original reports

Epcoritamab, a Novel, Subcutaneous CD3xCD2O Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

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abstract

PURPOSE Epcoritamab is a subcutaneously administered CD3xCD20 T-cell–engaging, bispecific antibody that activates T cells, directing them to kill malignant CD20$^+$ B cells. Single-agent epcoritamab previously demonstrated potent antitumor activity in dose escalation across B-cell non-Hodgkin lymphoma subtypes.

PATIENTS AND METHODS In the dose-expansion cohort of a phase I/II study (ClinicalTrials.gov identifier: NCT03625037), adults with relapsed or refractory CD20$^+$ large B-cell lymphoma and at least two prior therapy lines (including anti-CD20 therapies) received subcutaneous epcoritamab in 28-day cycles (once weekly step-up doses in weeks 1-3 of cycle 1, then full doses once weekly through cycle 3, once every 2 weeks in cycles 4-9, and once every 4 weeks in cycle 10 and thereafter) until disease progression or unacceptable toxicity. The primary end point was overall response rate by the independent review committee.

RESULTS As of January 31, 2022, 157 patients were treated (median age, 64 years [range, 20-83]; median of three [range, 2-11] prior therapy lines; primary refractory disease: 61.1%; prior chimeric antigen receptor (CAR) T-cell exposure: 38.9%). At a median follow-up of 10.7 months, the overall response rate was 63.1% (95% CI, 55.0 to 70.6) and the complete response rate was 38.9% (95% CI, 31.2 to 46.9). The median duration of response was 12.0 months (among complete responders: not reached). Overall and complete response rates were similar across key prespecified subgroups. The most common treatment-emergent adverse events were cytokine release syndrome (49.7%; grade 1 or 2: 47.1%; grade 3: 2.5%), pyrexia (23.6%), and fatigue (22.9%). Immune effector cell–associated neurotoxicity syndrome occurred in 6.4% of patients with one fatal event.

CONCLUSION Subcutaneous epcoritamab resulted in deep and durable responses and manageable safety in highly refractory patients with large B-cell lymphoma, including those with prior CAR T-cell exposure.

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INTRODUCTION

Large B-cell lymphoma (LBCL) is a heterogeneous group of hematologic malignancies.[1,2] Although new therapies have become available, management of relapsed or refractory LBCL remains a challenge.[3] Outcomes are poor, particularly among patients with early relapse or primary refractory disease. Response rates range from 20% to 39%, and the median overall survival (OS) was 6.3 months in 636 patients with LBCL who relapsed or were refractory to first-line chemoimmunotherapy.[3] Several therapies are approved in the United States, including polatuzumab vedotin in combination with bendamustine and rituximab, tafasitamab in combination with lenalidomide,

loncastuximab tesirine, selinexor, and chimeric antigen receptor (CAR) T-cell therapies. CAR T-cell therapy represents a major advancement; however, consistency of bioengineering, manufacturing timelines, and access are limited globally.[4,5] Thus, an unmet medical need still remains for effective, well-tolerated, and convenient therapies.

Epcoritamab (GEN3013) is a subcutaneously administered, bispecific antibody targeting CD3 and CD20 that redirects and activates T cells to kill CD20-expressing malignant cells.[6] In preclinical evaluation, epcoritamab resulted in potent and selective T-cell–mediated cytotoxic activity against CD20$^+$ malignant B cells.[6,7] The

CONTEXT

Key Objective
Outcomes are poor for patients with relapsed or refractory large B-cell lymphoma (LBCL). This study evaluated the efficacy and safety of subcutaneous epcoritamab, a bispecific antibody targeting CD3 and CD20, in a dose-expansion cohort of patients with relapsed or refractory LBCL.

Knowledge Generated
Single-agent epcoritamab demonstrated high overall response rates, including deep and durable complete responses. Adverse events were manageable, with few discontinuations; cytokine release syndrome was mostly low grade with predictable timing.

Relevance *(J.W. Friedberg)*
The observed high response rates with durability in patients with refractory LBCL treated with epcoritamab, including post–chimeric antigen receptor-T therapy, represent further evidence of the value of bispecific antibodies in this setting. Future studies need to evaluate feasibility of limited duration therapy, explore rational combinations, and incorporate this agent into earlier lines of treatment.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

dose-escalation portion met the primary end point, with the recommended phase II dose established and no dose-limiting toxicity in patients with relapsed or refractory CD20^{+} mature B-cell non-Hodgkin lymphoma.[8] Here, we report results from the LBCL expansion cohort.

METHODS

Study Design and Patients

This was a phase I/II, single-arm, multicenter, open-label, dose-escalation/dose-expansion study in patients with relapsed, progressive, and/or refractory mature B-cell lymphoma (EPCORE NHL-1; GCT3013-01; ClinicalTrials.gov identifier: NCT03625037).

Eligible patients were at least age 18 years with an Eastern Cooperative Oncology Group performance status of 0 to 2 and documented CD20^{+} mature B-cell neoplasm (diffuse large B-cell lymphoma [DLBCL] or other aggressive non-Hodgkin lymphoma, including primary mediastinal LBCL, high-grade B-cell lymphoma, or follicular lymphoma grade 3B).[1] Other inclusion criteria were relapsed or refractory disease, treatment with at least two prior lines of systemic therapy, including at least one anti-CD20–containing regimen, and prior failure or ineligibility for autologous stem-cell transplantation. Relapsed disease was defined as recurrence at least 6 months after completion of therapy, and refractory disease was defined as progression either during therapy or within 6 months of completion of therapy. Patients with prior CAR T-cell therapy were eligible (if ≥ 30 days since last treatment). There were no requirements for minimum life expectancy or absolute leukocyte count. Full inclusion and exclusion criteria are given in the Data Supplement (online only).

Patients received subcutaneous epcoritamab with cycle 1 step-up dosing consisting of a 0.16-mg priming dose once on day 1, followed by a 0.8-mg intermediate dose once on day 8, and subsequent full 48-mg doses once on day 15 and beyond until disease progression or unacceptable toxicity. Epcoritamab was administered as a 1-mL injection once weekly in cycles 1-3, once every 2 weeks during cycles 4-9 (days 1 and 15), and once every 4 weeks from cycle 10. No initial B-cell–depleting treatment was administered. During cycle 1, prophylaxis for cytokine release syndrome (CRS) included prednisolone 100 mg orally (or intravenous equivalent) administered 30-120 minutes before each epcoritamab dose (once daily on days 1-4 for the priming dose, once daily on days 8-11 for the intermediate dose, once daily on days 15-18 for the first full dose, and once daily on days 22-25 for the second full dose). In addition, diphenhydramine 50 mg orally or intravenously (or equivalent) and acetaminophen 650-1,000 mg orally were administered once daily on days 1, 8, 15, and 22 of cycle 1. If grade 2 or higher CRS occurred after the fourth epcoritamab administration during cycle 1, corticosteroids were given with epcoritamab for 4 days or until resolution of CRS occurred.

To ensure patient safety and to better characterize CRS, 24-hour inpatient monitoring was required for the first full epcoritamab dose.

The Protocol (online only) was approved by site-specific institutional review boards and/or institutional or central ethics committees before study initiation. The study was conducted in accordance with the International Council for Harmonisation E6 (R2) guidelines on good clinical practice and the principles of the Declaration of Helsinki. All patients reviewed and signed informed consent forms before enrollment.

End Points and Assessments

The primary end point was overall response rate (ORR) by the independent review committee (IRC) using Lugano criteria.[9] Secondary end points included duration of response (DOR), complete response (CR) rate, duration of CR, progression-free survival (PFS), time to response per IRC, and OS.

Subgroup analyses were prespecified. In addition, minimal residual disease (MRD) was assessed by circulating tumor DNA using the clonoSEQ MRD assay (Adaptive Biotechnologies, Seattle, WA; Data Supplement). Safety end points included adverse events (AEs) and laboratory abnormalities. Relatedness of AEs to treatment was designated by the investigator.

Imaging assessments for efficacy (mandatory fluorodeoxyglucose positron emission tomography and either computed tomography or magnetic resonance imaging), along with MRD evaluation and physical examination, took place at weeks 6, 12, 18, 24, 36, and 48 and every 24 weeks thereafter.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1, and severity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. CRS and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded using criteria from the American Society for Transplantation and Cellular Therapy criteria.[10] Clinical tumor lysis syndrome was graded using criteria by Cairo-Bishop.[11] Other assessments, including pharmacokinetics, antidrug antibodies, and patient-reported outcomes, are summarized in the Data Supplement.

Statistical Analysis

Enrollment occurred in two stages; 28 patients with DLBCL were enrolled in the first stage. Interim analysis was conducted when approximately 25 patients with DLBCL had follow-up of up to 12 weeks. Futility stopping criteria were not met; therefore, an additional 100 patients with DLBCL were enrolled in the second stage, with up to 30 additional patients having other types of aggressive non-Hodgkin lymphomas.

ORR was defined as the proportion of patients who achieved best overall response of CR or partial response (PR). Best overall response per response criteria before initiation of subsequent antilymphoma therapy was summarized. The primary analysis of ORR was IRC-assessed response per Lugano criteria in the full analysis population (all patients who received at least one dose of epcoritamab). The ORR and the corresponding 95% exact CI were calculated.

PFS was defined as time from day 1 of cycle 1 to first documented disease progression or death because of any cause, whichever occurred earlier. Patients who remained alive without disease progression at the cutoff date were censored at the date of last evaluable disease assessment before the start of subsequent antilymphoma therapy. For patients who remained alive with incomplete or no baseline tumor assessment, PFS was censored on day 1 of cycle 1.

Time-to-event end points (DOR, PFS, and OS) were analyzed using Kaplan-Meier estimates (median time and 95% CI) with the number and percentage of patients with an event or censoring reported. Efficacy analyses were performed on the full analysis set; the safety analysis set was identical to the full analysis set (all patients who received at least one dose of epcoritamab). A landmark analysis was conducted for PFS by MRD status up to cycle 3 day 1 (day 60, considering ± 3-day window). Data were analyzed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC; Data Supplement).

RESULTS

Patients and Treatment Exposure

Between June 19, 2020, and the data cutoff date of January 31, 2022, there were 157 patients who were enrolled at 54 global sites and treated with epcoritamab. At a median follow-up of 10.7 months, 106 patients discontinued study treatment: 83 (52.9%) because of disease progression, 11 (7.0%) because of AEs, seven (4.5%) because of decision to undergo allogeneic transplantation, four (2.5%) because of patient withdrawal, and one (0.6%) after achieving a PR to undergo CAR T-cell therapy. Demographic and baseline disease characteristics are given in Table 1. Patients had received a median of three prior lines of therapy (range, 2-11); 96 (61.1%) patients had primary refractory disease; 119 (75.8%) patients were refractory to two or more consecutive lines of therapy. The median time from initial diagnosis was 1.6 years (19 months). Sixty-one patients (38.9%) received prior CAR T-cell therapy, 46 (75.4%) of whom had progressive disease (PD) within 6 months of CAR T-cell therapy.

Patients received a median of five cycles (15 doses) of epcoritamab therapy (range, 1-20). As of the data cutoff date, 51 patients (32.5%) continued receiving study treatment; 56.1% continued into the follow-up period.

Efficacy

All 157 patients were efficacy and safety evaluable. The ORR per IRC using Lugano criteria was 63.1% (n/N = 99/157; 95% CI, 55.0 to 70.6), and the CR rate was 38.9% (n/N = 61/157; 95% CI, 31.2 to 46.9). Efficacy outcomes are summarized in Table 2. Best percentage changes from baseline in sum-of-product perpendicular diameters of target lesions are shown in Figure 1A. The median DOR (mDOR) per Kaplan-Meier estimates was 12.0 months in patients with LBCL (95% CI, 6.6 to not reached; Fig 1B). mDOR among complete responders was not reached. An estimated 88.7% of complete responders remained in response at 6 and 9 months. The median time to response was 1.4 months (range, 1.0-8.4). The median time to CR was 2.7 months (range, 1.2-11.1). Most CRs were achieved by the first or second assessment; however, nine patients converted from a PR to a CR at or after the week 36 tumor assessment (range, 32.3-48.1 weeks; Data Supplement).

The median PFS was 4.4 months (95% CI, 3.0 to 7.9; Fig 1C), and the PFS rate at 6 months was 43.9% (95% CI, 35.7 to 51.7). Median PFS among complete responders was not reached (95% CI, 14.5 to not reached). Twenty-eight patients had disease progression within the first

TABLE 1. Demographic and Clinical Characteristics at Baseline in Patients With LBCL

Characteristic	Patients (N = 157)
Age, years, median (range)	64 (20-83)
Age group, years, No. (%)	
< 65	80 (51.0)
65 to < 75	48 (30.6)
≥ 75	29 (18.5)
Male sex, No. (%)	94 (59.9)
ECOG performance status,[a] No. (%)	
0	74 (47.1)
1	78 (49.7)
2	5 (3.2)
Malignancy type	
DLBCL, No. (%)	139 (88.5)
De novo, No./n (%)	97/139 (69.8)
Transformed, No./n (%)	40/139 (28.8)
Unknown, No./n (%)	2/139 (1.4)
High-grade B-cell lymphoma, not otherwise specified, No. (%)	9 (5.7)
Primary mediastinal LBCL, No. (%)	4 (2.5)
Follicular lymphoma grade 3B, No. (%)	5 (3.2)
Central laboratory FISH analysis: Double-hit/triple-hit lymphoma (*MYC* and *BCL2* and/or *BCL6* rearrangement), No./n (%)	13/99 (13.1)
DLBCL cell of origin per local laboratory, No. (%)	
Germinal center B-cell	65 (41.4)
Activated B-cell/nongerminal center B-cell	56 (35.7)
Unknown	18 (11.5)
Not applicable	18 (11.5)
Ann Arbor stage, No. (%)	
I/II	39 (24.8)
III	21 (13.4)
IV	97 (61.8)
International Prognostic Index, No. (%)	
0-2	55 (35.0)
≥ 3	82 (52.2)
Unknown	2 (1.3)
Not applicable	18 (11.5)
Time from initial diagnosis to epcoritamab initiation, years, median (range)[b]	1.6 (0.0-28.4)
Time from end of last therapy to first dose, months, median (range)	2.4 (0.0-153.0)
Median prior lines of antilymphoma therapy, No. (range)	3 (2-11)
(continued in next column)	

TABLE 1. Demographic and Clinical Characteristics at Baseline in Patients With LBCL (continued)

Characteristic	Patients (N = 157)
Prior lines of antilymphoma therapy, No. (%)	
2	46 (29.3)
3	50 (31.8)
≥ 4	61 (38.9)
Primary refractory disease,[c] No. (%)	96 (61.1)
Refractory to last systemic therapy,[c] No. (%)	130 (82.8)
Refractory to ≥ 2 consecutive lines of therapy,[c] No. (%)	119 (75.8)
Prior autologous stem-cell transplant, No. (%)	31 (19.7)
Relapsed within 12 months after prior autologous stem-cell transplant, No./n (%)	18/31 (58.1)
Prior CAR T-cell therapy, No. (%)	61 (38.9)
Progressed within 6 months of CAR T-cell therapy, No./n (%)	46/61 (75.4)
Prior anthracycline therapy, No. (%)	154 (98.1)
First line	139 (88.5)
Second line	16 (10.2)

NOTE. Data cutoff: January 31, 2022.

Abbreviations: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; LBCL, large B-cell lymphoma.

[a]Patients had a baseline ECOG performance status of 0-2 (on a 5-point scale, with higher numbers indicating greater disability).

[b]Time from diagnosis of malignancy recorded at study entry.

[c]Disease progression or stable disease as best response to therapy or disease progression within 6 months after completion of therapy.

6 weeks of treatment, and eight deaths occurred within the first 6 weeks of treatment; reasons for these early deaths included PD in five patients and AEs in three patients (one each with COVID-19 disease, hepatotoxicity in a patient with PD in the liver, and myocardial infarction). Median OS was not reached (95% CI, 11.3 to not reached; Data Supplement). Of 107 MRD-evaluable patients, 49 (45.8%) were MRD-negative (95% CI, 36.1 to 55.7). An estimated 78.7% of these patients remained MRD-negative at 6 months. Patients who achieved MRD negativity had longer PFS versus those who were MRD-positive (Data Supplement).

Concordance between the IRC and investigator assessments was high at 82.8% (kappa: 0.77 [95% CI, 0.69 to 0.84]; Data Supplement). For key subgroups, benefit with epcoritamab was consistent with that of the overall population (Figs 2A and 2B). In patients with primary refractory disease (n = 96), the ORR was 55.2% and the CR rate was 30.2%. In patients who received prior CAR T-cell therapy (n = 61), the ORR was 54.1% and the CR rate was 34.4%, with a mDOR of 9.7 months (95% CI, 5.4 to not reached); mDOR in patients

TABLE 2. Summary of Efficacy End Points (per IRC; Lugano Criteria) in Patients With Large B-Cell Lymphoma

End Point	Patients (N = 157)
Best overall response per IRC, No. (%)	
Overall response of CR or PR, No. (%) [95% CI]	99 (63.1) [55.0 to 70.6]
CR	61 (38.9) [31.2 to 46.9]
PR	38 (24.2)
SD	5 (3.2)
PD	37 (23.6)
Nonevaluable[a]	16 (10.2)
DOR, months, median[b] (range) [95% CI]	12.0 (0.0+ to 15.5+) [6.6 to not reached]
DOR among complete responders, months, median[b] (range) [95% CI]	Not reached (1.4+ to 15.5+) [12.0 to not reached]
Duration of CR, months, median[b] (range) [95% CI]	12.0 (0.0 to 14.9+) [9.7 to not reached]
PFS, months, median[b] (range) [95% CI]	4.4 (0.0+ to 16.9+) [3.0 to 7.9]
OS, months, median[b] (range) [95% CI]	Not reached (0.3 to 17.9+) [11.3 to not reached]
Time to response, months, median (range) [No.]	1.4 (1.0-8.4) [99]
Time to CR, months, median (range) [No.]	2.7 (1.2-11.1) [61]

NOTE. Data cutoff: January 31, 2022. The + sign indicates censored value.

Abbreviations: CR, complete response; DOR, duration of response; IRC, independent review committee; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Of 16 nonevaluable patients, 14 had no response assessment before discontinuation, one patient had a response assessment after new anticancer therapy was initiated and was censored, and one patient had no evidence of disease at baseline and remains on treatment.

[b]On the basis of Kaplan-Meier estimate.

with CR was not reached. In patients who did not receive prior CAR T-cell therapy (n = 96), the ORR was 68.8% and the CR rate was 41.7%, with a mDOR of 12.0 months (95% CI, 5.6 to not reached); mDOR in patients with CR was not reached. Of note, regional differences in ORRs and CR rates were observed, likely because of a higher proportion of patients with prior CAR T-cell exposure in North America.

Safety

Treatment-emergent AEs observed with epcoritamab are summarized in Table 3. Grade 3 and higher AEs were observed in 61.1% of patients; treatment-related grade 3 and higher AEs were observed in 26.8% of patients. The most common treatment-related AEs were CRS (49.7%), injection site reaction (19.7%), and neutropenia (17.8%; Data Supplement). Most AEs (including treatment-related AEs) occurred in the first 12 weeks (cycles 1-3) of epcoritamab treatment, and the incidence of AEs declined after 12 weeks. Only one treatment-related serious AE occurred after week 12 (grade 1 CRS). Grade 3 or 4 infections are listed in the Data Supplement.

Treatment-emergent AEs leading to discontinuation occurred in 12 patients (7.6%); three patients discontinued because of treatment-related AEs, including worsening of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (see the description in the Data Supplement), CRS, and ICANS (one patient each). Nine patients (5.7%) had fatal treatment-emergent AEs, including COVID-19 disease in two patients and one case each with myocardial infarction, hepatotoxicity, progressive multifocal leukoencephalopathy, loss of consciousness, general health deterioration, pulmonary embolism, and ICANS. None of these AEs were considered related to epcoritamab by the investigator, except for the one fatal ICANS event, which had multiple concurrent confounding factors (Data Supplement). ICANS events occurred in 10 (6.4%) patients, including seven patients with grade 1, two patients with grade 2, and one fatal event. At least one event of CRS was observed in 49.7% of patients, mostly grade 1 in severity (n = 50; grade 2: n = 24; grade 3: n = 4); no grade 4 or 5 events were observed. Most CRS events occurred after the first full dose (Data Supplement) on day 15 of cycle 1 with a median time to onset of 0.8 days (20 hours). CRS resolved in 77 of 78 patients (98.7%); the median time to resolution from onset after first full dose was 2 days (48 hours). CRS was treated with tocilizumab in 22 (28.2%) patients and with corticosteroids (beyond those required for CRS prophylaxis) in 16 (20.5%) patients. Clinical tumor lysis syndrome occurred in two patients (grade 3 in severity) and was considered related to treatment. COVID-19–related events occurred in 10 (6.4%) patients; two of these cases were fatal but deemed to be unrelated to treatment.

The overall incidence of neutropenia was 21.7% (34 of 157). Febrile neutropenia was observed in four patients (2.5%) and was considered treatment-related in one patient (0.6%). Treatment with granulocyte colony-stimulating factor was required in 16 patients (10.2%).

Patient-Reported Outcomes

Patients reported improvements in their lymphoma-related symptoms and overall quality of life during treatment.
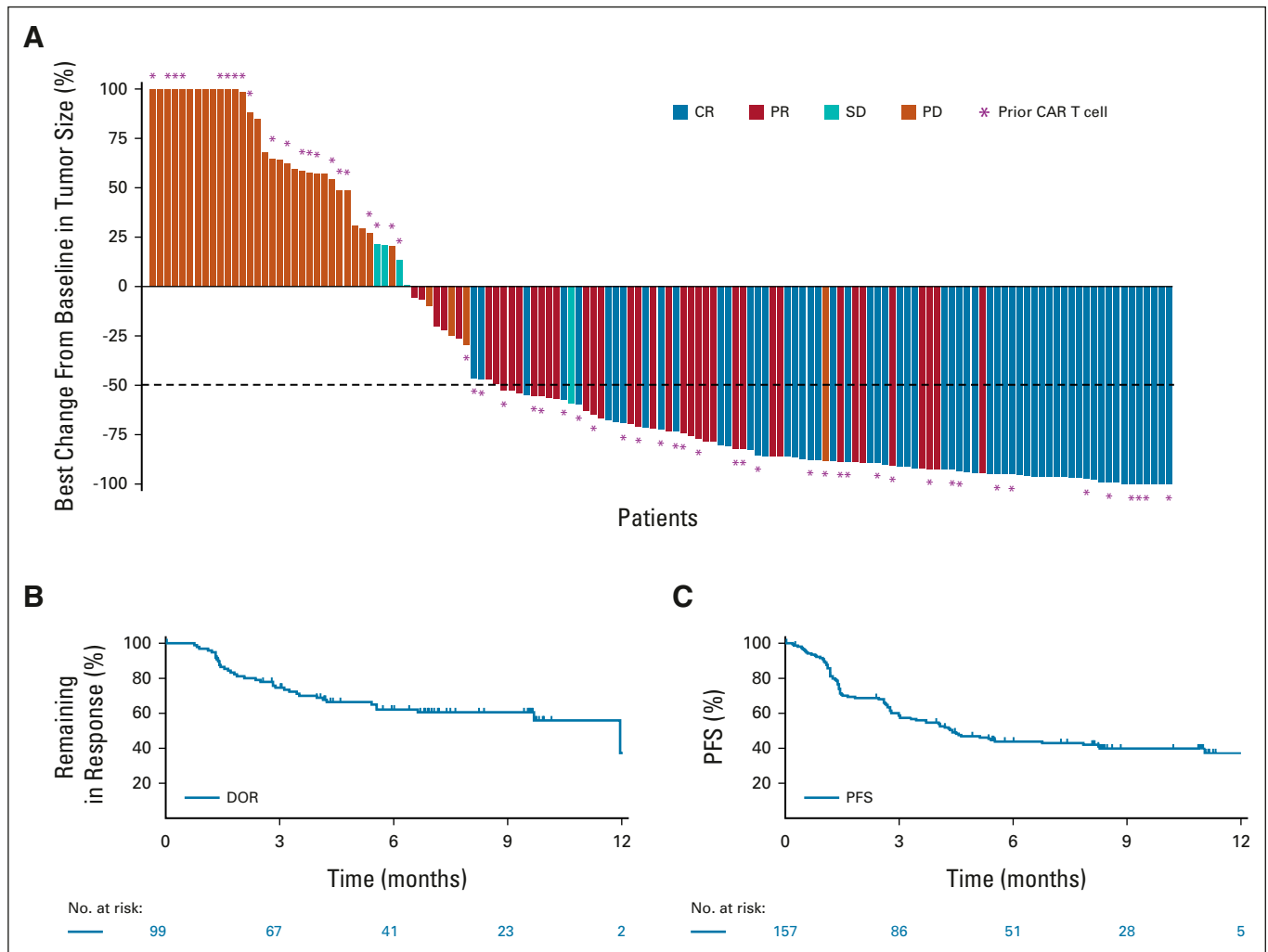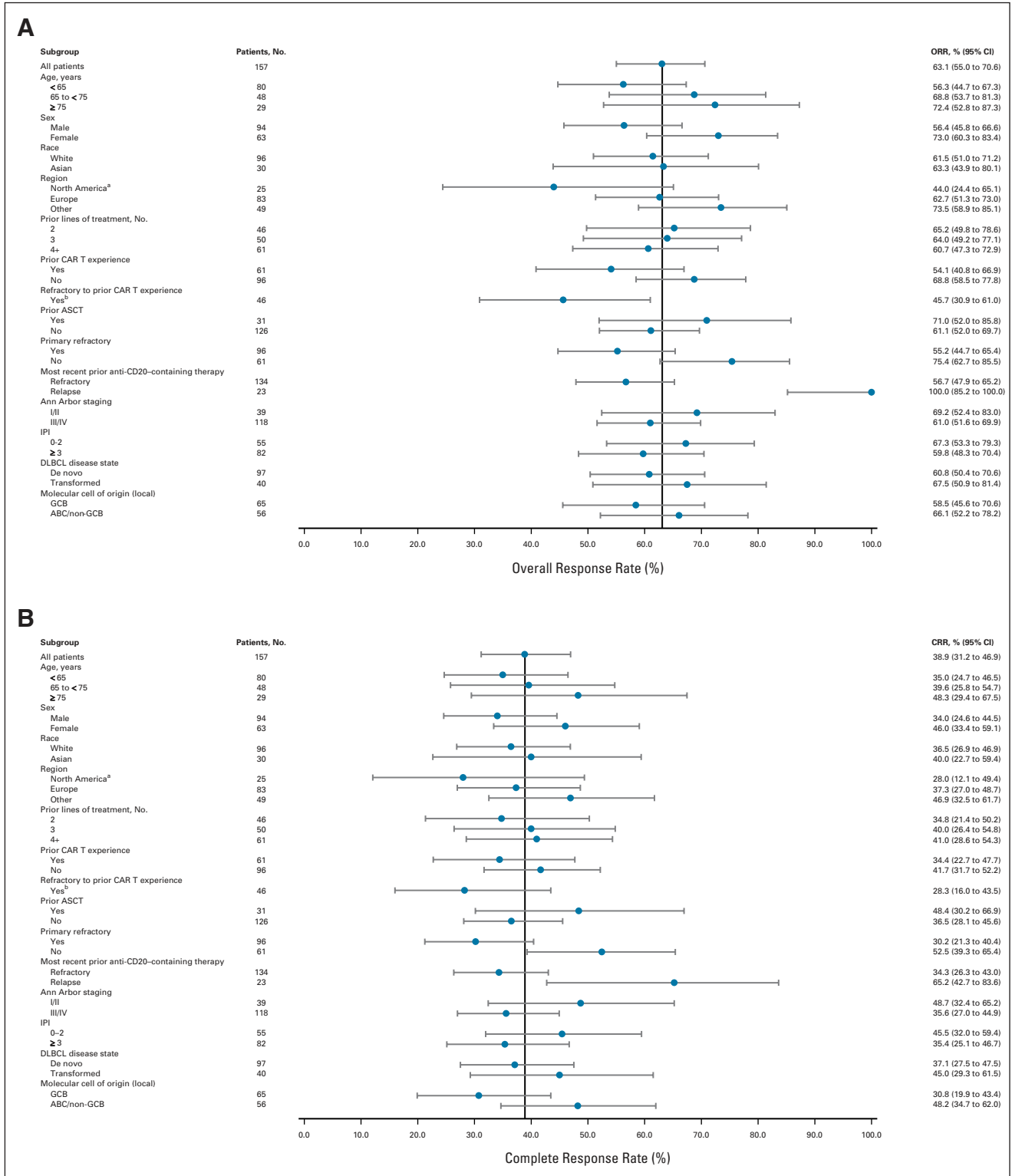
FIG 1. Efficacy results (per IRC; Lugano criteria) with epcoritamab in patients with LBCL. (A) shows best percentage change in sum-of-product perpendicular diameters of target lesions for patients with LBCL. Asterisks represent patients with prior exposure to CAR T-cell therapy. (B) shows the Kaplan-Meier curve for DOR. Results were similar in the DLBCL population (data not shown). (C) shows the Kaplan-Meier plot of PFS. A PFS ad hoc analysis using the Mantel-Byar approach showed a hazard ratio (95% CI) for patients with CR versus nonresponders of 0.11 (0.04 to 0.25) and a hazard ratio (95% CI) for patients with PR versus nonresponders of 0.47 (0.26 to 0.86). Thirty-six patients had disease progression (n = 28) or died (n = 8) within the first 6 weeks of treatment. Data cutoff: January 31, 2022. CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; IRC, independent review committee; LBCL, large B-cell lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Clinically meaningful improvements were reported in the Functional Assessment of Cancer Therapy-Lymphoma scores (ie, lymphoma subscale, trial outcome index, Functional Assessment of Cancer Therapy-General total score, and Functional Assessment of Cancer Therapy-Lymphoma total score) and the EuroQol-5 Dimensions-3 Levels health utility score and EuroQol visual analog scale from day 1 of cycle 1 to day 1 of cycle 9 (Data Supplement).

DISCUSSION

Subcutaneous epcoritamab achieved rapid, deep, and durable responses, including CRs and MRD negativity, in this cohort of patients with challenging-to-treat and highly refractory LBCL. Overall response and CR rates were 63.1% (95% CI, 55.0 to 70.6) and 38.9% (95% CI, 31.2 to

46.9), respectively. Responses were primarily observed early, by either the first or the second response assessment (scheduled at weeks 6 and 12). Among complete responders, mDOR was not reached at the time of analysis. Median PFS was not reached in complete responders, and median OS was not reached at the time of analysis. As of the data cutoff date, 32.5% of patients continued to receive study treatment and 56.1% continued into the follow-up period. This cohort represents a heavily pretreated, heterogeneous patient population. Patients had a median of three prior lines of therapy at a median of 19 months from diagnosis: 61.1% had primary refractory disease, 28.8% with DLBCL had transformed DLBCL, and 38.9% had received prior CAR T-cell therapy, 75.4% of whom were refractory to CAR T-cell therapy. The

A

Subgroup	Patients, No.	ORR, % (95% CI)
All patients	157	63.1 (55.0 to 70.6)
Age, years		
<65	80	56.3 (44.7 to 67.3)
65 to <75	48	68.8 (53.7 to 81.3)
≥75	29	72.4 (52.8 to 87.3)
Sex		
Male	94	56.4 (45.8 to 66.6)
Female	63	73.0 (60.3 to 83.4)
Race		
White	96	61.5 (51.0 to 71.2)
Asian	30	63.3 (43.9 to 80.1)
Region		
North America[a]	25	44.0 (24.4 to 65.1)
Europe	83	62.7 (51.3 to 73.0)
Other	49	73.5 (58.9 to 85.1)
Prior lines of treatment, No.		
2	46	65.2 (49.8 to 78.6)
3	50	64.0 (49.2 to 77.1)
4+	61	60.7 (47.3 to 72.9)
Prior CAR T experience		
Yes	61	54.1 (40.8 to 66.9)
No	96	68.8 (58.5 to 77.8)
Refractory to prior CAR T experience		
Yes[b]	46	45.7 (30.9 to 61.0)
Prior ASCT		
Yes	31	71.0 (52.0 to 85.8)
No	126	61.1 (52.0 to 69.7)
Primary refractory		
Yes	96	55.2 (44.7 to 65.4)
No	61	75.4 (62.7 to 85.5)
Most recent prior anti-CD20–containing therapy		
Refractory	134	56.7 (47.9 to 65.2)
Relapse	23	100.0 (85.2 to 100.0)
Ann Arbor staging		
I/II	39	69.2 (52.4 to 83.0)
III/IV	118	61.0 (51.6 to 69.9)
IPI		
0-2	55	67.3 (53.3 to 79.3)
≥3	82	59.8 (48.3 to 70.4)
DLBCL disease state		
De novo	97	60.8 (50.4 to 70.6)
Transformed	40	67.5 (50.9 to 81.4)
Molecular cell of origin (local)		
GCB	65	58.5 (45.6 to 70.6)
ABC/non-GCB	56	66.1 (52.2 to 78.2)

Overall Response Rate (%): 0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0 100.0

B

Subgroup	Patients, No.	CRR, % (95% CI)
All patients	157	38.9 (31.2 to 46.9)
Age, years		
<65	80	35.0 (24.7 to 46.5)
65 to <75	48	39.6 (25.8 to 54.7)
≥75	29	48.3 (29.4 to 67.5)
Sex		
Male	94	34.0 (24.6 to 44.5)
Female	63	46.0 (33.4 to 59.1)
Race		
White	96	36.5 (26.9 to 46.9)
Asian	30	40.0 (22.7 to 59.4)
Region		
North America[a]	25	28.0 (12.1 to 49.4)
Europe	83	37.3 (27.0 to 48.7)
Other	49	46.9 (32.5 to 61.7)
Prior lines of treatment, No.		
2	46	34.8 (21.4 to 50.2)
3	50	40.0 (26.4 to 54.8)
4+	61	41.0 (28.6 to 54.3)
Prior CAR T experience		
Yes	61	34.4 (22.7 to 47.7)
No	96	41.7 (31.7 to 52.2)
Refractory to prior CAR T experience		
Yes[b]	46	28.3 (16.0 to 43.5)
Prior ASCT		
Yes	31	48.4 (30.2 to 66.9)
No	126	36.5 (28.1 to 45.6)
Primary refractory		
Yes	96	30.2 (21.3 to 40.4)
No	61	52.5 (39.3 to 65.4)
Most recent prior anti-CD20–containing therapy		
Refractory	134	34.3 (26.3 to 43.0)
Relapse	23	65.2 (42.7 to 83.6)
Ann Arbor staging		
I/II	39	48.7 (32.4 to 65.2)
III/IV	118	35.6 (27.0 to 44.9)
IPI		
0–2	55	45.5 (32.0 to 59.4)
≥3	82	35.4 (25.1 to 46.7)
DLBCL disease state		
De novo	97	37.1 (27.5 to 47.5)
Transformed	40	45.0 (29.3 to 61.5)
Molecular cell of origin (local)		
GCB	65	30.8 (19.9 to 43.4)
ABC/non-GCB	56	48.2 (34.7 to 62.0)

Complete Response Rate (%): 0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0 100.0

FIG 2. Response (per IRC; Lugano criteria) in prespecified subgroups of patients with LBCL. (A) ORRs. (B) CR rates. Data cutoff: January 31, 2022. [a]A greater proportion of patients in North America had exposure to CAR T-cell therapy compared with other regions. [b]Per the statistical analysis plan, subgroup analyses were not performed on subgroups with fewer than 20 patients. The ORR in patients who were not refractory to prior CAR T-cell therapy (n = 15) was 80.0% (95% CI, 51.9 to 95.7). The CR rate in patients who were not refractory to prior CAR T-cell therapy (n = 15) was 53.0% (95% CI, 26.6 to 78.7). ABC, activated B-cell; ASCT, autologous stem-cell transplantation; CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; IPI, International Prognostic Index; IRC, independent review committee; LBCL, large B-cell lymphoma; ORR, overall response rate.

TABLE 3. Treatment-Emergent AEs by Worst Grade During the Treatment Period in Patients With LBCL

Patient	Any Grade (N = 157), No. (%)	Grade ≥ 3 (N = 157), No. (%)
Any AE	156 (99.4)	96 (61.1)
Any treatment-related AE	130 (82.8)	42 (26.8)
SAE	89 (56.7)	—
Serious treatment-related AE	55 (35.0)	—
Treatment-emergent AE leading to treatment discontinuation	12 (7.6)	11 (7.0)
Treatment-emergent AE in ≥ 10% of patients[a]		
CRS	78 (49.7)	4 (2.5)
Pyrexia[b]	37 (23.6)	0
Fatigue	36 (22.9)	3 (1.9)
Neutropenia	34 (21.7)	23 (14.6)
Diarrhea	32 (20.4)	0
Nausea	31 (19.7)	2 (1.3)
Injection site reaction	31 (19.7)	0
Anemia	28 (17.8)	16 (10.2)
Abdominal pain	22 (14.0)	3 (1.9)
Thrombocytopenia	21 (13.4)	9 (5.7)
Headache	21 (13.4)	1 (0.6)
Constipation	20 (12.7)	0
Decreased appetite	19 (12.1)	1 (0.6)
Vomiting	19 (12.1)	1 (0.6)
Peripheral edema	17 (10.8)	0
Back pain	16 (10.2)	1 (0.6)
AEs of special interest		
CRS[c]	78 (49.7)	4 (2.5)
ICANS[d]	10 (6.4)	1 (0.6)
Clinical tumor lysis syndrome	2 (1.3)	2 (1.3)

NOTE. Data cutoff: January 31, 2022.

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

[a]Classified using MedDRA version 24.1. CRS events and ICANS events were graded per Lee et al[10]; clinical tumor lysis syndrome was graded per Cairo-Bishop criteria.[11] All other events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

[b]Pyrexia not considered CRS by the investigator.

[c]Twenty-four patients had CRS that was a maximum of grade 2 in severity; of these, 19 patients had hypotension, including six with concurrent hypoxia and 13 without concurrent hypoxia, and did not receive vasopressor treatment.

[d]One fatal case of ICANS was reported.

aggressive disease of this patient population was further demonstrated in that 36 patients had disease progression (n = 28) or died (n = 8) within the first 6 weeks. Responses to epcoritamab were consistent across several prespecified subgroups, including age, line of therapy, primary refractory disease, and prior exposure to CAR T-cell therapy. Forty-nine

(45.8%) of 107 patients were MRD-negative per circulating tumor DNA analysis, with most (an estimated 78.7%) remaining MRD-negative after 6 months. Furthermore, MRD negativity was associated with longer PFS, highlighting the depth and durability of response to continuous epcoritamab treatment.

The safety profile of epcoritamab was consistent with previous reports. Notably, the majority of AEs occurred early (ie, in the first 12 weeks) in the treatment course. CRS, observed in 78 (49.7%) patients, was mostly low grade, predictable in terms of timing, and resolved. CRS occurred most frequently after the first full epcoritamab dose; tocilizumab was used to manage CRS in 22 of 78 (28.2%) patients. ICANS events were limited to mostly grade 1, and all resolved apart from the one fatal ICANS event in a patient with several confounding factors.

Results observed with epcoritamab in patients with relapsed or refractory LBCL favorably compare with those observed in approved antilymphoma immunotherapies, although differences in patient populations and study designs should be considered. CAR T-cell therapies (axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel) demonstrated high ORRs (52%-82%) and CR rates (40%-54%) in phase I/II studies.[12-14] However, many patients are ineligible for or do not receive CAR T-cell therapy because of rapidly progressing disease, complex manufacturing, limited accessibility, or patient preference.[4,15] Notably, 38.9% of patients in the present study received prior CAR T-cell therapy, to which most were refractory; the number of patients in our study with prior CAR T-cell exposure is among the largest reported to date in LBCL. Among patients with relapsed or refractory DLBCL who received CAR T-cell therapy, a 43% risk of relapse has been shown and outcomes after relapse are poor.[16] In the present study, epcoritamab showed clinical activity in patients who had received prior CAR T-cell therapy (n = 61), with an ORR of 54% and a CR rate of 34%. Numerically higher clinical activity was observed in patients without prior CAR T-cell therapy (n = 96), with an ORR of 69% and a CR rate of 42%. Recently approved therapies in the United States (polatuzumab vedotin plus bendamustine and rituximab, tafasitamab plus lenalidomide, selinexor, and loncastuximab tesirine) vary with regard to their mechanisms of action, safety profiles, and clinical activity.[17-22] In the pivotal studies for polatuzumab vedotin plus bendamustine and rituximab and tafasitamab plus lenalidomide, which enrolled patients with fewer lines of prior therapy and few patients with primary refractory disease or CAR T-cell exposure, response rates were 60%-63% in patients ineligible for transplantation with at least one prior systemic regimen, and CR rates were 43%-50%.[17,19] Despite shorter follow-up times, clinical activity observed with single-agent epcoritamab was comparable with that seen for CAR T-cell therapy and is favorable to other approved treatment options, considering the more refractory and difficult-to-treat population.

Subcutaneous administration of epcoritamab may be a convenient alternative to intravenous therapies for both long-term and first-line use.

CD3xCD20 bispecific antibodies are a treatment modality being developed for treatment of non-Hodgkin lymphomas, with one compound approved in the European Union for relapsed or refractory follicular lymphoma.[23-26] Responses with epcoritamab were shown to deepen from PR to CR at the week 36 assessment or later in nine patients, eight of whom had ongoing responses, thereby suggesting added clinical benefit with continuous treatment in a subset of patients.

Given the lack of direct comparison, there are currently no data to suggest whether the best outcome for heavily pretreated patients can be achieved by treating until disease progression or by stopping after a fixed number of treatment cycles. Treatment until progression ensures ongoing anti-CD20–directed, T-cell–mediated tumor suppression/surveillance. Continuation of subcutaneous epcoritamab at reduced frequency in later cycles may provide the greatest chance of durable remissions with limited burden for patients, but further studies would be helpful to determine the best treatment duration strategy for patients who achieve a CR. In this study, epcoritamab led to patient-reported improvements in their lymphoma-related symptoms and overall quality of life while receiving therapy. One limitation of our study is that it was a single-arm design with no control group for comparison.

Single-agent epcoritamab demonstrated a high ORR, including deep and durable CRs, in a challenging-to-treat and highly refractory patient population with relapsed or refractory LBCL. Efficacy was consistent across key subgroups. Epcoritamab was mostly well tolerated, with few discontinuations because of AEs. CRS was manageable, with predictable timing, and was mostly grade 1 or 2. As long-term treatment, epcoritamab is administered on a once monthly basis as a subcutaneous injection, making it an attractive and convenient off-the-shelf alternative to other antilymphoma immunotherapies. These results support ongoing and future clinical trials of epcoritamab both as monotherapy and in combination in late and earlier lines of treatment for B-cell non-Hodgkin lymphoma.

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DATA SHARING STATEMENT

Clinical trial data can be requested by qualified researchers for use in rigorous, independent scientific research as long as the trials are not part of an ongoing or planned regulatory submission. Sharing of data is subject to protection of patient privacy and respect for the patient's informed consent. The data will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. For approved requests, the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, contact clinicaltrials@genmab.com.

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Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

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