First-Line Lenvatinib Plus Pembrolizumab Versus Chemotherapy for Advanced Endometrial Cancer: A Randomized, Open-Label, Phase III Trial

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ABSTRACT

PURPOSE Lenvatinib plus pembrolizumab (len + pembro) significantly improved progression-free survival (PFS) and overall survival (OS) versus chemotherapy in previously treated advanced or recurrent endometrial cancer (aEC) in the phase III Study 309/KEYNOTE-775. We report results from the phase III, randomized, open-label European Network of Gynaecological Oncological Trial-en9/LEAP-001 study (ClinicalTrials.gov identifier: NCT03884101) that evaluated len + pembro versus chemotherapy in first-line aEC.

METHODS Patients with stage III to IV or recurrent, radiographically apparent EC and no previous chemotherapy or disease progression ≥6 months after neo/adjuvant platinum-based chemotherapy were randomly assigned 1:1 to lenvatinib 20 mg once daily plus pembrolizumab 200 mg once every 3 weeks or paclitaxel 175 mg/m² plus carboplatin AUC 6 mg/mL/min once every 3 weeks. Primary end points were PFS and OS, evaluated in the mismatch repair-proficient (pMMR) and all-comers populations. Noninferiority was assessed for OS at final analysis (FA) for len + pembro versus chemotherapy (multiplicity-adjusted, one-sided nominal alpha, .0159; null hypothesis–tested hazard ratio [HR], 1.1).

RESULTS Eight hundred forty-two patients were randomly assigned (len + pembro, n = 420 [pMMR population, n = 320]; chemotherapy, n = 422 [pMMR population, n = 322]). At FA (data cutoff, October 2, 2023), median PFS (95% CI) in the pMMR population was 9.6 (8.2 to 11.9) versus 10.2 (8.4 to 10.5) months with len + pembro versus chemotherapy (hazard ratio [HR], 0.99 [95% CI, 0.82 to 1.21]) and among all-comers was 12.5 (10.3 to 15.1) versus 10.2 (8.4 to 10.4) months (HR, 0.91 [95% CI, 0.76 to 1.09]; descriptive analyses). Median OS (95% CI) in the pMMR population was 30.9 (25.4 to 37.7) versus 29.4 (26.2 to 35.4) months with len + pembro versus chemotherapy (HR, 1.02 [95% CI, 0.83 to 1.26]; noninferiority $P = .246$, not statistically significant per multiplicity control strategy) and among all-comers was 37.7 (32.2 to 43.6) versus 32.1 (27.2 to 35.7) months (HR, 0.93 [95% CI, 0.77 to 1.12]). Grade ≥3 treatment-related adverse events occurred in 331/420 (79%) versus 274/411 (67%) treated patients.

CONCLUSION First-line len + pembro did not meet prespecified statistical criteria for PFS or OS versus chemotherapy in pMMR aEC.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

Endometrial cancer (EC) is the sixth most common cancer among women globally[1,2] and the fourth most common cancer among women in the United States and Europe.[3,4] There was a substantial increase in age-standardized incidence rates of EC in 26 of 43 populations worldwide between 1998 and 2013,[5] and Europe has been found to have the highest age-standardized death rate for EC among WHO regions.[2] Patients diagnosed with metastatic EC have a poor

CONTEXT

Key Objective

Is the combination of lenvatinib plus pembrolizumab superior to chemotherapy as first-line treatment for advanced or recurrent endometrial cancer?

Knowledge Generated

In the phase III, randomized, open-label European Network of Gynaecological Oncological Trial-en9/LEAP-001 study, lenvatinib plus pembrolizumab did not improve progression-free survival or overall survival over chemotherapy, either in all-comers or in patients with mismatch repair-proficient disease. Toxicity was manageable; no new safety signals were identified.

Relevance *(K.D. Miller)*

Negative trials are important and may inform practice as much as positive trials. Paclitaxel-carboplatin–containing regimens are standard-of-care initial treatment for advanced endometrial cancer. The lenvatinib/pembrolizumab combination is an effective option in patients with progression on or after previous chemotherapy.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

prognosis, with an estimated 5-year survival of <20%.[2,3] In the United States, mortality rates associated with EC have increased faster than any other cancer type, with an average annual increase of 1.7% between 2012 and 2021.[3]

The combination of the multitargeted tyrosine kinase inhibitor lenvatinib plus the anti–PD-1 monoclonal antibody pembrolizumab is an approved and established treatment for advanced or recurrent endometrial cancer (aEC), both in patients with mismatch repair-proficient (pMMR) tumors and regardless of MMR status, after disease progression (PD) on previous systemic therapy in any setting.[6,7] This is based on results from the phase I/II Study 111/KEYNOTE-146[8,9] and confirmatory phase III Study 309/KEYNOTE-775.[10,11] In Study 309/KEYNOTE-775, treatment with len + pembro significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus physician's choice chemotherapy in patients with previously treated advanced, metastatic, or recurrent EC.[10] Clinical benefit was also maintained with longer follow-up.[11] The safety profile of len + pembro was manageable and similar across Study 309/KEYNOTE-775 and Study 111/KEYNOTE-146.[8,9,11]

Chemotherapy-based regimens, including in combination with immunotherapy, are a standard treatment approach as first-line therapy for inoperable stage III to IV or recurrent EC. National Comprehensive Cancer Network recommendations for first-line immunotherapy plus paclitaxel-carboplatin stem from the phase III NRG-GY018[12] and RUBY[13] trials of anti–PD-1 monoclonal antibodies pembrolizumab and dostarlimab.[7] At initiation of the phase III European Network of Gynaecological Oncological Trial (ENGOT)-en9/LEAP-001 study, standard of care for first-line treatment of aEC was paclitaxel-carboplatin, as established by the GOG0209 study.[14] This study evaluated whether len + pembro can improve outcomes compared with paclitaxel-carboplatin in the first-line setting in patients with stage III to IV or recurrent EC. To our knowledge, ENGOT-en9/LEAP-001 is the first trial with registrational intent comparing the efficacy and safety of a novel chemotherapy-free combination treatment regimen with standard-of-care chemotherapy for the treatment of EC.

METHODS

Study Design and Patients

This global, open-label, randomized, phase III trial was conducted at 171 cancer treatment centers, in collaboration with ENGOT. The trial was conducted in accordance with local and national regulations and ethical requirements outlined in the Declaration of Helsinki. Institutional review boards or independent ethics committees at each study site approved the trial protocol and all amendments. All patients provided written informed consent before participation. Efficacy and safety data from the trial were monitored by an external data and safety monitoring committee.

The study design for ENGOT-en9/LEAP-001 has been previously described in detail.[15] Briefly, eligible patients were females age 18 years and older with stage III-IV or recurrent, histologically confirmed EC that was measurable or non-measurable per RECIST version 1.1[16] and radiographically apparent per blinded independent central review (BICR). Patients may have received one previous line of platinum-based chemotherapy as neo/adjuvant therapy (with/without radiation), if recurrence occurred ≥6 months after the last dose of chemotherapy. Additional details are provided in the Data Supplement (Supplementary Methods and section 5, online only) of the protocol.

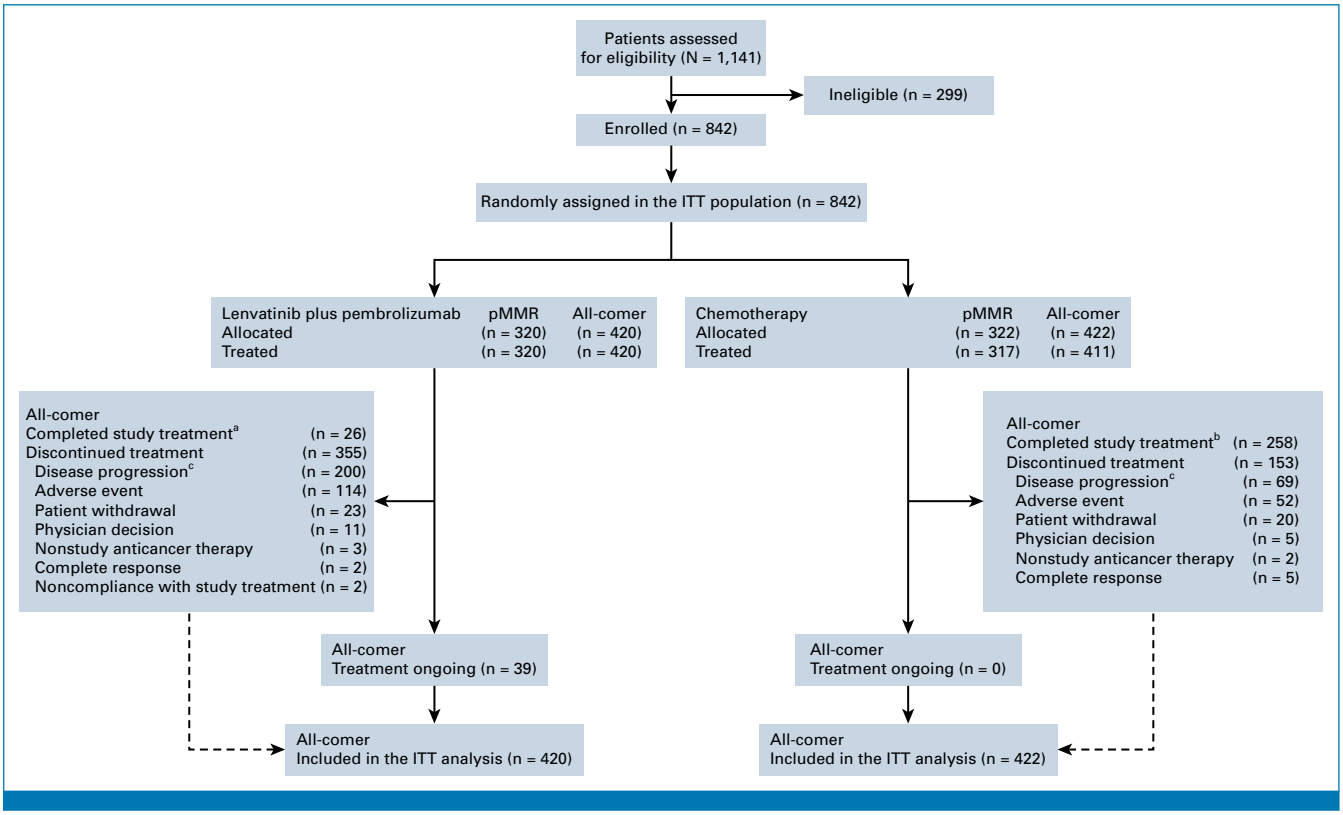


FIG 1. LEAP-001 trial profile. [a]Completed 35 infusions of pembrolizumab in cases where lenvatinib was discontinued before 35 infusions of pembrolizumab. [b]Received seven or more cycles of paclitaxel plus carboplatin, or per local standard. [c]Includes patients with clinical progression or progressive disease. ITT, intention-to-treat; pMMR, mismatch repair-proficient.

Treatment

Patients were randomly assigned 1:1 to lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously once every 3 weeks, or paclitaxel 175 mg/m² combined with carboplatin area under the concentration-time curve 6 mg/mL/min intravenously once every 3 weeks. Randomization was stratified first by MMR status (mismatch repair-deficient [dMMR] *v* pMMR), and then for those with pMMR tumors, by Eastern Cooperative Oncology Group performance status (0 *v* 1), measurable disease (yes *v* no), and previous chemotherapy or chemoradiation (yes *v* no). Patients received ≤35 cycles of pembrolizumab, but lenvatinib treatment could continue after discontinuation of pembrolizumab. Patients received ≤7 cycles of paclitaxel-carboplatin, although patients with ongoing clinical benefit could continue beyond seven cycles after sponsor consultation. Treatment continued for the specified duration or until PD, unacceptable toxicity, or withdrawal of consent.

Assessments

Tumor imaging was performed every 9 weeks from random assignment through week 54 and every 12 weeks thereafter or until PD, start of new anticancer treatment, patient withdrawal, or death. Adverse events (AEs) were assessed from random assignment through 90 days (120 days for serious AEs) after treatment discontinuation and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patient-reported outcomes (PROs) were evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire–Endometrial Cancer Module (QLQ-EN24). Additional details are provided in the Data Supplement (Supplementary Methods).

End Points

Dual primary end points were PFS as assessed by BICR using RECIST version 1.1 and OS. Secondary end points were ORR as assessed per RECIST version 1.1 by BICR, mean change from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) score, and safety. Duration of response (DOR) and disease control (defined as best overall response of complete or partial response, or stable disease achieved ≥7 weeks after random assignment) were exploratory end points.

Statistical Analysis

Two interim analyses and a final analysis (FA) were conducted per the study protocol (Data Supplement, Supplementary Methods). PFS results of the second interim

TABLE 1. Demographics and Disease Characteristics of All the Trial Patients at Baseline[a]

Characteristic	pMMR Population		All Patients	
	Lenvatinib Plus Pembrolizumab (n = 320)	Chemotherapy (n = 322)	Lenvatinib Plus Pembrolizumab (n = 420)	Chemotherapy (n = 422)
Age, years, median (range)	63.5 (22-87)	64.0 (32-88)	63.0 (22-93)	64.0 (32-88)
Age <65 years, No. (%)	172 (54)	162 (50)	232 (55)	216 (51)
Race, No. (%)				
White	217 (68)	217 (67)	288 (69)	300 (71)
Asian	88 (28)	88 (27)	114 (27)	102 (24)
Black or African American	8 (3)	12 (4)	10 (2)	14 (3)
Multiple, No. (%)				
Black or African American, White	4 (1)	1 (<1)	5 (1)	2 (<1)
American Indian or Alaska Native, White	3 (1)	2 (1)	3 (1)	2 (<1)
Black or African American, Native Hawaiian, or Other Pacific Islander	0	1 (<1)	0	1 (<1)
Native Hawaiian or Other Pacific Islander	0	1 (<1)	0	1 (<1)
Geographic region, No. (%)				
North America	70 (22)	74 (23)	98 (23)	104 (25)
Western Europe	57 (18)	55 (17)	83 (20)	78 (18)
Asia	76 (24)	80 (25)	99 (24)	92 (22)
Rest of the world	117 (37)	113 (35)	140 (33)	148 (35)
MMR status, No. (%)				
pMMR	320 (100)	322 (100)	320 (76)	322 (76)
dMMR	0	0	100 (24)	100 (24)
ECOG performance status, No. (%)[b]				
0	179 (56)	177 (55)	250 (60)	240 (57)
1	141 (44)	145 (45)	170 (40)	182 (43)
Measurable disease, No. (%)	318 (99)	317 (98)	418 (96)	416 (99)
Previous chemotherapy and/or chemoradiation, No. (%)	60 (19)	59 (18)	74 (18)	68 (16)
Chemoradiation alone	7 (2)	8 (2)	11 (3)	10 (2)
Neoadjuvant or adjuvant chemotherapy alone	52 (16)	50 (16)	62 (15)	57 (14)
Neoadjuvant or adjuvant chemotherapy and chemoradiation	1 (<1)	1 (<1)	1 (<1)	1 (<1)
None	260 (81)	263 (82)	346 (82)	354 (84)
Histology, No. (%)				
High-grade endometrioid carcinoma	98 (31)	90 (28)	139 (33)	127 (30)
Non–high-grade endometrioid carcinoma[c]	98 (31)	109 (34)	141 (34)	156 (37)
Clear cell carcinoma	11 (3)	19 (6)	12 (3)	19 (5)
Serous carcinoma[d]	76 (24)	76 (24)	77 (18)	80 (19)
Mixed	23 (7)	15 (5)	29 (7)	23 (5)
Other[e]	14 (4)	13 (4)	22 (5)	17 (4)
FIGO stage IVB at initial diagnosis, No. (%)	131 (41)	124 (39)	165 (39)	150 (36)

NOTE. Percentages may not total 100 because of rounding.

Abbreviations: dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; pMMR, mismatch repair-proficient.

[a]Key baseline characteristics were consistent between subgroups and the overall population.

[b]ECOG performance status is assessed on a 5-point scale, with higher scores indicating greater disability.

[c]Includes endometrioid carcinoma, endometrioid carcinoma with squamous differentiation, and low-grade endometrioid carcinoma.

[d]Includes serous carcinoma and high-grade serous carcinoma.

[e]Includes adenocarcinoma, high-grade mucinous carcinoma, low-grade mucinous carcinoma, neuroendocrine, undifferentiated histology, and other histologies.

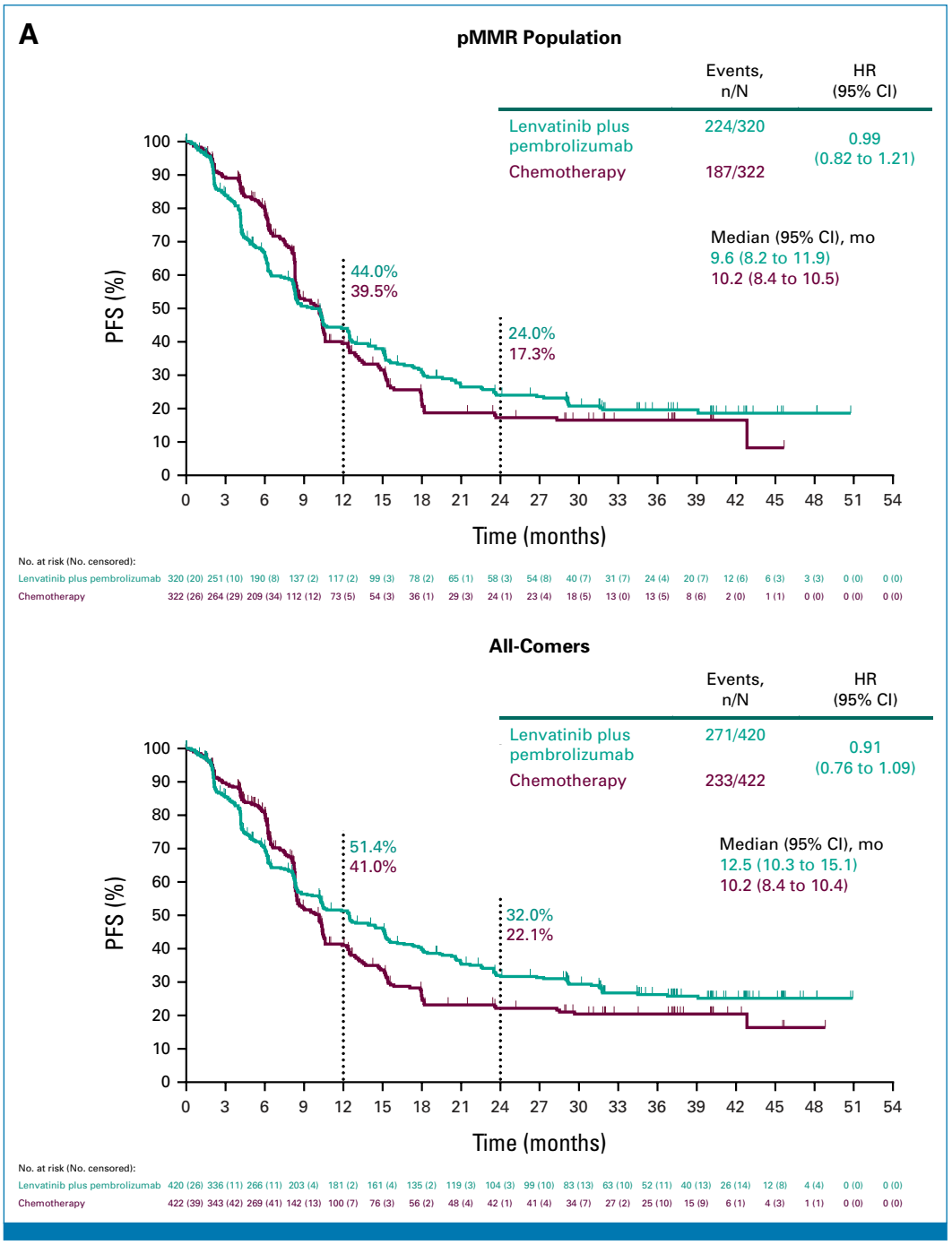
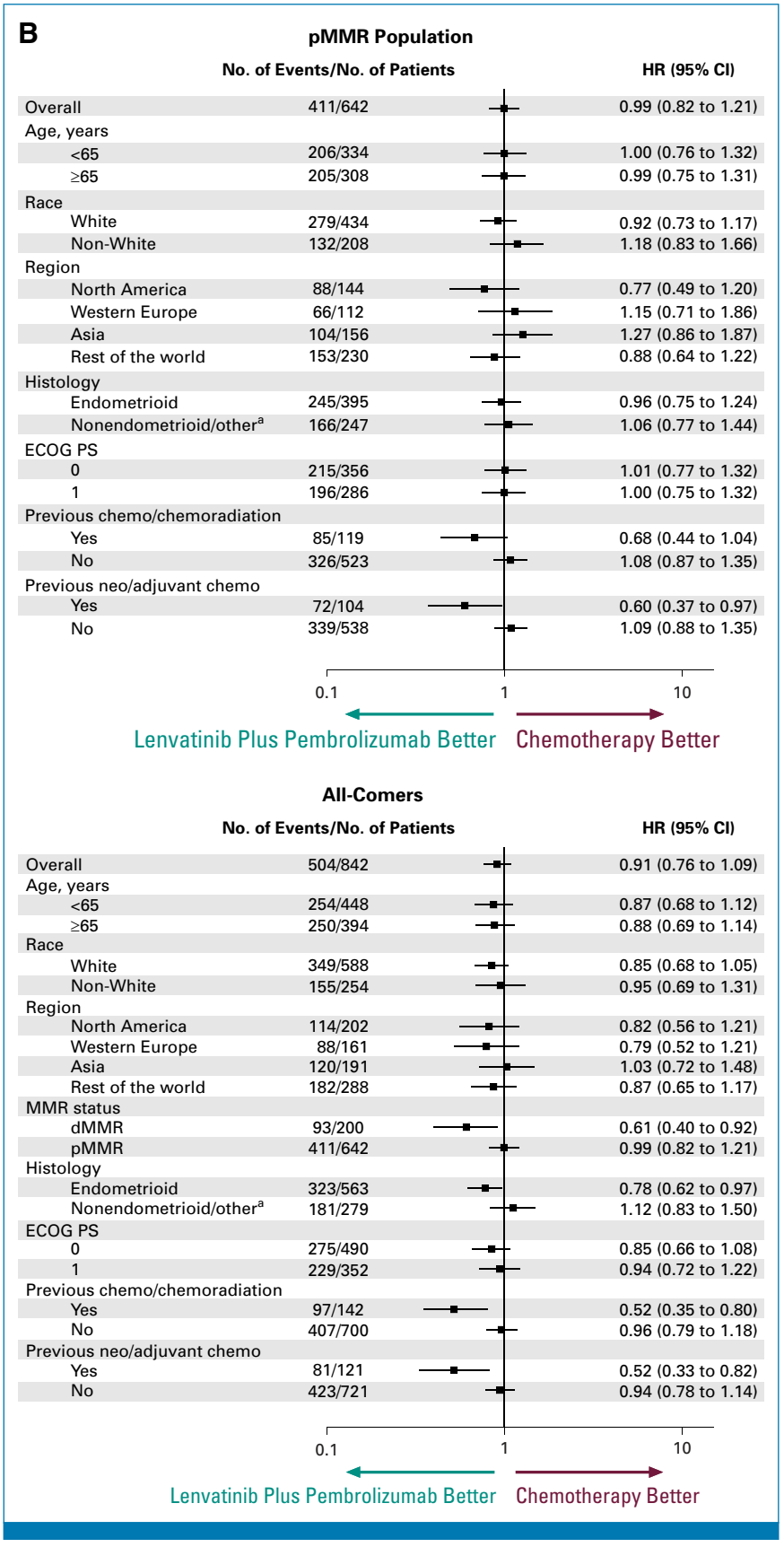


FIG 2. Descriptive analysis of PFS at the time of the final overall survival analysis. Kaplan-Meier estimates of PFS (A) in the pMMR population and among all-comers; (B) in key patient subgroups in the pMMR population and among all-comers; (C) in the dMMR subgroup; and (D) in the subgroup of patients in the pMMR and all-comers populations who had received previous neoadjuvant or adjuvant chemotherapy. Tick marks indicate censored data. [a]Includes nonendometrioid, adenocarcinoma with no further information (17 patients in the pMMR population; 22 patients among all-comers), and other histologies (two patients in the pMMR population; three patients among all-comers). dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MMR, mismatch repair; NR, not reached; PFS, progression-free survival; pMMR, mismatch repair-proficient. (continued on following page)

analysis (IA2; ie, the prespecified FA for PFS), and OS and PFS results of the FA (ie, the prespecified FA for OS), are reported. Efficacy was assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients, and was analyzed in the pMMR and all-comers populations. Safety was assessed in all randomly assigned patients who received ≥1 dose of study treatment. PROs were assessed in patients who received ≥1 dose of study treatment and



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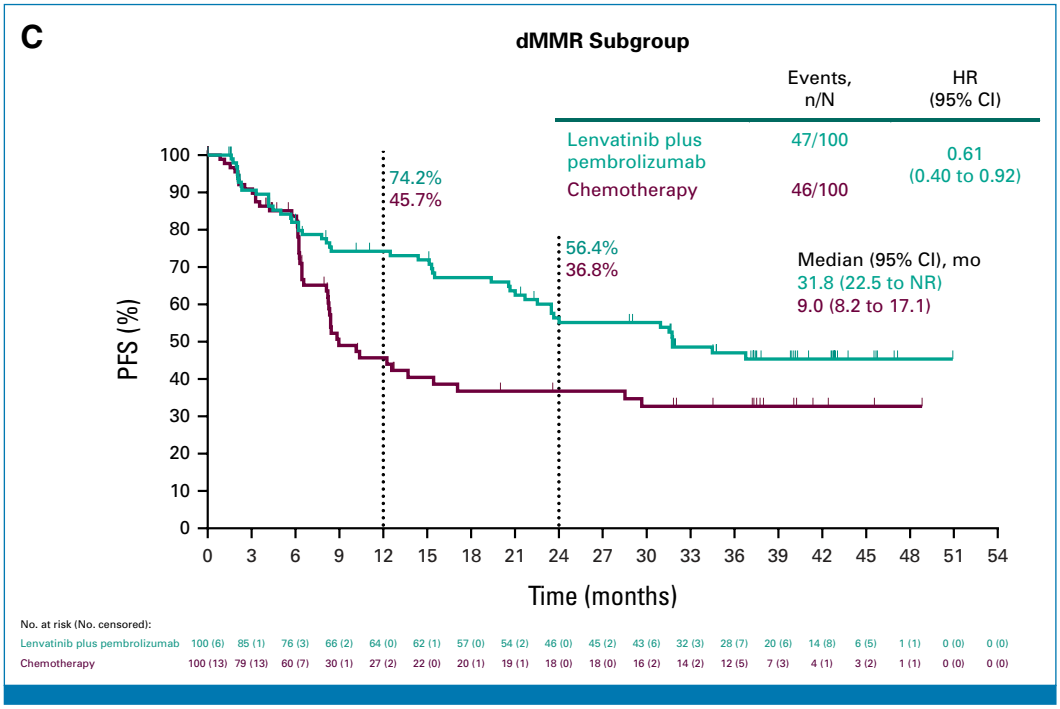

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had ≥1 health-related quality of life (HRQoL) assessment available. The planned sample size and power calculations were based on the pMMR population, with 612 planned patients. Additional details are provided in the Data Supplement (Supplementary Methods).

RESULTS

Patients

Between May 8, 2019, and March 25, 2021, 842 patients were randomly assigned to receive len + pembro (n = 420) or chemotherapy (n = 422), including 642 patients in the pMMR population (200 patients had dMMR tumors). All patients in the len + pembro group and 411 patients in the chemotherapy group received ≥1 dose of treatment (Fig 1). Median time from random assignment to the FA data cutoff date (October 2, 2023) was 38.4 (range, 30.3–52.9) months. Demographics and baseline disease characteristics were similar between treatment groups, in pMMR and all-comers populations (Table 1). In the pMMR population, 53 (17%) of 320 patients in the len + pembro group versus 51 (16%) of 322 in the chemotherapy group had received previous neo/adjuvant chemotherapy; among all-comers, 63 (15%) and 58 (14%) patients, respectively, had received previous neo/adjuvant chemotherapy.

At the FA data cutoff, 28 patients (9%) in the pMMR and 39 patients (9%) in the all-comers populations in the len + pembro group remained on study treatment; no patients in the chemotherapy group remained on study treatment. Among patients eligible for subsequent anticancer therapy, 156 patients (55%) in the len + pembro group and 192 (64%) in the chemotherapy group received such therapy in the pMMR population, including 13 (5%) and 84 (28%) patients, respectively, who received subsequent anti–PD-(L)1 therapy; 189 (53%) and 246 (63%) patients, respectively, received subsequent therapy among all-comers, including 13 (4%) and 115 (30%) patients who received subsequent anti–PD-(L)1 therapy (Data Supplement, Table S1). Additional subsequent therapy data for all patients randomly assigned are provided in the Data Supplement, (Table S2).

Efficacy

At IA2, the final prespecified formal analysis for PFS (data cutoff, December 19, 2022), 403 of 642 patients (63%) in the pMMR population experienced a PFS event. Median PFS (95% CI) was 9.6 (8.2 to 11.9) months in the len + pembro group versus 10.2 (8.4 to 10.4) months in the chemotherapy group (hazard ratio [HR], 1.01 [95% CI, 0.83 to 1.24]; Data Supplement, Fig S2A). Among all-comers (n = 842), 491 patients (58%) experienced a PFS event. Median PFS (95% CI) was 12.5 (10.3 to 15.1) versus 10.2 (8.4 to 10.4) months, respectively (HR, 0.92 [95% CI, 0.77 to 1.10]; Data Supplement, Fig S2B).

At the FA for OS (data cutoff, October 2, 2023), the PFS analysis was descriptive only. Of 642 patients in the pMMR population, 411 (64%) experienced a PFS event. Median PFS

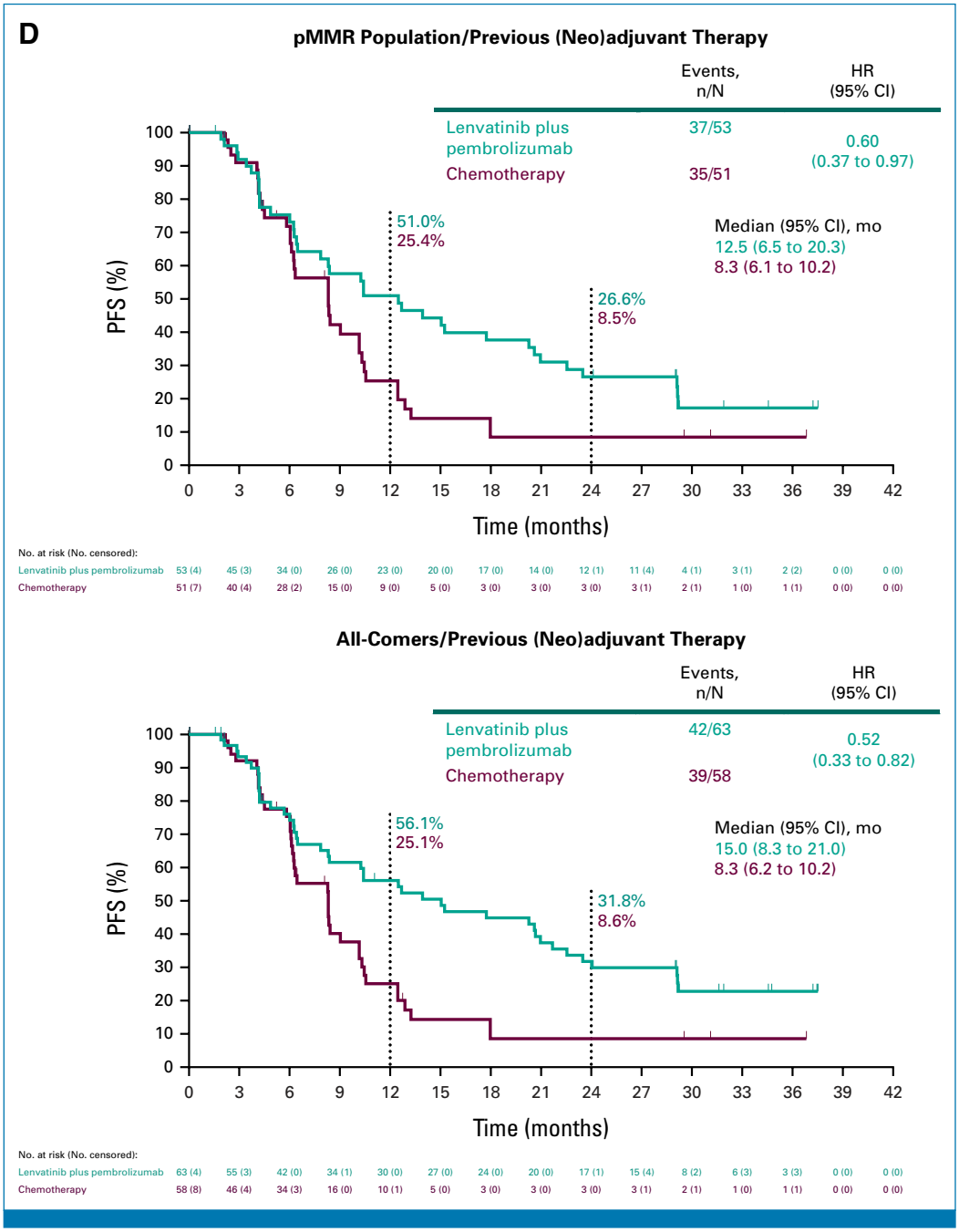


FIG 2. (Continued).

(95% CI) was 9.6 (8.2 to 11.9) months with len + pembro versus 10.2 (8.4 to 10.5) months with chemotherapy (HR, 0.99 [95% CI, 0.82 to 1.21]; Fig 2A). Among all-comers (n = 842), 504 patients (60%) experienced a PFS event. Median PFS (95% CI) was 12.5 (10.3 to 15.1) and 10.2 (8.4 to 10.4) months, respectively (HR, 0.91 [95% CI, 0.76 to 1.09]). PFS results were similar in most subgroups, except in patients who had received previous neo/adjuvant chemotherapy in the pMMR and all-comers populations, and the dMMR subgroup, where HRs favored len + pembro (Figs 2B-2D).

At FA of OS, 366 patients (57%) in the pMMR population had died. Median OS (95% CI) was 30.9 (25.4 to 37.7) months with len + pembro versus 29.4 (26.2 to 35.4) months with chemotherapy (HR, 1.02 [95% CI, 0.83 to 1.26]; 1-sided noninferiority $P = .246$, not statistically significant as prespecified OS noninferiority boundary was $P = .0159$ calculated on the basis of actual OS events at FA; Fig 3A). Among all-comers, 442 patients (52%) had died. Median OS (95% CI) was 37.7 (32.2 to 43.6) versus 32.1 (27.2 to 35.7) months, respectively (HR, 0.93 [95% CI, 0.77 to 1.12]). OS was similar

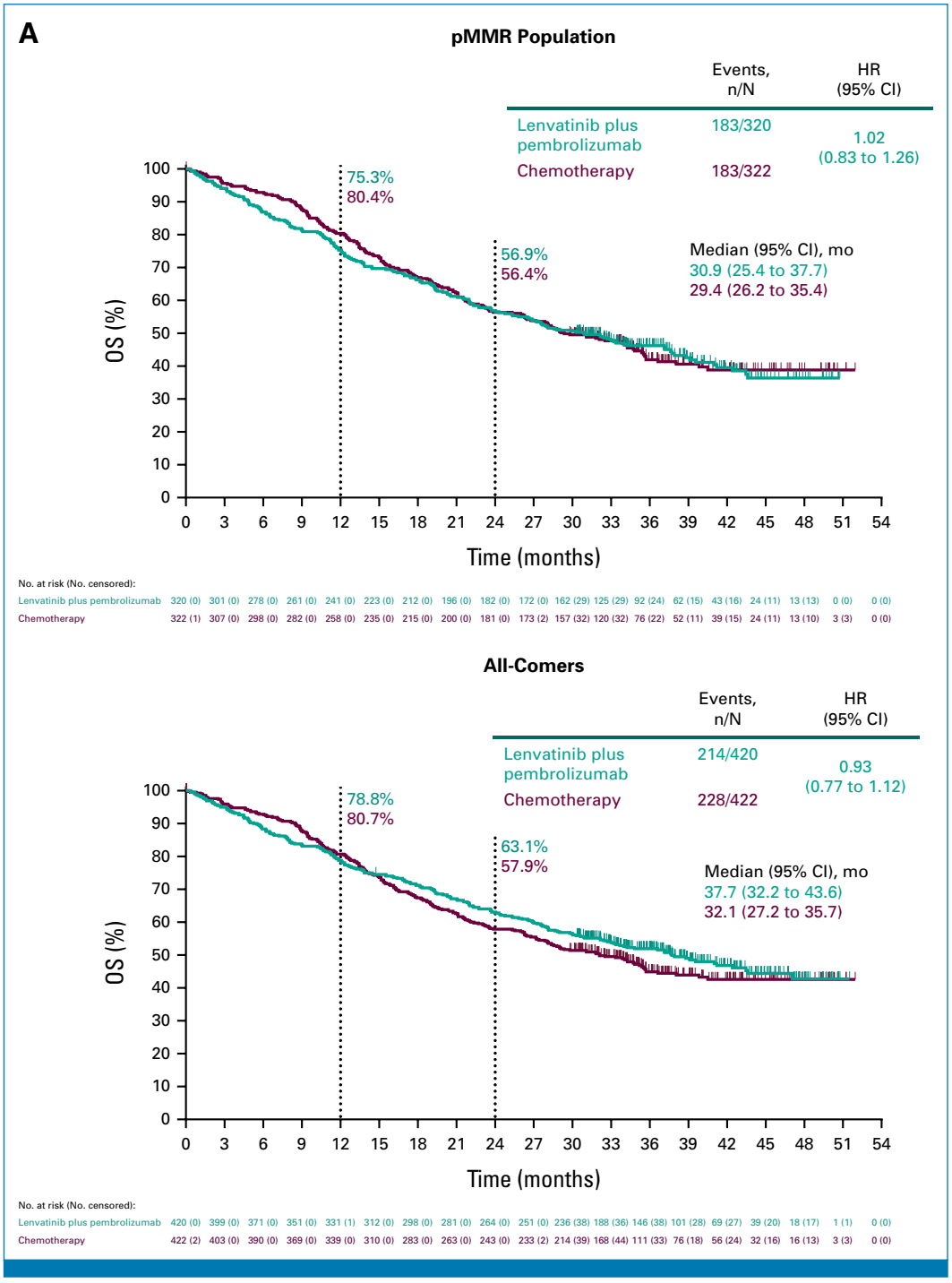
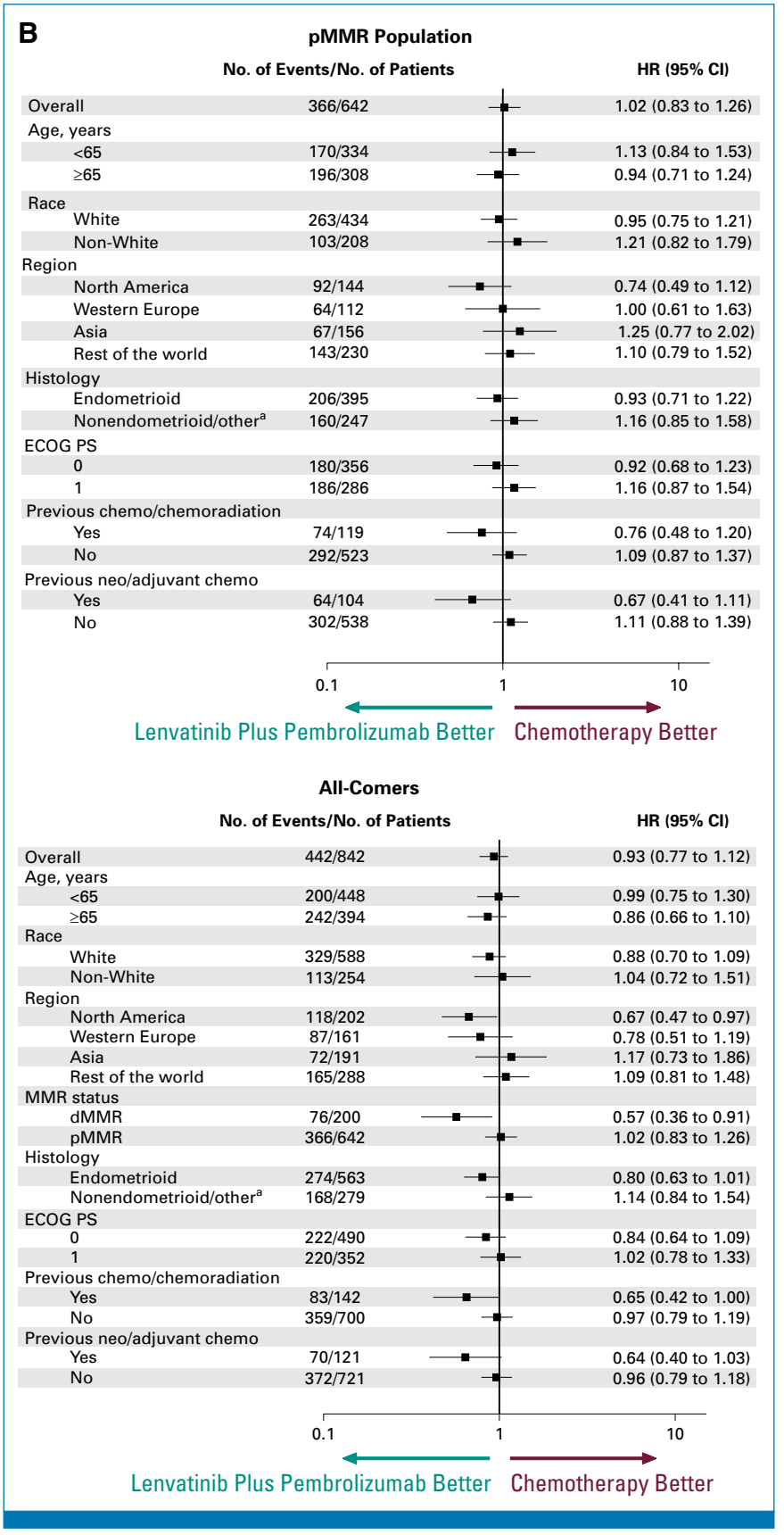


FIG 3. Kaplan-Meier estimates of OS (A) in the pMMR population and among all-comers; (B) in key patient subgroups in the pMMR population and among all-comers; (C) in the dMMR subgroup; and (D) in the subgroup of patients in the pMMR and all-comers populations who had received previous neoadjuvant or adjuvant chemotherapy. Tick marks indicate censored data. [a]Includes nonendometrioid, adenocarcinoma with no further information (17 patients in the pMMR population; 22 patients among all-comers), and other histologies (two patients in the pMMR population; three patients among all-comers). dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MMR, mismatch repair; NR, not reached; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair-proficient. (continued on following page)

between treatment groups for most patient subgroups, except, consistent with PFS results, HR point estimates favored len + pembro among patients who had received previous neo/adjuvant chemotherapy in the pMMR and all-comers populations, and in the dMMR subgroup (Figs 3B-3D).



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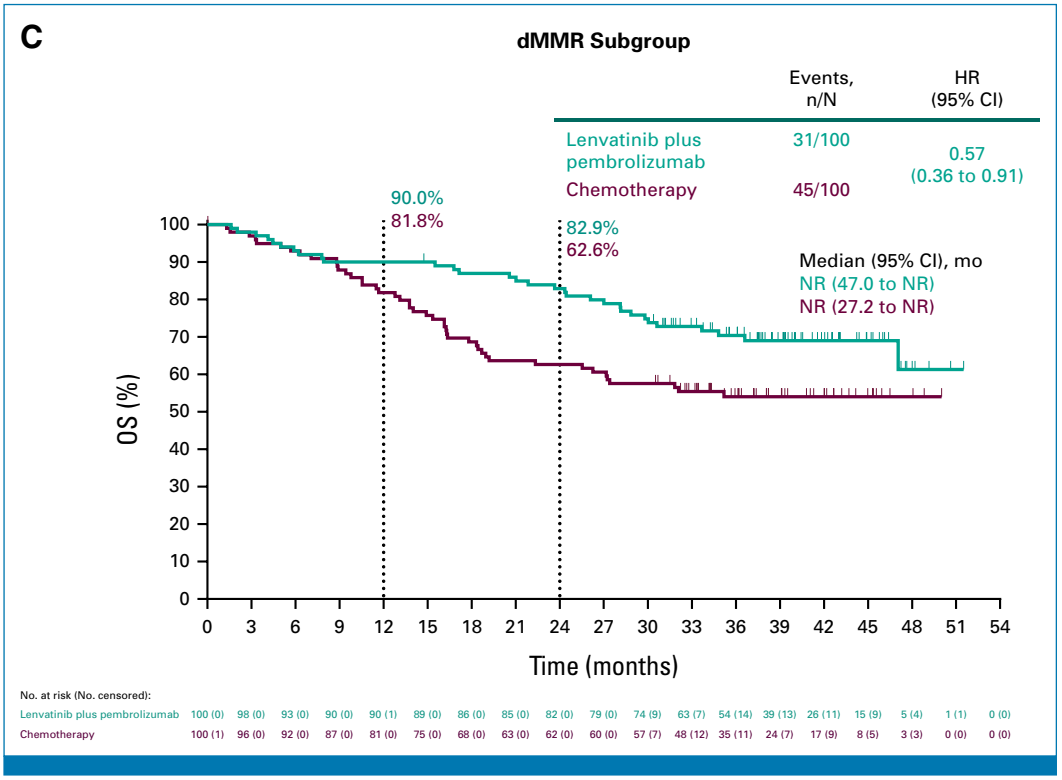

FIG 3. (Continued).

In the pMMR population, ORR (95% CI) was 51% (45 to 56) in the len + pembro group versus 55% (49 to 60) in the chemotherapy group (Fig 4A). Among all-comers, ORR (95% CI) was 56% (51 to 61) and 55% (51 to 60), respectively. In the pMMR population, disease control rates (95% CI) were 83% (78 to 87) versus 85% (81 to 89), and among all-comers were 84% (78 to 87) versus 84% (80 to 88), respectively. Median DOR was longer with len + pembro than with chemotherapy in the pMMR population (16.1 [range, 1.0+ to 48.7+] *v* 10.6 [range, 1.1+ to 43.8+] months; + indicates no PD at last disease assessment) and among all-comers (23.2 [range, 1.0+ to 49.0+] *v* 10.9 [range, 1.1+ to 46.9+] months). Among patients in the len + pembro group with measurable disease at baseline and ≥1 postbaseline tumor assessment, 277 of 299 patients (93%) in the pMMR and 370 of 396 (93%) in the all-comers populations had a reduction from baseline in target lesion size (Data Supplement, Figs S3A and S3B).

In exploratory analyses, PFS and OS improved with len + pembro versus chemotherapy in the subgroup of patients with dMMR tumors (PFS HR, 0.61 [95% CI, 0.40 to 0.92]; OS HR, 0.57 [95% CI, 0.36 to 0.91]; Figs 2C and 3C). ORR in this subgroup was higher with len + pembro versus chemotherapy (72% [95% CI, 62% to 81%] *v* 58% [95% CI, 48 to 68]) and median DOR was not reached (range, 2.8 to 49.0+ months) versus 11.7 (range, 2.1+ to 46.9+) months (Fig 4B). PFS and OS were also favorable with len + pembro versus chemotherapy in patients who had received previous neo/adjuvant chemotherapy in the pMMR (PFS HR, 0.60 [95% CI, 0.37 to 0.97]; OS HR, 0.67 [95% CI, 0.41 to 1.11]; Figs 2D and 3D) and all-comers (PFS HR, 0.52 [95% CI, 0.33 to 0.82]; OS HR, 0.64 [95% CI, 0.40 to 1.03]) populations. ORR was higher with len + pembro versus chemotherapy in the pMMR (60% *v* 43%) and all-comers (63% *v* 43%) populations, and median DOR was 16.6 (range, 2.1+ to 35.2+) versus 8.3 (range, 2.2+ to 30.6+) months in the pMMR and 19.9 (range, 2.1+ to 35.4+) versus 8.3 (range, 2.2+ to 30.6+) months in the all-comers populations (Fig 4C). Additional exploratory analyses demonstrated variable PFS and OS (Data Supplement, Figs S4A-S4D), and notable antitumor activity (Data Supplement, Figs S5A and S5B) across histologic subtypes, although patient numbers were limited and the study was not designed or powered to demonstrate differences in these subgroups.

Safety

The median duration of treatment was 316.5 (range, 1.0–1,568.0) days in the len + pembro group and 126.0 (range, 1.0–554.0) days in the chemotherapy group (drug exposure and lenvatinib dose reductions are further summarized in the Data Supplement, Tables S3-S5). Among patients who received ≥1 dose of treatment, 411 patients (98%) in the len + pembro group and 398 (97%) in the chemotherapy group experienced treatment-related AEs of any grade (Table 2). Grade 3 to 4 treatment-related AEs occurred in 321 patients

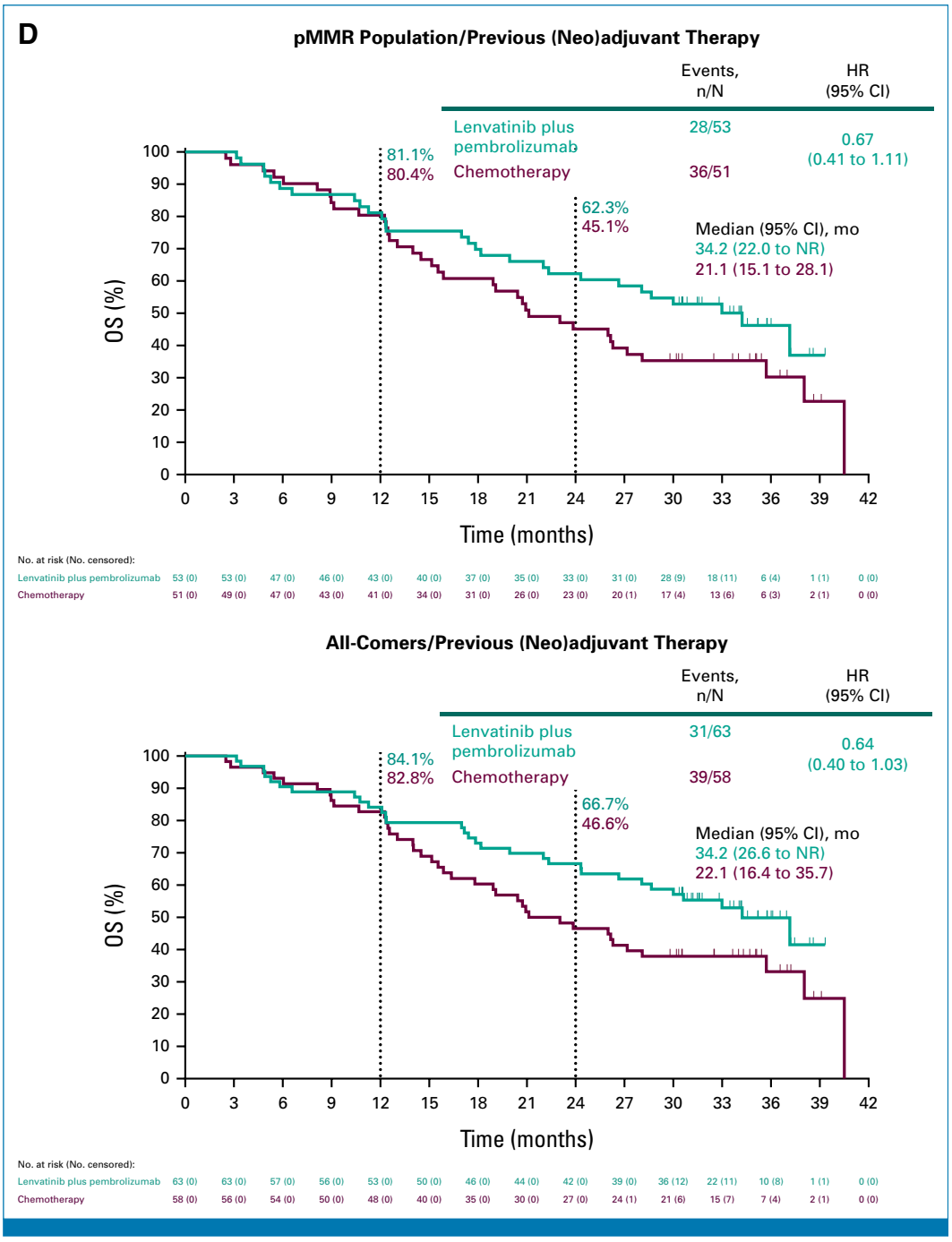

FIG 3. (Continued).

(76%) and 272 patients (66%), respectively. Grade 5 AEs are summarized in the Data Supplement (Table S6). Ten patients (2%) in the len + pembro group and two patients (<1%) in the chemotherapy group died due to treatment-related AEs (len + pembro group: cerebrovascular accident [n = 2]; large intestine perforation, death [general disorder], cerebral hemorrhage, hemorrhagic stroke, intracranial hematoma, acute respiratory failure, pneumonitis, and subcutaneous hemorrhage [n = 1 each]; chemotherapy group: pneumonia aspiration and sepsis [n = 1 each]). In the len + pembro group, the median time from onset of AEs leading to death, to date of death was 3.5 days (range, 1-214 days). Treatment-related AEs that led to discontinuation of any study treatment occurred in 165 patients (39%; 23 [5%] discontinued both lenvatinib and pembrolizumab) and 70 patients (17%), respectively. AEs of any cause resulted in lenvatinib dose reductions in 267 patients (64%), and resulted in dose reductions of any study treatment in 91 patients (22%) in the chemotherapy group (Data Supplement, Table S7). AEs of any cause led to interruption of any

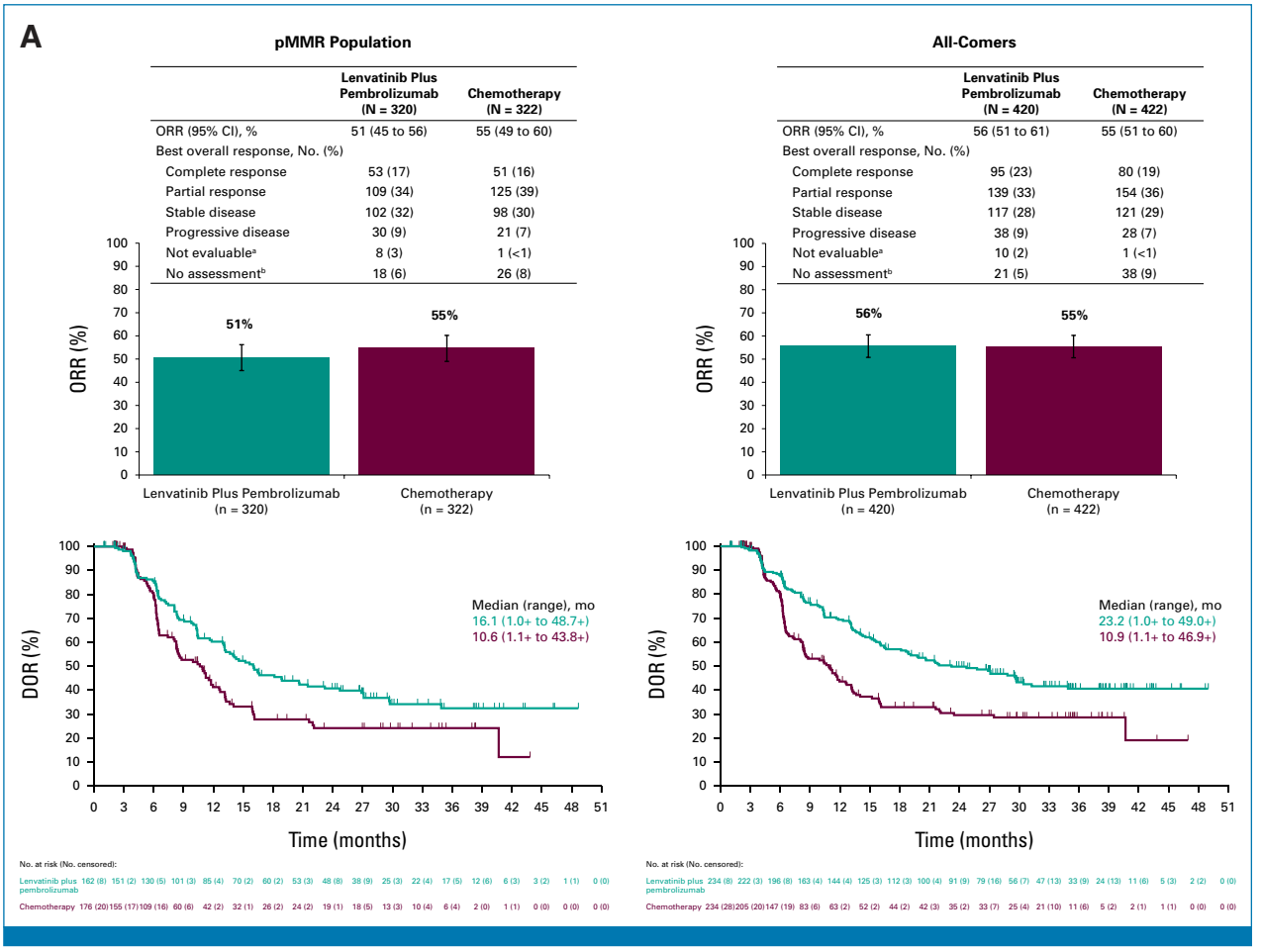

FIG 4. Confirmed tumor responses. Objective response rates and duration of response among patients with a complete or partial response (A) in the pMMR population and among all-comers; (B) in the dMMR subgroup; and (C) in the subgroup of patients who had received previous neoadjuvant or adjuvant chemotherapy. [a]Postbaseline assessment(s) available, but not evaluable. [b]No postbaseline assessment available for response evaluation. dMMR, mismatch repair-deficient; DOR, duration of response; ORR, objective response rate; pMMR, mismatch repair-proficient. (continued on following page)

study treatment in 301 patients (72%) in the len + pembro group and 168 patients (41%) in the chemotherapy group, and led to discontinuation of any study treatment in 199 (47%) and 80 patients (19%), respectively (Data Supplement, Table S7). AEs on the basis of MMR status are summarized in the Data Supplement (Table S8). The rate of study drug exposure–adjusted AEs of any cause was 147.5 events per 100 person-months of exposure versus 220.4 events per 100 person-months of exposure, respectively (Data Supplement, Table S9).

AEs of special interest for pembrolizumab, assessed irrespective of attribution to study intervention, occurred in 315 patients (75%) in the len + pembro group and 56 patients (14%) in the chemotherapy group, including 67 (16%) and 19 patients (5%), respectively, who had grade 3 to 5 AEs. One patient (<1%) in the len + pembro group died from an immune-mediated AE of pneumonitis (Data Supplement, Table S10). Clinically significant AEs for lenvatinib, assessed irrespective of attribution to study intervention, occurred in 403 patients (96%) in the len + pembro group and 192 patients (47%) in the chemotherapy group, including 272 (65%) and 60 patients (15%), respectively, who had grade 3-5 AEs. Grade 5 events, assessed irrespective of attribution to study intervention, occurred in 12 patients (3%) and one patient (<1%), respectively (Data Supplement, Table S11).

Patient-Reported Outcomes

Among 820 patients in the PRO population (len + pembro, n = 417; chemotherapy, n = 403), rates of completion and compliance with the EORTC QLQ-C30 and QLQ-EN24 instruments were >60% and >80% at 18 weeks, respectively, in both treatment groups. Mean changes from baseline to week 18 on the EORTC QLQ-C30 and QLQ-EN24 scales, including GHS/QoL, functional, and symptom scales, were generally similar between treatment groups in pMMR and all-comers populations, except outcomes were better with len + pembro for neuropathy, alopecia,

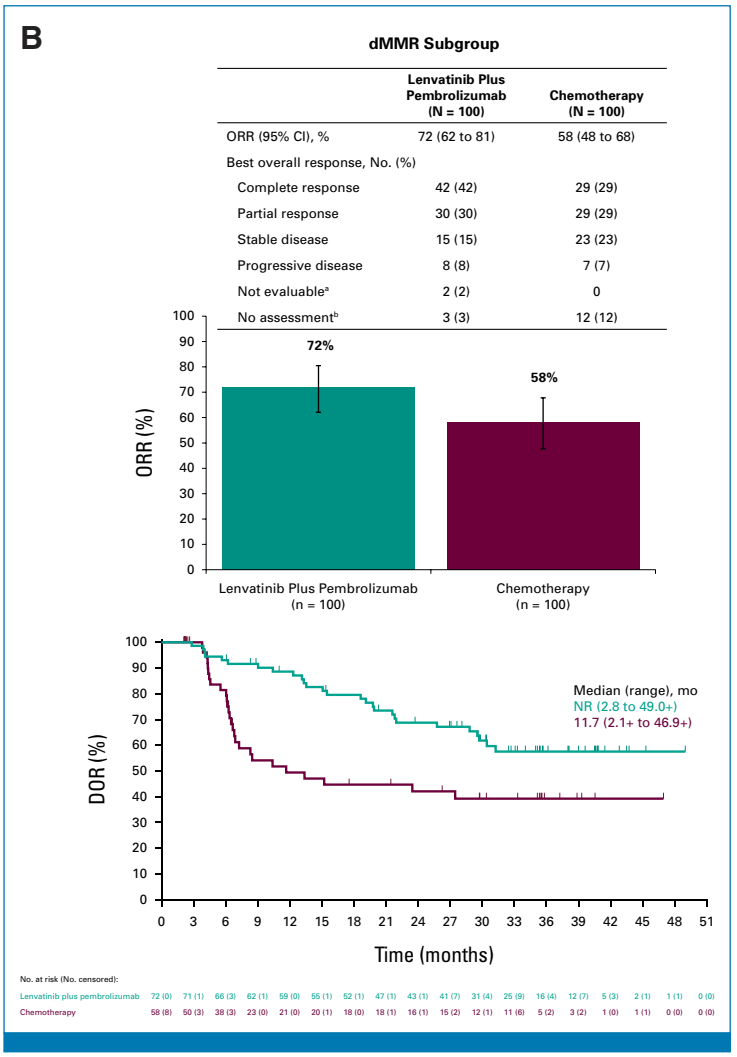

FIG 4. (Continued).

poor body image, and dyspnea (Data Supplement, Figs S6A-S6D).

DISCUSSION

This phase III trial of len + pembro versus paclitaxel-carboplatin did not meet the prespecified statistical criteria for PFS or OS as first-line treatment for patients with pMMR aEC. In the pMMR population, the prespecified statistical criterion for PFS was not met for superiority at IA1 or IA2 (ie, the FA for PFS). Furthermore, the prespecified statistical criterion for OS was not met for noninferiority at the FA. Response rates were generally similar between treatment groups in the pMMR population, although median DOR was numerically longer with len + pembro than with paclitaxel–carboplatin (16.1 *v* 10.6 months).

Our findings underscore the challenges of replacing rather than adding to the entrenched standard of care, paclitaxel-carboplatin, in aEC in the first-line setting. The benefits observed with len + pembro in the 14% of patients who had received previous neo/adjuvant chemotherapy who were being considered for platinum rechallenge were consistent with previously described positive results with len + pembro in Study 111/KEYNOTE-146[8,9] and Study 309/KEYNOTE-775,[10,11] where patients were considered to receive single-agent chemotherapy after previous platinum therapy in any setting. In ENGOT-en9/LEAP-001, for patients who had previously received neo/adjuvant chemotherapy, the combination prolonged PFS and demonstrated favorable OS, a higher ORR, and longer median DOR in the pMMR and all-comers populations. Len + pembro also prolonged PFS and OS and demonstrated higher ORR and longer median DOR in the dMMR subgroup.

No new safety signals were identified with either treatment regimen in our trial. It is difficult to compare results between trials because of numerous factors. However, the types and rates of AEs that occurred were consistent with previous findings with len + pembro[8-11] and paclitaxel-carboplatin[12-14,17] in patients with EC. The safety profile of len + pembro was also consistent regardless of MMR status.

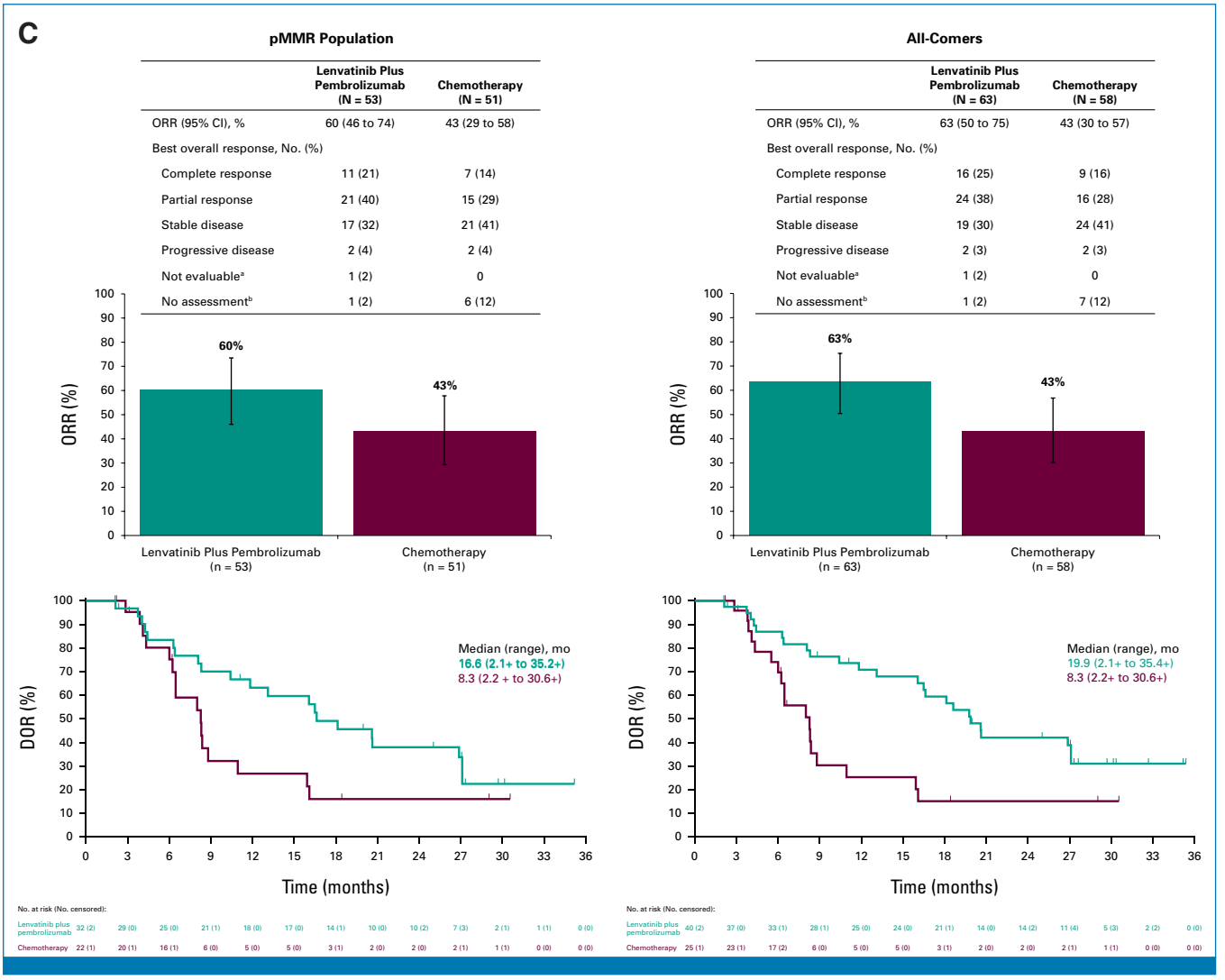

FIG 4. (Continued).

The incidence of treatment-related grade ≥3 AEs, including events leading to death, was higher with len + pembro compared with paclitaxel-carboplatin in our trial, which may be due in part to the longer duration of treatment in the len + pembro group. Notably, when accounting for increased drug exposure in the len + pembro group, the rate of exposure-adjusted AEs was higher in the chemotherapy group. Importantly, although lenvatinib dose reductions were observed, data across lenvatinib clinical trials demonstrate the importance of initiating treatment at the recommended dose, with subsequent dose modifications as necessary, to optimize clinical benefit[18]; dose modifications are also common with other tyrosine kinase inhibitors.[19–22] Similar proportions of patients in both treatment groups were able to make the transition to subsequent anticancer therapy, suggesting that len + pembro was not associated with safety concerns that prohibited further therapy. HRQoL was similar between treatment groups across most QoL scales, although results for neuropathy, alopecia, poor body image, and dyspnea symptom scales were better with len + pembro.

To our knowledge, ENGOT-en9/LEAP-001 is the first registrational-intent trial to compare a novel combination treatment strategy with chemotherapy for the first-line treatment of aEC. In our trial, the efficacy results with the chemotherapy regimen were as expected for the treatment of aEC as first-line therapy,[12–14,17] with len + pembro providing similar clinical benefit compared with this standard of care, although the combination did not meet the predefined statistical criterion required for declaring noninferiority. Although no definitive conclusions can be made, the preplanned subgroup analysis for patients with previous chemotherapy showed meaningful clinical benefit with len + pembro. Notably, Study 309/KEYNOTE-775[10] demonstrated benefit for patients with EC after previous systemic therapy in any setting (including neo/adjuvant). Results from LEAP-001 further suggest this benefit may extend to patients being considered for rechallenge with platinum doublet therapy because of recurrence ≥6 months after previous neo/adjuvant chemotherapy, given the apparent attenuated benefit of platinum rechallenge[23] and the

TABLE 2. Incidence of Treatment-Related Adverse Events Among All Patients as Treated

TRAE	Lenvatinib Plus Pembrolizumab (n = 420)		Chemotherapy (n = 411)	
Any TRAE, No. (%)	411 (98)		398 (97)	
Grade 3 to 4	321 (76)		272 (66)	
Grade 5[a]	10 (2)		2 (<1)	
Serious	120 (29)		45 (11)	
TRAEs that led to discontinuation of any treatment, No. (%)	165 (39)		70 (17)	
Lenvatinib	124 (30)		—	
Pembrolizumab	77 (18)		—	
Both lenvatinib and pembrolizumab	23 (5)		—	
TRAEs with incidence ≥20% in either treatment group, No. (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	263 (63)	179 (43)	11 (3)	5 (1)
Hypothyroidism	248 (59)	4 (1)	2 (<1)	0
Diarrhea	177 (42)	33 (8)	67 (16)	2 (<1)
Proteinuria	129 (31)	29 (7)	4 (1)	1 (<1)
Fatigue	121 (29)	18 (4)	109 (27)	5 (1)
Nausea	118 (28)	7 (2)	165 (40)	3 (<1)
Decreased appetite	103 (25)	10 (2)	72 (18)	3 (<1)
ALT increased	91 (22)	17 (4)	40 (10)	4 (1)
AST increased	87 (21)	15 (4)	24 (6)	1 (<1)
Arthralgia	72 (17)	6 (1)	83 (20)	3 (<1)
Anemia	41 (10)	2 (<1)	198 (48)	62 (15)
Alopecia	26 (6)	0	216 (53)	3 (<1)
Neutrophil count decreased	21 (5)	7 (2)	122 (30)	106 (26)
Neutropenia	17 (4)	5 (1)	125 (30)	96 (23)
WBC count decreased	14 (3)	0	102 (25)	62 (15)
Peripheral neuropathy	7 (2)	0	107 (26)	7 (2)
Peripheral sensory neuropathy	4 (1)	0	89 (22)	6 (1)

Abbreviation: TRAEs, treatment-related adverse events.
[a]Grade 5 TRAEs in the lenvatinib plus pembrolizumab group: cerebrovascular accident (n = 2) and large intestine perforation, death (general disorder), cerebral hemorrhage, hemorrhagic stroke, intracranial hematoma, acute respiratory failure, pneumonitis, and subcutaneous hemorrhage (n = 1 each); and in the chemotherapy group: pneumonia aspiration and sepsis (n = 1 each).

consistent activity of len + pembro regardless of previous neo/adjuvant treatment.

In conclusion, len + pembro did not meet the prespecified statistical criteria for PFS or OS versus paclitaxel-carboplatin in patients with aEC in the first-line setting. The safety profile of len + pembro was manageable and consistent with that established for the combination. Despite not meeting its primary end points, evidence of meaningful antitumor activity was observed with len + pembro. The study was not designed to statistically assess the postadjuvant subgroup; however, the combination demonstrated benefit over paclitaxel-carboplatin in that subgroup, with prolonged PFS and favorable OS. On the basis of the results from Study 309/KEYNOTE-775, len + pembro remains a standard-of-care therapy for patients with aEC that has progressed after systemic therapy in any setting.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and the European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First-Line Lenvatinib Plus Pembrolizumab Versus Chemotherapy for Advanced Endometrial Cancer: A Randomized, Open-Label, Phase III Trial

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Robert Orlowski
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Stock and Other Ownership Interests: Merck Sharp & Dohme, Nektar, Bluebird Bio, 2Seventy Bio
Research Funding: Merck Sharp & Dohme
Travel, Accommodations, Expenses: Merck Sharpe & Dohm

Vivek Khemka
Employment: Merck
Stock and Other Ownership Interests: Merck
Travel, Accommodations, Expenses: Merck

Lucy Gilbert
Honoraria: Merck, GlaxoSmithKline
Consulting or Advisory Role: GlaxoSmithKline, Merck/Eisai, Eisai, Kora Healthcare, Corcept Therapeutics, Repare Therapeutics
Research Funding: Merck Sharp & Dohme (Inst), IMV (Inst), AstraZeneca (Inst), Immunogen (Inst), Karyopharm Therapeutics (Inst), Alkermes (Inst), OncoQuest (Inst), Novocure (Inst), Esperas Pharma (Inst), Mersana (Inst), Roche (Inst), Tesaro (Inst), K-Group Beta (Inst), GlaxoSmithKline (Inst), Sutro BioPharma Inc (Inst), Corcept Therapeutics (Inst), Shattuck Labs (Inst), GOG Foundation (Inst), Ascendis Pharma (Inst), Repare Therapeutics (Inst), Seagen (Inst)
Travel, Accommodations, Expenses: Zentalis, GlaxoSmithKline, Merck, GOG Foundation, Corcept Therapeutics, EndomEra

Vicky Makker
Consulting or Advisory Role: Eisai, Merck, Karyopharm Therapeutics, Takeda, ArQule, IBM, GlaxoSmithKline, Clovis Oncology, Faeth Therapeutics, Novartis, DualityBio, ITeos Therapeutics, Kartos Therapeutics, Lilly
Research Funding: Lilly (Inst), AstraZeneca (Inst), Eisai (Inst), Merck (Inst), Bristol Myers Squibb (Inst), Karyopharm Therapeutics (Inst), Takeda (Inst), Clovis Oncology (Inst), Bayer (Inst), Zymeworks (Inst), DualityBio (Inst), Faeth Therapeutics (Inst)
Travel, Accommodations, Expenses: Eisai, Merck, AstraZeneca, ESMO Congress
Other Relationship: IBM

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Principal Investigators Who Randomly Assigned Patients in the ENGOT-en9/LEAP-001 Study

Country/Region	Site Name	Principal Investigator
Argentina	Centro Oncologico Riojano Integral	Kaen, Diego Lucas
	Hospital Aleman	Gomez Abuin, Gonzalo
	Hospital Italiano de Buenos Aires	Zamora, Liliana Beatriz
	IDIM Instituto de Diagnostico e Investigaciones Metabolicas	Alfie, Margarita Sonia
	Instituto de Investigaciones Clinicas Mar del Plata	Casarini, Ignacio Alfredo
Australia	Chris O'Brien Lifehouse	Harrison, Michelle
	Epworth Freemasons Hospital	Ananda, Sumitra
	Mater Misericordiae Ltd	Shannon, Catherine Margaret
	Monash Health	Frentzas, Sophia
	Prince of Wales Hospital	Friedlander, Michael
	Sir Charles Gairdner Hospital	Meniawy, Tarek
	The Crown Princess Mary Cancer Centre—Westmead Hospital	Gao, Bo
	Royal North Shore Hospital, St Leonards	Baron-Hay, Sally; Diakos, Connie
Austria	Medizinische Universitat Innsbruck	Marth, Christian
	Medizinische Universitat Wien	Polterauer, Stephan
	Universitatsklinik fuer Frauenheilkunde und Geburtshilfe	Petru, Edgar
Belgium	AZ Delta	De Bock, Marlies
	AZ Maria Middelares Gent	Vulsteke, Christof
	Cliniques Universitaires Saint-Luc	Baurain, Jean-Francois
	UZ Leuven	Van Gorp, Toon
	UZA University Hospital Antwerp	Altintas, Sevilay
Brazil	A.C. Camargo Cancer Center	Lima, Joao Paulo da Silveira Nogueira
	Clinica de Pesquisas e Ctro de Estudos Onc. Ginecol. e Mamaria Ltda	Mattar, Andre
	Hospital Araujo Jorge Associacao de Combate ao Cancer de Goias	de Freitas Junior, Ruffo
	Instituto do Cancer do Ceara	Santana, Rosane O.
	Instituto Nacional do Cancer II	de Melo, Andreia Cristina
	ONCOSITE—Centro de Pesquisa Clinica em Oncologia	Franke, Fabio Andre
	Real e Benemerita Associacao Portuguesa de Beneficencia	Zibetti Dal Molin, Graziela
	Uniao Brasileira de Educacao e Assistencia Hospital Sao Lucas da Pucrs	Damian, Fernanda Bronzon
	Hospital de Base de Sao Jose de Rio Preto, Hospital de Base/2° andar/Centro Integrado de Pesquisa São José do Rio Preto	Guedes, João Daniel Cardoso
Canada	BC Cancer-Kelowna—Sindi Ahluwalia Hawkins Centre	Ellard, Susan
	BC Cancer-Vancouver Center	Tinker, Anna
	Centre Hospitalier de l Universite de Montreal (CHUM)	Samouëlian, Vanessa
	CIUSSS de l Est de L Ile de Montreal—Hopital Maisonneuve-Rosemont	Fortin, Suzanne
	CIUSSS de l Estrie—Centre Hosp. Univ. Sherbrooke (CHUS)	Bessette, Paul
	Cross Cancer Institute	Kolinsky, Michael
	Juravinski Cancer Centre	Kumar Tyagi, Nidhi
	Kingston Health Sciences Centre	Ethier, Josee-Lyne
	McGill University Health Centre	Gilbert, Lucy
	Princess Margaret Cancer Centre	Lheureux, Stephanie
	Sunnybrook Research Institute	MacKay, Helen
	The Credit Valley Hospital	Lim, Charles

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TABLE A1. List of Principal Investigators Who Randomly Assigned Patients in the ENGOT-en9/LEAP-001 Study (continued)

Country/Region	Site Name	Principal Investigator
China	Fudan University Shanghai Cancer Center	Wu, Xiaohua
	Peking Union Medical College Hospital	Pan, Lingya
	The first affiliated Hospital of Xi an Jiaotong University	An, Ruifang
	Obstetrics and Gynecology Hosp. Fudan University	Chen, Xiaojun
	Beijing Cancer Hospital	Zheng, Hong
	Beijing Obstetrics and Gynecology Hospital Capital Medical University	Wu, Yumei
	Zhejiang Cancer Hospital	Zhu, Jianqing
	The First Affiliated Hospital, Sun Yat-sen University	Yao, Shuzhong
	Nanjing Maternity and Child Health Care Hospital	Jia, Xuemei
	Hubei Cancer Hospital	Huang, Yi
	Women's Hospital School of Medicine Zhejiang University	Lv, Weiguo
	Xiangya Hospital Central South University	Zhang, Yu
	Chongqing Cancer Hospital	Zhou, Qi
	The First Affiliated Hospital of Xinjiang Medical University	Ma, Cailing
Germany	Charite Universitaetsmedizin Berlin	Chekerov, Radoslav
	Universitaetsklinikum Essen	Mach, Pawel
	Universitaetsklinikum Muenster	Witteler, Ralf
	Universitaetsmedizin Mannheim. Klinik fuer Kinder und Jugendmedizin	Marmè, Frederik
Ireland	St James Hospital	Cadoo, Karen
Israel	Chaim Sheba Medical Center	Korach, Jacob
	Edith Wolfson Medical Center	Levy, Talia
	Meir Medical Center	Beiner, Mario
	Rambam Medical Center	Amnon, Amit
Italy	Azienda Ospedaliera per l Emergenza Cannizzaro	Scollo, Paolo
	IRCCS Giovanni Paolo II Ospedale Oncologico	Naglieri, Emanuele
	Istituto Nazionale Tumori Fondazione Pascale	Pignata, Sandro
	Ospedale Policlinico S. Orsola-Malpighi	Zamagni, Claudio
	Policlinico Universitario Agostino Gemelli	Salutari, Vanda
Japan	Ehime University Hospital	Usami, Tomoka
	Gunma Prefectural Cancer Center	Nakamura, Kazuto
	Hyogo Cancer Center	Matsumoto, Koji
	Keio University Hospital	Yamagami, Wataru
	Kyorin University Hospital	Kobayashi, Yoichi
	National Defense Medical College Hospital	Takano, Masashi
	National Hospital Organization Hokkaido Cancer Center	Kato, Hidenori
	National Hospital Organization Kyushu Cancer Center	Sonoda, Kenzo
	Niigata Cancer Center Hospital	Kikuchi, Akira
	Nippon Medical School Musashi Kosugi Hospital	Katsumata, Noriyuki
	Osaka International Cancer Institute	Kamiura, Shoji
	Saitama Cancer Center	Horie, Koji
	Saitama Medical University International Medical Center	Hasegawa, Kosei
	Showa University Hospital	Tsunoda, Takuya
	St Marianna University School of Medicine Hospital	Suzuki, Nao
	The Cancer Institute Hospital of JFCR	Yunokawa, Mayu
	Kurume University Hospital	Nishio, Shin
	University of the Ryukyus Hospital	Kudaka, Wataru

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TABLE A1. List of Principal Investigators Who Randomly Assigned Patients in the ENGOT-en9/LEAP-001 Study (continued)

Country/Region	Site Name	Principal Investigator
Mexico	Centro de Investigacion Clinica Gramel	Guerrero Cabrera, Fernando Felix
	Centro Estatal de Cancerologia de Chihuahua	Gonzalez Mendoza, Rene Lazaro
	Centro Oncologico Internacional, SEDNA	Magallanes Maciel, Manuel Ernesto
	Consultorio Dentro de la Torre Medica Dalinde Oncologia Medica	Villalobos Valencia, Ricardo
	Hospital San Lucas Cardiologica del Sureste	Escobar Penagos, Jose
	Ican Oncology SA de SV	Lopez Chuken, Yamil Alonso
Poland	Bialostockie Centrum Onkologii	Mackowiak-Matejczyk, Beata
	Centrum Onkologii Instytut im. MSC Oddział w Gliwicach	Tarnawski, Rafal
	Instytut Centrum Zdrowia Matki Polki	Kalinka, Ewa
	Narodowy Instytut Onkologii im. Marii Sklodowskiej-Curie—Panstwowy Instytut Badawczy w Warszawie	Bidzinski, Mariusz
	Samodzielny Publiczny Szpital Kliniczny Nr 1 w Lublinie	Bednarek, Wieslawa
	Szpital Kliniczny im Ks Anny Mazowieckiej	Danska-Bidzinska, Anna
	Szpital Specjalistyczny im. Ludwika Rydygiera w Krakowie	Koralewski, Piotr
	Wielkopolskie Centrum Onkologii im.M.Sklodowskiej-Curie	Roszak, Andrzej
Russian Federation	FSBI-FRCC of Special Types Med. Care and Technologies FMBA of Russia	Kedrova, Anna
	Krasnoyarsk Regional Clinical oncology dispensary	Musaeva, Natalia
	National Medical Research Center of Oncology N.A. N.N. Petrov	Urmancheeva, Adiliya Fettekhovna
	Railway Hospital of OJSC	Vasiliev, Aleksandr Gennadievich
	Republican Clinical Oncology Dispensary of Tatarstan MoH	Safina, Sufia Zievna
	SPb SBHI City Clinical Oncological Dispensary	Lisyanskaya, Alla Sergeevna
	St. Petersburg Clinical Hospital RAS	Rykov, Ivan V.
	Russian Oncological Research Center n.a. N.N.Blokhin of MoH	Rumyantsev, Alexey Alexandrovich
	Medical Rehabilitation Center	Belonogov, Aleksandr
	Samara Regional Clinical Oncology Center	Makarycheva, Yulia
Republic of Korea	Asan Medical Center	Kim, Yong Man
	Samsung Medical Center	Choi, Chel Hun
	Seoul National University Bundang Hospital	Kim, Yong Beom
	Seoul National University Hospital	Kim, Hee Seung
	Severance Hospital Yonsei University Health System	Kim, Sang Wun
Spain	Complejo Hospitalario Universitario A Coruna. CHUAC	Quindos Varela, Maria
	Hospital Clinico San Carlos	Casado Herraez, Antonio
	Hospital Materno Infantil [Malaga]	Diaz Redondo, Tamara
	Hospital Universitario Reina Sofia	Rubio Perez, Maria Jesus
	Institut Catala d Oncologia Badalona	Romeo Marin, Margarita
	Instituto Valenciano de Oncologia (IVO)	Romero Noguera, Ignacio
	Parc de Salut Mar	Taus Garcia, Alvaro
Taiwan	China Medical University Hospital	Lin, Wu-Chou
	Linkou Chang Gung Memorial Hospital	Chou, Hung-Hsueh
	National Taiwan University Hospital	Cheng, Wen-Fang
	Taichung Veterans General Hospital	Lu, Chien-Hsing
	Taipei Veterans General Hospital	Wang, Peng-Hui
Türkiye	Akdeniz Universitesi Tıp Fakultesi	Simsek, Tayup
	Baskent Universitesi Adana Uygulama ve Arastirma Hastanesi	Kose, Fatih
	Baskent Universitesi Ankara Hastanesi	Ayhan, Ali
	Cukurova Uni. Tip Fakultesi	Vardar, Mehmet Ali
	Uludag Universitesi Tip Fakultesi	Ozerkan, Kemal

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TABLE A1. List of Principal Investigators Who Randomly Assigned Patients in the ENGOT-en9/LEAP-001 Study (continued)

Country/Region	Site Name	Principal Investigator
United Kingdom	Northern Centre for Cancer Care	Hughes, Andrew
	Western General Hospital	Stillie, Alison
	UCLH NHS Foundation Trust	Eminowicz, Gemma
	Mount Vernon Cancer Centre	Khalique, Saira
Ukraine	Communal non-profit enterprise Regional Clinical Oncology Center	Shalkova, Mariia
	Grigoriev Institute for Medical Radiology NAMS of Ukraine	Sukhina, Olena
	Khmelnitskiy Regional Onkology Dispensary	Piatnytska, Tetiana
	Medical and Diagnostic Centre LLC Dobryi Prognoz	Averina, Hanna
	Medical Center Asklepion LLC	Kulyaba, Yaroslav
	MI Precarpathian Clinical Oncology Center	Kryzhanivska, Anna
	Municipal Non-Profit Enterprise City Clinical Hospital 4 of Dnipro City Council	Bondarenko, Igor
	National Cancer Institute of the MoH of Ukraine	Svintsitsky, Valentyn
	MI Odessa Regional Oncological Centre	Krasnohrud, Yuliia
	Kyiv City Clinical Oncology Centre	Voitko, Nataliia
United States	Arizona Oncology Associates PC—HOPE	Buscema, Joseph
	Georgia Cancer Center at Augusta University	Ghamande, Sharad
	Holy Name Medical Center	Lewin, Sharyn
	John Theurer Cancer Center at Hackensack University Medical Center	Graham, Deena M.
	Memorial Sloan Kettering Cancer Center	Makker, Vicky
	Memorial Sloan Kettering Cancer Center—Nassau	Makker, Vicky
	Memorial Sloan Kettering Cancer Center—West Harrison	Makker, Vicky
	Memorial Sloan Kettering Cancer Center—Monmouth	Makker, Vicky
	MSKCC-Bergen	Makker, Vicky
	Sanford Cancer Center Oncology Clinic	Bell, Maria
	Smilow Cancer Hospital at Yale New Haven	Santin, Alessandro
	Texas Oncology-The Woodlands	Lee, Christine
	The Blavatnik Family—Chelsea Medical Center at Mount Sinai	Blank, Stephanie
	UCLA Hematology and Oncology Clinic (Westwood)	Konecny, Gottfried E.
	University of Colorado Cancer Center	Corr, Bradley
	University of North Carolina at Chapel Hill	Van Le, Linda
	University of Rochester	Moore, Richard G.
	University of South Alabama, Mitchell Cancer Institute	Scalici, Jennifer
	Willamette Valley Cancer Institute and Research Center	Anderson, Charles
	Women's Cancer Care	Braly, Patricia
	Legacy Salmon Creek Medical Center	Fehniger, Julia; Westhoff, Gina
	Minnesota Oncology Hematology, PA	Bollinger, Lauren