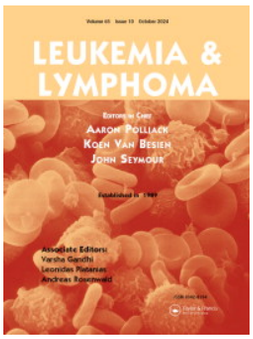

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ORIGINAL ARTICLE

Outcomes of patients aged ≥26 years with relapsed or refractory B-cell acute lymphoblastic leukemia in ZUMA-3 and historical trials

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ABSTRACT

Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 CAR T-cell therapy approved in the USA and European Union (EU) for adults with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL; aged ≥26 years in EU). Here, outcomes for patients with R/R B-ALL aged ≥26 years in ZUMA-3 treated with brexu-cel were compared with historical standard-of-care (SOC) therapy. After median follow-up of 26.8 months, the overall complete remission (CR) rate among patients treated with brexu-cel in Phase 2 (N = 43) was 72% and median overall survival (OS) was 25.4 months (95% CI, 15.9-NE). Median OS was improved in Phase 2 patients *versus* matched historical SOC-treated patients. Compared with aggregate historical trial data, Phase 1 and 2 patients had improved OS versus blinatumomab, inotuzumab, and chemotherapy in a matching-adjusted indirect comparison (MAIC) study. These data demonstrate clinical benefit of brexu-cel relative to SOC in patients ≥26 years with R/R B-ALL.

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Introduction

Among patients with acute lymphoblastic leukemia (ALL), the 5-year survival rate is high for patients aged <20 years (90%) [1]. Long-term survival decreases in patients aged ≥20 years (81% in patients aged <50 years), with 5-year survival rates decreasing to 44% among patients aged 40–64 years and 24% among patients aged ≥65 years [1]. Newer treatment options for patients with relapsed or refractory (R/R) B-cell ALL (B-ALL) include blinatumomab and inotuzumab ozogamicin, which have improved outcomes; however, median overall survival (OS) with these therapies is <8 months, highlighting an important unmet need [2,3]. Additionally, 2 CD19-directed chimeric antigen receptor (CAR) T-cell therapies, tisagenlecleucel and brexucabtagene autoleucel (brexu-cel, formerly KTE-X19) are approved in the R/R B-ALL setting. Tisagenlecleucel is approved in the United States (USA) and the European Union (EU) to treat patients with R/R B-ALL who are <26 years of age [4,5], whereas brexu-cel is approved in the USA for the treatment of patients ≥18 years of age and in the EU for patients ≥26 years of age [6,7].

After 2 years of follow-up in the multicenter, single-arm, Phase 2 ZUMA-3 study, 55 adult patients aged ≥18 years with R/R B-ALL treated with brexu-cel had an overall complete remission (CR) and CR with incomplete hematologic recovery (CRi) rate of 71% (95% confidence interval [CI], 57–82) and a median OS of 25.4 months (95% CI: 16.2-not estimable [NE]) in all treated patients and not reached among those who achieved a CR (n = 31). In addition, brexu-cel demonstrated a tolerable safety profile despite high disease burden and heavy pretreatment in the study patient population [8]. Here, we report outcomes for patients with R/R B-ALL who were ≥26 years on treatment initiation in ZUMA-3 after 2 years of follow-up.

In the absence of a control arm, two different retrospective study methodologies were used to contextualize ZUMA-3 results in patients aged ≥26 years with standard-of-care (SOC) regimens used in historical clinical trials (HCTs) in the R/R B-ALL setting. First, a subgroup analysis of the previously described retrospective, external historical control study, SCHOLAR-3 (a propensity-scoring analysis that matched individual patient data for adult patients with R/R B-ALL treated with SOC

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regimens in HCTs with treated patients in ZUMA-3), was conducted to estimate the benefit of brexu-cel in ZUMA-3 compared with SOC in patients aged ≥26 years with R/R B-ALL [8]. A previous SCHOLAR-3 analysis of patients aged ≥18 years with R/R ALL who were blinatumomab- and inotuzumab ozogamicin-naive demonstrated a CR/CRi rate of 85% (95% CI: 62.1–96.8; n = 20) for patients treated in ZUMA-3 *versus* 35% (95% CI: 15.4–59.2; n = 20) for patients treated with SOC regimens [8]. Additionally, the median OS was 25.4 months (95% CI: 15.9 months-NE) for all matched ZUMA-3 patients (N = 49) *versus* 5.5 months (95% CI: 3.3–9.2 months) for all matched historical control patients (N = 40; hazard ratio [HR]: 0.32; 95% CI: 0.18–0.58) [8]. It is important to note that most of the historical control patients in SCHOLAR-3 received SOC chemotherapy as study treatment rather than blinatumomab or inotuzumab ozogamicin. Here we report outcomes of the SCHOLAR-3 analysis limited to patients ≥26 years of age for both the HCT and ZUMA-3 datasets, using matched patient-level data.

Second, a matching-adjusted indirect comparison (MAIC) study, employing published aggregate trial data, was used to estimate the relative survival benefit associated with brexu-cel in ZUMA-3 patients aged ≥26 years compared with individual SOC therapies including blinatumomab, inotuzumab ozogamicin, and SOC chemotherapy. A similar MAIC was used to compare patients aged ≥18 years who received brexu-cel with these SOC therapies, and it was found that OS was significantly improved in the brexu-cel arm relative to SOC [9]. The comparator trials for this study included a much larger number of patients who received blinatumomab or inotuzumab ozogamicin as study treatment than were included in SCHOLAR-3, enabling a more direct comparison of survival outcomes for patients in ZUMA-3 to patients receiving targeted immunotherapies. Due to the aggregate nature of the data in the HCTs used in the MAIC, it was not possible to examine outcomes only for patients aged ≥26 years. Thus, the MAIC compared ZUMA-3 patients aged ≥26 years to HCT patients aged ≥18 years.

Patients and methods

ZUMA-3 study design and patients

The ZUMA-3 study (NCT02614066) included patients aged ≥18 years who had R/R B-ALL with morphological disease in the bone marrow (>5% blasts) at study entry. The study start date was 7 March 2016. Comprehensive details on the ZUMA-3 methodology have been reported previously [10], and details are provided in the Supplemental Appendix. Only those patients aged ≥26 years at time of treatment initiation were included here. Patients who were or were not previously treated with blinatumomab and/or inotuzumab ozogamicin, as well those who had or had not received a prior allogeneic stem cell transplant (alloSCT) were eligible. ZUMA-3 was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board or independent ethics committee at each study site and all patients provided signed written informed consent.

Procedures

Patients in ZUMA-3 underwent brexu-cel treatment as previously described [10]. Briefly, patients underwent leukapheresis followed by lymphodepleting chemotherapy (fludarabine 25 mg/m^2/d on Days −4, −3, −2 and cyclophosphamide 900 mg/m^2/d on Day −2) and a single infusion of 1×10^6 CAR T cells/kg on Day 0. Bridging therapy was allowed per physician's discretion as outlined in the protocol. AlloSCT was allowed as subsequent consolidative therapy following brexu-cel at physician's discretion but was not protocol-defined.

Outcomes

The primary endpoint for ZUMA-3 was overall CR/CRi rate per central assessment. Key secondary endpoints for ZUMA-3 included OS, minimal residual disease negativity rates, duration of remission (DOR; censored at subsequent therapy, including alloSCT), relapse-free survival (RFS; censored at subsequent therapy, including alloSCT), and safety.

Statistical analyses

Efficacy and safety endpoints were reported in Phase 2-treated patients and combined Phase 1 and 2 patients treated with the Phase 2 dose of brexu-cel (1×10^6 CAR T cells/kg). Time-to-event endpoints were analyzed using the Kaplan–Meier method, and subgroup analyses were descriptive in nature.

SCHOLAR-3 analysis

Propensity-score matching was used to match patients with R/R B-ALL treated with SOC in HCTs with brexu-cel–treated patients from Phase 2 of ZUMA-3 based on key baseline characteristics and prior therapies. Full methodology for SCHOLAR-3 was previously described [8]. Three cohorts for ZUMA-3 were matched

to three synthetic control arms (SCAs) from SCHOLAR-3 that were created based on the prior blinatumomab and inotuzumab treatment status at time of enrollment: blinatumomab- and inotuzumab-naive patients (SCA-1), blinatumomab- and inotuzumab-treated patients (SCA-2), and a combined SCA-1 and SCA-2 dataset (SCA-combined). Full statistical analysis details, including details of the propensity-score matching, are included in the Supplemental Appendix (SCHOLAR-3 Supplementary Methods). The primary endpoint of SCHOLAR-3 was overall CR/CRi rate for SCA-1, with OS as a secondary endpoint for all three cohorts.

MAIC analysis

Relative treatment effects associated with brexu-cel compared with SOC therapies including blinatumomab, inotuzumab ozogamicin, and chemotherapy were also estimated using published studies. For brexu-cel, individual patient-level data from patients in Phase 1 and 2 of ZUMA-3 aged ≥26 years who received the Phase 2 dose of brexu-cel (1×10^6 CAR T cells/kg) were reweighted so that their mean characteristics matched those from aggregate data from published studies of clinical trials where patients received SOC therapy. For SOC therapies, a systematic literature review (SLR) was conducted to identify randomized controlled trials and non-randomized trials that evaluated the clinical efficacy and safety of relevant SOC therapies for adults with R/R B-ALL (Figure S1). The search was originally executed on 12 June 2019, with an updated search performed in November 2020. The study start years for the 12 studies, examining 13 trials, included in the final SLR ranged from 2012 to 2015 (Table S1). Between-study differences are summarized in the Supplemental Appendix (MAIC Supplementary Methods).

Of the 12 studies included in the SLR, only the INO-VATE (inotuzumab ozogamicin *versus* chemotherapy) and TOWER (blinatumomab versus chemotherapy) studies were included in the final comparisons. The rationale for excluding the other studies and full statistical analysis details are included in the Supplemental Appendix (MAIC Supplementary Methods). The endpoint of interest was OS in the ZUMA-3 Phase 1- and 2-treated population *versus* SOC.

Results

ZUMA-3 patient characteristics

Among ZUMA-3 Phase 2 patients aged ≥26 years at time of enrollment, 58 were enrolled and leukapheresed (Phase 2 ITT population) and 43 received brexu-cel (Phase 2-treated population). Among combined ZUMA-3 Phase 1 and 2 patients aged ≥26 years who received the pivotal dose of brexu-cel, 81 were enrolled and leukapheresed (combined Phase 1 and 2 ITT population) and 63 received brexu-cel (combined Phase 1- and 2-treated population). The median follow-up time for Phase 2-treated patients was 26.8 months (range, 20.7–32.6) and was 29.6 months (range, 20.7–58.3) for Phase 1- and 2-treated patients as of the data cutoff date (23 July 2021). Most Phase 2-treated patients and combined Phase 1- and 2-treated patients had ECOG performance status of 1 (72% and 71%, respectively), were R/R to ≥2 lines of prior therapy (81% and 78%, respectively), had >25% bone marrow blasts at screening (70% and 73%, respectively), and a substantial group had received prior alloSCT (44% and 38%, respectively) and were Ph+ (35% and 25%, respectively; Table S1).

ZUMA-3 efficacy outcomes

In treated Phase 2 and combined Phase 1 and 2 patients ≥26 years, the overall CR/CRi rates by central assessment were 72% (95% CI: 56–85; n = 43) and 73% (95% CI: 60–83; n = 63), respectively (Table 1). The CR rates were 56% (95% CI: 40–71) and 60% (95% CI: 47–72), respectively. Rates of subsequent alloSCT were 19% among Phase 2-treated patients and 17% among Phase 1- and 2-treated patients.

Table 1. Efficacy outcomes based on Central assessment in ZUMA-3 phase 2-treated patients aged ≥26 years and combined phase 1 and 2 patients treated at pivotal dose aged ≥26 years.

	Phase 2-treated patients (N=43)	Combined Phase 1 and 2 patients treated at Phase 2 dose (N=63)
Overall CR/CRi rate, % (95% CI)	72.1 (56–85)	73.0 (60–83)
CR rate, % (95% CI)	55.8 (40–71)	60.3 (47–72)
CRi rate, % (95% CI)	16.3 (7–31)	12.7 (6–23)
MRD negative rate, % (95% CI)	79 (64–90)	81 (69–90)
Median duration of remission, months (95% CI)	12.8 (5.2–NE)	20.0 (9.4–NE)
Median relapse-free survival, months (95% CI)	10.3 (2.3–22.1)	11.6 (5.6–22.1)
Median overall survival, months (95% CI)	25.4 (15.9–NE)	26.0 (15.9–NE)
Subsequent alloSCT rate, n (%)	8 (19)	11 (17)
Subsequent alloSCT rate for patients with CR, n (%)	7 (16)	10 (16)

alloSCT: allogeneic stem cell transplant; CI: confidence interval; CR: complete remission; CRi: CR with incomplete hematologic recovery; MRD: minimal residual disease; NE: not estimable

Overall CR/CRi rates by central assessment were similar in key subgroups for combined Phase 1 and 2 patients but were numerically higher among patients aged ≥65 years compared with the overall population (100%; 95% CI: 74–100; Figure S2).

Phase 2 patients who received subsequent alloSCT in ZUMA-3 were censored for DOR (7 patients) and RFS (7 patients) in the KM analyses, along with combined Phase 1 and 2 patients ($n = 10$ for DOR and RFS). The median DOR by central assessment was 12.8 months (95% CI: 5.2–NE; $n = 31$) for Phase 2 patients and 20.0 months (95% CI: 9.4-NE; $n = 46$) for Phase 1 and 2 patients (Figure 1(A)). At data cutoff, among the 16 Phase 2-treated patients with CR/CRi who were censored for DOR, 6 (38%) were in ongoing remission without subsequent therapy, 7 (44%) proceeded to subsequent alloSCT per physician's discretion, and 3 (19%) proceeded to other anticancer therapies (reasons for starting subsequent therapy included a positive minimal residual disease measurement [$n = 2$] and relapse by unscheduled bone marrow examination [$n = 1$]). For the 27 Phase 1- and 2-treated patients with CR/CRi who were censored for DOR, 12 (44%) were in ongoing remission without subsequent therapy, 10 (37%) proceeded to subsequent alloSCT per physician's discretion (1 of these patients had prior alloSCT), 4 (15%) proceeded to other anticancer therapies (reason for Phase 1 patient starting subsequent therapy is unknown), and 1 (4%) was lost to follow-up.

The median RFS in Phase 2 and Phase 1 and 2 patients was 10.3 (95% CI: 2.3–22.1) and 11.6 months (95% CI: 5.6–22.1), respectively (Figure 1(B)), and the median OS was 25.4 (95% CI: 15.9-NE) and 26.0 months (95% CI: 15.9–NE), respectively (Figure 1(C)). Among the 31 Phase 2-treated patients with CR/CRi, the median OS was 26.0 months (95% CI: 21.9-NE). Among the seven Phase 2-treated patients with CR/CRi who proceeded to subsequent alloSCT, the median OS was not reached (95% CI: 7.6–NE), and the median OS was 26.0 months (95% CI: 18.6–NE) among the 24 patients with CR/CRi who did not proceed to subsequent alloSCT (Figure S3). Subgroup analyses of OS rates at 24 months for the ZUMA-3 Phase 1 and 2 population were similar to the overall population, though patients with both prior blinatumomab and inotuzumab ozogamicin had a numerically smaller 24-month OS rate (Figure S4).

In the ZUMA-3 Phase 2 ITT population ($N = 58$), the overall CR/CRi rate by central assessment was 53.4% (95% CI: 40–67). The median DOR was 12.8 months (95%CI, 5.2–NE), and the median RFS and OS were 3.4 months (95% CI: 0.0-12.4) and 23.1 months (95% CI: 9.3–NE), respectively.

ZUMA-3 safety

In the ZUMA-3 Phase 2 population (≥26 years), 95% of patients experienced Grade ≥3 treatment-emergent adverse events (TEAEs), and 88% experienced Grade ≥3 brexu-cel–related TEAEs. TEAEs of all Grades and Grade ≥ 3 occurred at similar rates to all ZUMA-3 Phase 2-treated patients aged ≥18 years [10] (Table 2**)**. Grade ≥3 CRS was reported in 23% of patients in the ZUMA-3 Phase 2 population (≥26 years), and Grade ≥3 neurologic events were reported in 21%. Grade 5 TEAEs were experienced by 9 (21%) patients in this population (4 [9%] due to disease progression), 1 (2%) of which was deemed to be brexu-cel related (brain herniation). Other Grade 5 TEAEs included one instance each of graft versus host disease, pneumonia fungal, respiratory failure, and sepsis. TEAEs in the combined Phase 1 and 2 populations were consistent with the Phase 2 population (Table S3).

SCHOLAR-3 efficacy analysis

A total of 78 treated patients aged ≥26 years, 39 each from ZUMA-3 (Phase 2) and 13 HCTs, were included in this SCHOLAR-3 efficacy analysis. Four of the total 43 treated patients from ZUMA-3 were not able to be matched to patients from HCTs and were excluded from this analysis. Among these 78 treated patients, 16 patients from ZUMA-3 were matched to 16 patients from SCA-1 who had not received prior blinatumomab or inotuzumab ozogamicin therapy. Additionally, 23 patients from ZUMA-3 were matched to 23 patients from SCA-2 who had received prior blinatumomab or inotuzumab ozogamicin therapy. The baseline characteristics for all matched treated patients after propensity-score matching along with baseline characteristics and outcomes for all matched ITT patients are detailed in the Supplementary Appendix (Tables S4 and S5). In SCA-1, 9.1 (56.7%) of treated patients received blinatumomab as study treatment and 6.9 (43.3%) received SOC chemotherapy. In SCA-2, 3.0 (13%) of treated patients received blinatumomab or inotuzumab as study treatment and 20.0 (87%) received SOC chemotherapy. Among all treated patients in the SCA-combined cohort, 12.1 (30.9%) received blinatumomab or inotuzumab as study treatment and 26.9 (69.1%) received SOC chemotherapy.

The primary endpoint of overall CR/CRi rates among blinatumomab- and inotuzumab ozogamicin-naive patients were 81.3% (95% CI: 62–100; $n = 16$) for ZUMA-3 and 42.3% (95% CI: 18–67; $n = 16$) for SCA-1. The CR rates were 68.8% (95% CI: 46–92) and 38.1% (95% CI: 14–62), respectively. Treatment with brexu-cel

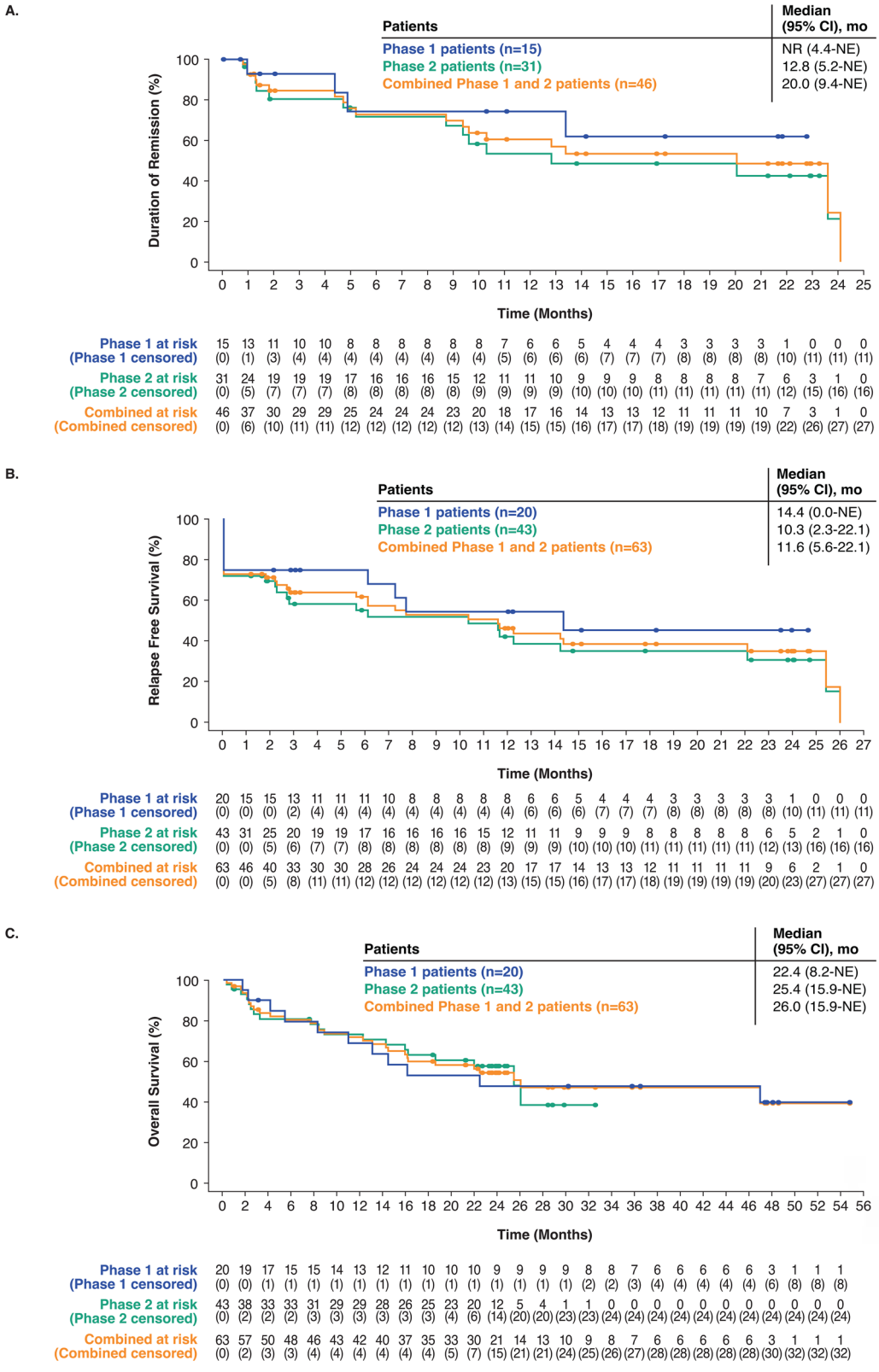

Figure 1. DOR, censored at subsequent therapy, including alloSCT, (A) RFS, censored at subsequent therapy, including alloSCT, (B) and OS (C) KM curves for ZUMA-3 Phase 1, Phase 2, and Phase 1 and 2 combined patients aged ≥26 years. alloSCT, allogeneic stem-cell transplant. CI: confidence interval; DOR: duration of remission; KM, Kaplan–Meier; mo: months; NE: not estimable; NR: not reached; OS: overall survival; RFS: remission-free survival.

Table 2. Adverse events occurring in ≥20% of patients, cytokine release syndrome, and neurologic events in ZUMA-3 phase 2-treated patients aged ≥26 years ($N = 43$).

	Any grade	Grade 3/4	Grade 5
Any adverse event	43 (100)	32 (74)	9 (21)
Pyrexia	42 (98)	15 (35)	0 (0)
Hypotension	27 (63)	14 (33)	0 (0)
Anemia	22 (51)	21 (49)	0 (0)
Nausea	17 (40)	0 (0)	0 (0)
Sinus tachycardia	15 (35)	3 (7)	0 (0)
Headache	15 (35)	0 (0)	0 (0)
Chills	12 (28)	0 (0)	0 (0)
Platelet count decreased	13 (30)	12 (28)	0 (0)
Hypoxia	13 (30)	8 (19)	0 (0)
Fatigue	13 (30)	0 (0)	0 (0)
Hypokalemia	11 (26)	3 (7)	0 (0)
Hypophosphatemia	11 (26)	8 (19)	0 (0)
Neutrophil count decreased	12 (28)	12 (28)	0 (0)
Tremor	11 (26)	1 (2)	0 (0)
White blood cell count decreased	11 (26)	10 (23)	0 (0)
Confusional state	10 (23)	1 (2)	0 (0)
Diarrhea	10 (23)	2 (5)	0 (0)
Hypomagnesemia	10 (23)	0 (0)	0 (0)
Tachycardia	9 (21)	0 (0)	0 (0)
Encephalopathy	9 (21)	3 (7)	0 (0)
Cytokine release syndrome[a]	37 (86)	10 (23)	0 (0)
Neurological events[b]	25 (58)	8 (19)	1 (2)

[a]Cytokine release syndrome is graded per the revised grading system proposed by Lee and colleagues [12].
[b]Neurologic events are identified based on a modification of criteria proposed by Topp and colleagues [13].

Table 3. Comparison of efficacy outcomes in matched treated patients aged ≥26 years who were previously naive to blinatumomab and inotuzumab ozogamicin in ZUMA-3 and SCA-1.

	ZUMA-3–matched patients ($n = 16$)	SCA-1 ($n = 16$)
Overall CR/CRi rate, % (95% CI)	81.3 (62.1–100.0)	42.3 (18.1–66.5)
Treatment difference (95% CI)	39.0 (8.1–69.8)	
Odds ratio (95% CI)	5.9 (1.2–29.3)	
P value	0.0234	
CR rate, % (95% CI)	68.8 (46.0–91.5)	38.1 (14.3–61.9)
Treatment difference (95% CI)	30.6 (−2.3 to 63.5)	
Odds ratio (95% CI)	3.6 (0.8–15.4)	
P Value	0.0825	
alloSCT rate, % (95% CI)	31.3 (8.5–54.0)	38.5 (14.7–62.4)
Treatment difference (95% CI)	−7.3 (−40.2 to 25.6)	
Odds ratio (95% CI)	0.7 (0.2–3.1)	
P Value	0.6652	

alloSCT: allogeneic stem cell transplant; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; SCA: synthetic control arm

resulted in 5.9 (95% CI 1.2, 29.3) and 3.6 (95% CI: 0.8–15.4) times higher odds of achieving CR/CRi and CR, respectively, *versus* SOC therapy. The rates of alloSCT were not significantly different between ZUMA-3 and SCHOLAR-3 patients (Table 3). Comparison of overall CR/CRi rates by subgroup in matched blinatumomab- or inotuzumab ozogamicin-naive patients enrolled in ZUMA-3 or HCTs are presented in the Supplementary Appendix (Figure S5).

Among blinatumomab- or inotuzumab ozogamicin-naive patients, the median OS was not reached (95% CI: 16.2–NE; $n = 16$) for ZUMA-3 patients (median follow-up for OS: 23.9 months; 95% CI: 21.2–24.8) and 12.1 months (95% CI: 2.8–24.9; $n = 16$) for SCA-1 patients (median follow-up for OS: 24.9; 95% CI: 2.8–24.9). Among blinatumomab- or inotuzumab ozogamicin-treated patients, the median OS was 15.9 months (95% CI: 2.7–26.0; $n = 23$) for ZUMA-3 patients (median follow-up for OS: 23.9 months; 95% CI: 22.3–NE) and 4.5 months (95% CI: 3.1–6.8; $n = 23$) for SCA-2 patients (median follow-up for OS: 17.9 months; 95% CI: 6.1–NE). The treatments received by the SCA-combined patients ($n = 39$) included blinatumomab and/or inotuzumab ozogamicin (30.9%) and SOC chemotherapy (69.1%). the median OS was 25.4 months (95% CI: 14.2–NE; $n = 39$) for all treated ZUMA-3 patients (median follow-up for OS: 23.9 months; 95% CI: 22.7–24.2) and was 6.2 months (95% CI: 3.5–10.5; $n = 39$) for SCA-combined patients (median follow-up for OS: 24.4 months; 95% CI: NE–NE; HR: 0.35; 95% CI: 0.18–0.70; Figure 2).

MAIC efficacy analysis

The comparison with published sources included 63 patients aged ≥26 years treated with the Phase 2 dose of brexu-cel from ZUMA-3 (combined Phase 1 and 2; median follow-up: 24.1 months [range, 23.8–NE]), 164 patients aged ≥18 years treated with inotuzumab ozogamicin from the INO-VATE clinical trial (median follow-up, 29.6 months [range, 1.7–49.7]), 271 patients aged ≥18 years in the blinatumomab arm ($n = 267$ [99%] treated) from the TOWER clinical trial (median follow-up not available), and 296 patients aged ≥18 years in the chemotherapy arms from INO-VATE and TOWER ($n = 252$ [85%] treated) The baseline characteristics for these patients are included in the Supplementary Appendix (Table S6).

The median OS for the inotuzumab ozogamicin-treated population was 7.5 months (95% CI: 6.1–9.3; $n = 164$) and not reached (7.6 months–NE; effective sample size [ESS] = 19.5) in the MAIC-adjusted ZUMA-3 population, with an HR of 0.44 (95% CI: 0.22–0.89; Figure 3(a)). The median OS for the blinatumomab-treated population was 7.7 months (95% CI: 5.7-9.6; $n = 271$) and 22.4 months (95% CI: 7.6–NE; ESS = 27.3) in the MAIC-adjusted ZUMA-3 population, with an HR of 0.48 (95% CI: 0.27–0.86) Figure 3(b)). The median OS for the chemotherapy-treated population was

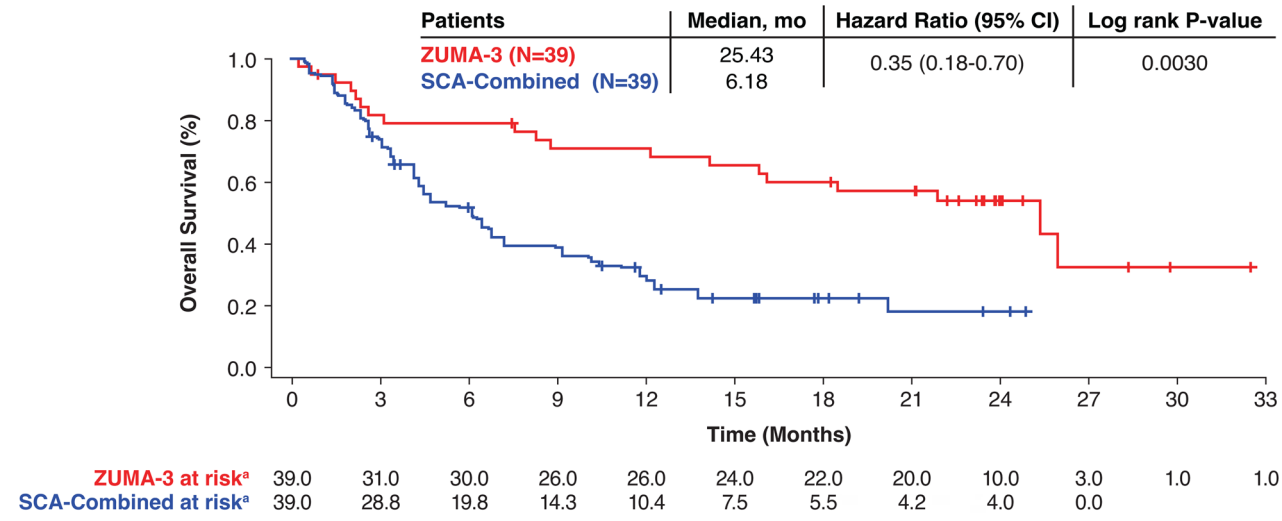

Figure 2. Kaplan–Meier curve of OS for SCHOLAR-3 all matched patients ≥26 years. [a]An optimal full matching algorithm along with weighted analysis was used for creating the SCA, which led to non-integer patients at risk in the SCA-combined group. CI: confidence interval; mo: months; OS: overall survival; SCA: synthetic control arm.

5.3 months (95% CI: 4.5–6.3; $n = 296$) and 22.4 months (7.6–NE; ESS = 25.2) in the MAIC-adjusted ZUMA-3 population, with an HR of 0.34 (95% CI: 0.18–0.63; Figure 3(c)).

Discussion

Brexu-cel is the first and only CAR T-cell therapy currently approved for the treatment of patients aged ≥26 years with R/R B-ALL in the EU. As such, it is important to understand the efficacy of this treatment relative to SOC therapy in this population. In this analysis, considerable benefit was observed in ZUMA-3 Phase 2 patients aged ≥26 years with R/R B-ALL who received brexu-cel therapy, with an overall CR/CRi rate of 72%, CR rate of 56%, median RFS of 10.3 months, and median OS of 25.4 months. This efficacy is comparable with the ZUMA-3 Phase 2 patients aged ≥18 years as previously published [11]. There was no significant difference in safety in this population versus the overall ZUMA-3 Phase 2 population [11]. In addition, efficacy and safety results in patients ≥26 years were corroborated by a larger population of combined Phase 1 and 2 patients. These data further support the recent European Medicines Agency approval of brexu-cel for patients aged ≥26 years with R/R B-ALL and continued use in this patient population.

Given that ZUMA-3 is a single-arm study, we used two different methods (SCHOLAR-3 and an MAIC) to assess the benefit of ZUMA-3 relative to SOC therapies in patients with R/R B-ALL. Both methods have different limitations that are considered below and, in the absence of direct comparative evidence, these two comparisons were used in a complementary fashion. In SCHOLAR-3, a comparison of patient outcomes was conducted in 39 patients from HCTs successfully matched to 39 patients from ZUMA-3. This analysis showed that brexu-cel demonstrated better response rates in patients aged ≥26 years with R/R B-ALL who were not previously treated with blinatumomab or inotuzumab ozogamicin than in patients treated with SOC therapies, mostly consisting of chemotherapy. Among all matched patients treated with brexu-cel, the median OS appeared extended compared with that reported for SOC therapies, with a 56% reduction in risk of death versus inotuzumab ozogamicin, a 52% reduction in risk of death versus blinatumomab, and a 66% reduction in risk of death *versus* chemotherapy. These results suggest that brexu-cel delivers a meaningful clinical improvement versus SOC therapy in this patient population.

The MAIC used published sources, whereby ZUMA-3 individual patient-level data for patients aged ≥26 years were compared with aggregate data from historical SOC trials (for patients aged ≥18 years), which also showed improvement in OS with brexu-cel relative to blinatumomab, inotuzumab ozogamicin, and SOC chemotherapy regimens. These data therefore complement and reinforce the conclusions from the comparison used in the SCHOLAR-3 analysis.

A limitation of ZUMA-3 was the single-arm design. However, SCHOLAR-3 and the MAIC helped contextualize these results using two different methodological approaches that provided consistent outcomes with OS HR favoring brexu-cel in treated patients over SOC chemotherapy (SCHOLAR-3) and over targeted agents, such as blinatumomab and

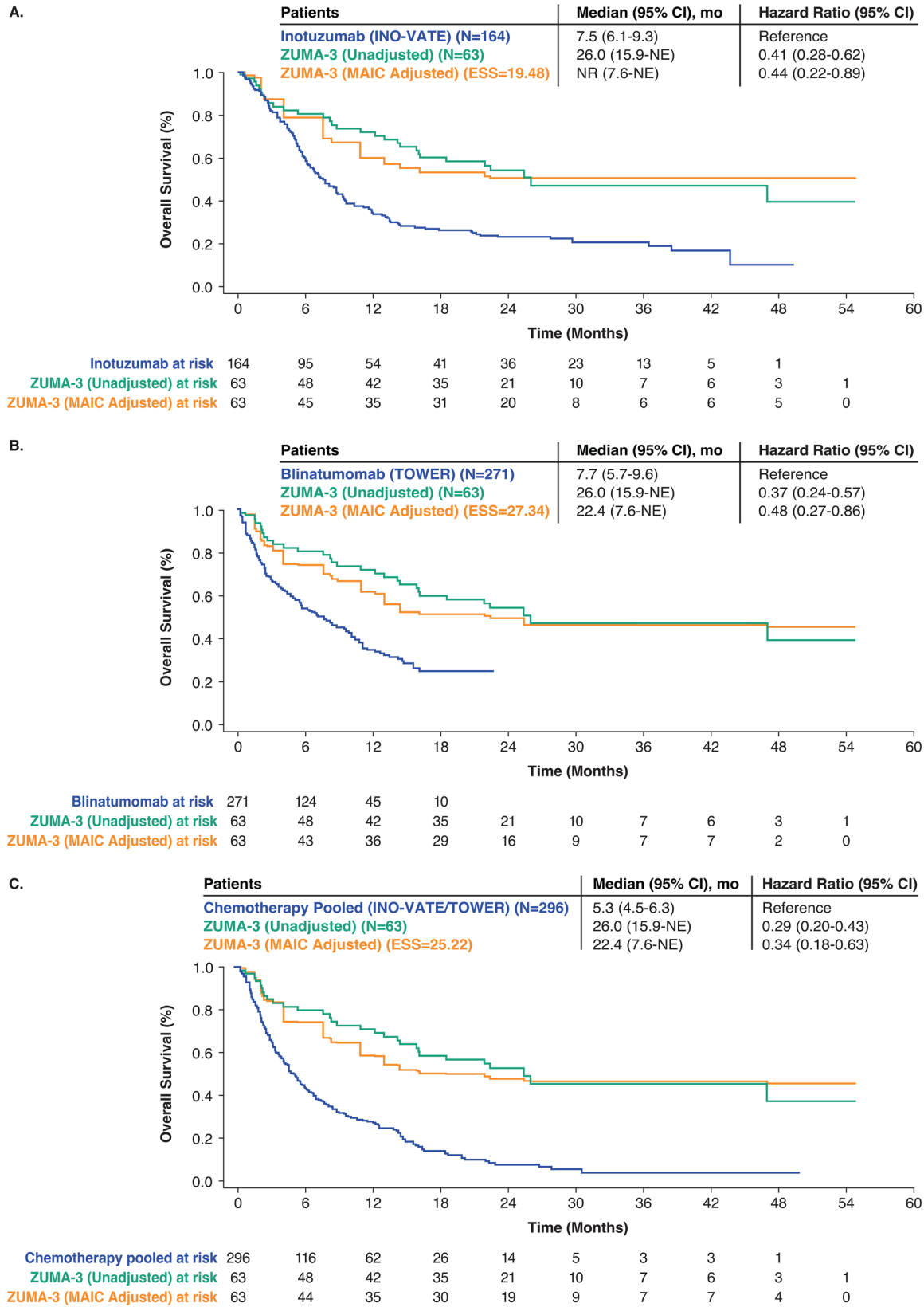

Figure 3. OS curve combined Phase 1 and 2 matched patients aged ≥26 years treated at pivotal dose versus patients treated with inotuzumab ozogamicin in the INO-VATE clinical trial (A), patients treated with blinatumomab in the TOWER clinical trial (B), and patients treated with chemotherapy in the INO-VATE and TOWER clinical trials (C). CI: confidence interval; ESS: effective sample size; MAIC: matching-adjusted indirect comparison; mo: months; NE: not estimable; NR: not reached; OS: overall survival.

inotuzumab ozogamicin (MAIC). Limitations of the SCHOLAR-3 analysis include its retrospective nature, which includes variation in follow-up times between the studies examined. Other limitations include a small sample size due to the heterogeneity of the ZUMA-3 study to which the patients from HCTs were matched, and lack of available overall CR/CRi and CR rate information for patients previously treated with blinatumomab or inotuzumab ozogamicin (owing to only having long-term efficacy outcomes reported for these patients). We note that most patients in the SCA-1 and SCA-2 arms received study treatment of chemotherapy and not targeted agents. For the MAIC analysis, in addition to its retrospective nature, the lack of individual patient-level data in the comparator studies limits the interpretations of the results. Most notably, patients from comparator studies in the MAIC could not be limited only to those aged ≥26 years, and so only a comparison with patients aged ≥18 years could be made, which relied on the reported aggregate patient population characteristics.

In summary, this analysis demonstrated that patients in ZUMA-3 aged ≥26 years benefited from brexu-cel with similar efficacy and safety to the overall patient population [8]. Additionally, the benefit of brexu-cel versus SOC therapy was substantial in patients aged ≥26 years as examined using two complementary analytical approaches to compare ZUMA-3 outcomes with other studies.

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Author contributions

Collected data: MCM; SK; BDS
Completed the statistical analysis: XY; RD; SK; JEP; LZ; JJW
All authors were involved in the interpretation of the data and writing of the article and provided final approval to submit for publication.

Disclosure statement

MCM reports consulting or advisory role for Bristol Myers Squibb, CDR-life, GSK, and Janssen-Cilag (institution); speakers' bureau participation for Bristol Myers Squibb, Janssen-Cilag, Pfizer, and Siemens; research funding from BeiGene (institution) and travel accommodations and expenses from Bristol Myers Squibb. XY reports employment with and stock or other ownership in Medidata Solutions, a Dassault Systèmes company. RD reports employment with, stock or other ownership in, research funding, travel support from and received funds from Medidata; stock or other ownership with Dassault Systèmes. SK reports employment with PRECISIONheor, which received funding from Kite, a Gilead Company, to conduct these analyses. JEP reports employment with PRECISIONheor, which received funding from Kite, a Gilead Company, to conduct these analyses. TI reports employment with Kite, a Gilead Company, and stock or other ownership in Gilead Sciences TH reports employment with, stock or other ownership in Kite, a Gilead Company. J-CG reports employment with and stock or other ownership in Kite, a Gilead Company. RDK reports employment with, stock or other ownership in, and travel support from Kite, a Gilead Company. LZ reports employment with Kite, a Gilead Company; and owned AbbVie RSU or stock in the past 2 years. JJW reports employment with and stock or other ownership in Kite, a Gilead Company; and stock or other ownership in Abbott, AbbVie, Amgen, Avid, Curis, and Viracta. BDS reports consultancy or advisory role for Adaptive, Amgen, Autolus, BeiGene, Bristol Myers Squibb, Century Therapeutics, Deciphera, Jazz, Kite, a Gilead Company, Lilly, Novartis, Precision Biosciences, Pfizer, and Takeda; research funding from Jazz Pharmaceuticals, Kite and Servier; and other relationship with PeproMene Bio.

Data sharing statement

Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com.

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