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Extended Follow-Up Beyond 2.5 Years Demonstrates Long-Term Efficacy in Complete Responders Following Epcoritamab Monotherapy in Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL)

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OBJECTIVE

- To present long-term results from the pivotal expansion cohort in R/R LBCL, with a focus on CR patients, and preliminary results from the C1 optimization part

CONCLUSIONS

- Long-term results demonstrate that epcoritamab drives deep responses beyond 2.5 y, leading to favorable long-term outcomes
  - At 30 mo, an estimated 54% of complete responders remained in CR
  - 30-mo PFS and OS estimates (censored for COVID-19) among complete responders were 69% and 85%, respectively
- MRD-negativity rates were high among complete responders
  - 80% at C3D1; 92% overall
- Safety findings were consistent with prior reports[3]
- Preliminary results indicate that simple measures of prophylactic dexamethasone and hydration in C1 decreased rates and severity of CRS, with no mandatory hospitalization
- These outcomes underscore the long-term benefit of epcoritamab monotherapy given until progression for the treatment of R/R LBCL

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Abbreviations

AE, adverse event; ASCT, autologous stem cell transplant; C, cycle; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; cfDNA, circulating tumor DNA; d, day(s); DHTH, double-hit or triple-hit; DLBCL, diffuse large B-cell lymphoma; DLBCL-TL, DLBCL transformed from indolent lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOI, end of induction; FDG, fluorodeoxyglucose; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; HGBCL-TL, HGBCL transformed from indolent lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; IV, intravenous; KM, Kaplan–Meier; L, liter(s); LBCL, large B-cell lymphoma; mAb, monoclonal antibody; mo, month(s); MRD, minimal residual disease; MRL, relapsed lymphoma outgoing; NOS, not otherwise specified; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; R/R, relapsed or refractory; RP2D, recommended phase 2 dose; SC, subcutaneous; SoD, step-up dose; TEAE, treatment-emerged adverse event; wk, week(s); y, year(s).

Disclosures

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BACKGROUND

- R/R LBCL remains difficult to treat, especially for patients in later lines of therapy[1]
- T-cell–engaging therapies are an emerging class of treatment for R/R LBCL, but CRS is an expected adverse event; strategies for CRS risk mitigation need to be optimized[2]
- Epcoritamab, a subcutaneous CD3xCD20 bispecific antibody, has demonstrated high rates of CR and MRD negativity with durable responses and manageable safety in patients with R/R LBCL in the EPCORE NHL-1 phase 2 pivotal trial[3]
  - Approved for the treatment of adults with different types of R/R LBCL after ≥2 lines of systemic therapy in various geographies, including the US, Europe, and Japan, and the treatment of adults with R/R FL after ≥2 lines of systemic therapy in the US[a-c,4-6]
  - Epcoritamab may allow for rapid T-cell engagement without the need for debulking and its treatment-to-progression strategy may allow for sustained inhibition of CD20$^+$ malignant B cells[7,8]

[a]Approved in the US for the treatment of adults with R/R DLBCL, NOS, including DLBCL arising from indolent lymphoma, HGBCL, and FL after ≥2 lines of systemic therapy. [b]Approved in Europe and the UK for the treatment of adults with R/R DLBCL after ≥2 lines of systemic therapy. [c]Approved in Japan for the treatment of adults with the following R/R LBCL: DLBCL, HGBCL, PMBCL, and FL G3B after ≥2 lines of systemic therapy.

STUDY DESIGN: EPCORE® NHL-1

Key inclusion criteria:
- R/R CD20$^+$ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of systemic antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed

Step-up dosing[a]

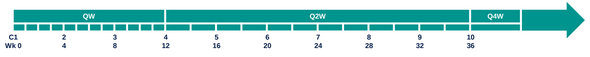
Expansion
Data cutoff: October 16, 2023

Epcoritamab SC RP2D 48 mg
Treatment until PD or unacceptable toxicity
LBCL cohort, N=157
DLBCL, HGBCL, PMBCL, and FL G3B

Step-up dosing[a]

Cycle 1 optimization
Data cutoff: December 6, 2023

Epcoritamab SC 48 mg
Treatment until PD or unacceptable toxicity
DLBCL cohort, N=81
DLBCL, NOS (de novo or transformed from FL)



- For this follow-up analysis, efficacy was based on investigator assessment
- Time-to-event endpoints (ie, DOCR, PFS, OS) were analyzed by response using the Kaplan–Meier method
- Sensitivity analyses for PFS and OS were carried out based on an adjusted population excluding patients with COVID-19–related deaths on study
- Exploratory MRD analyses were performed using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA, USA) next-generation sequencing assay to evaluate ctDNA in plasma
- Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter

Expansion
To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study

C1 optimization
Recommendations[b]: Dexamethasone 15 mg premedication[c]; administer 500 mL of isotonic IV fluids on the day of each dose prior to administration; hospitalization not required but patients must remain in close proximity to treatment facility for 24 h following first full dose

[a]SUD 1: priming, 0.16 mg; SUD 2: intermediate, 0.8 mg. Corticosteroid prophylaxis was used in C1 to mitigate CRS. [b]Other recommendations include 2–3 L of fluid intake during the 24 h prior to and following each dose, holding antihypertensive medications for 24 h prior to each dose, and self-monitoring of temperature 3 times daily for 4 d following each dose. [c]On D1, D8, D15, and D22 and prophylaxis on D2–4, D9–11, D16–18, and D23–25. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

RESULTS

Baseline Characteristics and Prior Treatments

	LBCL N=157	LBCL Complete Responders, n=65
Median age (range), y	64 (20–83)	68 (20–83)
≥75 y, n (%)	29 (18)	15 (23)
ECOG PS, n (%)		
0	74 (47)	36 (55)
1	78 (50)	29 (45)
2	5 (3)	0
DLBCL,[a] n (%)	139 (89)	58 (89)
De novo, n/n (%)	97/139 (70)	39/58 (67)
Transformed, n/n (%)	40/139 (29)	19/58 (33)
Ann Arbor stage IV disease, n (%)	96 (61)	38 (58)
Median time from initial diagnosis to first dose, y	1.6	2.1
Median time from end of last therapy to first dose, mo	2.4	2.9
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)
≥3 prior lines of therapy, n (%)	110 (70)	47 (72)
Primary refractory[b] disease, n (%)	95 (61)	31 (48)
Refractory[b] to last systemic therapy, n (%)	130 (83)	48 (74)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	118 (75)	45 (69)
Prior ASCT, n (%)	31 (20)	15 (23)
Prior CAR T-cell therapy, n (%)	61 (39)	22 (34)

[a]Other disease types were FL G3B (n=5; CR, n=3), HGBCL (n=9; CR, n=2), and PMBCL (n=4; CR, n=2). DLBCL type was unknown in 2 patients. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within 6 mo of completion of therapy.

Patient Disposition and Exposure

	LBCL N=157	LBCL Complete Responders, n=65
Median follow-up (range), mo	30.6 (0.3 to 38.8+)	31.3 (5.3+ to 38.8+)
Mean number of treatment cycles	11	21
Mean number of doses administered	21	36
Ongoing treatment with epcoritamab, n (%)	24 (15)	24 (37)
Discontinued treatment, n (%)	133 (85)	41 (63)
AE	23 (15)	14 (22)
PD	90 (57)	12 (18)
Decision to proceed with transplant	7 (4)	7 (11)
Withdrawal by patient	6 (4)	2 (3)
Maximum clinical benefit[a]	1 (1)	1 (2)
Other	6 (4)	5 (8)

Symbol '+' indicates a censored value. [a]Decision due to investigator assessment that maximum clinical benefit was obtained.

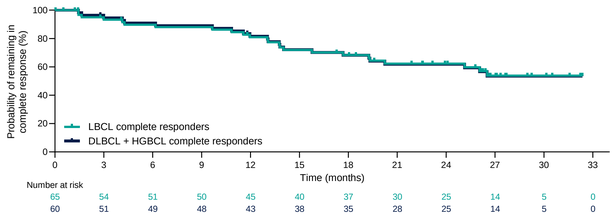
High Rates of Response and Durable CRs per Investigator

	LBCL N=157[a]	DLBCL + HGBCL[b] n=148[c]
ORR, n (%)	92 (59)	85 (57)
CR	65 (41)	60 (41)
PR	27 (17)	25 (17)
Median DOCR, mo	NR	NR
24-mo KM estimate, %	62	62
30-mo KM estimate, %	54	54
Median follow-up, mo	26.4	26.7

[a]Median study follow-up: 30.6 mo (range, 0.3 to 38.8+). [b]Population based on the FDA-approved indication of epcoritamab; 127 patients had DLBCL and 21 patients had HGBCL (including 12 patients who were enrolled with DLBCL but reclassified based on DH/TH status). [c]Median study follow-up: 31.1 mo (range, 0.3+ to 38.8).

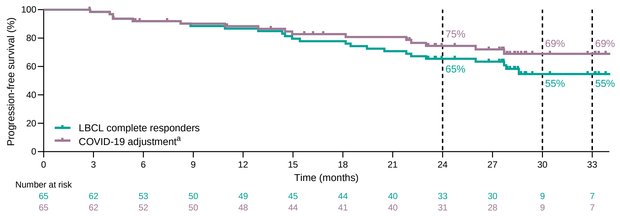
Efficacy Results in Complete Responders

CRs Sustained Over Time

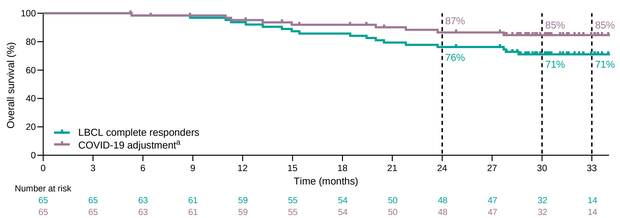


Kaplan–Meier estimates are shown. Neither median was reached.

Favorable Long-Term Outcomes Among Complete Responders



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.

MRD Negativity in Complete Responders

MRD-Negativity Rate, n (%)	LBCL, n=49[a]
At C3D1	39 (80)
At any time	45 (92)

[a]Based on MRD-evaluable patients (patients had ≥1 baseline or on-treatment MRD result and MRD was not negative at baseline) with complete response.

Safety Profile

Patients, n (%)	LBCL, N=157
Most common (>20%) TEAEs	
CRS	80 (51)
Fatigue	39 (25)
Pyrexia	39 (25)
Neutropenia	37 (24)
Diarrhea	35 (22)
Nausea	34 (22)
Anemia	33 (21)
COVID-19	32 (20)

- Infections on study:
  - 46 patients (29%) had G≥3 serious infections
  - Of 12 G5 infections, 9 were COVID-19; 2 of 3 treatment-related G5 AEs were infections: COVID-19 pneumonia and bacterial pneumonia
  - Rates of treatment-related G≥3 infections were low for 12-wk treatment intervals up to week 144 (range, 0%–7%)
  - 15 patients (10%) discontinued treatment due to infection
  - It is well-described that there is an increased risk of morbidity and mortality due to infections for patients with hematologic malignancies being treated with B-cell–depleting therapies
- 17 patients (11%) had fatal TEAEs
- 10 patients (6%) had ICANS; all events were G1–2 except one (G5)

Cycle 1 Optimization

- 81 patients were enrolled (median follow-up: 5.4 mo)
- Baseline characteristics indicated a higher proportion of patients with prior CAR T-cell therapy (51%) or aged ≥75 years (26%), and a lower proportion of patients with an ECOG PS of 0 (36%)

	Expansion N=157	C1 Optimization N=81
CRS, n (%)[a]	80 (51)	30 (37)
G1	50 (32)	21 (26)
G2	25 (16)	8 (10)
G3	5 (3)	1 (1)
Treated with tocilizumab, n/n (%)[b]	23/80 (29)	13/30 (43)
Treated with corticosteroid,[c] n/n (%)[b]	17/80 (21)	6/30 (20)
Leading to treatment discontinuation, n (%)	1 (1)	0
CRS resolution, n/n (%)[b]	78/80 (98)	30/30 (100)
Median time to resolution (range),[b] d	2 (1–27)	2 (1–15)

[a]Graded by Lee et al 2019 criteria.[3] [b]Among patients with CRS. [c]Corticosteroids beyond those required per protocol for prophylaxis.

- Among the 78 patients in C1 optimization who received the first full dose, pretreatment prior to first full dose included: dexamethasone (86%); IV fluid (81%); IV fluid and dexamethasone (69%); other corticosteroids (14%)
- C1 optimization reduced the incidence and severity of CRS
- Most CRS events occurred following the first full dose

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