Single-Agent Epcoritamab Leads to Deep, Durable Responses in R/R FL: Pivotal Data From EPCORE NHL-1

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OBJECTIVE

Pivotal trial reporting on the efficacy and safety of epcoritamab monotherapy in patients with R/R FL

CONCLUSIONS

In this pivotal data from the EPCORE NHL-1 FL expansion cohort, epcoritamab SC led to deep and durable responses in a challenging-to-treat R/R FL population

ORR 82%, CR rate 63%, 67% MRD negativity

High ORRs and CR rates were observed regardless of high-risk features

Depth of response, including MRD negativity, was correlated with favorable long-term outcomes

Cycle 1 optimization with 3-step SUD substantially reduced risk and severity of CRS (no grade ≥3 events) and ICANS (no events)

Safety profile was predictable and epcoritamab was generally well tolerated

Results add to the growing body of evidence of the single-agent activity of epcoritamab across B-cell non-Hodgkin lymphoma histologies

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Disclosures

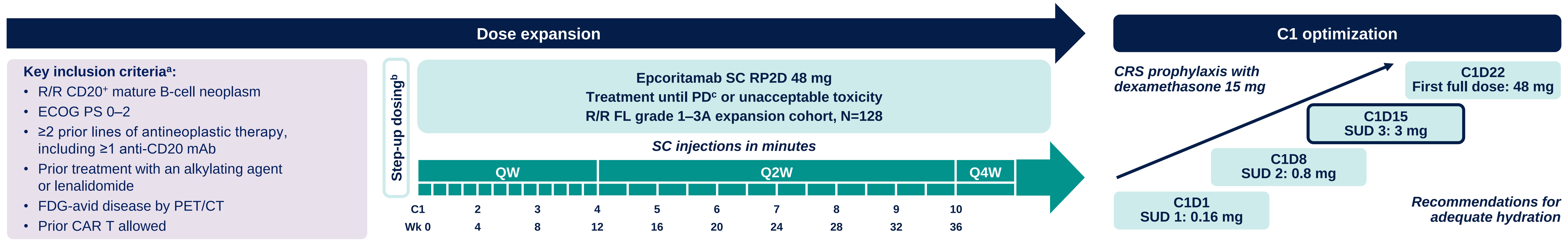
Linton: Genmab: Member of the Epcoritamab Global Council; AbbVie, BeiGene, BMS, Celgene, Genmab, Kite/Gilead, Roche: Consulting or Advisory Role; AbbVie, Celgene: Speakers Bureau; AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, BMS, Celgene, CellCentric, Genmab, Janssen, Kite/Gilead, MorphoSys, MSD, Nurix, Regeneron, Roche, Step Pharma, Viracta: Research Funding (Paid to Institution); Celgene: Travel Expenses. **Jurczak:** AbbVie, Roche: Research Funding, Consultancy. **Lugtenburg:** Takeda, Servier: Research Grants; Celgene, Roche, Takeda, Genmab, AbbVie, Incyte, Regeneron: Advisory Honoraria; Y-mAbs Therapeutics: Consultancy Honoraria. **Gyan:** AbbVie, Amgen, Gilead, Roche, Sanofi: Congress/Travel Fees, Hospitality; MSD, Novartis, Sandoz, Sanofi: Research Funding; Astellas, Pharmacyclics, Roche: Coordinating Investigator for Industry-Sponsored Studies; Alexion, BMS, EUSA Pharma, Gilead, Jazz Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi: Honoraria. **Sureda:** Takeda, BMS/Celgene, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite, Mundipharma: Consultancy; Takeda, BMS/Celgene, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite: Honoraria; Takeda, BMS/Celgene, Novartis, Janssen, Amgen, Bluebird, Sanofi, Kite: Membership on an Entity's Board of Directors or Advisory Committees; Takeda, BMS/Celgene, Roche: Travel Expenses; Takeda: Research Funding; Takeda, BMS/Celgene, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite: Speakers Bureau. **Christensen:** There are no relationships to disclose. **Hess:** ADC Therapeutics, BMS: Membership on an Entity's Board of Directors or Advisory Committees. **Tilly:** ADC Therapeutics, BMS, Roche: Membership on an Entity's Board of Directors or Advisory Committees; Roche: Honoraria; Roche: Research Funding. **Cordoba:** AbbVie, Janssen, AstraZeneca, Kite, BMS, Genmab, Roche, Takeda, Kyowa Kirin, BeiGene, Lilly: Consultancy; AbbVie, Janssen, AstraZeneca, Kite, BMS, Roche, Takeda: Speakers Bureau; Pfizer: Research Funding. **Lewis:** Janssen, Lilly, Roche, BeiGene, Kite: Advisory Boards, Consultancy. **Okada:** There are no relationships to disclose. **Hutchings:** AbbVie, Celgene, Genmab, Janssen, Roche, Takeda: Scientific Advisory Boards; Celgene, Genentech, Genmab, Incyte, Janssen, Novartis, Roche, Takeda: Research Support (Paid to Institution). **Clausen:** AbbVie, Janssen, Gilead, AstraZeneca, Genmab, Incyte: Consultancy; AbbVie, Janssen, Gilead, Genmab: Advisory; AbbVie, Janssen, AstraZeneca, Genmab, Roche: Travel Expenses. **Favaro:** Genmab: Current Employment. **Thieblemont:** BMS/Celgene, Hospira, Roche: Research Funding; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Kite, Novartis, Roche: Consultancy; AbbVie, Amgen, Bayer, Cellectis, Gilead Sciences, Incyte, Janssen, Kite, Novartis, Takeda: Honoraria; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Incyte, Janssen, Kite, Novartis, Roche, Takeda: Membership on an Entity's Board of Directors or Advisory Committees; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Kite, Novartis, Roche: Travel Expenses.

BACKGROUND

- Despite recent advances in therapy, patients with relapsed/refractory follicular lymphoma (R/R FL) are still underserved by current treatment options; there remains a need for highly efficacious, easy-to-administer therapies that induce durable remissions, particularly in later lines of therapy[1-3]
- Particularly poor outcomes are observed in patients with POD24, double-refractory disease, and disease refractory to the last prior therapy[4-7]
- Epcoritamab is the only approved subcutaneously administered (SC) CD3xCD20 bispecific antibody
  – Approved for the treatment of adults with different types of R/R large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy in various geographies, including the US, Europe, and Japan[a-c,8-12]
- We report the efficacy and safety of epcoritamab monotherapy in patients with R/R FL from the pivotal EPCORE NHL-1 trial

[a]Approved in the US for the treatment of adults with R/R diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBCL) after ≥2 lines of systemic therapy. [b]Approved in Europe and the UK for the treatment of adults with R/R DLBCL after ≥2 lines of systemic therapy. [c]Approved in Japan for the treatment of adults with the following R/R LBCL: DLBCL, HGBCL, primary mediastinal large B-cell lymphoma, and FL grade 3B after ≥2 lines of systemic therapy.

TRIAL DESIGN: PIVOTAL EPCORE™ NHL-1 STUDY


Dose expansion
Key inclusion criteria[a]:
R/R CD20+ mature B-cell neoplasm
ECOG PS 0–2
≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
Prior treatment with an alkylating agent or lenalidomide
FDG-avid disease by PET/CT
Prior CAR T allowed
Step-up dosing[b]
Epcoritamab SC RP2D 48 mg
Treatment until PD[c] or unacceptable toxicity
R/R FL grade 1–3A expansion cohort, N=128
SC injections in minutes
QW
Q2W
Q4W
C1 2 3 4 5 6 7 8 9 10
Wk 0 4 8 12 16 20 24 28 32 36
C1 optimization
CRS prophylaxis with dexamethasone 15 mg
C1D1 SUD 1: 0.16 mg
C1D8 SUD 2: 0.8 mg
C1D15 SUD 3: 3 mg
C1D22 First full dose: 48 mg
Recommendations for adequate hydration

Data cutoff: April 21, 2023
Median follow-up: 17.4 mo

- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** CR rate, MRD[d], DOR, TTR, PFS, OS, and safety/tolerability

- Hospitalization not mandated
- **Primary objective:** Assess impact on incidence and severity of CRS

Phase 1/2 trial. [a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [d]MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

RESULTS

Baseline Characteristics and Prior Treatments

Demographics	N=128
Median age, y (range)	65 (39–84)
Male, n (%)	79 (62)
Ann Arbor stage, n (%)[a]	
III	32 (25)
IV	77 (60)
FLIPI, n (%)[b]	
2	31 (24)
3–5	78 (61)
Beta-2 microglobulin, n (%)[c]	
High	79 (62)

[a]Ann Arbor stage was I–II in 19 patients. [b]FLIPI was 0–1 in 17 patients, unknown for 1 patient, and not applicable for 1 patient. FLIPI was prior to first dose on study. [c]Beta-2 microglobulin was normal in 45 patients and missing for 4 patients.

Treatment History	N=128
Median time from diagnosis to first dose, y (range)	5.8 (0.6–35)
Median time from end of last line of therapy to first dose, mo (range)	5.2 (1–105)
Median time from end of last anti-CD20 therapy to first dose, mo (range)	10.3 (1–159)
Median number of prior lines of therapy (range)	3 (2–9)
≥3 prior lines, n (%)	81 (63)
≥4 prior lines, n (%)	40 (31)
POD24,[a] n (%)	54 (42)
Double refractory,[b,c] n (%)	90 (70)
Primary refractory,[b] n (%)	69 (54)
Refractory[b] to last prior systemic therapy, n (%)	88 (69)

[a]Progression within 2 y of initiating first-line chemoimmunotherapy. [b]Refractory: No response or relapse within 6 mo after therapy. [c]Double refractory: Refractory to both anti-CD20 and an alkylating agent.

- All patients had ≥2 prior lines of therapy, including an anti-CD20 mAb and an alkylating agent
- Other prior systemic treatments included anthracyclines (77%), bendamustine (63%), nucleotides (48%), topoisomerase inhibitors (36%), IMiDs (31%), PI3K inhibitors (23%), and CAR T-cell therapy (5%)

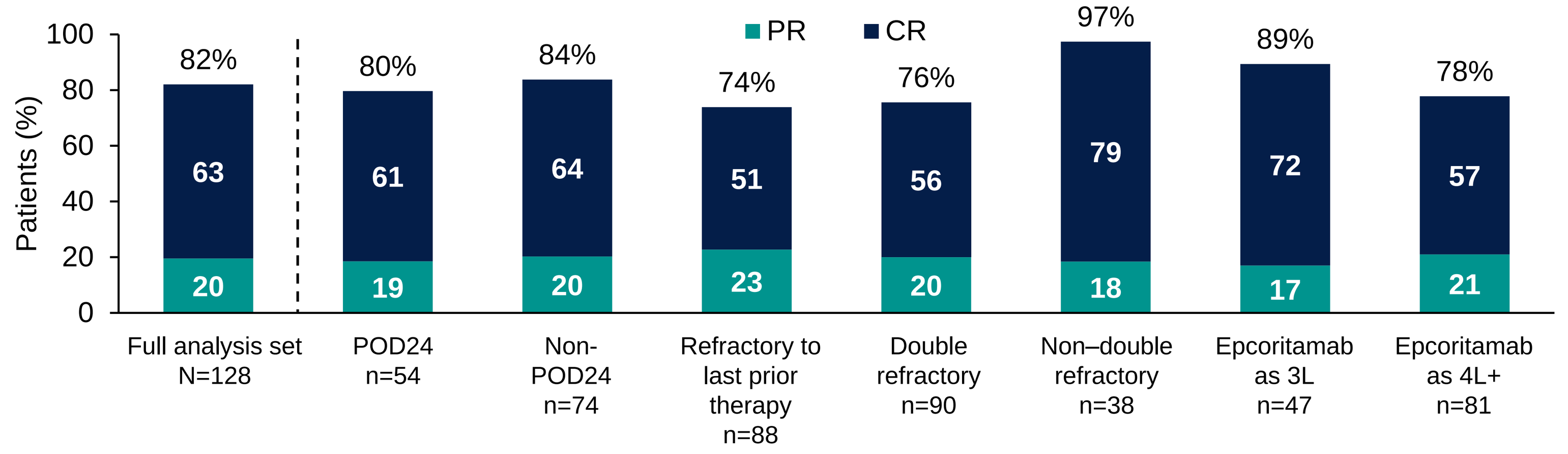
Treatment Exposure and Follow-Up

	N=128
Median follow-up, mo (range)	17.4 (0.2+ to 30.1)
Epcoritamab treatment exposure	
Median number of treatment cycles initiated (range)	8 (1–33)
Median duration of treatment, mo (range)	8.3 (0.03–30)
Ongoing treatment, n (%)	47 (37)
Discontinued treatment, n (%)	81 (63)
PD	44 (34)
AE	24 (19)
COVID-19[a]	12 (9)
Decision to proceed to transplant	4 (3)
Patient withdrawal	3 (2)
Other	6 (5)

[a]Includes COVID-19 pneumonia.

Efficacy Results

High ORRs and CR Rates Regardless of Subgroup


PR
CR
Patients (%)
82% 80% 84% 74% 76% 97% 89% 78%
63 61 64 51 56 79 72 57
20 19 20 23 20 18 17 21
Full analysis set N=128
POD24 n=54
Non-POD24 n=74
Refractory to last prior therapy n=88
Double refractory n=90
Non–double refractory n=38
Epcoritamab as 3L n=47
Epcoritamab as 4L+ n=81

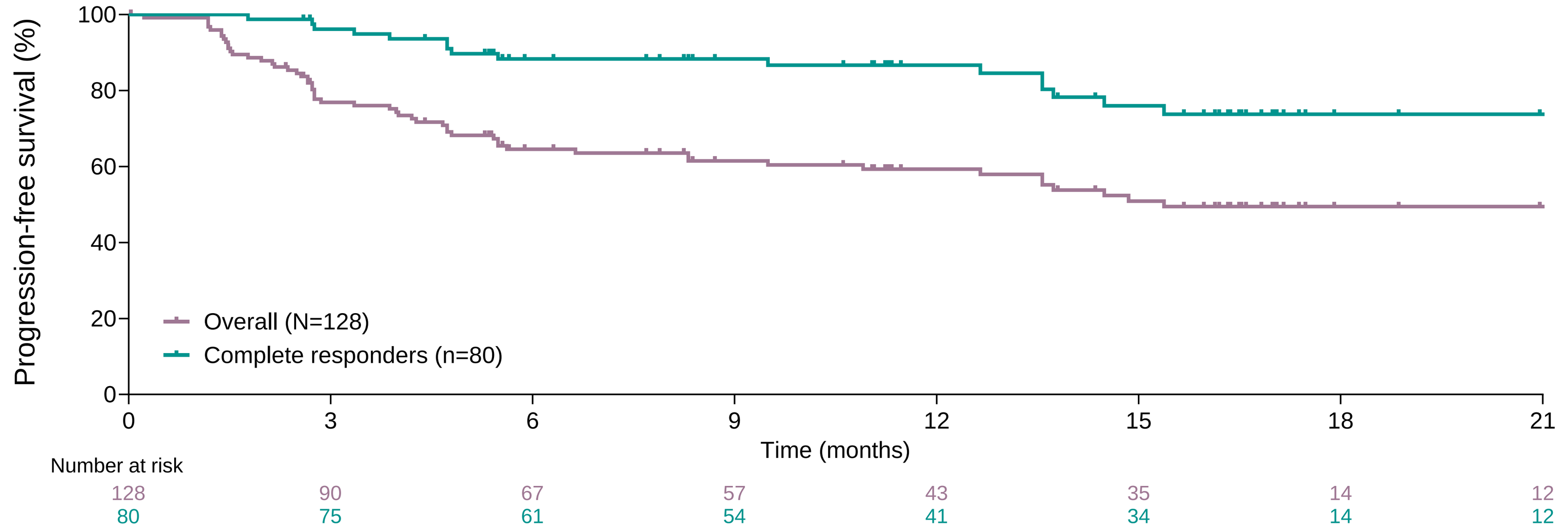
Responses Were Early, Deep, and Durable

Efficacy Parameters	N=128
Median time to response, mo (range)	1.4 (1.0–3.0)
Median time to complete response, mo (range)	1.5 (1.2–11.1)
Median duration of response, mo (95% CI)[a]	NR (13.7–NR)
Median duration of complete response, mo (95% CI)[a]	NR (21.4–NR)
MRD negativity, n (%)[b]	61 (67)
Median progression-free survival, mo (95% CI)[a]	
Overall (N=128)	15.4 (10.9–NR)
Complete responders (n=80)	NR (22.8–NR)
MRD-negative patients (n=61)	NR (22.8–NR)
Median overall survival, mo (95% CI)[a]	NR (NR–NR)
Median time to next therapy, mo (range)[a]	NR (0.2+ to 30.0+)

MRD, minimal residual disease; NR, not reached. [a]Based on Kaplan–Meier estimate. [b]Based on MRD-evaluable set (n=91) per clonoSEQ® PBMC assay with 10^{-6} cutoff.

- High MRD-negativity rate observed
- MRD negativity was associated with improved progression-free and overall survival
- 71 patients remained in complete response as of data cutoff

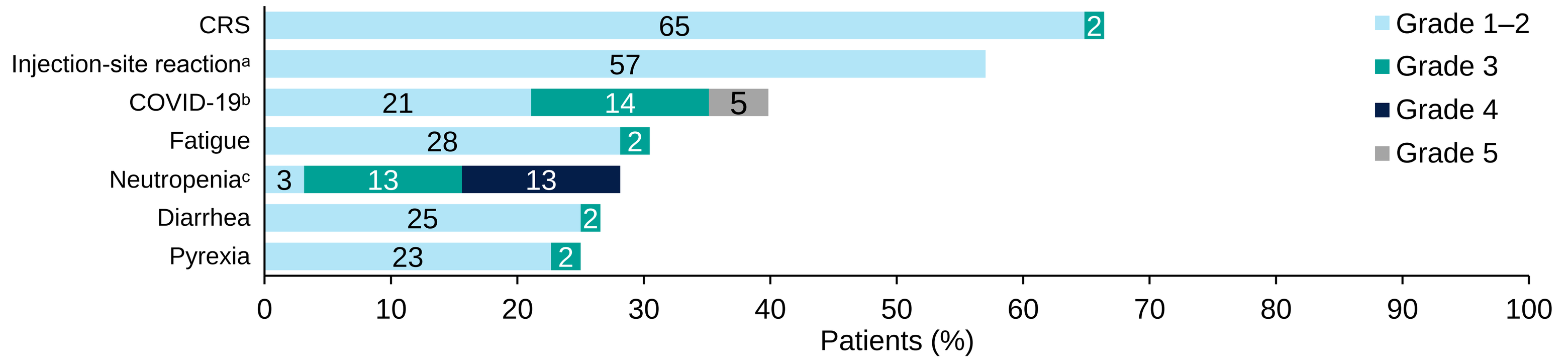
Complete Response Associated With Favorable Long-Term Outcomes



Progression-free survival assessed by IRC.

Safety Profile

Common (>20%) TEAEs Mostly Low Grade



[a]Combined term includes injection-site reaction, erythema, inflammation, nodule, pain, pruritus, rash, and swelling. [b]Combined term includes COVID-19 and COVID-19 pneumonia. [c]Combined term includes neutropenia and neutrophil count decreased.

- Safety findings were generally consistent with previous reports of epcoritamab
- Grade ≥3 TEAEs occurred in 88 patients (69%); 48 patients (38%) had grade ≥3 TEAEs reported as related to epcoritamab
  – Febrile neutropenia was reported in 4 patients (3%; all grade 3)
- The trial, conducted during the global COVID-19 pandemic, was impacted by prevailing COVID-19 trends, including the highly infectious Omicron variant
  – The outcomes of COVID-19 cases were consistent with expected outcomes based on well-known risk factors for severe COVID-19 (eg, age and other comorbidities)
- TEAEs led to treatment discontinuation in 24 patients (19%); half of these TEAEs were due to COVID-19
  – 5 patients (4%) discontinued treatment due to TEAEs reported as related to epcoritamab: 1 patient each with COVID-19, pneumonitis, enteritis, and diarrhea; 1 patient with both fatigue and malaise
- 13 patients (10%) had fatal TEAEs, and 6 (5%) were due to COVID-19
- No clinical tumor lysis syndrome was reported

C1 Optimization With 3 SUD Substantially Reduced Risk and Severity of CRS

	Pivotal Cohort N=128	C1 Optimization Cohort[a] N=50
CRS, n (%)[b]	85 (66)	24 (48)
Grade 1	51 (40)	20 (40)
Grade 2	32 (25)	4 (8)
Grade 3	2 (2)	0
Treated with tocilizumab, n (%)	31 (24)	6 (12)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**24/24 (100)**
Median time to resolution, d (range)	2 (1–54)	3 (1–14)

[a]Data cutoff: September 21, 2023. Median follow-up: 3.8 mo (range, 1.9–8.7). [b]Graded by Lee et al 2019 criteria.[13]

- Baseline characteristics were consistent between cohorts
- In both cohorts, CRS was mostly confined to C1
- Similar response rates were observed in the C1 optimization cohort
- There were no cases of ICANS in the C1 optimization cohort; 8 cases were observed in the pivotal cohort (all grade 1–2 and resolved; none led to discontinuation)

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