Early Results From the Phase 1b/2 EPCORE CLL-1 Trial: Subcutaneous Epcoritamab in Patients With Richter's Syndrome

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OBJECTIVE

To evaluate the preliminary clinical efficacy and safety of epcoritamab in patients with RS-DLBCL

CONCLUSIONS

In a difficult-to-treat, high-risk RS-DLBCL patient population, single-agent epcoritamab showed promising activity (high response rates: ORR 60%; CMR 50%) with a tolerable safety profile (only low-grade CRS, all resolved; no ICANS events; no discontinuations due to TEAEs)

This first standalone dataset for a bispecific antibody in RS supports further clinical exploration of epcoritamab in this aggressive disease with limited treatment options

The EPCORE CLL-1 study is ongoing and recruiting patients with CLL or RS (NCT04623541)

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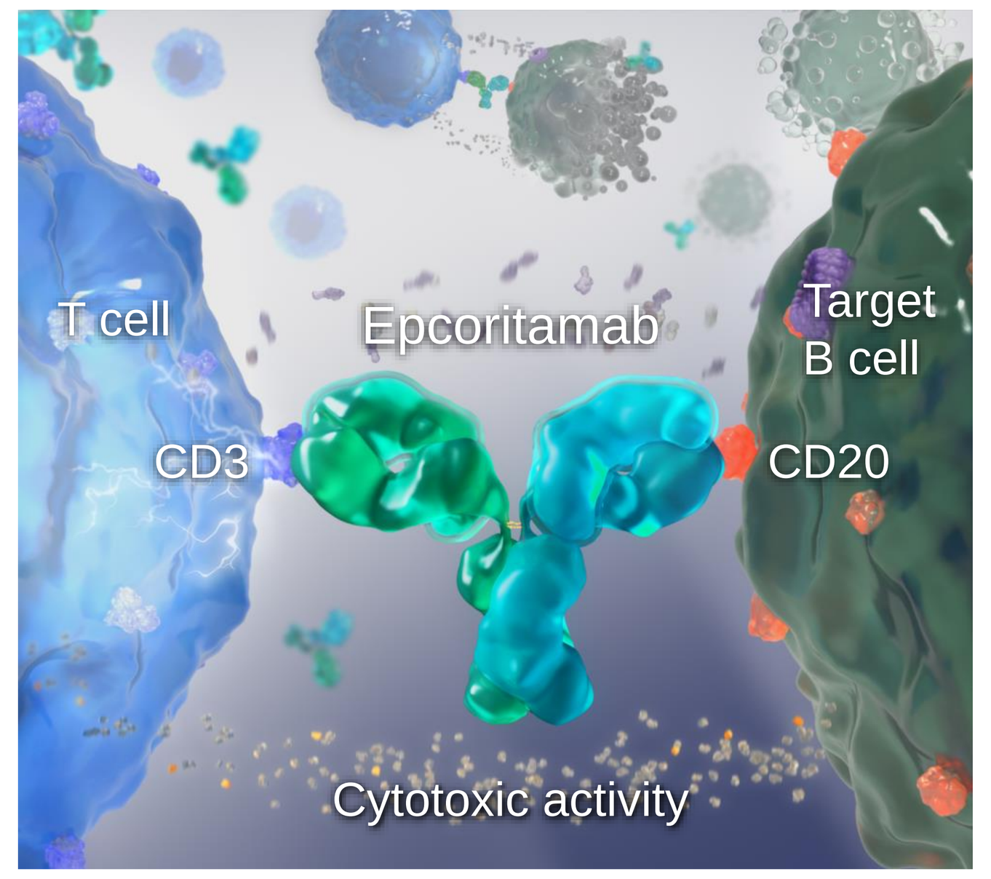
BACKGROUND

- Richter's syndrome (RS) is the development of an aggressive lymphoma from underlying chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
  - Occurs in approximately 2–10% of patients with CLL/SLL,[1] and most commonly, disease transforms to CD20+ diffuse large B-cell lymphoma (DLBCL)
- RS-DLBCL is characterized by sudden clinical deterioration
  - Poor prognostic factors include prior treatment for CLL/SLL, elevated lactate dehydrogenase, and adverse molecular abnormalities or cytogenetics (eg, *TP53*, *NOTCH1*, trisomy 12, and del17p)[1,2]
  - Chemoimmunotherapies have limited responses[3,4]
  - Median overall survival ranges from a few months to approximately 1 year[1,4,5]
  - There is no established standard of care; current guidelines recommend clinical trials
- High unmet medical need exists for novel, efficacious, and well-tolerated therapies
- Epcoritamab (DuoBody®-CD3xCD20) is a subcutaneous bispecific antibody that binds to CD3 on T cells and CD20 on B cells to induce T-cell–mediated killing of CD20+ malignant B cells[6,7]
- Single-agent epcoritamab in large B-cell lymphoma (LBCL) in the EPCORE NHL-1 pivotal trial:
  - Epcoritamab demonstrated substantial antitumor efficacy with a well-tolerated safety profile in relapsed or refractory, including heavily pretreated, patients with LBCL[8,9]; trial included one patient with RS-DLBCL
- Herein, we present initial data from the RS cohort in the ongoing phase 1b/2 EPCORE CLL-1 trial, the first standalone dataset for a bispecific antibody in Richter's syndrome



STUDY DESIGN: EPCORE CLL-1 RS Expansion Cohort

Dose escalation → **Median follow-up: 4.9 mo (range, 0.6–9.3)**

CLL[10]
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key RS inclusion criteria
- Ineligible for or voluntarily declined chemotherapy
- ≤1 prior line of therapy for RS-DLBCL
- Biopsy-proven transformation to CD20+ RS-DLBCL
- Prior clinical history of CLL or SLL
- ECOG PS 0–2
- Measurable disease by PET and/or CT/MRI

RS-DLBCL expansion, N=10

Step-up dosing[a]: **Epcoritamab (SC) 48 mg** 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 at first 4 doses of epcoritamab
- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete metabolic response (CMR) rate, time to response (TTR), and safety/tolerability

Data cutoffs: September 8, 2022 (efficacy); September 16, 2022 (safety). Epcoritamab was administered in 28-d cycles as shown. [a]Patients received SC epcoritamab 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.

RESULTS

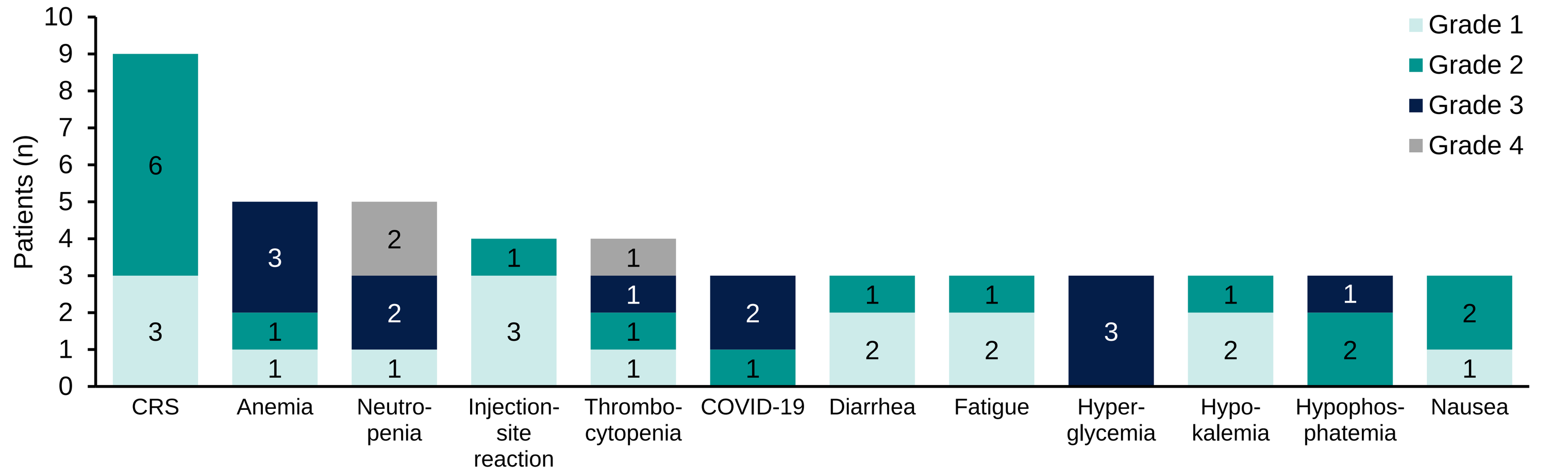
Patient Characteristics and Treatment History

CLL Characteristic, n (%)	Total, N=10
IGHV unmutated[a]	8 (80)
TP53 mutation[b]	5 (50)
NOTCH1 mutation[c]	2 (20)
FISH	
Trisomy 12[d]	1 (10)
Del17p[e]	3 (30)
Del11q[f]	3 (30)
Del13q[g]	4 (40)
RS Characteristic	**Total, N=10**
Median age, y (range)	70 (53–79)
Male, n (%)	7 (70)
Ann Arbor stage, n (%)	
IE	1 (10)
II	1 (10)
III	3 (30)
IV	5 (50)
Elevated lactate dehydrogenase, n (%)	8 (80)
Cell of origin, n (%)[h]	
Germinal center B-cell	1 (10)
Non–germinal center/Activated B-cell	6 (60)
Characteristic of Prior CLL Therapy	**Total, N=10**
Median time from initial CLL diagnosis to first dose, y (range)	12 (2.6–24.0)
Median number of prior lines of therapy for CLL (range)	**3 (0–7)**
Prior CLL/SLL therapy, n (%)	7 (70)
Chemoimmunotherapies	7 (70)
Targeted agents	6 (60)
BCL2 inhibitor	5 (50)
BTK inhibitor	5 (50)
CAR T-cell therapy	1 (10)
Median time from last CLL treatment to first dose, mo (range)	12 (0.2–61.8)
Characteristic of Prior RS-DLBCL Therapy	**Total, N=10**
1 prior line of RS-DLBCL therapy, n (%)	**5 (50)**
R-CHOP	3 (30)
No response	2 (20)
R-DHAP	1 (10)
No response	1 (10)
VR-EPOCH[i]	1 (10)
Median time from disease transformation to first dose, mo (range)	3.4 (0.5–21.4)
Median time from end of last line of RS-DLBCL therapy to first dose, mo (range)	2 (0.5–5.4)

Data cutoff: September 16, 2022. Data for CLL characteristics were obtained from local laboratories. [a]*IGHV* mutation status unknown for 2 patients. [b]*TP53* mutation status unmutated for 4 patients and unknown for 1 patient. [c]*NOTCH1* mutation status unmutated for 4 patients and unknown for 4 patients. [d]Trisomy 12 status negative for 8 patients and unknown for 1 patient. [e]Del17p status negative for 7 patients. [f]Del11q status negative for 7 patients. [g]Del13q status negative for 4 patients and unknown for 2 patients. [h]Cell of origin was unknown for 3 patients. [i]Response to VR-EPOCH unknown. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; VR-EPOCH, venetoclax plus dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

- Prior novel therapies for CLL indicate a modern, difficult-to-treat, high-risk RS-DLBCL patient population; 1 patient received prior CAR T-cell therapy

Treatment-Emergent AEs (≥30%)



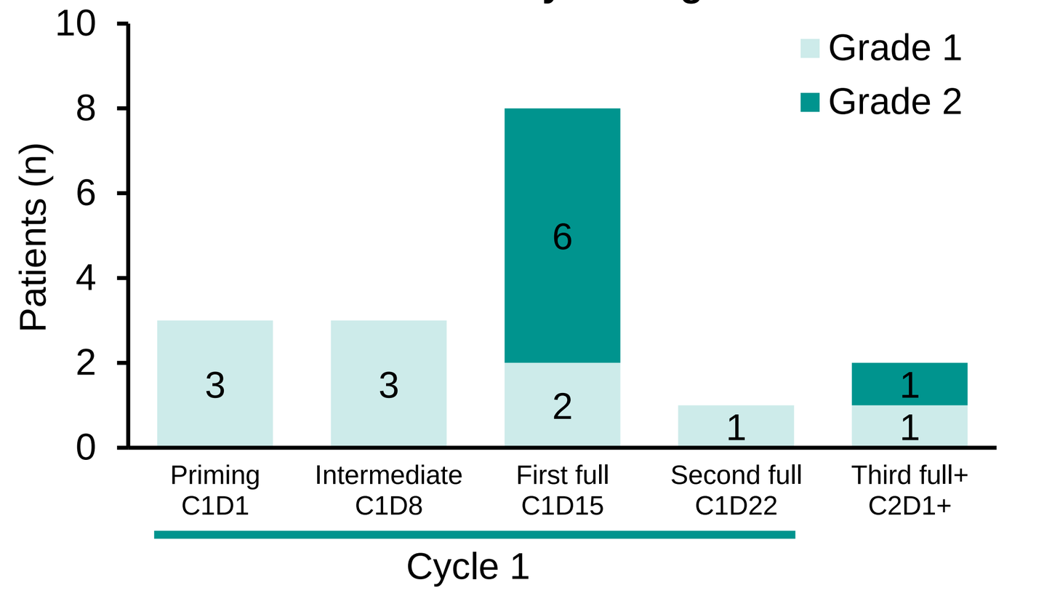
Data cutoff: September 16, 2022. Median duration of treatment: 3.5 mo (range, 0.5–9.3). Median cycles (28 d) of epcoritamab: 4 (range, 1–11).

- AEs were primarily low grade, including CRS; no ICANS events were observed
- One case of clinical tumor lysis syndrome (grade 2); resolved in 3 days
- One grade 5 (fatal) TEAE (general physical health deterioration in the setting of PD, unrelated to epcoritamab)
- Six patients experienced dose delay due to TEAE
- No TEAEs leading to discontinuation

CRS Events

	Total, N=10
CRS, n (%)[a]	9 (90)
Grade 1	3 (30)
Grade 2	6 (60)
CRS resolution, n/n (%)	**9/9 (100)**
Median time to onset after first full dose, h (range)	12.5 (8–394)
Median time to resolution, d (range)[b]	3 (2–9)
Treated with tocilizumab, n (%)	7 (70)
Leading to treatment discontinuation, n (%)	**0**

Data cutoff: September 16, 2022. [a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.



Data cutoff: September 16, 2022.

- Occurrence was predictable, with most cases following the first full dose
- No grade ≥3 CRS events
- All CRS events resolved, and none led to discontinuation

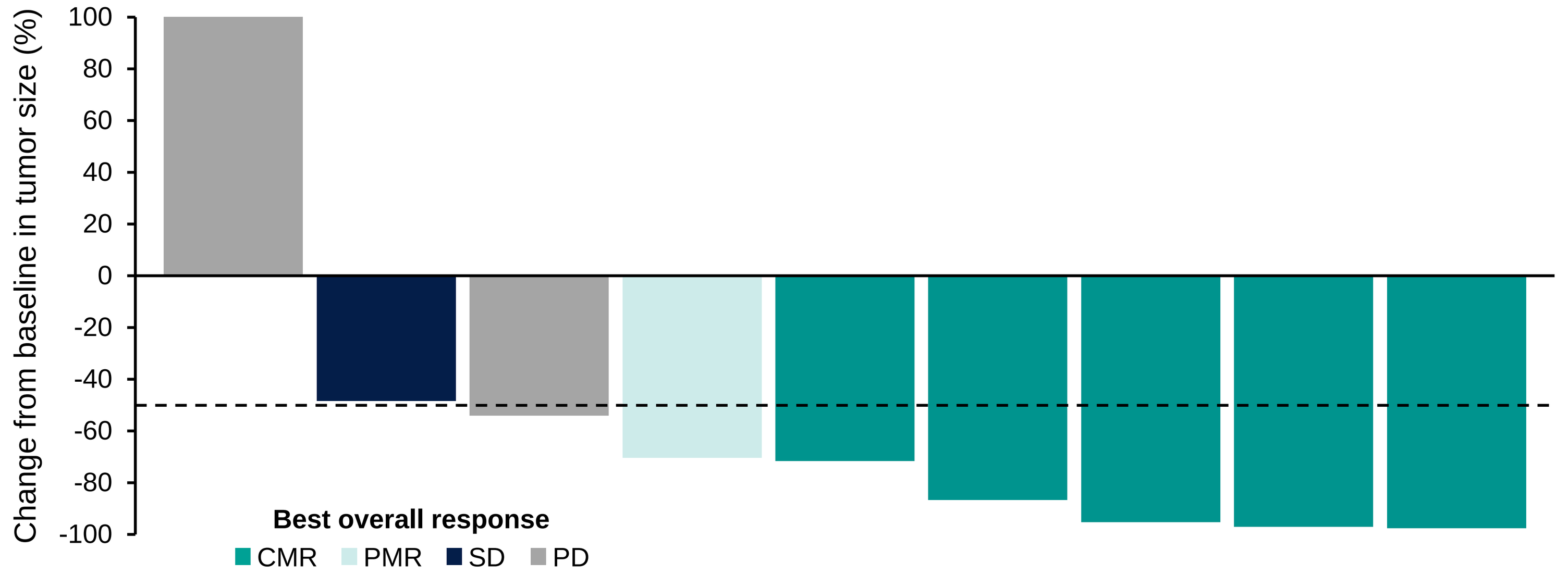
Best Overall Response

Response, n (%)[a]	Total Efficacy Evaluable, N=10
Overall response[b]	**6 (60)**
Complete metabolic response (CMR)	5 (50)
Partial metabolic response (PMR)	1 (10)
Stable disease	1 (10)
Progressive disease	2 (20)
Not evaluable	1 (10)[c]

Data cutoff: September 8, 2022. Median follow-up: 4.9 mo (range, 0.6–9.3).
[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.
[b]Response assessment according to Lugano 2014 criteria. [c]Patient stopped treatment on C1D15 due to progression and did not receive any scans.

- High overall and complete metabolic response rates observed

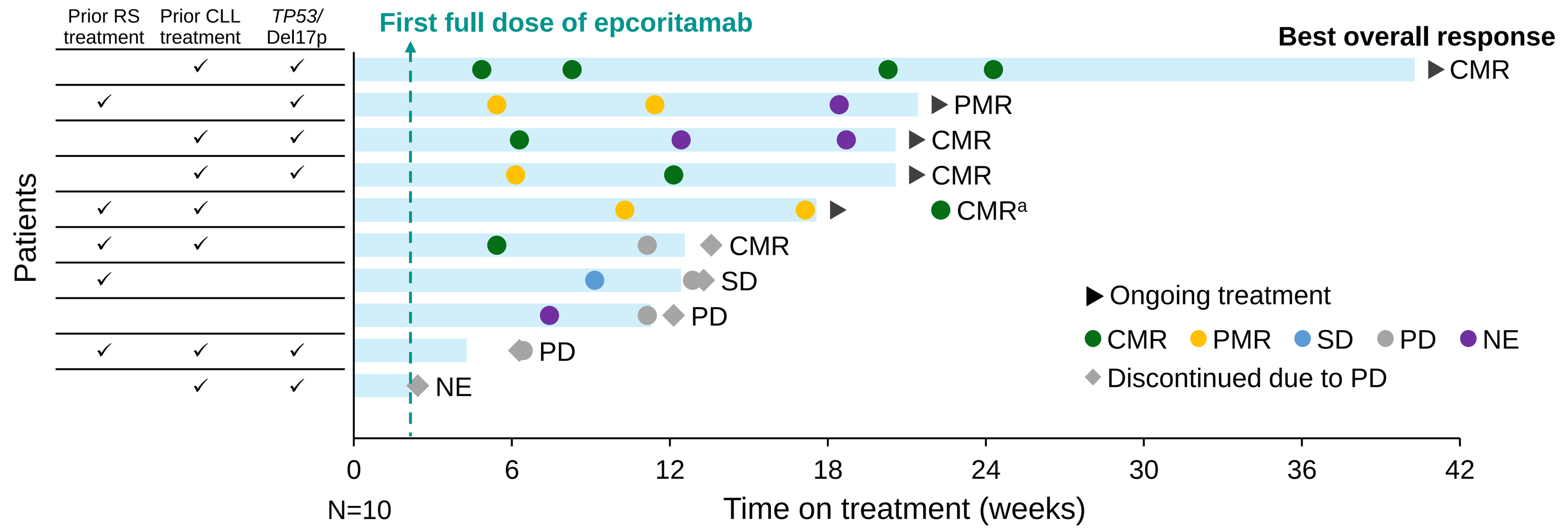
Best Tumor Reduction From Baseline



Data cutoff: September 8, 2022.

- Nearly all patients achieved at least 50% reduction in tumor size from baseline

Depth and Duration of Response



Data cutoff: September 8, 2022. Median follow-up: 4.9 mo (range, 0.6–9.3). Tumor response was evaluated by PET-CT obtained Q6W until wk 24, and then Q24W until disease progression. Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD. Check marks indicate patient characteristics. [a]Response was verified as CMR post data cutoff, with updated bone marrow results, while patient was receiving 40 mg of prednisone.

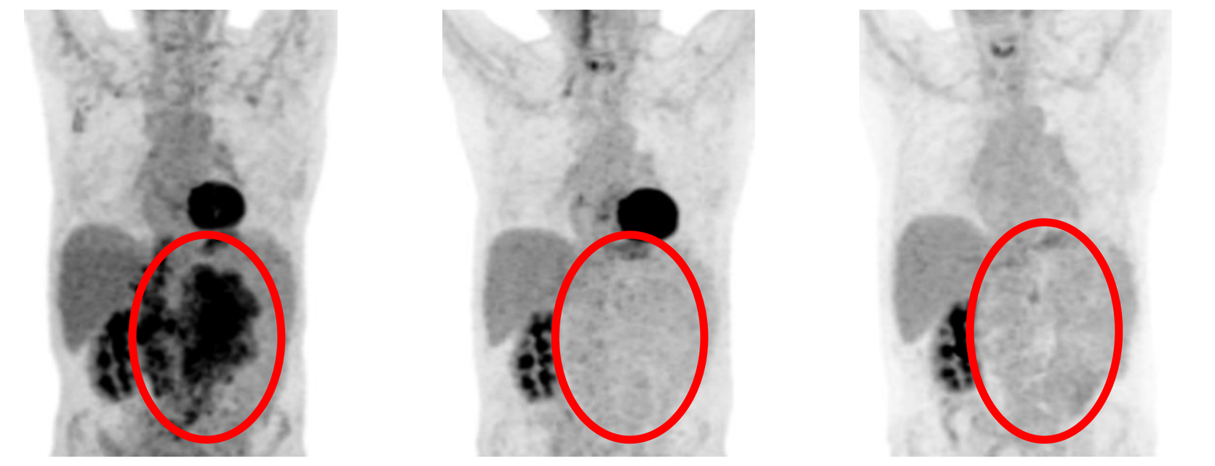
- Median time to response was 1.3 mo (range, 1.1–2.4)
- Median time to complete response was 1.4 mo (range, 1.1–2.8)

EPCORE NHL-1 Clinical Case Study: RS-DLBCL

Patient history
- 76-year-old male
- Diagnosed with SLL in Jul 2019, started on ibrutinib
- Transformed to RS-DLBCL in Oct 2020
- RS-DLBCL treated with 3 cycles of R-CHOP, mixed response

Epcoritamab treatment
- First dose: Feb 2021 (SPD = 105 cm²)
- CR at week 6, 12, 17, 23, 36, 48, 62, 76 (DS = 1, SPD = 2.8 cm²)
- Patient has been in sustained CR for over 70 weeks and is still on treatment (last dose C22D1)

Baseline PET/CT scan | 12-week PET/CT scan | 76-week PET/CT scan



Mesenteric mass: 11.6 x 7.2 cm; SUV max 6.3 in abdominal/pelvic mass | Mesenteric mass: 0.5 x 0.5 cm; SUV max 2.0 in abdominal/pelvic mass | Mesenteric mass: 0.5 x 0.5 cm; Background uptake only

Courtesy of Dr. Yasmin H. Karimi.

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