CLL-280

Epcoritamab Induces Deep Responses in Patients With Richter's Transformation (RT): Primary Results From the EPCORE CLL-1 Trial

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OBJECTIVE

- To report the first data from the fully enrolled RT monotherapy expansion cohort of the EPCORE CLL-1 trial, in which patients received single-agent epcoritamab

CONCLUSIONS

- Single-agent epcoritamab showed promising efficacy with a manageable safety profile in a large cohort of patients with high-risk RT
  - High overall response rate (ORR 53%, CR rate 42%), with encouraging outcomes observed in patients with 1L RT (ORR 60%, CR rate 50%)
  - CRS events were mostly low grade; none led to treatment discontinuation
- These data support further evaluation of epcoritamab in RT
- The EPCORE CLL-1 study is exploring epcoritamab combinations in RT and CLL (NCT04623541)

EPCORE CLL-1 Combinations	
RT	**CLL**
Epcoritamab + R-CHOP Epcoritamab + lenalidomide	Epcoritamab + venetoclax

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Abbreviations

1L, previously untreated (i.e., second line or later; AE, adverse event; BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; *C. cycle*, CAR, chimeric antigen receptor; CAV, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; CTLS, clinical tumor lysis syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOMP, epcoritamab, obinutuzumab, lenalidomide, and prednisone; ICANS, immune cell-associated neurotoxicity syndrome; IRC, independent review committee; IVL, single-cell lymphoma; mo, month(s); MRI, magnetic resonance imaging; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PDL1, programmed cell death protein 1; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q2W, every week; Q4W, every 2 weeks; Q6W, every 4 weeks; Q8W, every 6 weeks; Q12W, every 12 weeks; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EMA, rituximab, dexamethasone, cytarabine, and cisplatin; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; R/R, relapsed or refractory; RT, Richter's transformation; SD, stable disease; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.

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BACKGROUND

Novel Treatment Options Are Needed for Patients With RT

- Approximately 2%–10% of patients with CLL/SLL develop RT, most commonly CD20+ DLBCL[1]
- Poor prognostic factors:
  - Prior CLL/SLL treatment
  - Adverse cytogenetic and molecular abnormalities (eg, *TP53* aberrations, *NOTCH1,* trisomy 12)[1,2]
- Chemoimmunotherapy (R-CHOP or R-EPOCH) is the most widely used treatment[1]; **however, no standard of care for RT currently exists**
  - CR rates are often ≤20%[3]
  - Overall survival is frequently several months to approximately 1 year[4,5]
- Preliminary data suggest that (re)activation of autologous T cells (eg, anti-PD-1 therapy) is a promising approach[6]; however, an unmet need remains for novel, efficacious, and well-tolerated treatment options

Epcoritamab, a Subcutaneous Bispecific Antibody

- Epcoritamab binds to CD3 on T cells and CD20 on B cells to induce T-cell–mediated killing of CD20+ B cells[7,8]
  - Approved in the US, Europe, the UK, and Japan for adults with R/R DLBCL and different subtypes of LBCL and in the US for FL after ≥2 lines of systemic therapy[9-12]
- Previously showed promising single-agent antitumor activity in difficult-to-treat, high-risk patients with R/R CLL: ORR 62%, CR rate 33%[13]
- Initial data from 10 patients with RT treated with single-agent epcoritamab showed promising antitumor activity (ORR 60%) with a manageable safety profile[14]

First disclosure of data from the fully enrolled RT monotherapy expansion cohort

STUDY DESIGN: EPCORE® CLL-1 RT Expansion Cohort

Key RT inclusion criteria

- Prior clinical history of CLL or SLL
- Biopsy-proven transformation to CD20+ DLBCL
- Measurable disease by PET and/or CT/MRI
- ≤2 prior lines of therapy for RT
- Ineligible for or declined chemotherapy
- ECOG PS 0–2

Median follow-up: 12.9 mo (range, 0.5+ to 28.6)

RT expansion, N=42 (fully enrolled)

2 step-up doses[a] → **Epcoritamab 48 mg 28-d cycles** QW C1–3, Q2W C4–9, Q4W C10+ → Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter → Treatment until disease progression

- To ensure patient safety and better characterize CRS, inpatient monitoring was required for 24 h after the first full dose of epcoritamab (C1D15)
- **Primary endpoint:** ORR by IRC
- **Key secondary endpoints:** CR rate, time to response, and safety/tolerability

Data cutoff: April 12, 2024. [a]Patients received subcutaneous epcoritamab with 2 step-up doses (ie, 0.16-mg priming and 0.8-mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS.

RESULTS

Baseline Characteristics

Characteristic	Total N=42
Median age, y (range)	69 (50–80)
Male, n (%)	32 (76)
Ann Arbor stage, n (%)[a]	
I	2 (5)
II	1 (2)
III	**15 (36)**
IV	**23 (55)**
TP53 aberration	
Yes[b]	**19 (45)**
No[c]	13 (31)
Missing	10 (24)
Median time from initial CLL/SLL diagnosis to disease transformation, y (range)	8 (0–23.9)
Median time from disease transformation to first dose, mo (range)	2 (0.4–86.5)

Characteristic	Total N=42
Prior CLL/SLL or RT therapy, n (%)[d]	**40 (95)**
Median number of prior lines of CLL/SLL therapy (range)[e]	**2 (1–7)**
Prior CLL/SLL therapy, n (%)	**31 (74)**
Chemoimmunotherapy, n/n (%)	23/31 (74)
Targeted agents, n/n (%)	23/31 (74)
BCL-2 inhibitor, n/n (%)	17/31 (55)
BTK inhibitor, n/n (%)	21/31 (68)
CAR T-cell therapy, n/n (%)	1/31 (3)
Prior RT therapy, n (%)	**20 (48)**
Chemoimmunotherapy, n/n (%)[f]	20/20 (100)
R-CHOP, n/n (%)	15/20 (75)
Targeted agents, n/n (%)	8/20 (40)
BCL-2 inhibitor, n/n (%)	4/20 (20)
BTK inhibitor, n/n (%)	6/20 (30)

[a]Ann Arbor stage was missing for 1 patient. [b]*TP53* mutated or del17p positive. [c]Both *TP53* wild type and del17p negative. [d]Two patients had neither prior CLL/SLL therapy nor prior RT therapy. [e]Among 31 patients who received prior CLL/SLL therapy. [f]Two patients received R-EPOCH and 1 patient each received hyper-CVAD and R-DHAP.

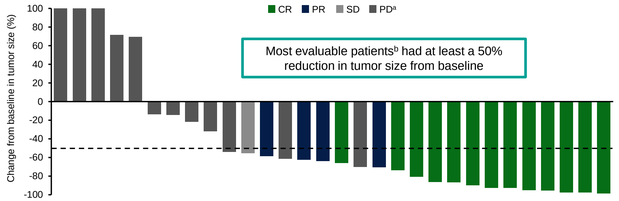
Best Overall Response and by Line of Therapy

Response, n (%)[a]	Total Efficacy Evaluable n=38[b]	1L RT n=20	2L+ RT n=18
Overall response	**20 (53)**	**12 (60)**	**8 (44)**
Complete response	16 (42)	10 (50)	6 (33)
Partial response	4 (11)	2 (10)	2 (11)
Stable disease	1 (3)	0	1 (6)
Progressive disease	14 (37)	6 (30)	8 (44)

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and/or patients who died within 60 d of first dose. Response assessment according to Lugano 2014 criteria.[15] [b]Three patients died without postbaseline assessment (2 in the 1L RT population and 1 in the 2L+ RT population).

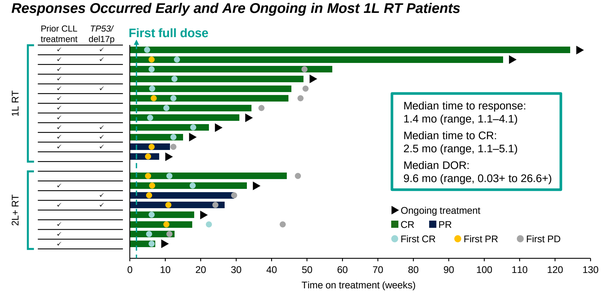
High response rates observed, particularly in 1L RT patients

Best Tumor Reduction From Baseline



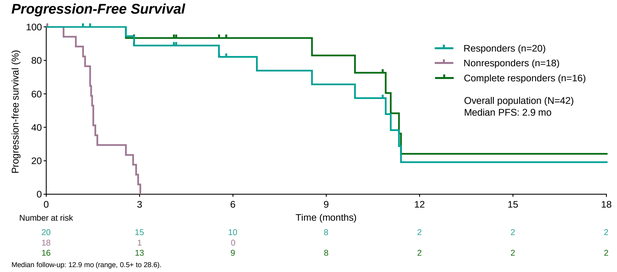
Response assessed using PET-CT per Lugano criteria.[15] CR was complete metabolic response. [a]Patients with a reduction in tumor size may have had new lesions per PET-CT. [b]Includes patients evaluable for postbaseline sum of perpendicular diameters.

Responses Occurred Early and Are Ongoing in Most 1L RT Patients



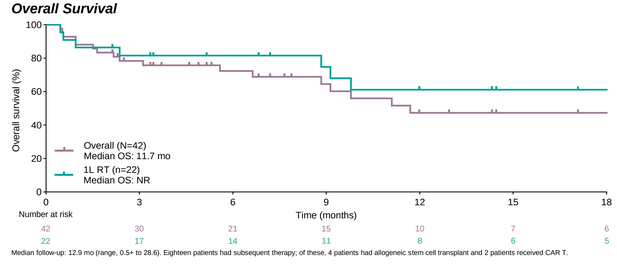
Median follow-up: 12.9 mo (range, 0.5+ to 28.6). Median number of treatment cycles initiated (range): 3 (1–32). Median duration of treatment (range): 2.7 mo (0.3–28.6). Tumor response was evaluated by PET-CT obtained Q6W until week 24, and then Q24W until disease progression. Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD. Patient characteristics are shown at left.

Progression-Free Survival



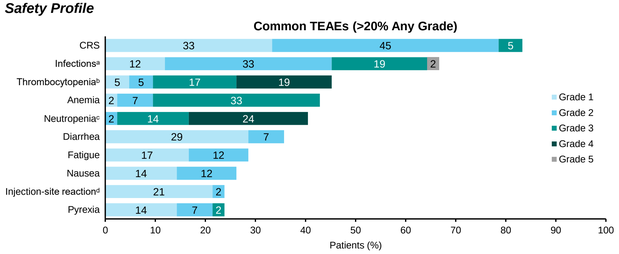
Median follow-up: 12.9 mo (range, 0.5+ to 28.6).

Overall Survival



Median follow-up: 12.9 mo (range, 0.5+ to 28.6). Eighteen patients had subsequent therapy; of these, 4 patients had allogeneic stem cell transplant and 2 patients received CAR T.

Safety Profile



Baseline Cytopenia in Patients With Reported Hematologic Events, n/n (%)	Total N=42
Anemia	16/18 (89)
Thrombocytopenia	16/19 (84)
Neutropenia	6/17 (35)

- 1 nonfatal TEAE led to treatment discontinuation[e]
- 3 fatal TEAEs reported[f]; none were considered related to epcoritamab

Nonhematologic TEAEs were primarily low grade (grade 1–2)

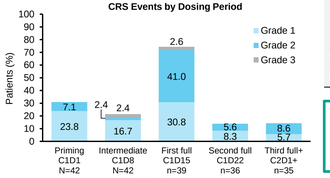
Median duration of treatment: 2.7 mo (range, 0.3–28.6). Median cycles (28 d) of epcoritamab initiated: 3 (range, 1–32). N=42. Additional grade 3 TEAEs occurring in >1 patient: Hyperglycemia (n=4); dyspnea, pneumonia (both n=3); generalized edema, rhinovirus infection (both n=2). No additional grade 4 TEAEs occurred in >1 patient. [a]COVID-19: 7% grade 1, 10% grade 2, 5% grade 3. [b]Combined term includes thrombocytopenia and decreased platelet count. [c]Combined term includes neutropenia and decreased neutrophil count. Two cases of febrile neutropenia (both grade 3) were reported. [d]Combined term includes injection-site reaction, erythema, bruising, and rash. [e]Interstitial lung disease (considered related to treatment). [f]General physical health deterioration in the context of PD (n=2) and sepsis (n=1).

AEs of Special Interest

CRS[a]	Total N=42
CRS, n (%)	**35 (83)**
Grade 1	14 (33)
Grade 2	19 (45)
Grade 3	2 (5)
Median time to onset after first full dose, h (range)	14 (3–480)
Median time to resolution, d (range)[b]	3.5 (1–16)
Treated with tocilizumab, n (%)	20 (48)
CRS resolution, n/n (%)	34/35 (97)[c]

ICANS[a] & CTLS[d]	Total N=42
ICANS, n (%)[e]	**5 (12)**
Grade 1	2 (5)
Grade 2	3 (7)
ICANS resolution, n/n (%)	4/5 (80)[c]
Median time to resolution, d (range)[b]	2 (1–11)
Tumor lysis syndrome, n (%)	**4 (10)**
Laboratory only	1 (2)
Clinical – grade 2	2 (5)
Clinical – grade 3	1 (2)
CTLS resolution, n/n (%)	2/3 (67)
Median time to CTLS resolution, d (range)[b]	3 (3–3)

CRS Events by Dosing Period



- CRS occurrence was predictable, with cases primarily occurring following the first full dose
- No AEs of special interest led to discontinuation

[a]Graded by Lee et al 2019 criteria.[16] [b]Median is based on longest event duration in patients with event. [c]The patient for whom CRS and ICANS did not resolve developed CRS and ICANS in the setting of a fatal TEAE (sepsis; considered unrelated to epcoritamab by investigator). [d]Graded by Cairo–Bishop criteria. [e]All ICANS events occurred with concurrent grade 2 CRS events.

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