ABCL-417

First Data From Subcutaneous Epcoritamab + Polatuzumab Vedotin, Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) for First-Line Diffuse Large B-Cell Lymphoma (DLBCL): EPCORE NHL-5

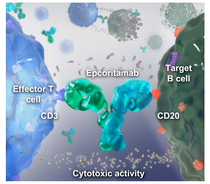
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BACKGROUND

- No therapies have provided improved cure rates since the introduction of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for first-line (1L) diffuse large B-cell lymphoma (DLBCL)[1,2]
  - Polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) demonstrated improved response rates (objective response rate [ORR] 86% vs 83.8%, complete response rate [CRR] 78% vs 74%) and improved 2-year progression-free survival rate (77% vs 70.2%) vs R-CHOP, but did not significantly improve overall survival[2]
- Epcoritamab administered subcutaneously (SC) is a CD3xCD20 bispecific antibody[3]
  - Approved as monotherapy for relapsed or refractory (R/R) DLBCL[4-6]
  - Demonstrated high response rates with a manageable safety profile when combined with R-CHOP in patients with 1L DLBCL[7]

Epcoritamab mechanism of action



STUDY DESIGN: EPCORE NHL-5 (NCT05283720)

Key Inclusion Criteria: Arm 3
- Adults ≥18 y
- Histologically confirmed CD20+ DLBCL[a]
  - DLBCL, NOS including de novo or histologically transformed from FL or MZL
  - HGBCL with *MYC* and *BCL-2* and/or *BCL-6* translocations (double-hit or triple-hit lymphoma)
  - FL grade 3B
- Newly diagnosed, treatment-naive disease
- No prior treatment with CD3/CD20 bispecific antibodies
- ECOG PS 0–2
- IPI score 2–5
- Measurable disease

Data cutoff: February 29, 2024 | Median follow-up: 7.4 months

Epcoritamab + pola-R-CHP 1L DLBCL: Dose escalation and dose expansion (21-day cycle)

Agent	C1	C2	C3	C4	C5	C6	C7	C8
Epcoritamab	Step-up dosing (SUD): D1: SUD1 (0.16 mg) D8: SUD2 (0.8 mg) D15: full dose (24 or 48 mg)	D1, 8, 15: full dose (24 or 48 mg)			D1: full dose (24 or 48 mg)			
pola-R-CHP: Polatuzumab vedotin	D1 (1.8 mg/kg)							
pola-R-CHP: Rituximab	D1 (375 mg/m²)							
pola-R-CHP: Cyclophosphamide	D1 (750 mg/m²)							
pola-R-CHP: Doxorubicin	D1 (50 mg/m²)							
pola-R-CHP: Prednisone	D1–5 (100 mg)							

Premedication and CRS prophylaxis
- Diphenhydramine, acetaminophen, and corticosteroids were mandatory for CRS prophylaxis with the first 4 epcoritamab doses
  - Prednisone 100 mg for 4 days was initially recommended
  - Current recommendation is dexamethasone 15 mg for 4 days[b,c]
- G-CSF or pegylated G-CSF was mandatory and administered per local standard

Primary endpoint: DLTs of epcoritamab in combination with antineoplastic agents

[a]Per WHO 2016 classification. [b]Additional information can be found in the following presentation: Vose J, et al. ASH 2023, abstract 1729. [c]Dexamethasone recommended on days when pola-R-CHP was not administered. C, cycle; CRS, cytokine release syndrome; D, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; G-CSF, granulocyte colony-stimulating factor; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; SUD, step up dose.

RESULTS

Demographic and Baseline Characteristics

Characteristic	Arm 3 (N=37[a])
Age, median (range), y	64 (24–76)
≥65 y, n (%)	18 (49)
Female, n (%)	19 (51)
Ann Arbor stage, n (%)	
II	5 (14)
III	8 (22)
IV	24 (65)
Subtype, n (%)	
DLBCL	34 (92)
HGBCL – triple-hit[b]	1 (3)
FL grade 3B	1 (3)
FL grade 3A	1 (3)
DLBCL type, n (%)	
De novo	33 (89)
Transformed	2 (5)
Molecular classification,[c] n (%)	
GCB	19 (51)
ABC, non-GCB, or unclassified	15 (41)
Unknown	1 (3)
Bulky disease, n (%)	
<6 cm	27 (73)
≥6 cm	10 (27)
ECOG PS, n (%)	
0	21 (57)
1	12 (32)
2	4 (11)
IPI,[d] n (%)	
0–1	2 (5)
2	7 (19)
3	17 (46)
4–5	10 (27)
Extranodal disease at screening,[e] n (%)	30 (81)
Bone	15 (41)
Bone marrow	13 (35)
Spleen	8 (22)
Head and neck	6 (16)
Lung	6 (16)
Time from initial diagnosis to first epcoritamab dose, median (range), mo	0.8 (0.0, 3.4)

Data cutoff: February 29, 2024. Percentages are based on non-missing values; characteristics not totaling 100% are due to rounding. [b]Included 1 with inclusion criteria not met retroactively (patient with FL grade 3A). [c]Assessed by local pathology. [d]Assessed by investigator; applicable for DLBCL, HGBCL – DH/TH. [e]IPI risk factors included: age >60 years, Ann Arbor stage III or IV, elevated lactate dehydrogenase (LDH), >1 extranodal disease site, and ECOG PS ≥2; 1 point each for a maximum sum of 5 points for each patient. *The 5 most common sites are shown. ABC, activated B cell; GCB, germinal center B-cell.

Patient Disposition

	Arm 3 (N=37[a])
Study follow-up, median (range), mo	7.4 (0.3–16.6)
Ongoing epcoritamab treatment	9 (24)
Completed epcoritamab treatment	24 (65)
Discontinued epcoritamab treatment[a]	4 (11)
AE	2 (5)
Physician discretion	1 (3)
Ongoing pola-R-CHP treatment	8 (22)
Completed pola-R-CHP treatment	24 (65)
Discontinued pola-R-CHP treatment	5 (14)

Data cutoff: February 29, 2024. Data shown as n (%) unless otherwise specified. [a]Included 1 patient with inclusion criteria not met retroactively (patient with FL grade 3A). AE, adverse event.

Treatment Exposure

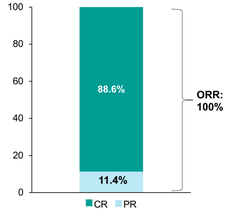
	Arm 3 (N=37)
Epcoritamab exposure	
Duration, median (range), mo	5.0 (0.03–6.5)
Number of cycles, median (range)	8 (1–8)
Epcoritamab delay/interruption due to AE, n (%)	24 (65)
Pola-R-CHP exposure	
Median duration, mo (range)	3.7 (0.16–4.8)
Number of cycles, median (range)	6 (1–6)
Pola-CHP dose reduction due to AE,[a,b] n (%)	3 (8)
Polatuzumab vedotin dose reduction due to AE	3 (8)
Cyclophosphamide dose reduction due to AE	1 (3)
Doxorubicin dose reduction due to AE	1 (3)
Prednisone dose reduction due to AE	0

Data cutoff: February 29, 2024. [a]The pola-R-CHP regimen is dosed once per 21-day cycle. [b]Dose reductions were not allowed for rituximab. Rituximab was held for any rituximab-related, clinically significant, unmanageable grade 3 AE, or any grade 4 AE, until the AE returned to baseline or resolved completely.

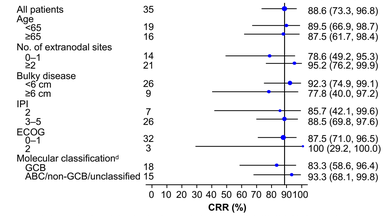
- Median relative dose intensities were high (85–100%) for all study drugs
- The most common AEs leading to dose delay were:
  - Neutropenia, 17 (46%); all patients (100%) successfully restarted epcoritamab
  - Infections, 13 (35%); 12/13 (92%) successfully restarted epcoritamab

Frequent and Deep Responses Observed (n=35)

Best overall response[a]



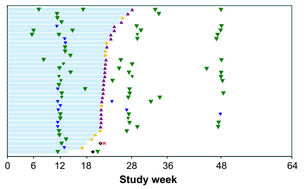
Complete response in subgroups[b,c]



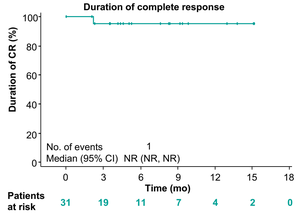
Data cutoff: February 29, 2024. [a]Based on response-evaluable population (patients with measurable disease at baseline and ≥1 postbaseline disease evaluation, or who had died within 60 d of the first dose of study drug without a postbaseline assessment) that excluded 1 patient without a post baseline assessment; also excluded 1 patient with FL grade 3A. [b]Based on investigator assessment per Lugano criteria. [c]Subgroup categories with <3 patients not shown. [d]Applicable for DLBCL, double-hit/triple-hit lymphoma. CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Early and Durable Responses Observed[a]

Patients with response (n=35)[b]



Duration of complete response



Data cutoff: February 29, 2024. [a]Based on investigator assessment per Lugano criteria. [b]Radiographic response assessments occurred at screening (within 28 d of first dose of study drug), at the end of cycle 4, at the later of week 28 or 6 weeks after cycle 8 day 1, at week 48 then every 24 weeks through week 96, then every 48 weeks thereafter until 5 years after the last subject enrolled in arm 3 or progressive disease, whichever occurred first. EOT, end of treatment; NR, not reached.

- Median time to response was 2.7 mo (range: 1.3–3.3)
- Median time to CR was 2.8 mo (range: 1.3–7.4)
- Median duration of CR was not reached

Adverse Event Profile Was Consistent With Previous Findings

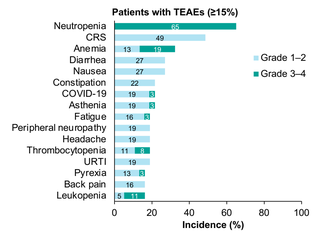
- No DLTs, immune effector cell–associated neurotoxicity syndrome (ICANS), or clinical tumor lysis syndrome (CTLS) were observed
- One patient experienced grade 4 hemophagocytic lymphohistiocytosis, which resolved, and the patient completed treatment
- Febrile neutropenia (all grade 3–4) occurred in 3 (8%) patients
- The most common grade ≥3 treatment-emergent adverse event (TEAE) was neutropenia (65%); no neutropenia events led to epcoritamab discontinuation
- Rates of infection were low

	Arm 3 (N=37[a])
Any-grade TEAE	36 (97)
Related to epcoritamab	34 (92)
Grade 3–4 TEAE	28 (76)
Related to epcoritamab	21 (57)
Serious AE	20 (54)
Related to epcoritamab	17 (46)
Discontinued epcoritamab due to TEAE[b]	2 (5)
Related to epcoritamab[b]	1 (3)
Grade 5 TEAE[c]	1 (3)
Related to epcoritamab	0

Data shown as n (%) unless otherwise specified. [a]Included 1 ineligible patient with FL grade 3A who was excluded from efficacy analyses. [b]TEAEs leading to epcoritamab discontinuation included hypomania and increased aspartate aminotransferase (possibly related to epcoritamab). [c]There was 1 grade 5 TEAE (urosepsis).

Data cutoff: February 29, 2024. URTI, upper respiratory tract infection.

Patients with TEAEs (≥15%)



CRS: Primarily Low Grade and All Resolved

- No grade ≥3 CRS events were observed in this arm
- Rates of CRS were lower with prophylactic dexamethasone vs prednisone

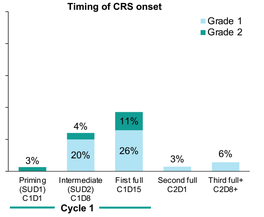
	Arm 3 (N=37[a])
CRS grade,[b] n (%)	18 (49)
1	12 (32)
2	6 (16)
3	0
Time to onset of first CRS event, median (range), d	16 (2–39)
CRS resolution,[c] n (%)	18 (100)
Time to resolution,[d] median (range), d	2 (1–6)
CRS prophylaxis, n (%)	
Dexamethasone	11 (30)
Prednisone	25 (68)
IV fluid	9 (24)
Dexamethasone + IV fluid	3 (8)
Prednisone + IV fluid	6 (16)
CRS interventions,[c] n (%)	
Tocilizumab	7 (39)
Corticosteroid	3 (17)
Tocilizumab + corticosteroid	1 (6)
IV fluid	2 (11)
Leading to epcoritamab discontinuation, n (%)	0

Data cutoff: February 29, 2024. [a]Included 1 ineligible patient with FL grade 3A who was excluded from efficacy analyses. [b]Maximum CRS grade is presented for patients with >1 CRS event. [c]Percentage calculated based on patients with ≥1 CRS event. [d]Based on longest recorded CRS duration for patients with >1 CRS event. IV, intravenous.

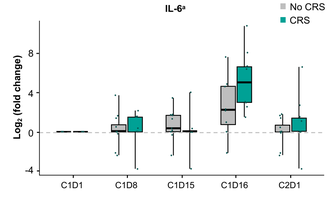
IL-6 Peaked After First Full Dose of Epcoritamab

- Predictable timing of CRS onset; most events occurred after first full dose (C1D15) and were primarily confined to C1
- IL-6 levels peaked 24 hours after the first full dose of epcoritamab (C1D16) and trended toward a greater increase in patients who experienced a CRS event versus patients without a CRS event

Timing of CRS onset



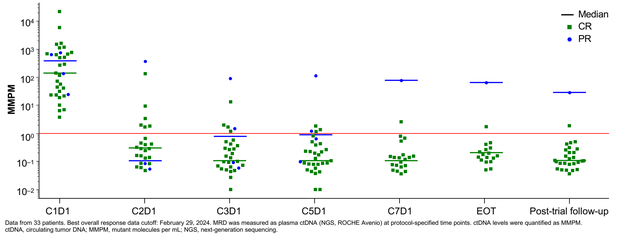
IL-6[a]



Data cutoff: February 29, 2024. [a]Data from patients treated with epcoritamab 48 mg. IL, interleukin; SUD, step-up dose.

Rapid Decline in ctDNA and Sustained MRD Negativity in Patients With CR

- 29 patients had CR, 4 had PR
- Most patients achieved minimal residual disease (MRD)-negative CR after 2 cycles of treatment
- All evaluable CR patients except 1 patient reached MRD-negativity by EOT



Data from 33 patients. Best overall response data cutoff: February 29, 2024. MRD was measured as plasma ctDNA (NGS, ROCHE Avenio) at protocol-specified time points. ctDNA levels were quantified as MMPM. ctDNA, circulating tumor DNA; MMPM, mutant molecules per mL; NGS, next-generation sequencing.

OBJECTIVE

We present the first results of epcoritamab plus pola-R-CHP as 1L treatment for patients with DLBCL from arm 3 of the Phase 1b/2 EPCORE NHL-5 trial

CONCLUSIONS

Fixed treatment duration epcoritamab + pola-R-CHP showed deep and durable responses in 1L DLBCL patients: ORR: 100%; CR: 89%
- Consistent high response rates across subgroups
- Median duration of CR was not reached
- MRD negativity was achieved early and was sustained throughout treatment in the majority of patients with CR

Demonstrated a manageable safety profile with no new safety signals identified
- Most CRS events were low grade and had predictable timing; all events resolved
- The most common grade >3 TEAE was neutropenia (65%), however there were no discontinuations due to neutropenia and rates of infection were low

These data are the second dataset to show that epcoritamab can be combined with 1L standard of care for DLBCL[7]

Data for epcoritamab + pola-R-CHP compares favorably to 1L treatment of DLBCL with both pola-R-CHP and R-CHOP alone and these results support further exploration of epcoritamab + pola-R-CHP in these patients[2]

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Disclosures

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