Epcoritamab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia: Results From the Phase 1b/2 EPCORE CLL-1 Trial Expansion Cohort

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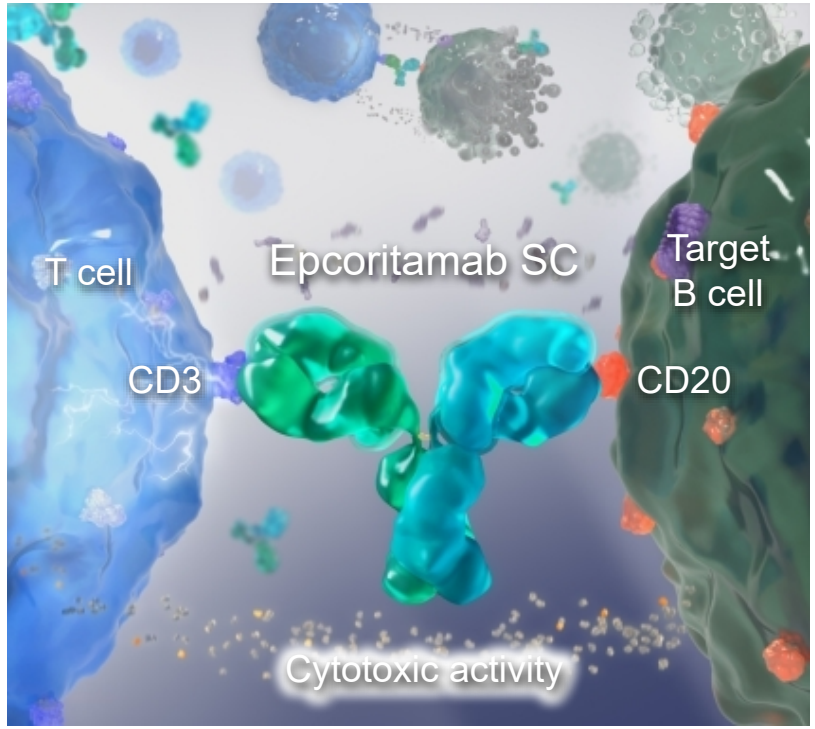
Novel Treatment Options Are Needed for Patients With R/R CLL

- Bruton tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL-2) inhibitors have improved outcomes in R/R CLL; however, they are not considered curative[1,2]
- An increasing number of patients with R/R CLL are double-exposed to these agents, and there is a lack of effective salvage options, leading to very poor outcomes[3]
- Novel, efficacious therapies are needed for these patients, who often have poor prognostic factors, including *TP53* aberrations and/or unmutated *IGHV*, and have experienced clonal evolution[1,2]



Epcoritamab is a novel subcutaneous CD3xCD20 bispecific antibody

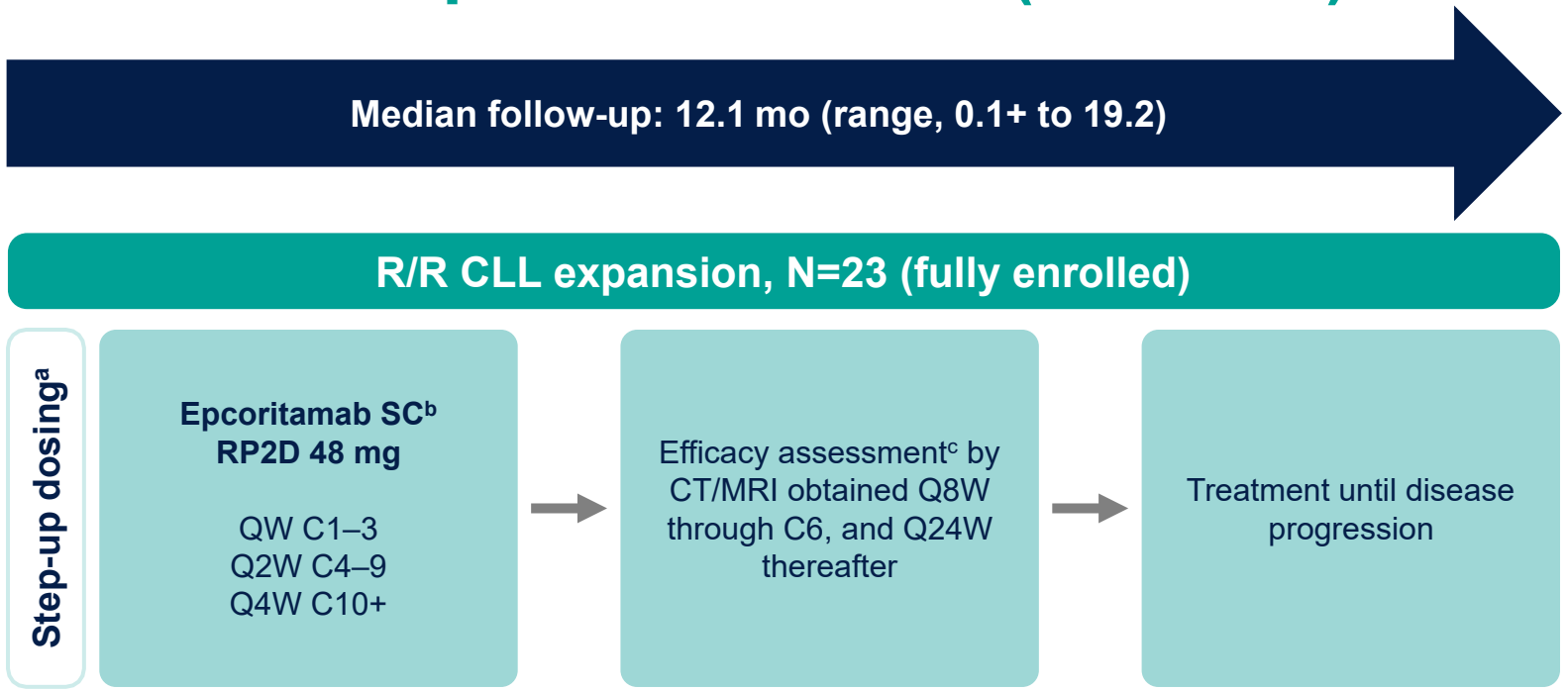
- Approved by the US FDA for the treatment of adults with R/R DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after ≥2 lines of systemic therapy[4]
- Previous reports from EPCORE CLL-1 showed encouraging efficacy and manageable safety in R/R CLL (dose escalation) and Richter's syndrome (dose expansion)[5,6]

1. Hallek M, et al. *Lancet*. 2018;391:1524-37. **2.** Dreger P, et al. *Blood*. 2018;132:892-902. **3.** Martens AWJ, et al. *Leukemia*. 2023;37:606-16. **4.** EPKINLY [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2023. **5.** Kater AP, et al. ASH 2021. Abstract 2627. **6.** Kater AP, et al. ASH 2022. Abstract 348.

Study Design: EPCORE CLL-1 Expansion Cohort (R/R CLL)

Key inclusion criteria

- CD20^{+} R/R CLL
- ≥2 prior lines of systemic therapy, including treatment with or intolerance to a BTK inhibitor
- ECOG PS 0–2
- Requiring treatment per iwCLL criteria
- Measurable disease with ≥5×10^{9}/L B lymphocytes or measurable lymphadenopathy or organomegaly
- No minimum life expectancy required



- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete response (CR) rate, time to response, and safety/tolerability

Data cutoff: July 5, 2023. Epcoritamab was administered in 28-d cycles. [a]Patients received epcoritamab SC with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS. [b]To ensure patient safety and better characterize CRS, inpatient monitoring was required for the first 4 doses of epcoritamab. [c]Based on iwCLL guidelines.

Patient Characteristics and Treatment History

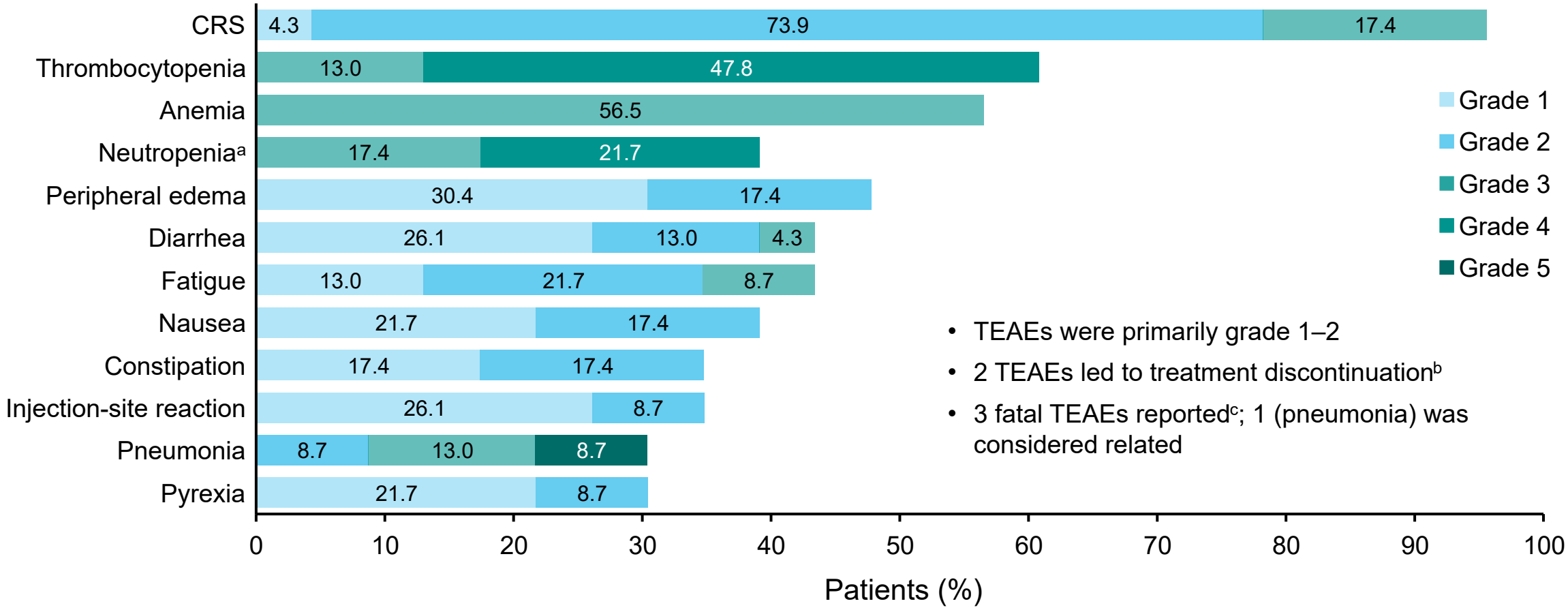
Characteristic	Total N=23
Median age, y (range)	72 (55–83)
Male, n (%)	17 (74)
CLL characteristic, n (%)	
IGHV unmutated[a]	16 (70)
TP53 aberration[b]	15 (65)

Treatment History	Total N=23
Median time from initial diagnosis to first dose, y (range)	13 (5.5–19.5)
Median number of prior lines of therapy (range)	**4 (2–10)**
≥4 prior lines of therapy, n (%)	15 (65)
Prior therapy, n (%)	23 (100)
Chemoimmunotherapy	23 (100)
Small molecules	23 (100)
BTK inhibitor	23 (100)
Discontinuation due to progression	17 (74)
BCL-2 inhibitor	19 (83)
CAR T-cell therapy	1 (4)
Median time from last treatment to first dose, mo (range)	1.0 (0.1–49.4)

Prior therapies and key CLL characteristics reflect a modern R/R CLL patient population

Data for CLL characteristics were obtained from local laboratories. [a]*IGHV* status mutated for 4 patients and unknown for 3 patients. [b]*TP53*/del17p status unmutated/negative for 6 patients and unknown for 2 patients.

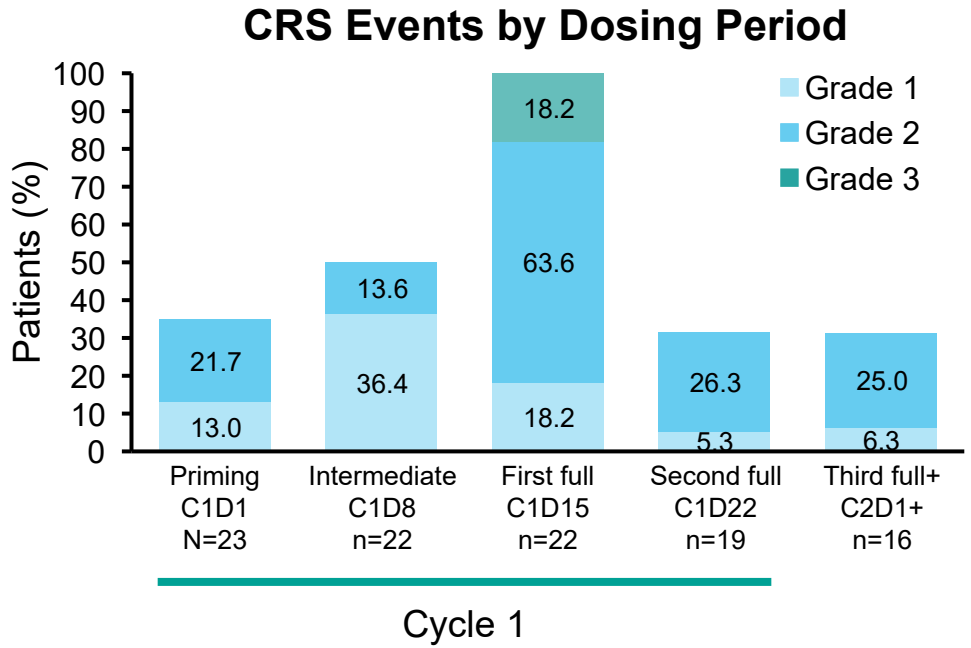
Common (>30%) Treatment-Emergent AEs



N=23. Additional grade 3 TEAEs: Alanine aminotransferase increased, aspartate aminotransferase increased (both n=3); arthralgia, hypertension, hypokalemia, pleural effusion (all n=2); acute sinusitis, capillary leak syndrome, COVID-19, dyspnea, epistaxis, headache, hematoma, hematuria, hepatotoxicity, herpes zoster reactivation, hyperglycemia, hypertriglyceridemia, hypotension, infection, intestinal abscess, leukocytosis, leukopenia, musculoskeletal pain, *Pneumocystis jirovecii* pneumonia, presyncope, syncope (all n=1). Additional grade 4 TEAEs: Cerebrovascular accident, hyperkalemia (both n=1). [a]Two cases of febrile neutropenia were reported. [b]Pneumonia (n=2); 1 was considered related to treatment. [c]Pneumonia (n=2) and squamous cell carcinoma of the skin (n=1).

AEs of Special Interest Were Manageable

CRS[a]	Total, N=23
CRS resolution, n/n (%)	22/22 (100)
Median time to onset after first full dose, h (range)	7.3 (1–99)
Median time to resolution, d (range)[b]	3 (1–16)
Treated with tocilizumab, n (%)	19 (83)



ICANS & Clinical Tumor Lysis Syndrome	Total, N=23
ICANS, n (%)[c]	**3 (13)**
Grade 1	1 (4)
Grade 2	2 (9)
ICANS resolution, n/n (%)	3/3 (100)
Median time to resolution, d (range)	3 (3–4)
Tumor lysis syndrome, n (%)	**1 (4)**
Laboratory	0
Clinical – grade 2	1 (4)
Clinical tumor lysis syndrome resolution, n/n (%)	1/1 (100)
Time to resolution, d	11

- CRS occurrence was predictable, with most cases following the first full dose
- No AEs of special interest led to discontinuation, and all resolved

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. [c]All ICANS events occurred with grade 2 CRS.

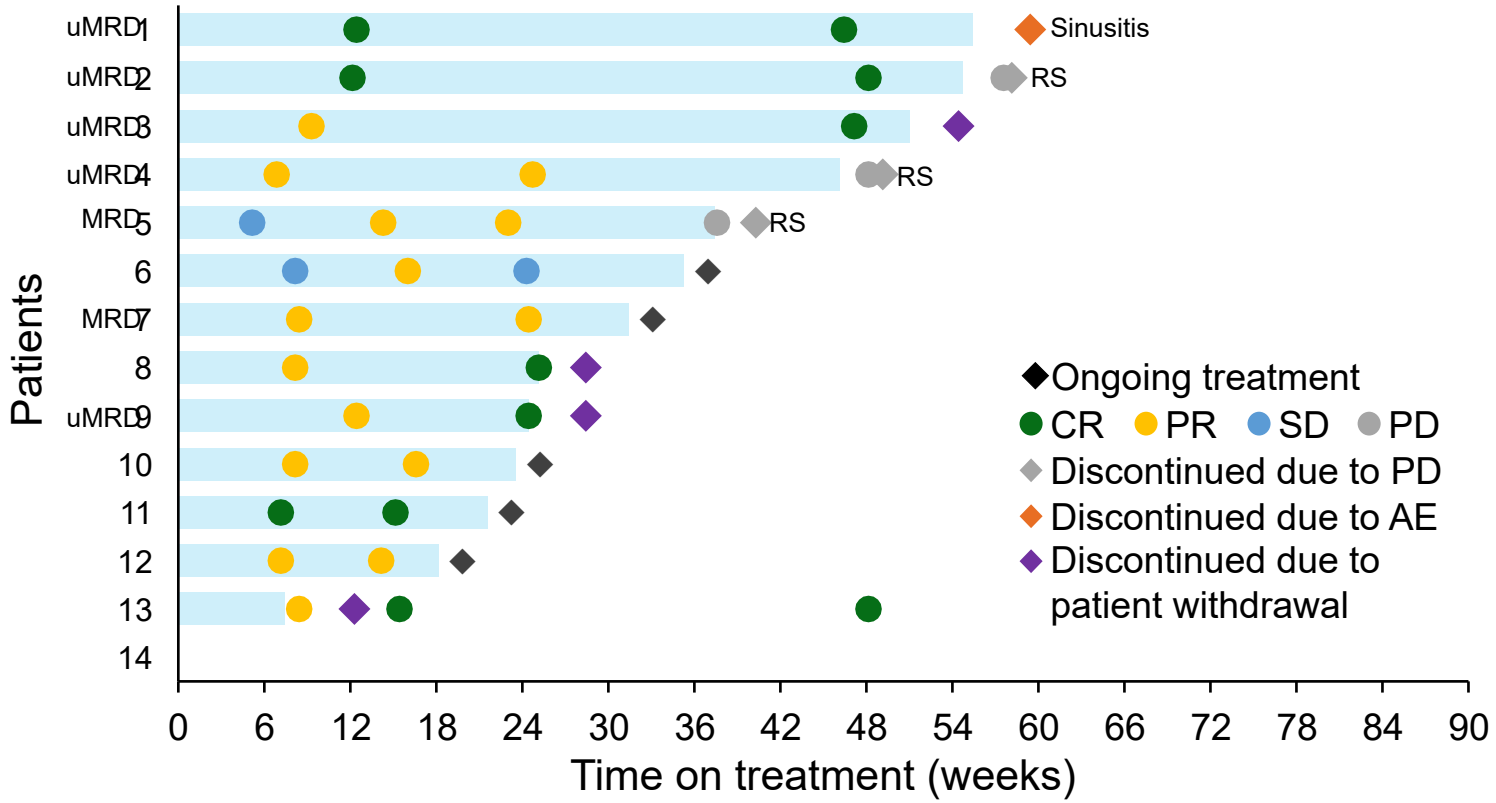
High Overall and Complete Response Rates

Response, n (%)[a]	Total Efficacy Evaluable n=21	*TP53* Aberration n=14	Double-Exposed[b] n=17
Overall response[c]	**13 (62)**	**9 (64)**	**9 (53)**
Complete response	7 (33)	4 (29)	5 (29)
Partial response	6 (29)	5 (36)	4 (24)
Stable disease	4 (19)	2 (14)	4 (24)
Progressive disease	1 (5)	1 (7)	1 (6)
Not evaluable/no assessment[d]	3 (14)	2 (14)	3 (18)

Very encouraging overall and complete response rates observed, including in difficult-to-treat, high-risk R/R CLL patients

[a]Based on response-evaluable population, defined as patients who received ≥1 full dose of epcoritamab, had ≥1 postbaseline response evaluation, or died within 60 d of first dose.[b]Patients previously treated with both a BTK and a BCL-2 inhibitor. [c]Response assessment according to iwCLL criteria. [d]Two patients died without postbaseline assessment.

Deep and Durable Responses



	Efficacy Evaluable n=21
Median time to response, mo (range)	1.9 (1.6–3.7)
Median time to CR, mo (range)	3.6 (1.6–10.8)
Estimated DOR at 9 mo,[a] %	83
Estimated PFS at 9 mo,[a] %	67
Estimated OS at 9 mo,[a] %	81

[a]Kaplan–Meier estimates.

Responses occurred early, were deep, and appear durable

Median follow-up, mo (range): 12.1 (0.1+ to 19.2). Median number of treatment cycles initiated (range): 5 (1–14). Median duration of treatment, mo (range): 5.0 (0.03+12.7). Seven responders (4 CR; 3 PR) were tested for MRD in peripheral blood. All 4 patients with CR had undetectable MRD (uMRD) to 10^{-4} (<1 CLL cell in 10^4 leukocytes). One patient with PR had uMRD to 10^{-4}.
RS, Richter's syndrome.

Conclusions

In a difficult-to-treat, high-risk population of patients with R/R CLL, most of whom had been double-exposed, single-agent epcoritamab SC showed promising antitumor activity

- Responses were seen early and frequently (ORR 62%; CR rate 33%) and appear durable, with an estimated 83% of responders remaining in response at 9 mo

Safety was manageable and consistent with T-cell–engaging strategies; there were no new safety signals

- CRS events were mostly low grade, all were transient, and none led to discontinuation

The findings support the continued exploration of epcoritamab SC

EPCORE CLL-1 is enrolling patients with R/R CLL/small lymphocytic lymphoma (SLL) or Richter's syndrome (NCT04623541)

- In this trial, epcoritamab is combined with:
  - Venetoclax for R/R CLL/SLL
  - Lenalidomide or R-CHOP for Richter's syndrome

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