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Epcoritamab plus rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin induces deep and durable responses in transplant-eligible patients with relapsed or refractory diffuse large B-cell lymphoma: results from the EPCORE NHL-2 trial

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Running head: Epcoritamab + R-DHAX/C induces high response rates in R/R DLBCL

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Abstract (250/250 words)

The treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) remains challenging, with inadequate responses to salvage chemoimmunotherapy limiting patients' ability to receive potentially curative treatments like autologous stem cell transplantation (ASCT). Epcoritamab, a subcutaneous CD3×CD20 bispecific antibody, has demonstrated antitumor activity in R/R DLBCL as a monotherapy and in combination with chemotherapy.

In Arm 4 of the EPCORE® NHL-2 phase 1b/2 trial (NCT04663347), transplant-eligible patients with CD20+ R/R DLBCL received epcoritamab plus rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin (R-DHAX/C). Patients could continue epcoritamab until ASCT or progression.

Twenty-nine patients received epcoritamab plus R-DHAX/C; 72% had stage IV disease; 66% had primary refractory disease. As of January 15, 2025 (median follow-up 40.4 months), overall response rate (primary endpoint) was 79%, and complete response rate was 69%. Sixteen patients (55%) proceeded to ASCT and five remained on epcoritamab monotherapy. At 36 months, an estimated 70% of responses were ongoing, 59% of patients were progression-free, and 76% were alive. Common treatment-emergent adverse events (TEAE) were thrombocytopenia (90%), anemia (66%), and neutropenia (59%). Cytokine release syndrome occurred in 45% of patients; all were grade 1–2 and resolved after a median of 2 days. Immune effector cell-associated neurotoxicity syndrome occurred in one patient. No fatal TEAE or clinical tumor lysis syndrome were observed.

Epcoritamab plus R-DHAX/C achieved deep, durable responses with manageable safety. Over half of patients proceeded to ASCT, a potentially curative treatment. These findings suggest the potential of epcoritamab combined with standard chemoimmunotherapy as an effective salvage treatment for patients with R/R DLBCL.

Introduction

Salvage chemoimmunotherapy (CIT) followed by consolidation with high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) is a standard second-line (2L) treatment for patients with diffuse large B-cell lymphoma (DLBCL) who experience relapse more than 12 months after initial therapy, and can be curative in this setting. Approximately 50% of HDT-ASCT-eligible patients undergo transplantation after initial salvage therapy and achieve disease remission, with an overall cure rate of up to 35%.[1] However, 40–60% of patients do not achieve an adequate response to salvage CIT, which limits their ability to proceed to HDT-ASCT and leads to poor outcomes.[2–4] Patients with DLBCL treated with R-DHAX/C (rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin) have previously shown complete response (CR) rates of approximately 50%.[5] For other salvage CIT regimens, such as dexamethasone, high-dose cytarabine, cisplatin (DHAP), dexamethasone, high-dose cytarabine, carboplatin (DHAC), ifosfamide, carboplatin, etoposide (ICE), gemcitabine, dexamethasone, cisplatin (GDP), and gemcitabine, oxaliplatin (GemOx), reported overall response (OR) rates ranged from 40% to 60%, even with the addition of rituximab.[6] Patients who achieve CR with salvage CIT regimens may be able to proceed to HDT-ASCT, thereby achieving improved outcomes compared with patients who continue with CIT.[7] Patients undergoing ASCT without achieving CR during salvage therapy experience shorter progression-free survival (PFS) and overall survival (OS) compared with those undergoing ASCT while in a CR.[8]

Chimeric antigen receptor (CAR) T-cell therapies, including lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel), are approved for the treatment of patients with LBCL who have refractory disease to first-line (1L) CIT or relapse within 12 months of 1L CIT, based on results from the phase 3 TRANSFORM and ZUMA-7 clinical trials.[9,10] CAR T-cell therapies have become the standard of care (SoC) for patients who progress within 12 months of 1L therapy and have been associated with longer survival compared with salvage CIT.[11] However, CAR T-

cell therapy use is constrained by clinical and logistical challenges for physicians, patients, and care partners; based on survey results obtained between 2022 and 2024, only around 25% of eligible patients with LBCL received 2L CAR T-cell therapy in the US.[12] Treatment is typically delayed by the lengthy manufacturing process required before infusion, and access is limited to specialized treatment or academic centers.[13,14] Additional barriers include the need for bridging therapy, patient ineligibility, and high costs. Furthermore, CAR T-cell therapies are largely unavailable in many regions of the globe, with approvals currently limited to high- and middle-income countries.[15]

While CAR T-cell therapy is approved as 2L treatment for patients with R/R DLBCL who relapse within 12 months after 1L therapy, ASCT remains a curative option for patients with R/R DLBCL who relapse after 12 months and for those without access to CAR T-cell therapy.[14] Therefore, there is still a need for effective, accessible salvage regimens that improve transplant eligibility and enable more patients to proceed to ASCT.

Epcoritamab is a subcutaneous CD3×CD20 bispecific antibody (bsAb) that induces T-cell–mediated killing of CD20+ malignant B cells and is approved for treatment of adult patients with R/R DLBCL, and DLBCL not otherwise specified (NOS) including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBCL; US only), after ≥2 lines of systemic therapy.[16–20] Owing to its distinct mechanism of action and manageable safety profile, epcoritamab is a promising candidate for combination with salvage CITs .[20–24] Previously, epcoritamab plus R-GemOx demonstrated high OR (85%) and CR (61%) rates, and manageable safety, supporting the clinical benefit of combining epcoritamab with chemotherapy regimens in HDT-ASCT-ineligible patients with 2L+ DLBCL.[25] Here, we report efficacy and safety results from Arm 4 of the EPCORE NHL-2 trial, which evaluated epcoritamab plus R-DHAX/C in HDT-ASCT-eligible patients with R/R DLBCL.

Methods (499/500 words)

Study design and patients

EPCORE NHL-2 (NCT04663347) is a phase 1b/2, open-label, multicenter, multicohort trial in patients with CD20+ non-Hodgkin lymphoma. In Arm 4, eligible patients were ≥18 years of age, had histologically confirmed CD20+ DLBCL (including double-hit/triple-hit DLBCL, classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* translocations), had R/R disease after ≥1 prior line of therapy (pLOT), were HDT-ASCT-eligible, had ECOG PS of 0–2, and measurable disease by CT-MRI.

The study consisted of dose-escalation and dose-expansion parts. In dose escalation, patients received 24- or 48-mg full doses of epcoritamab in the same schedule as dose expansion. In dose expansion, subcutaneous epcoritamab 48 mg was administered once weekly (QW) in 21-day cycles ([C]1–3) in combination with R-DHAX/C (rituximab 375 mg/m^2 intravenously [IV] every 3 weeks (Q3W); dexamethasone 40 mg/d IV or orally on Day (D) 1–4; cytarabine 2 g/m^2 IV repeated after 12 hours Q3W; carboplatin AUC=5 mg/mL × min [Calvert formula] or oxaliplatin 100 mg/m^2 IV Q3W). Epcoritamab monotherapy continued QW in C4 (21-day cycles), then in 28-day cycles (Q2W, C5–9; Q4W, C10+) until HDT-ASCT, progressive disease, or unacceptable toxicity.

During C1, two step-up doses (0.16 mg on D1 and 0.8 mg on D8) followed by full 48-mg doses of epcoritamab were administered; patients were hospitalized for ≥24 hours after the first full dose. Patients received corticosteroid prophylaxis (prednisolone 100 mg PO or equivalent on D1–4, D8 –11, and D15–18) for cytokine release syndrome (CRS).[23] Premedication with diphenhydramine 50 mg, acetaminophen 650–1000 mg, and prednisolone 100 mg orally (or equivalent) was mandatory in C1. Patients with recurrent cases of grade ≥3 neutropenia were mandated to receive granulocyte colony-stimulating factor (G-CSF).

Endpoints

The primary endpoint was investigator-assessed OR rate (Lugano criteria).[26] Secondary endpoints included CR rate, time to response (TTR), time to CR (TTCR), duration of response (DoR), duration of CR (DoCR), PFS, OS, time to next anti-lymphoma therapy (TTNT), adverse events (AE), serious AE (SAE), and AE of special interest.

Assessments

Tumor response was evaluated by FDG PET-CT Q6W for the first 24 weeks, Q12W through Week 48, and Q24W thereafter, relative to the first day of any trial drug administration. The first on-treatment response assessment occurred at Week 6.

AE were assessed from first treatment dose for a maximum of 60 days after the last dose of epcoritamab and 30 days after last dose of SoC or start of a new line of lymphoma therapy. SAE were reported throughout the study; SAE considered related to epcoritamab were reported continuously after the safety follow-up visit (>60 days after the last dose).

Statistical analysis

All analyses were descriptive and based on the full analysis set (patients who received ≥1 dose of study treatment); safety analyses were conducted in the safety population (same definition as full analysis set). OR and CR rates were summarized with 95% confidence intervals (CI) using the Clopper–Pearson method. Time-to-event endpoints were analyzed using Kaplan–Meier methods. Additional details are provided in the *Online Supplementary Methods*.

Ethics approval

The study was approved by the institutional review board or central ethics committee at each participating institution and was conducted according to the ethical principles that have their

origin in the Declaration of Helsinki, the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice, and applicable regulatory requirements.

Results

Study population and treatment exposure

Twenty-nine patients were enrolled between February and September 2021, and all were treated with epcoritamab plus R-DHAX/C. Three patients received epcoritamab 24 mg and 26 received epcoritamab 48 mg as the full dose across dose escalation and expansion. The median age was 58 years (range, 28–75); 83% (24/29) of patients were male at birth, 72% (21/29) had Ann Arbor stage IV disease, 66% (19/29) had primary refractory disease, and 83% (24/29) had extranodal involvement (Table 1). Five of 19 (26%) patients with available data had HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit/triple-hit lymphoma) per central laboratory analysis. The median number of pLOT was 1 (range, 1–3), 76% (22/29) of patients had received 1 pLOT, 83% (24/29) had progressed within 12 months of 1L therapy, and 10% (3/29) had received prior CAR T-cell therapy. As of the data cutoff (January 15, 2025), median study follow-up was 40.4 months (range, 2.0+ to 45.5).

Among the 29 patients, 21 (72%) completed epcoritamab plus R-DHAX/C treatment per protocol (Figures 1 and 2). Of these, 16 patients proceeded to ASCT and five continued epcoritamab monotherapy. Reasons for continuing epcoritamab monotherapy and not proceeding to ASCT were patient choice (3/5) and infectious AE (2/5). Among the 8 (28%) patients who discontinued treatment, reasons for discontinuation were progressive disease (PD; 21%; 6/29) and AE (7%; 2/29). Six of the eight patients who discontinued trial treatment subsequently received CAR T-cell therapy; of these, two underwent allogenic stem cell transplantation. Four of the six patients who received CAR T-cell therapy had subsequent PD.

Patients received a median of 4 (range, 1–41) epcoritamab cycles, with a median relative dose intensity of 88% and a median epcoritamab treatment duration of 2.7 months (range, 0–39.4). The median number of R-DHAX/C cycles was 3 (range, 1–3). Median relative dose intensities were 98% for rituximab, 99% for oxaliplatin, 86% for carboplatin, and 93% for cytarabine. Among patients who proceeded to HDT-ASCT (n=16), median number of R-DHAX/C cycles was 3 (range 2–3) and median number of epcoritamab cycles was 4 (range, 3–7). Median time from last epcoritamab dose to HDT-ASCT was 14 days (range, 2–52). Among patients who stayed on epcoritamab (n=5), median number of R-DHAX/C cycles was 3 (range, 1–3) and median number of epcoritamab cycles was 24 (range, 10–41). Among patients who discontinued treatment due to other reasons (n=8), median number of R-DHAX/C cycles was 2.5 (range, 1–3) and median number of epcoritamab cycles was 3 (range, 1–4).

Efficacy

In the overall study population (N=29), the OR rate was 79% (23/29; 95% CI: 60.3–92.0) and the CR rate was 69% (20/29; 95% CI: 49.2–84.7). Three (10%) patients had partial response (PR) as best response, and stable disease (SD) and PD were observed as best response in two (7%) patients each. Two patients were not evaluable and classified as non-responders, as they discontinued the trial prior to their first lymphoma assessment. At the first protocol-scheduled response assessment at Week 6, the OR rate was 72% (21/29), including a CR rate of 45% (13/29).

Response rates were consistently high among prespecified subgroups. Among patients with primary refractory disease (n=19), the OR rate was 68% (95% CI: 43–87) and the CR rate was 53% (95% CI: 29–76). OR and CR rates in patients who relapsed within 12 months of initial therapy (n=24) were 75% (95% CI: 53–90) and 63% (95% CI: 41–81), respectively. Among patients who relapsed after 12 months of initial therapy (n=5), OR and CR rates were both

100% (95% CI: 48–100). In those with 1 prior line of therapy (n=22), OR rate was 77% (95% CI: 55–92) and CR rate was 68% (95% CI: 45–86).

Overall, median TTR and TTCR were 1.4 months (range, 1.2–3.9) and 1.5 months (range, 1.2–15.5), respectively. Median DoR, DoCR, OS (Figures 3 and 4), and TTNT were not reached (NR); median PFS was 38.7 months (95% CI, 11.5–NR). At 36 months, an estimated 70% of responders remained in response, 71% of complete responses were ongoing, 59% of patients were progression-free, and 76% were alive. Seven of the eight patients who discontinued epcoritamab plus R-DHAX/C treatment had died by the data cutoff, three of whom had reportedly died due to PD.

Among the 16 patients who proceeded to ASCT, 14 (88%) had a CR and two (13%) had a PR at the time of transplant (Figure 2). One patient in PR converted to CR after HDT-ASCT, resulting in a post-transplant CR rate of 94%. Seven of the 16 patients (44%) received plerixafor for mobilization for stem-cell harvest, of whom one (6%) did not mobilize until a second attempt with G-CSF, and four (25%) underwent apheresis over 2 days, compared to 1 day for all other patients. Consistent with what was observed in the overall population, median DoR, DoCR, PFS, OS (Figures 3 and 4), and TTNT were NR in patients who proceeded to ASCT. At 36 months, an estimated 83% of patients who received HDT-ASCT remained in response and 75% remained in CR.

Five (17%) patients continued with epcoritamab treatment and did not undergo ASCT, and all five achieved a CR: three during the combination treatment, and two had a PR with combination treatment and converted to a CR after staying on epcoritamab monotherapy. At the data cutoff, all five patients had discontinued treatment due to AE (n=2), PD (n=1), and by patient request (n=2). Three patients remained in CR (durations, 35.1+, 37.5+, and 42.2+ months), and two had progressed after remaining in CR for 7.1 months and 16.2 months.

Safety

All 29 patients had a treatment-emergent adverse event (TEAE), with grade 3 or 4 events reported in 97% (28/29) of patients and SAE in 52% (15/29). The most common TEAE were thrombocytopenia (90%; 26/29), anemia (66%; 19/29), neutropenia (59%; 17/29), and nausea (52%; 15/29) (Table 2). CRS occurred in 45% (13/29) of patients; all events were low grade (grade 1: 34% [10/29], grade 2: 10% [3/29]), and fever was the most common symptom (100% [13/13]), followed by hypotension (15% [2/13]) and hypoxia (15% [2/13]). CRS was most common after the first full dose (33% [9/27]). All CRS events resolved, and median time to resolution was 2 days (range, 1–7). No patients discontinued treatment due to CRS. One (3%) patient had grade 2 immune effector cell-associated neurotoxicity syndrome (ICANS), which led to epcoritamab discontinuation, and which resolved within 37 days. Febrile neutropenia was reported in 17% (5/29) of patients. Overall, 16 (55%) patients received granulocyte-colony stimulating factor (G-CSF) as prophylaxis. Grade 1 peripheral neuropathy was reported in 10% (3/29) of patients, and there were no clinical tumor lysis syndrome events.

Infections of any grade were reported in 41% (12/29) of patients, with grade 3 or 4 infections in 17% (5/29) and 7% (2/29), respectively. Infections were mostly viral (21%, 6/29; COVID-19 [14%; 4/29], cytomegalovirus colitis, viral gastroenteritis, oral herpes, and herpes zoster [3% each; 1/29]), followed by bacterial infections (14%, 4/29; cellulitis, Escherichia urinary tract infection, folliculitis, lower respiratory tract infection, pseudomonal pneumonia, Staphylococcal skin infection, Streptococcal endocarditis [3% each; 1/29]), and fungal infections (14%, 4/29; 1 pulmonary aspergillosis [post-ASCT; 3%] and 3 superficial fungal [oral candidiasis, genital infection, skin infection; 3% each]). No deaths occurred due to infection.

TEAE led to epcoritamab dose delays in 59% (17/29) of patients. Three patients discontinued epcoritamab due to TEAEs; 2 discontinued due to TEAEs (ICANS and Guillain–Barré syndrome) during co-administration with R-DHAX/C, and another patient who remained on

epcoritamab monotherapy discontinued due to respiratory tract infection (*Online Supplementary Table S1*). No fatal TEAE were reported. No transplant-related deaths were reported.

Discussion

HDT followed by ASCT remains a curative option for patients with R/R DLBCL in the 2L setting, with treatment failure more than 12 months after 1L therapy. However, the lack of response to salvage CIT continues to limit transplant applicability. Thus, effective and widely available salvage regimens are needed to improve response rates and to enable more patients to proceed to ASCT. In this study, epcoritamab combined with R-DHAX/C as salvage therapy led to a notable increase in response rates, with an OR rate of 79%, compared with historic response rates of 40–60% with CIT/R-DHAX/C alone.[2,29,30] An encouraging CR rate of 69% was observed in the overall population, and responses occurred early, with many observed at the first assessment. Overall, 55% of patients proceeded to ASCT, and the majority (83%) of patients with a response remained in response at 3 years.

While sample sizes are small, deep and durable responses were observed across subgroups, including in patients with historically poor outcomes (e.g., those with primary refractory disease or early relapse following 1L therapy), suggesting promising efficacy in challenging-to-treat patients. Of particular interest, responses were durable among the five patients who did not proceed to ASCT and continued epcoritamab monotherapy; three patients remained in CR at data cutoff. After a median follow-up of 40.4 months, median DoR, PFS, and OS were NR in both transplanted and non-transplanted subgroups. These results suggest that the addition of epcoritamab to salvage CIT may improve response rates and transplant eligibility, while potentially offering durable disease control in patients not proceeding to ASCT.

Combinations of a bsAb plus CIT regimens have demonstrated promise as effective treatment options in the transplant-eligible and transplant-ineligible 2L+ setting. The combination of

epcoritamab with GemOx assessed in the EPCORE NHL-2 trial led to high OR and CR rates of 85% and 61%, respectively, in patients with ASCT-ineligible R/R DLBCL (median follow-up, 13.2 months).[25] Compared to epcoritamab and GemOx, which led to median PFS of 11.2 months, longer median PFS of 38.7 months was observed in the present study, which may be reflective of the transplant-eligible population.[25] Similarly, an OR rate of 68% was observed in patients who received glofitamab plus GemOx in the STARGLO trial (median follow-up, 20.7 months),[30] and preliminary results from the GO43693 trial suggest that glofitamab plus R-ICE yields an OR rate of 78%.[31] However, there remains a need for salvage regimens capable of inducing rapid, deep responses leading to HDT-ASCT. Epcoritamab in combination with other salvage CIT regimens, such as R-ICE and GDP, have also achieved high response and transplant rates. Epcoritamab plus R-ICE resulted in an OR rate of 87%, with 65% of patients proceeding to HDT-ASCT,[32] while epcoritamab plus GDP led to an OR rate of 79%.[33] Collectively, these findings underscore the potential of bsAb and CIT combinations in R/R DLBCL.

The proportion of patients who proceeded to ASCT in this study was similar to historic rates, such as the CORAL study where 50–54% of patients proceeded to ASCT.[2] While 55% (16/29) of patients proceeded to ASCT following epcoritamab plus R-DHAX/C, an additional 5 patients remained on epcoritamab monotherapy due to patient choice or an AE; therefore, 72% (21/29) of patients benefited from the study treatment. Notably, this patient cohort represented a challenging-to-treat population, with 83% of patients progressing within 12 months of prior therapy, 10% receiving prior CAR T-cell therapy, and 26% harboring double-hit or triple-hit lymphoma, features that are typically associated with poor outcomes.[1] Additionally, the higher CR rate achieved in current study (69%) and 3-year PFS (59%) compared to CORAL (48–53% CR rate, 37% 3-year event-free survival) highlights the importance of increasing CR rates prior to ASCT, often resulting in improved long-term outcomes.[2,8]

Our findings should be viewed in the context of other contemporary trials evaluating 2L treatment strategies for R/R DLBCL, particularly with the advent of CAR T-cell therapies. The current study enrolled patients prior to the 2022 approval of axi-cel and liso-cel CAR T-cell therapies for 2L treatment of R/R DLBCL in 2022.[34,35] The ZUMA-7 trial has since compared investigator-selected SoC CIT followed by HDT-ASCT versus CAR T-cell therapy (axi-cel).[10] At a median follow-up of 24.9 months, the CR rate was 65% in the axi-cel group and 32% in the SoC group; 36% of patients assigned to SoC proceeded to ASCT and 49% did not receive ASCT due to PD or SD. The estimated OS at 4 years was 55% with axi-cel and 46% with SoC; estimated 4-year PFS rate was 42% with axi-cel versus 24% with SoC.[36] The TRANSFORM trial compared SoC (R-DHAP, R-ICE, or R-GDP plus ASCT) with liso-cel.[9] At a median follow-up of 33.9 months, the CR rates were 74% in the liso-cel group and 43% in the SoC group; 47% of patients assigned to SoC proceeded to ASCT.[37] At 36 months, OS rates were higher for liso-cel (63%) compared with SoC (52%); 36-month PFS rates were 51% for liso-cel and 27% for SoC.[37]

While CAR T-cell therapy is a proven effective treatment for patients who progress within 12 months of 1L therapy, in the present study, patients with challenging-to-treat disease (66% primary refractory, 26% with double-hit/triple-hit lymphoma, and 10% with prior CAR T-cell therapy) achieved a promising OR rate of 79% with bsAb treatment combined with platinum-based salvage CIT followed by ASCT. This suggests that HDT-ASCT may remain a viable treatment option in patients with early progression when CAR T-cell therapy is not feasible or available. Moreover, while CAR T-cell therapies are now SoC for patients with early progression, there is an ongoing need for effective treatment options for patients with later relapse. As ASCT is associated with improved long-term survival over salvage CIT alone in patients with late relapses, increasing the number of patients who can undergo HDT-ASCT still represents an attractive strategy in this setting.[38] Additionally, achieving CR prior to ASCT can

lead to improved long-term outcomes, as prior studies have noted that patients who proceed to ASCT without achieving CR often have shorter survival rates and poorer outcomes.[2,8]

The safety profile of epcoritamab plus R-DHAX/C was manageable and aligned with the known effects of the individual agents and no new safety signals emerged. CRS events were predictable (occurring most often after the first full dose), low grade (grade 1–2), and resolved without treatment discontinuation within a median of 2 days. Infections were generally viral. No treatment-related deaths occurred.

Among patients who received ASCT, seven out of 16 (44%) required plerixafor. Plerixafor use was not protocol-mandated and was administered at investigators' discretion, typically in patients with poor initial mobilization. Mobilization practices were not standardized across participating sites, and institutional variation in thresholds for introducing plerixafor may have contributed to the frequency observed. Given the small sample size, the impact of the treatment regimen on stem-cell mobilization or plerixafor requirements remains unknown. Importantly, all patients were successfully mobilized, and no patient failed to proceed to ASCT due to mobilization failure in this study.

This study has several strengths, including enrollment of a 2L+ DLBCL population with features indicative of poor prognosis, a setting in which effective salvage treatment options remain limited. The extended median follow-up (40.4 months) allowed for meaningful evaluation of long-term outcomes, including durability of responses and survival outcomes. The analysis across transplanted and non-transplanted cohorts, reflecting real-world clinical decision-making, suggesting the versatility of epcoritamab both as part of a CIT regimen or as monotherapy. Encouraging results were seen in patients with challenging-to-treat primary refractory disease. Further investigation is warranted to determine the optimal placement of bsAb therapy combined with salvage CIT and HDT-ASCT in the treatment paradigm.

However, study limitations should also be acknowledged, including the single-arm design, limited sample size (thereby resulting in wide confidence intervals), and lack of power to differentiate the relative contributions of epcoritamab versus CIT or isolate the contribution of ASCT. Additionally, because the study enrolled patients prior to the 2L approval of CAR T-cell therapies,[35,36] comparisons with more recent standards are limited.

In summary, epcoritamab plus R-DHAX/C delivered high response rates in this 2L+ transplant-eligible patient population with R/R DLBCL. Durable responses were observed in both transplanted and non-transplanted patients, although interpretation of outcomes in the latter group is limited by the small sample size. Despite the single-arm design, these results support the potential benefit of adding epcoritamab to salvage therapy regimens and warrant further evaluation in larger, controlled studies.

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TABLES

Table 1. Baseline demographic and clinical characteristics

Characteristics	**All patients N=29**
Median age, years (range) <65, n (%)	58 (28–75) 21 (72.4)
Male at birth, n (%)	24 (82.8)
Race, n (%) Asian Black or African American White Not reported	 1 (3.4) 1 (3.4) 25 (86.2) 2 (6.9)
ECOG PS, n (%) 0 1 2	 11 (37.9) 18 (62.1) 0
Disease type at study entry, n (%) DLBCL FL grade 3B	 28 (96.6) 1 (3.4)
DLBCL type,[a] n (%) De novo Transformed	 18 (62.1) 11 (37.9)
Cell of origin, n (%) GCB Non-GCB/ABC Unknown/missing	 15 (51.7) 10 (34.5) 4 (13.8)
Extranodal disease, n (%)[b]	24 (82.8)
DH/TH status with chromosomal alteration per central lab, n/n (%)	5/19 (26.3)
Ann Arbor stage, n (%) II III IV	 4 (13.8) 4 (13.8) 21 (72.4)
IPI, n (%) 0–2 3 4–5	 13 (44.8) 10 (34.5) 6 (20.7)
Bulky disease status, n (%)	

Characteristics	**All patients N=29**
<7 cm ≥7 cm	22 (75.9) 7 (24.1)
Primary refractory disease, n (%)	19 (65.5)
Median prior lines of anti-lymphoma therapy (range)	1.0 (1–3)
Prior lines of anti-lymphoma therapy, n (%) 1 2 3	 22 (75.9) 5 (17.2)[c] 2 (6.9)[d]
Prior CAR T-cell therapy, n (%)	3 (10.3)
Median time from end of last anti-lymphoma therapy to first dose, mo (range)	6.34 (0.6–48.8)
1L response status, n (%) Refractory No response Relapsed within 6 mo after therapy Relapsed Progressed within 12 mo after therapy	 19 (65.5) 4 (13.8) 15 (51.7) 10 (34.5) 24 (82.8)
Best response to last line of therapy, n (%)[e] CR PR SD PD	 18 (62.1) 7 (24.1) 1 (3.4) 2 (6.9)
Refractory to anti-CD20, n (%)	19 (65.5)

[a]DLBCL subtypes include: DLBCL not otherwise specified, double-hit and triple-hit DLBCL (high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations), FL grade 3B, and T-cell/histiocyte-rich DLBCL. [b]Assessment based on non-nodal sites. [c]Two patients had received CAR-T cell therapy, two patients received R-CHOP (both had transformed DLBCL), and one patient received R-GDP as their last treatment. [d]One patient had received R-CHOP, R-DHAP, and R-bendamustine for prior FL and one patient with transformed DLBCL had received R-CHOP, R-GDP, and CAR T-cell therapy. [e]Two additional patients (7%) discontinued due to AE before their first tumor assessment.

1L: first line; ABC: activated B-cell; AE: adverse event; CAR: chimeric antigen receptor; CR: complete response; DLBCL: diffuse large B-cell lymphoma; DH/TH: double-hit/triple-hit; ECOG PS: Eastern Cooperative Oncology Group performance status; FL: follicular lymphoma; GCB: germinal center B-cell; IPI: International Prognostic Index; mo: month(s); PD: progressive disease; PR: partial response; R-bendamustine: rituximab, bendamustine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, cisplatin; SD: stable disease.

Table 2. Treatment-emergent adverse events

	All patients N=29
TEAE Any grade Grade 3/4 Grade 5	 29 (100) 28 (96.6) 0
Serious TEAE	15 (51.7)
TEAE leading to any trial drug discontinuation TEAE leading to epcoritamab discontinuation	4 (13.8) 3 (10.3)
TEAE leading to dose delay TEAE leading to epcoritamab dose delay	17 (58.6) 17 (58.6)
Fatal TEAE	0
Most common TEAE in ≥20% of patients	
Thrombocytopenia[a]	26 (89.7)
Anemia[b]	19 (65.5)
Neutropenia[c]	17 (58.6)
Nausea	15 (51.7)
Cytokine release syndrome	13 (44.8)
Fatigue	11 (37.9)
Diarrhea	10 (34.5)
Headache	8 (27.6)
Constipation	7 (24.1)
Aspartate aminotransferase increased	6 (20.7)
Cough	6 (20.7)
Pyrexia	6 (20.7)
Serious infections[d]	6 (20.7)

AE were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[27]

TEAE were reported up to 60 days after the last dose of epcoritamab. CRS and ICANS were graded using American Society for Transplantation and Cellular Therapy consensus grading criteria.[28] [a]Thrombocytopenia includes hematopoietic thrombocytopenia using SMQ narrow search. [b]Neutropenia includes neutropenia or neutrophil count decreased. [c]Anemia includes anemia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased. [d]Serious infections include serious TEAE in the SOC of infections and infestations. In total, six patients had serious infections (pneumonia [n=3], bronchitis, pulmonary aspergillosis, COVID-19, cellulitis, Escherichia urinary tract infection, gastroenteritis viral, periodontitis, sepsis, sinusitis, streptococcal endocarditis, and upper respiratory tract infection [n=1, each]).

AE: adverse event; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; SMQ: standardized MedDRA query; SOC, System Organ Class; TEAE: treatment-emergent adverse event.

FIGURE LEGENDS

Figure 1. Patient flow diagram

Figure 2. Responses by investigator assessment per Lugano criteria over time in patients receiving epcoritamab plus R-DHAX/C (full analysis set)

Figure 3. Durability of responses in patients receiving epcoritamab plus R-DHAX/C. (A) Duration of response for all patients, patients who proceeded to autologous stem cell transplantation, patients who stayed on epcoritamab, and patients who discontinued treatment. (B) Duration of complete response for all patients, patients who proceeded to autologous stem cell transplantation, and patients who stayed on epcoritamab.

Figure 4. Survival outcomes in patients receiving epcoritamab plus R-DHAX/C. (A) Progression-free survival for all patients, patients who proceeded to autologous stem cell transplantation, patients who stayed on epcoritamab, and patients who discontinued treatment. (B) Overall survival for all patients, patients who proceeded to autologous stem cell transplantation, patients who stayed on epcoritamab, and patients who discontinued treatment.

Figure 1

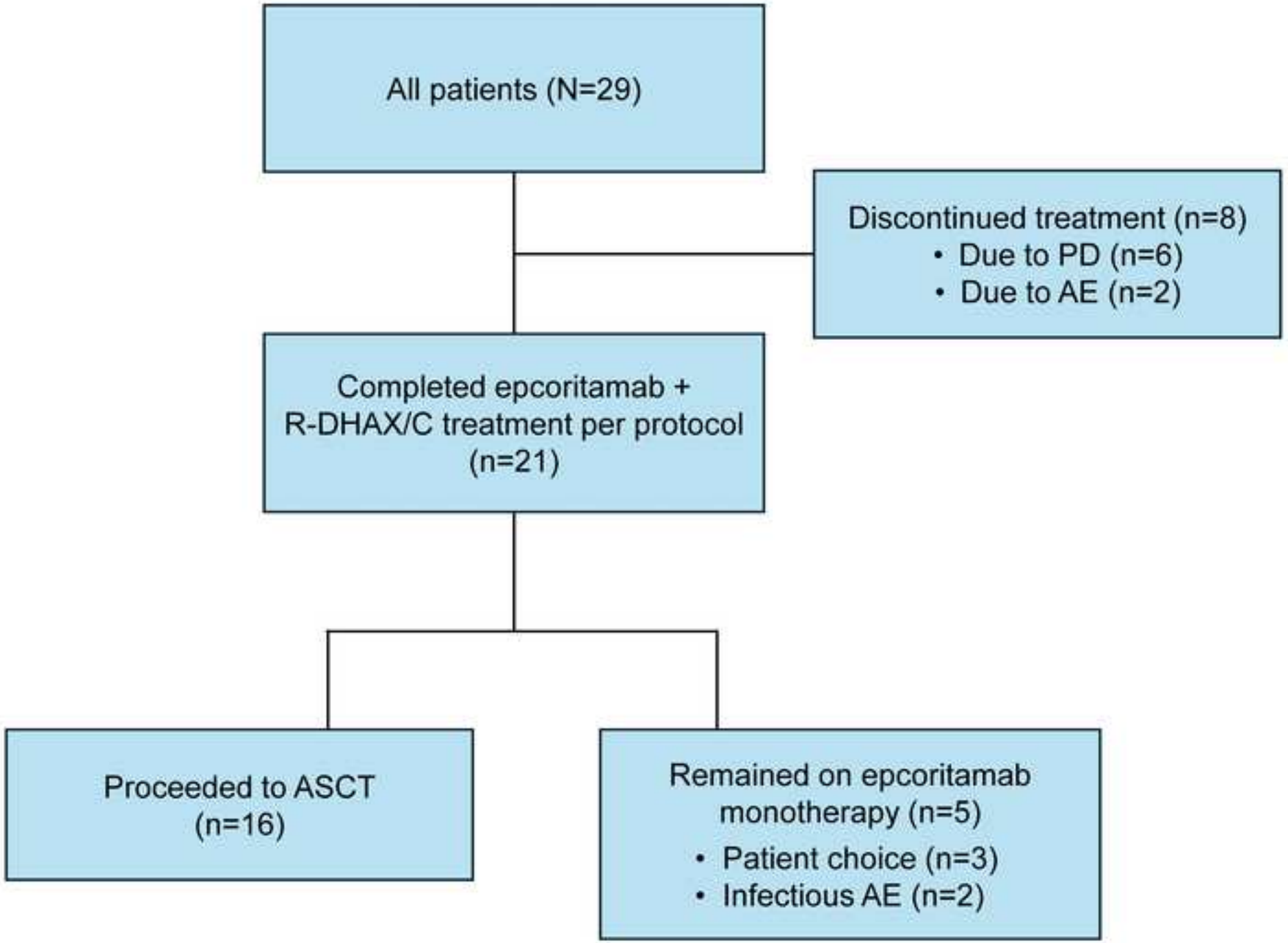


Figure 2

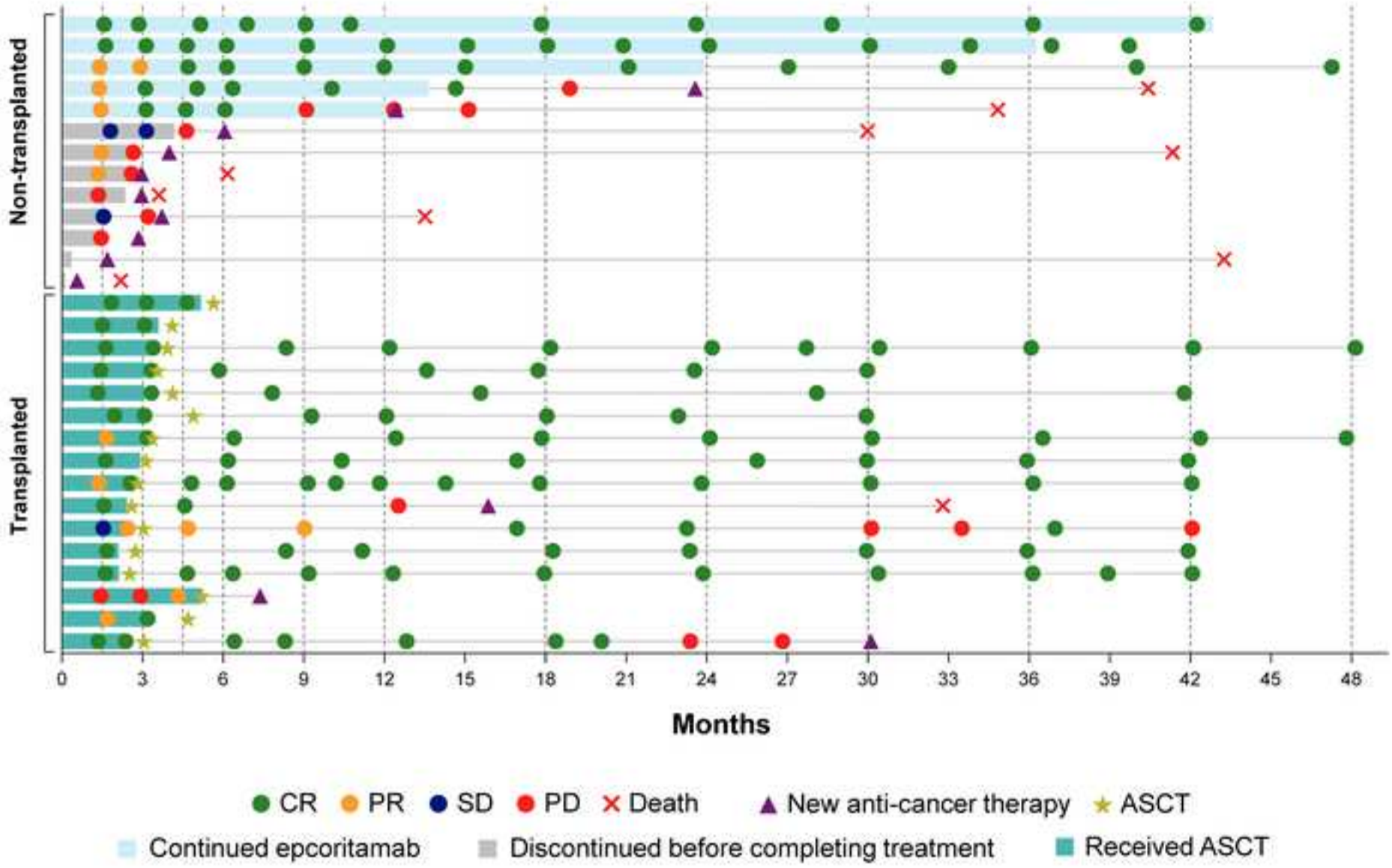
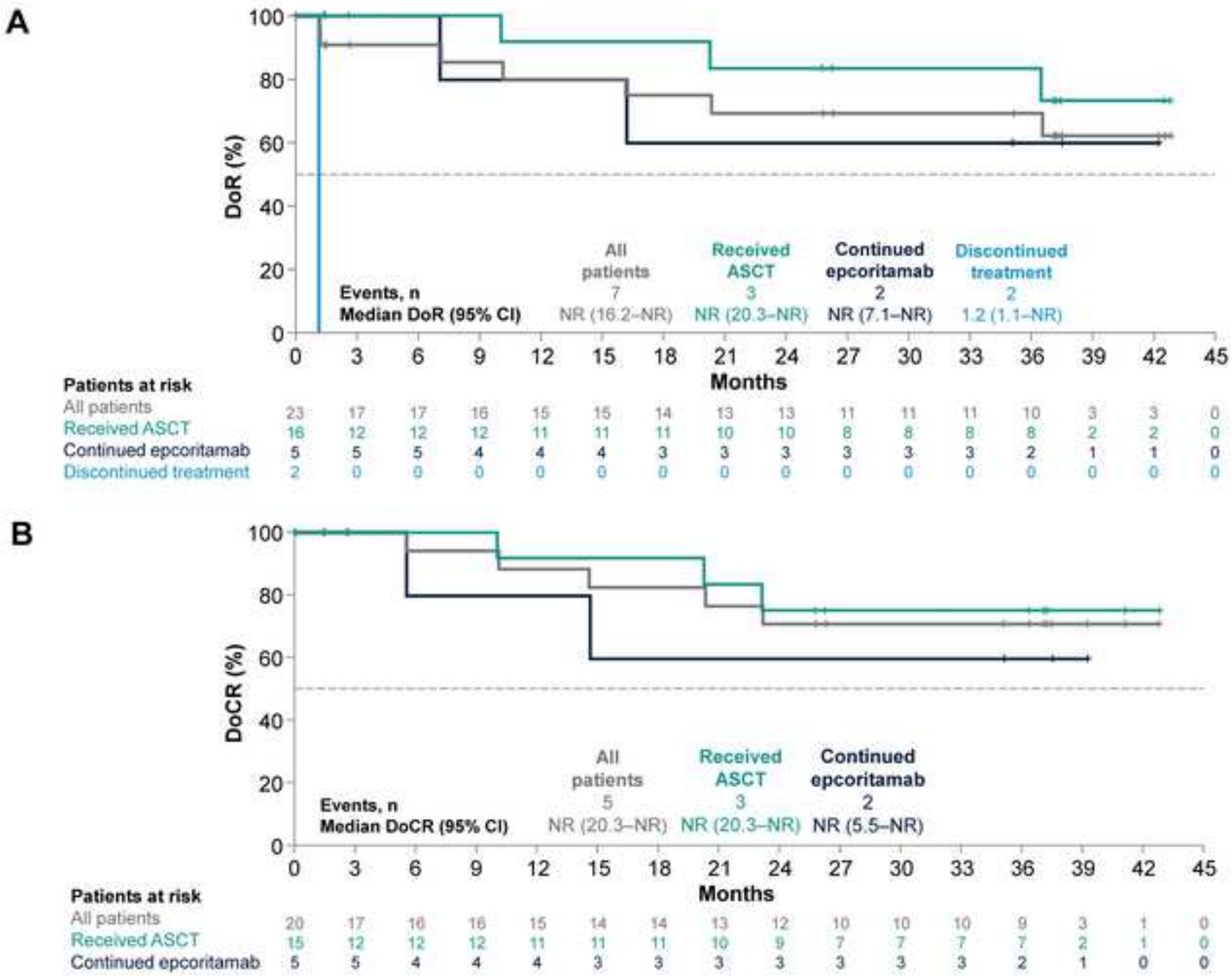
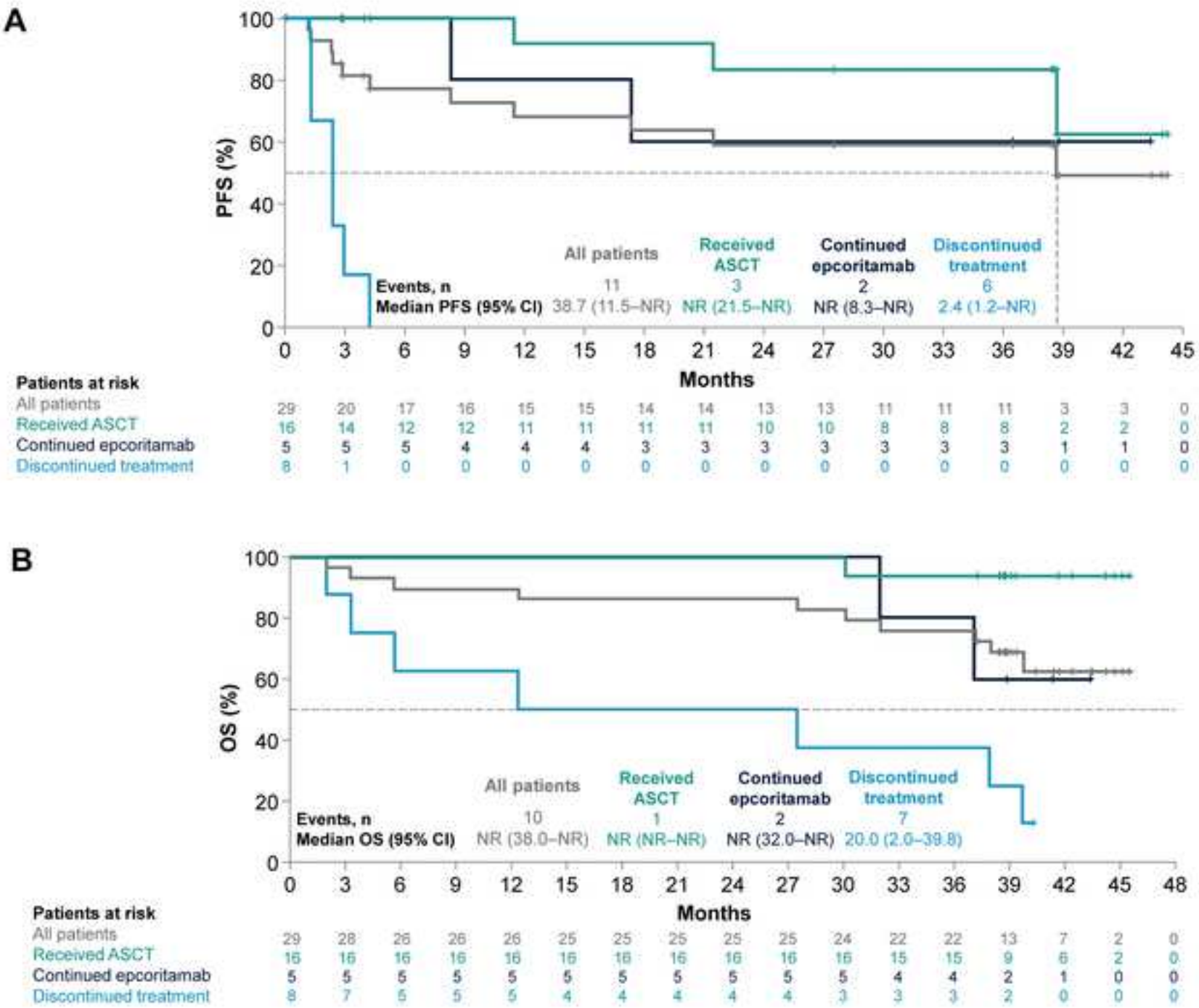


Figure 3





SUPPLEMENTAL METHODS

Patient eligibility criteria

In Arm 4 of the EPCORE® NHL-2 trial, eligible patients were adults (≥18 years of age) with histologically confirmed CD20+ diffuse large B cell lymphoma (DLBCL) that was de novo or histologically transformed from follicular lymphoma or nodal marginal zone lymphoma, based on World Health Organization 2016 classification[1] (DLBCL not otherwise specified; double-hit or triple-hit DLBCL classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* translocations; follicular lymphoma grade 3B; or T-cell/histiocyte-rich DLBCL).

Dosing regimen

In the dose escalation, patients received subcutaneous epcoritamab in 2 step-up doses, followed by either 24- or 48-mg full doses, administered weekly in 21-day cycles (C) during C1–3; patients could continue epcoritamab monotherapy (once weekly [QW] during a 21-day C4, then in 28-day C: Q2W in C5–9; Q4W in C10+) until high-dose therapy and autologous stem cell transplantation or progressive disease (PD). Rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin (R-DHAX/C) was administered every C, in 21-day C (C1–3): rituximab at 375 mg/m^2 intravenously (IV); dexamethasone at 40 mg/d IV or orally on days 1–4; cytarabine 2 g/m^2 IV repeated after 12 hours; carboplatin AUC=5 mg/mL x min (Calvert[2] formula) or oxaliplatin 100 mg/m^2 IV.

Endpoints

Additional secondary endpoints assessed in Arm 4 of the EPCORE NHL-2 study were safety and tolerability, including incidence and severity of adverse events (AE), serious AE (SAE), and AE of special interest (i.e., cytokine release syndrome [CRS], immune effector cell-associated neurotoxicity syndrome, clinical tumor lysis syndrome).

Assessments

Tumor response was assessed by fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT), or by CT/magnetic resonance imaging (MRI) and FDG PET if PET-CT is not available at weeks 6, 12, 18, 24, 36, and 48, and every 24 weeks thereafter until PD.

AE were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[3] CRS and immune effector cell-associated neurotoxicity syndrome were graded using American Society for Transplantation and Cellular Therapy consensus grading criteria.[4] Clinical tumor lysis syndrome was graded according to Cairo–Bishop criteria.[5] AE were

assessed throughout the study from the first treatment dose until the maximum of 60 days after the last dose of epcoritamab and 30 days after the last dose of standard of care, or start of new therapy, whichever occurred first. All SAE were reported over the duration of the study until the safety follow-up visit (>60 days after the last dose), after which only SAE considered by the investigator as related to epcoritamab were reported.

Statistical analysis

All analyses were descriptive and based on the full analysis set, which included all patients who received ≥1 dose of study treatment. Time-to-event endpoints (duration of response, duration of complete response (CR), progression-free survival, overall survival [OS], and time to next anti-lymphoma therapy [TTNT]) were analyzed using Kaplan–Meier methods; time to response and time to CR were analyzed with descriptive methods. For duration of response, duration of CR, and progression-free survival, progression at the date of PD scan and death prior to progression on the date of death were considered events. Date of PD is defined as the earliest date of documented progression after which there is no more partial response or CR assessment. Patients were censored at the first dosing date if there were no or incomplete baseline tumor assessments or no post-baseline assessments and the patient was alive. Patients were censored at the last adequate disease assessment date if they had no progression, death, or, if they had PD or died after 2 or more consecutive missing disease assessments. Patients were also censored at the last adequate disease assessment date before start of subsequent anti-cancer therapy if they started subsequent anti-cancer therapy prior to PD or death.

OS was defined as the time from C1D1 to death from any cause. For OS analysis, patients for whom death was not reported were censored at the latest date they were known to be alive.

For TTNT, death due to PD was considered an event and death due to other reasons was censored at the death date. The subsequent anti-lymphoma therapies for TTNT events consisted of systemic anti-lymphoma therapy, stem cell transplantation, CAR T-cell therapy, surgery to target lesions and radiotherapy to target lesion(s), with the exception of censoring subjects with partial response or CR while receiving subsequent stem cell transplantation after responding to epcoritamab, to be consistent with the intent to measure duration of clinical benefit using TTNT. Patients who were alive and without initiation of subsequent anti-lymphoma therapy were censored at the last known alive date.

Safety analyses were conducted in the safety population, which included all patients who received ≥1 dose of study treatment. AE, including treatment-emergent AE (TEAE), SAE, grade ≥3 AE, AE of special interest, and AE leading to dose modifications or treatment

discontinuation, were summarized descriptively by frequency, severity (grade), and relationship to study treatment. AE incidence was additionally evaluated by analysis period, where applicable.

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Supplementary Table S1. Treatment-emergent adverse events leading to epcoritamab discontinuation or dose modification of any drug

	All TEAE
TEAE leading to epcoritamab treatment discontinuation, n (%)	3 (10.3)[a]
Guillain–Barré syndrome	1 (3.4)
ICANS	1 (3.4)
Thrombocytopenia	1 (3.4)
Lower respiratory tract infection bacterial	1 (3.4)
Pneumonia	1 (3.4)
TEAE leading to dose modification of any drug, n (%)	18 (62.1)
Thrombocytopenia	9 (31.0)
Neutropenia	4 (13.8)
COVID-19	2 (6.9)
Fatigue	2 (6.9)
Febrile neutropenia	2 (6.9)
Platelet count decreased	2 (6.9)
Acute pulmonary oedema	1 (3.4)
Alanine aminotransferase increased	1 (3.4)
Anemia	1 (3.4)
Blood creatinine increased	1 (3.4)
Bronchitis	1 (3.4)
Cholecystitis	1 (3.4)
Coronary artery disease	1 (3.4)
Cough	1 (3.4)
Cushingoid	1 (3.4)
Cytokine release syndrome	1 (3.4)
Cytomegalovirus colitis	1 (3.4)
Eczema	1 (3.4)
Heart failure with reduced ejection fraction	1 (3.4)
Infusion related reaction	1 (3.4)
Insomnia	1 (3.4)
Mucosal inflammation	1 (3.4)
Neutrophil count decreased	1 (3.4)
Pancytopenia	1 (3.4)
Periodontitis	1 (3.4)
Pneumonia	1 (3.4)
Pneumonia pseudomonal	1 (3.4)
Post procedural hemorrhage	1 (3.4)
Rash maculo-papular	1 (3.4)
Sepsis	1 (3.4)
Streptococcal endocarditis	1 (3.4)
Tumor associated fever	1 (3.4)
Upper respiratory tract infection	1 (3.4)
Vomiting	1 (3.4)

Percentages are calculated based on number of patients in the safety analysis set. Adverse events are classified using MedDRA v27.1 and are counted only once per SOC and only

once per preferred term. [a]Two patients discontinued epcoritamab in Cycle 1; one patient discontinued epcoritamab after long-term treatment.

COVID 19: coronavirus disease 2019; ICANS: Immune effector cell-associated neurotoxicity syndrome; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class; TEAE: treatment emergent adverse events.