Subcutaneous Epcoritamab Plus Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma From EPCORE NHL-5

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OBJECTIVES

To evaluate the safety and anti-tumor activity of epcoritamab plus lenalidomide in patients with R/R DLBCL from EPCORE NHL-5

CONCLUSIONS

Epcoritamab + lenalidomide showed deep and durable responses in patients with R/R DLBCL, including those with high-risk disease (eg, primary refractory, elderly, prior CAR T therapy)

Epcoritamab + lenalidomide had a manageable safety profile with no new safety signals identified; most CRS events were low grade, had predictable timing, and all CRS events resolved

Cytokine peaks occurred immediately after the first full dose

MRD negativity was achieved early and was sustained throughout treatment

These data are the first results of a bispecific antibody in combination with lenalidomide for R/R DLBCL and support further exploration of epcoritamab + lenalidomide in these patients

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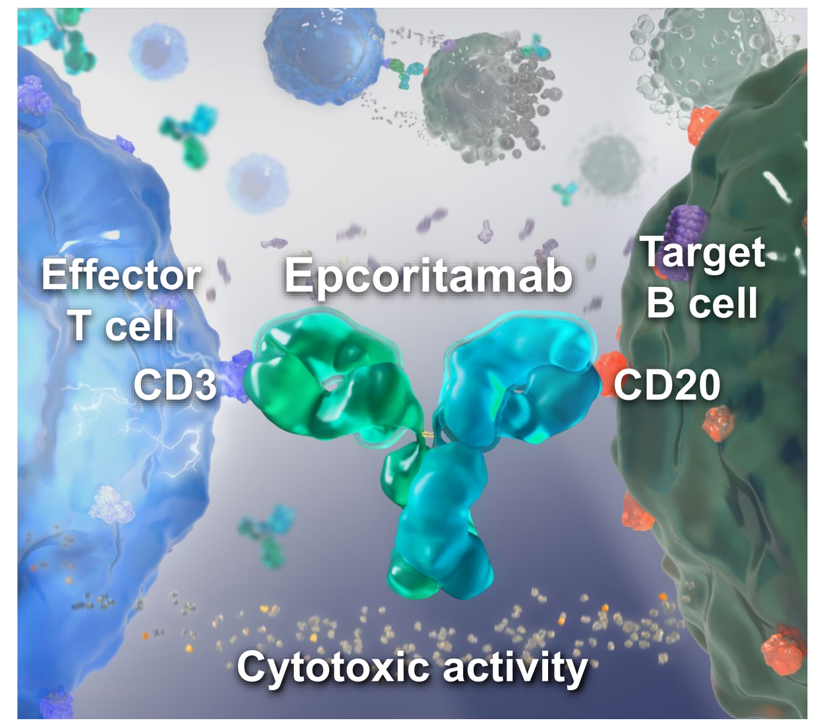
BACKGROUND

- Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have poor outcomes[1,2]
- Epcoritamab SC is a CD3xCD20 bispecific antibody developed using the DuoBody® platform[3,4]
- Epcoritamab demonstrated deep and durable responses and a manageable safety profile as monotherapy in patients with R/R B-cell lymphoma in the EPCORE NHL-1 trial[5] and in different lines of therapy and combinations[6,7]
- EPCORE NHL-1 (large B-cell lymphoma cohort)[5]:
  - Overall response rate (ORR): 63%; complete response: 40%
  - Median overall survival: 18.5 mo
  - Median duration of complete response (CR): 20.8 mo
- Epcoritamab is approved in the US,[7] Europe,[8] Japan,[9] and other regions; in the US, epcoritamab is approved 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[7]
- Lenalidomide activates and enhances T-cell and natural killer cell proliferation, which may complement the T-cell–mediated cytotoxicity of epcoritamab[9]
- Here we present the first results of epcoritamab plus lenalidomide in patients with R/R DLBCL from arm 1 of EPCORE NHL-5

Epcoritamab mechanism of action



STUDY DESIGN: EPCORE NHL-5 PHASE 1b/2 TRIAL (NCT05283720)

Key inclusion criteria: arm 1

- Adults ≥18 y
- Histologically confirmed CD20+ DLBCL[a]
  - DLBCL, NOS
  - High-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* translocations
  - FL grade 3B
- R/R disease[b] with ≥1 prior anti-CD20 mAb–containing systemic therapy
- ASCT ineligible or failed prior ASCT
- Prior CAR T allowed, but prior CD3/CD20 bispecific antibodies not allowed
- ECOG PS 0–2
- Measurable disease

Data cutoff: Oct 6, 2023
Median follow-up: 8.2 mo

Dose escalation and dose expansion

- **Arm 1** Epcoritamab + lenalidomide (12 x 28-day cycles) R/R DLBCL
- Arm 2 Epcoritamab + ibrutinib + lenalidomide R/R DLBCL
- Arm 3 Epcoritamab + polatuzumab + R-CHP 1L DLBCL
- Arms 4–5 Epcoritamab + CC-99282 (CELMoD) R/R DLBCL, R/R FL
- Arms 6–7 Epcoritamab + ibrutinib ± venetoclax R/R MCL, 1L MCL

Epcoritamab dosing schedule

Step-up dosing (SUD)
- Cycle 1, day 1: SUD1 (0.16 mg)
- Cycle 1, day 8: SUD2 (0.8 mg)
- Cycle 1, days 15, 22: full dose (48 mg)
- Cycles 2–3, days 1, 8, 15, 22: full dose (48 mg)
- Cycles 4–12, day 1: full dose (48 mg)

Lenalidomide dosing schedule

Cycles 1–12: 25 mg once daily on days 1–21

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[c]

Objectives

Dose escalation: safety, tolerability, and identify expansion dose (RP2D)
Dose expansion: safety, tolerability, and antitumor activity

[a]Per WHO 2016 classification.
[b]Relapsed disease is defined as disease that previously responded to therapy but progressed ≥6 mo after completion of therapy. Refractory disease is defined as disease that either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed within 6 mo after completion of therapy (including maintenance therapy).
[c]Additional information can be found in Vose JM, et al. *Blood*. 2023;142(Supplement 1):1729.

RESULTS

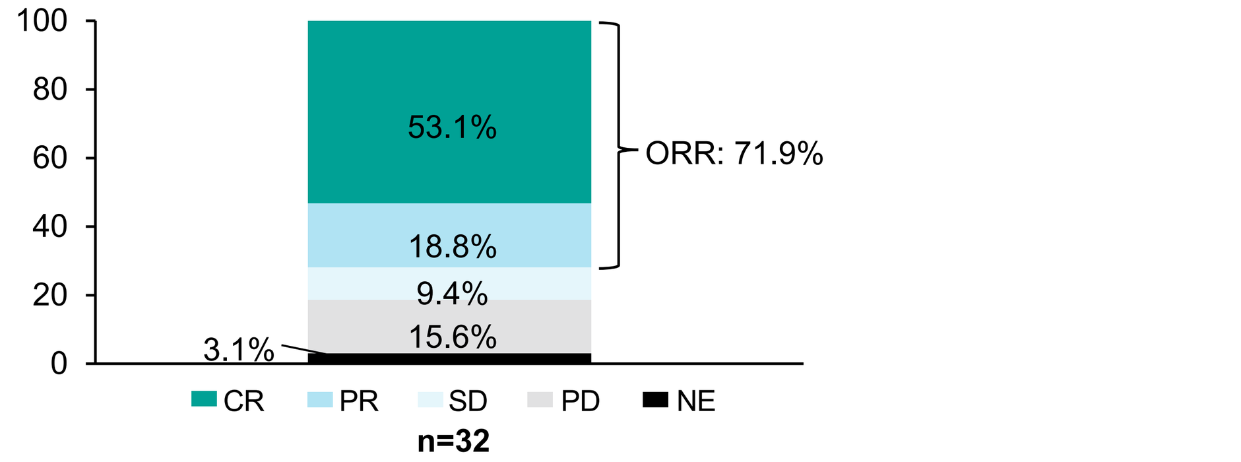
Baseline Characteristics

- As of October 6, 2023, 35 patients were enrolled

Demographics	Total N=35
Age, median (range), y	72 (41–85)
≥75 y, n (%)	13 (37)
Male, n (%)	21 (60)
Ann Arbor stage, n (%)	
I–II	11 (31)
III	7 (20)
IV	17 (49)
Subtype, n (%)	
DLBCL	31 (89)
Follicular lymphoma grade 3B	3 (9)
Double-hit lymphoma	0
Triple-hit lymphoma	1 (3)
ECOG performance status, n (%)	
0	24 (69)
1	10 (29)
2	1 (3)
R-IPI, n (%)	
0	2 (6)
1–2	10 (29)
3–5	18 (51)
Unknown	2 (6)
Extra-nodal disease at screening, n (%)	22 (63)
Treatment history and prior system therapies	**Total N=35**
Number of prior lines of anticancer therapy, median (range)	2 (1–4)
Prior lines of therapy, n (%)	
1	17 (49)
2	11 (31)
3	5 (14)
≥4	2 (6)
Time from last prior anticancer therapy to first epcoritamab dose, median (range), mo	5.5 (0.7–150.6)
Prior systemic therapies, n (%)	
Prior CAR T therapy	8 (23)
Prior stem cell transplant	2 (6)
Refractory disease, n (%)	
Primary refractory	15 (43)
Refractory to ≥2 consecutive lines of anticancer therapy	8 (23)
Treatment exposure and disposition	**Total N=35**
Study follow-up, median (range), mo	8.2 (1.2–12.7)
Epcoritamab exposure	
Duration, median (range), mo	3.9 (0.03–11.4)
Number of cycles, median (range)	5 (1–2)
Ongoing epcoritamab treatment, n (%)	17 (49)
Completed epcoritamab treatment, n (%)	1 (3)
Discontinued epcoritamab treatment, n (%)	17 (49)
Progressive disease	10 (29)
Patient withdrawal	3 (9)
No longer achieving clinical benefit	2 (6)
AE	2 (6)
Lenalidomide exposure	
Duration, median (range), mo	4.2 (0.13–11.4)
Number of cycles, median (range)	5 (1–12)
No lenalidomide dose reduction due to AEs, n (%)	24 (69)
Discontinued lenalidomide only due to AE,[a] n (%)	2 (6)

[a]Two additional patients discontinued both epcoritamab and lenalidomide due to AEs.

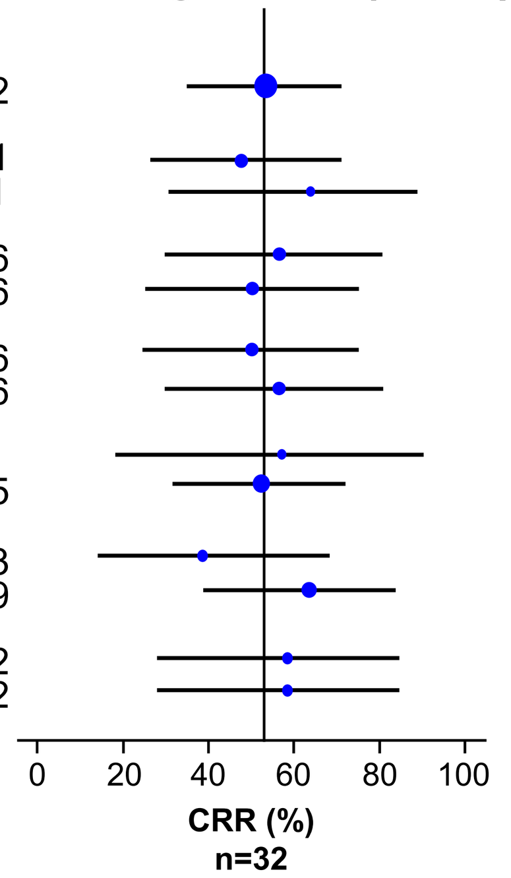
Frequent and Deep Responses Observed[a] (n=32)



[a]Based on response-evaluable population, defined as 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.

Complete Responses in Patient Subgroups (n=32)

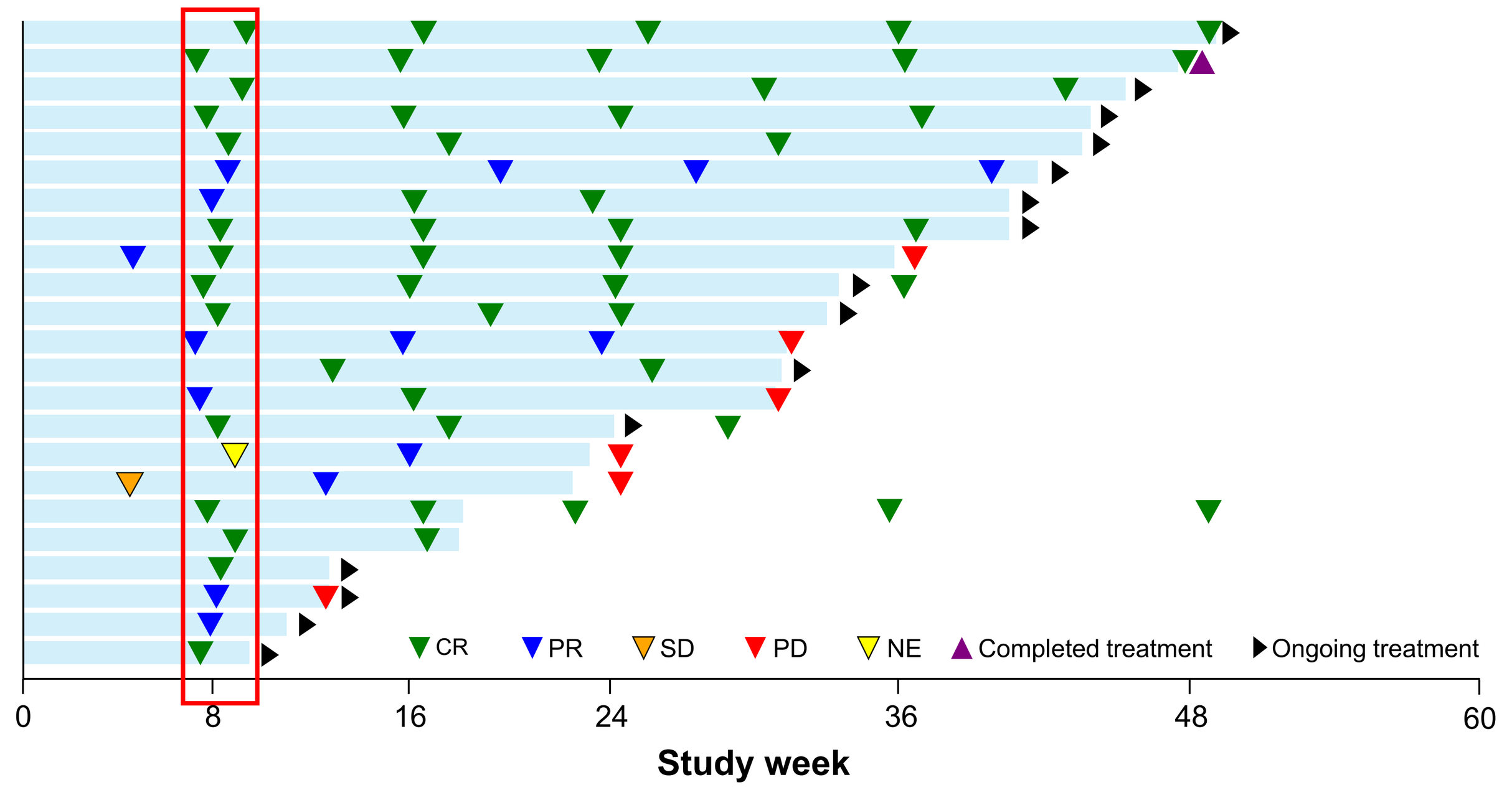
Subgroup	N	CRR, % (95% CI)
All patients	32	53.1 (34.7, 70.9)
Age		
<75 y	21	47.6 (25.7, 70.2)
≥75 y	11	63.6 (30.8, 89.1)
Prior lines of therapy		
1	16	56.3 (29.9, 80.2)
≥2	16	50.0 (24.7, 75.3)
Time from end of last therapy to 1st dose		
<6 mo	16	50.0 (24.7, 75.3)
≥6 mo	16	56.3 (29.9, 80.2)
Prior CAR T therapy		
Yes	7	57.1 (18.4, 90.1)
No	25	52.0 (31.3, 72.2)
Primary refractory status		
Yes	13	38.5 (13.9, 68.4)
No	19	63.2 (38.4, 83.7)
Molecular classification		
GCB	12	58.3 (27.7, 84.8)
ABC/non-GCB	12	58.3 (27.7, 84.8)



- Early and durable investigator-assessed responses
  - Median time to response was 1.8 mo (range: 1.0–3.6)
  - Median time to complete response was 1.9 mo (range: 1.6–3.6)

Investigator-Assessed Responses in Patients With Responses[a,b] (n=32)

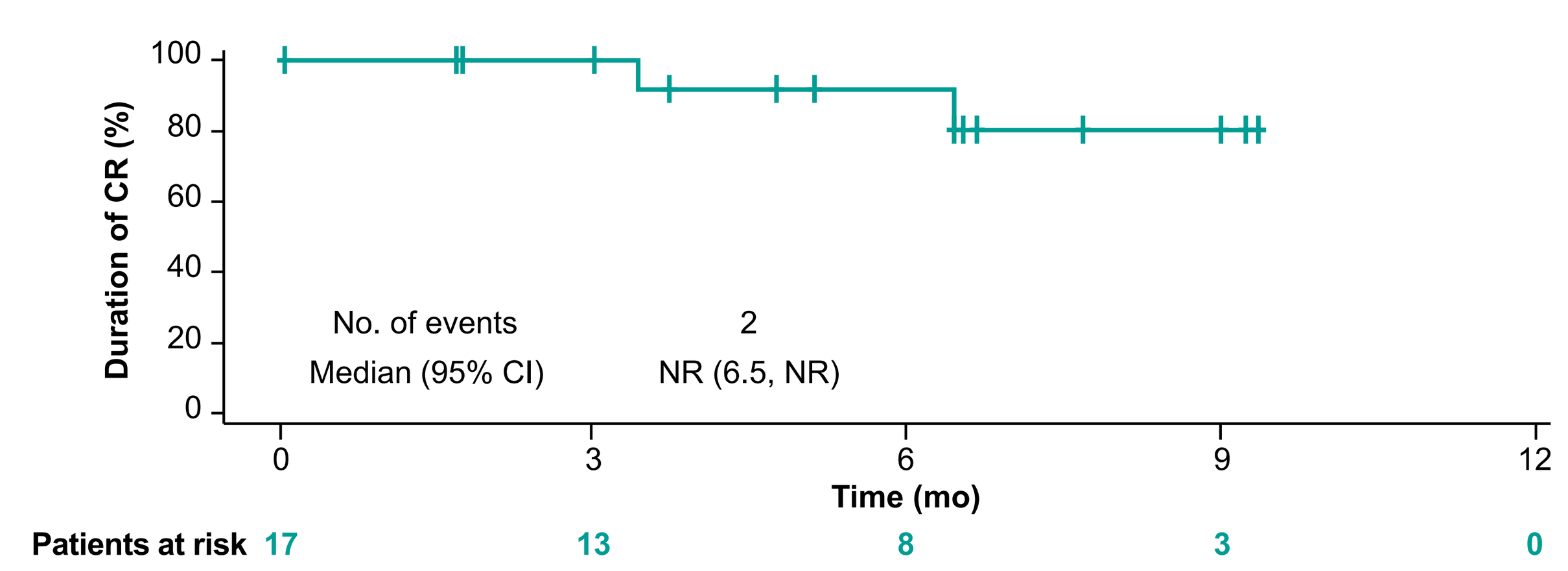
First tumor response assessment at week 8, n=23



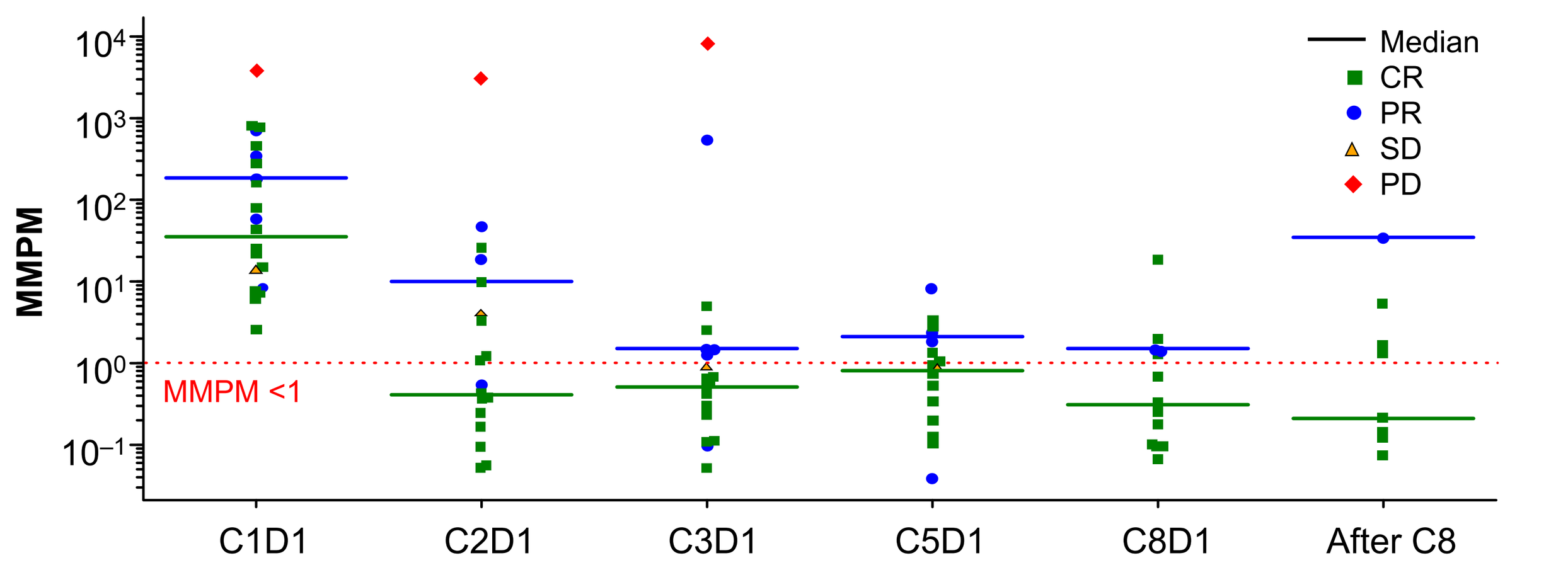
[a]Based on investigator assessment per Lugano criteria.
[b]Radiographic response assessments occurred Q8W for 24 weeks, Q12W through week 48, then Q24W, and as clinically indicated, until disease progression.

Duration of Complete Response

- Median duration of complete response was not reached



Rapid and Sustained Decline in ctDNA



High MRD Negativity Rates

- Most patients achieved MRD-negative CR after 2 cycles of treatment

Best overall response	MRD negative at C3D1, n (%)	Total
Complete response	10 (83)	12
Partial response	1 (20)	5
Stable disease	1 (100)	1
Progressive disease	0	1
Not evaluable	0	1

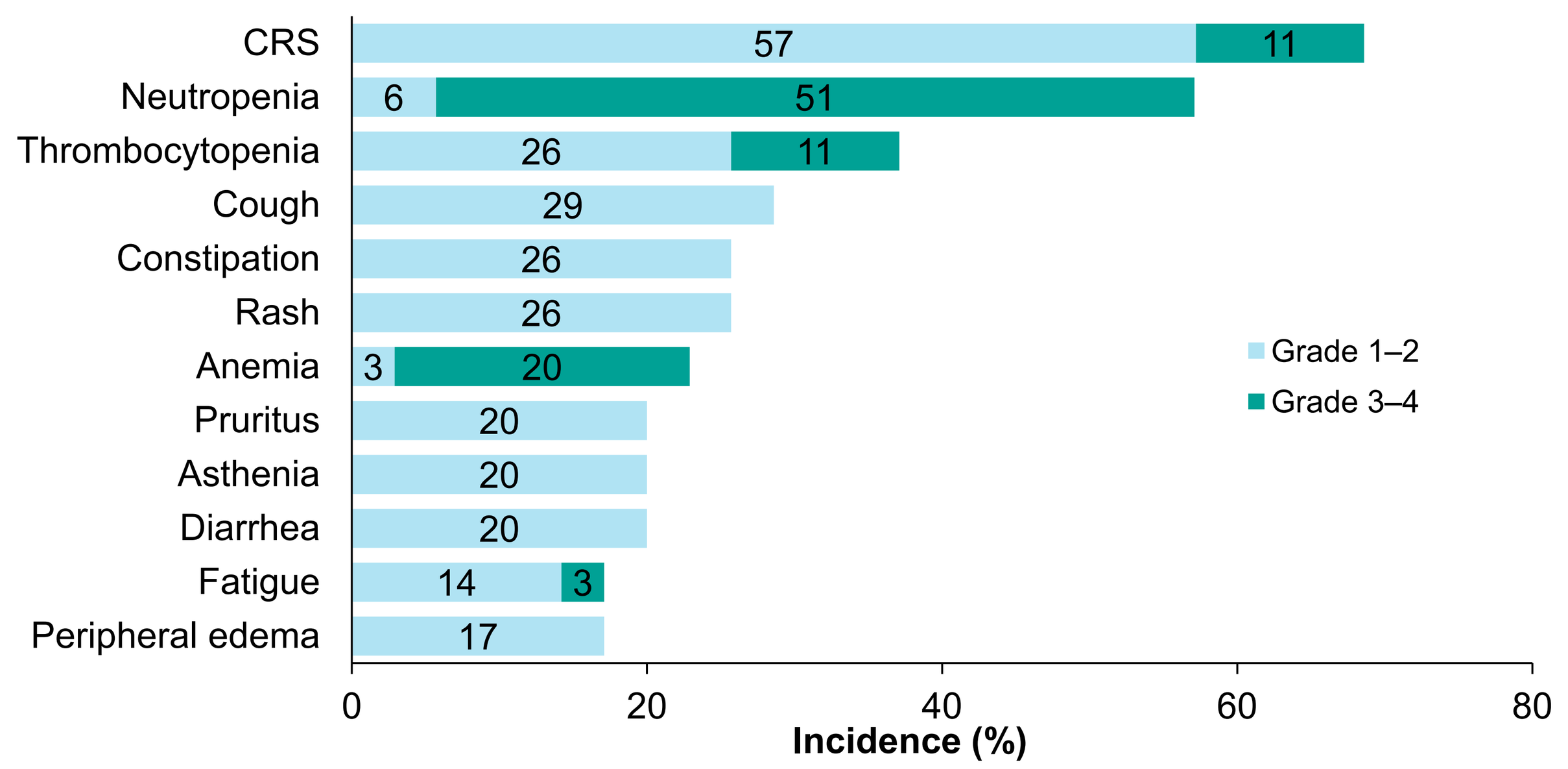
Safety Was Consistent With Established Profiles

- One patient experienced ICANS (grade 3), which resolved after 2 days
- One patient experienced CTLS (grade 1)
- The most common grade ≥3 TEAE was neutropenia (51%); no neutropenia events led to epcoritamab discontinuation

n (%)	Total N=35
Any-grade TEAE	35 (100)
Related to epcoritamab	31 (89)
Grade 3–4 TEAE	30 (86)
Related to epcoritamab	23 (66)
Serious AE	26 (74)
Related to epcoritamab	23 (66)
Epcoritamab delay or interruption due to TEAE	28 (80)
Discontinued epcoritamab due to TEAE	2 (6)
Related to epcoritamab	1 (3)
Grade 5 TEAE[a]	3 (9)
Related to epcoritamab	0

[a]All observed grade 5 TEAEs were due to disease progression.

Patients With TEAEs (≥15%)

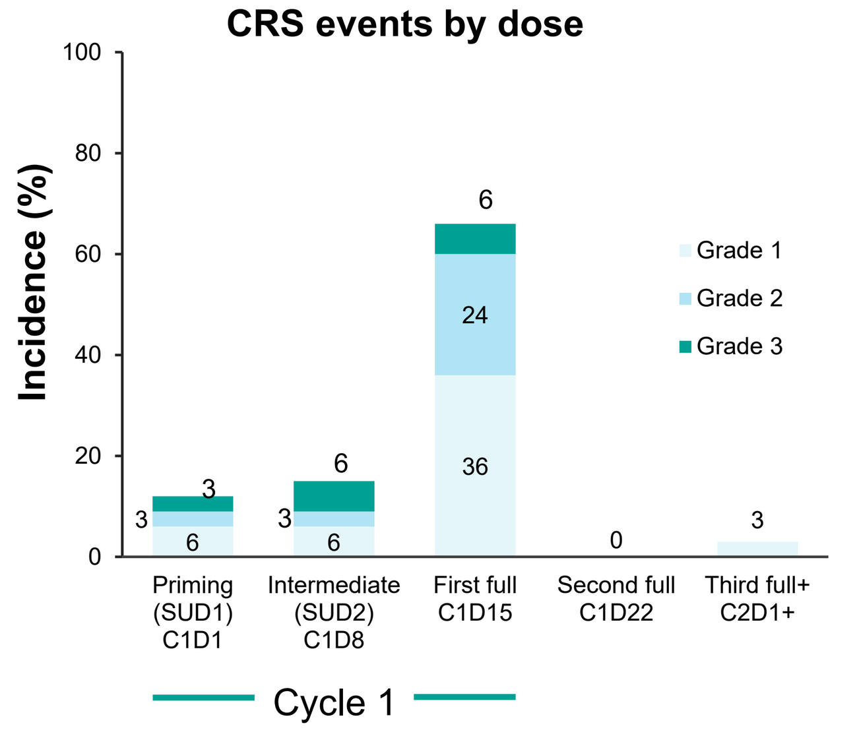


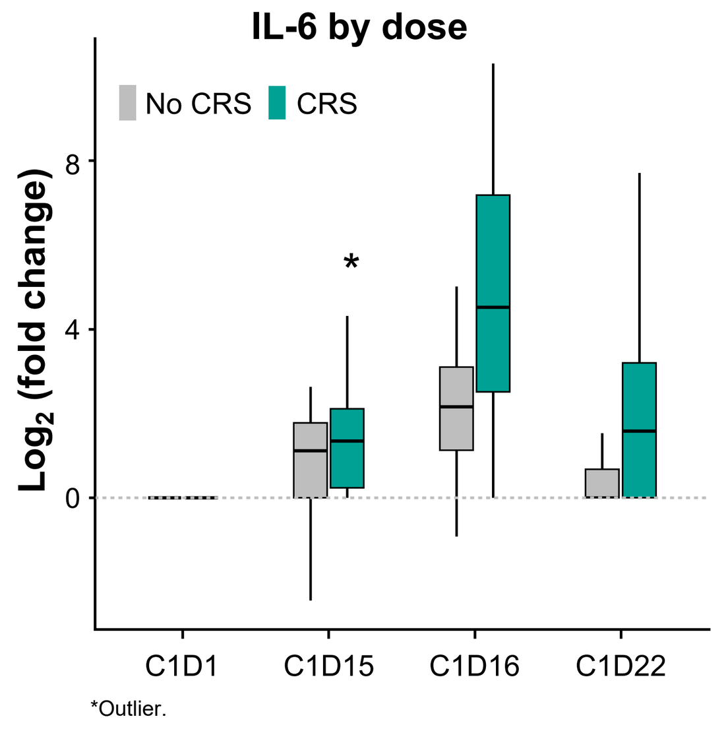
CRS Was Primarily Low Grade and All Resolved

	Total N=35
CRS, n (%)[a]	24 (69)
Grade 1	12 (34)
Grade 2	8 (23)
Grade 3	4 (11)
Time to onset of first CRS event, median (range), d	16 (2–45)
CRS resolution, n (%)[b]	24 (100)
Time to resolution, median (range), d[c]	2 (16)
CRS interventions, n (%)	
Treated with tocilizumab	13 (54)
Treated with corticosteroid	10 (42)
Treated with tocilizumab + corticosteroid	7 (29)
Leading to epcoritamab discontinuation, n (%)	0

[a]Maximum CRS grade is presented for patients with >1 CRS event. [b]Percentages calculated based on patients with ≥1 CRS event. [c]Based on longest recorded CRS duration for patients with >1 CRS event.

- 5 of 9 patients (56%) receiving prophylactic dexamethasone had CRS
- Timing of CRS onset was predictable; most events occurred after first full dose and were primarily confined to C1
- IL-6 peak occurred at C1D16
- Similar results were seen for IFN-γ and IL-2





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