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Epcoritamab Monotherapy Demonstrates Deep and Durable Responses at 3-Year Follow-Up in Patients With Relapsed/Refractory Follicular Lymphoma

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OBJECTIVES

- To report results from the 3-year follow-up of the pooled NHL-1 and NHL-3 EXP cohorts and present updated findings from the NHL-1 C1 OPT cohort
- To present outcomes in patients who discontinued early while in CR

CONCLUSIONS

- With over 3 years of follow-up, epcoritamab monotherapy showed deep, durable responses in a large, diverse population including heavily pretreated patients with 3L+ R/R FL
  - Median DOCR, OS, and PFS in patients with CR were NR
  - With data still maturing, median TTNT was 45 months with a median epcoritamab exposure of 9.7 months
  - MRD-negativity rates were high (70%) and durable
  - CRs were maintained in patients who discontinued epcoritamab treatment for reasons other than PD or death, demonstrating response durability following treatment cessation
- Long-term follow-up confirmed a manageable and predictable safety profile, with reduced rates and severity of CRS and ICANS in the C1 OPT cohort without compromised efficacy

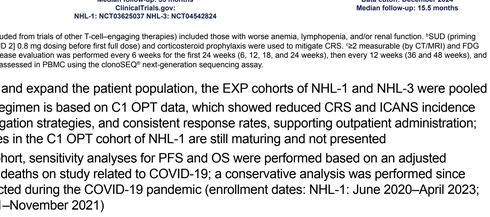
BACKGROUND

- Targeted agents and immunotherapies offer alternatives to CIT for patients with FL, especially for patients who are ineligible for or R/R to treatment; however, many treatments have shown suboptimal CR rates[1–3]
- There is a need to further improve long-term outcomes and expand treatment choices for broad patient populations[4–6]
- Epcoritamab, a CD3×CD20 T-cell–engaging bsAb, is the only bsAb approved as a monotherapy in 2 indications: R/R FL and R/R DLBCL after ≥2 prior LOTs (3L+)
  - Approvals were based on the results from the EPCORE® NHL-1 (US/EU; NCT03625037) and NHL-3 (Japan; NCT04542824) trials[7–10]

EPCORE NHL-1 AND NHL-3 STUDY DESIGN

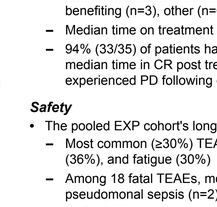
Key inclusion criteria[a]:

- R/R CD20+ FL grade 1–3A
- ECOG PS score 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T cell therapy allowed



Primary objective: ORR by IRC
Key secondary endpoints: MRD[d], DOR, TTR, PFS, OS, CR rate, and safety/tolerability

Data cutoff: December 2024 (NHL-1) and July 2024 (NHL-3)
Median follow-up: 35 months
ClinicalTrials.gov:
NHL-1: NCT03625037 NHL-3: NCT04542824



Primary objective:
Assess incidence and severity of CRS

Data cutoff: December 2024
Median follow-up: 15.5 months

[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]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 weeks for the first 24 weeks (6, 12, 18, and 24 weeks), then every 12 weeks (36 and 48 weeks), and every 6 months thereafter. [d]MRD was assessed in PBMC using the clonoSEQ® next-generation sequencing assay.

- To increase diversity and expand the patient population, the EXP cohorts of NHL-1 and NHL-3 were pooled
- The approved SUD regimen is based on C1 OPT data, which showed reduced CRS and ICANS incidence and severity with mitigation strategies, and consistent response rates, supporting outpatient administration; time-to-event analyses in the C1 OPT cohort of NHL-1 are still maturing and not presented
- In the pooled EXP cohort, sensitivity analyses for PFS and OS were performed based on an adjusted population excluding deaths on study related to COVID-19; a conservative analysis was performed since the study was conducted during the COVID-19 pandemic (enrollment dates: NHL-1: June 2020–April 2023; NHL-3: January 2021–November 2021)

RESULTS

Baseline Characteristics and Prior Treatments

Demographics	Pooled EXP (N=149)	C1 OPT (N=86)
Median age, years (range)	65 (39–84)	64 (33–90)
≥75 years, n (%)	19 (13)	10 (12)
Geography, n (%)		
Japan	21 (14)	0
North America	22 (15)	17 (20)
Europe	91 (61)	61 (71)
Rest of world	15 (10)	8 (9)
Ann Arbor stage, n (%)		
III/IV	126 (85)	79 (92)
FLIPI score, n (%)		
3–5	89 (60)	44 (51)

Treatment history	Pooled EXP (N=149)	C1 OPT (N=86)
Median prior LOTs, n (range)	3 (2–10)	2 (2–9)
≥3 prior LOTs, n (%)	94 (63)	41 (48)
≥4 prior LOTs, n (%)	51 (34)	17 (20)
POD24, n (%)[a]	79 (53)	42 (49)
Double refractory, n (%)[b,c]	102 (68)	54 (63)
Primary refractory, n (%)[b]	75 (50)	38 (44)
Refractory to ≥2 consecutive lines of prior anti-lymphoma therapy, n (%)	77 (52)	37 (43)

[a]Progression within 2 years of initiating any 1L therapy. [b]No response or relapse within 6 months after therapy. [c]Refractory to both an anti-CD20 mAb and an alkylating agent.
Data cutoff: December 2024. Population based on FDA-approved indication of epcoritamab (N=127) had a median age of 65 years, with 85% of patients having Ann Arbor stage III/IV disease, and 61% with a FLIPI score of 3–5. Additionally, 31% had received ≥4 prior LOTs, 52% experienced POD24, 70% were double refractory, and 55% were refractory to ≥2 consecutive lines of prior anti-lymphoma therapy.

- Median follow-up was 35 months in the pooled EXP (N=149) and 15.5 months in the C1 OPT (N=86) cohorts

Treatment Exposure and Disposition

	Pooled EXP (N=149)	C1 OPT (N=86)
Median follow-up, months (95% CI)	35.3 (33.5–36.9)	15.5 (14.1–16.6)
Epcoritamab treatment exposure		
Median treatment cycles initiated, n (range)	10.0 (1.0–53.0)	12.0 (1.0–23.0)
Median duration of treatment, months (range)	9.7 (0.03–48.6)	11.4 (0.3–22.1)
Ongoing treatment, n (%)	22 (15)	39 (45)
Discontinued treatment, n (%)	127 (85)	47 (55)
PD	54 (36)	31 (36)
AE	45 (30)	10 (12)
COVID-19	18 (12)	1 (1)
Other	28 (19)	6 (7)

Data cutoff: December 2024. Population based on FDA-approved indication of epcoritamab (N=127) had a median follow-up of 35.4 months, a median of 10.0 treatment cycles initiated, and a median treatment duration of 9.6 months. At the time of analysis, 15% of patients remained on treatment, while 85% had discontinued – most commonly due to PD (37%), AEs (30%), or other reasons (18%).

Acknowledgments

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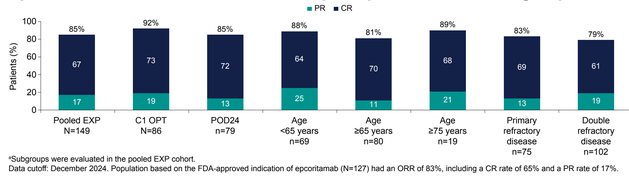
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Abbreviations

1L, first line; 3L+, third line or later; AE, adverse event; bsAb, bispecific antibody; C, cycle; C1 OPT, cycle 1 optimization; CAR, chimeric antigen receptor; CI, confidence interval; CIT, chemoimmunotherapy; COVID-19, Coronavirus disease 2019; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; D, day; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; EXP, expansion; FDA, Food and Drug Administration; FDG, fluorodeoxyglucose; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ICANS, immune effector cell-associated neurotoxicity syndrome; IgG, immunoglobulin G; IRC, independent review committee; LOT, line of treatment; mAb, monoclonal antibody; MRD, minimal residual disease; MRI, magnetic resonance imaging; NR, not reached; OPT, optimization; ORR, overall response rate; OS, overall survival; PBMC, peripheral blood mononuclear cells; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; POD24, progression of disease within 2 years; PR, partial response; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SUD, step-up dosing; TEAE, treatment-emergent adverse event; TTNT, time to next treatment; TTR, time to response; US, United States.

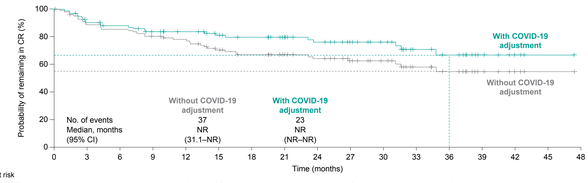
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Epcoritamab Treatment Resulted in Deep Responses Across Subgroups[a]



[a]Subgroups were evaluated in the pooled EXP cohort.
Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had an ORR of 83%, including a CR rate of 65% and a PR rate of 17%.

Median DOCR was NR in the Pooled EXP Cohort



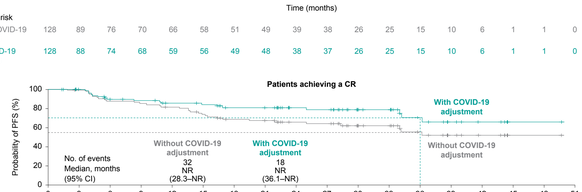
Number at risk

Without COVID-19 adjustment	100	85	82	76	72	62	56	50	45	36	31	20	16	7	3	1	0
With COVID-19 adjustment	100	84	80	72	66	60	56	50	44	36	31	20	16	7	3	1	0

Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had a median DOCR of NR (95% CI, 34.8–NR; 18 events) with COVID-19 adjustment, and NR (95% CI, 31.1–NR; 31 events) without COVID-19 adjustment. Median DOR in the pooled EXP cohort (N=149) was NR (95% CI, 31.6–NR; 46 events) with COVID-19 adjustment and 31.6 (95% CI, 14.0–NR; 59 events) without COVID-19 adjustment. Median DOR for the FDA-approved indication of epcoritamab (N=127) was NR (95% CI, 31.6–NR; 38 events) with COVID-19 adjustment and 31.6 (95% CI, 13.7–NR; 51 events) without COVID-19 adjustment.

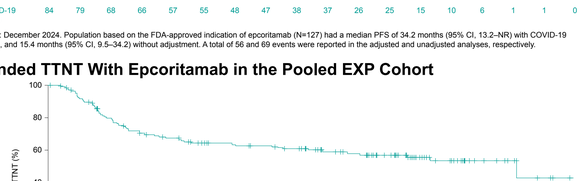
- In the pooled EXP cohort, median PFS was 15.4 months (95% CI, 9.5–34), however after adjustment for COVID-19 deaths it was 34.2 months (95% CI, 13.2–NR) in the EXP cohort and NR in patients with CR from the EXP cohort
- In the pooled EXP cohort, median OS was NR regardless of COVID adjustment; the estimated COVID-adjusted 30-month OS rate was 79% (95% CI, 71.5–85.4)

Sustained PFS With Epcoritamab in the Pooled EXP Cohort



Number at risk

Without COVID-19 adjustment	128	89	76	70	66	58	51	49	39	38	26	25	15	10	6	1	1	0
With COVID-19 adjustment	128	88	74	68	59	56	49	48	38	37	26	25	15	10	6	1	1	0

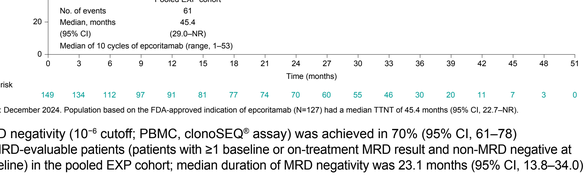


Number at risk

Without COVID-19 adjustment	84	80	70	68	64	57	50	48	39	38	26	25	15	10	6	1	1	0
With COVID-19 adjustment	84	79	68	66	57	55	48	47	38	37	26	25	15	10	6	1	1	0

Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had a median PFS of 34.2 months (95% CI, 13.2–NR) with COVID-19 adjustment, and 15.4 months (95% CI, 9.5–34.2) without adjustment. A total of 56 and 69 events were reported in the adjusted and unadjusted analyses, respectively.

Extended TTNT With Epcoritamab in the Pooled EXP Cohort



Number at risk

	149	134	112	97	91	81	77	74	70	60	55	46	30	20	11	7	3	0

Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had a median TTNT of 45.4 months (95% CI, 22.7–NR).

- MRD negativity (10^{-6} cutoff; PBMC, clonoSEQ® assay) was achieved in 70% (95% CI, 61–78) of MRD-evaluable patients (patients with ≥1 baseline or on-treatment MRD result and non-MRD negative at baseline) in the pooled EXP cohort; median duration of MRD negativity was 23.1 months (95% CI, 13.8–34.0)

Treatment Discontinuations While in CR

- In the pooled EXP cohort, 35 patients discontinued epcoritamab treatment while in CR for a reason other than PD or death, and had ≥1 response measurement following treatment discontinuation
  - Reasons for discontinuation included AEs (n=16), withdrawal by patient (n=9), no longer clinically benefiting (n=3), other (n=6), and decision to proceed with transplant (n=1; transplant not received)
  - Median time on treatment was 15.9 months (range, 1.5–36.2)
  - 94% (33/35) of patients had sustained CR on a subsequent scan after treatment discontinuation; median time in CR post treatment discontinuation was 13.1 months (range, 0.4–28.3); 2 patients experienced PD following discontinuation

Safety

- The pooled EXP cohort's long-term safety profile was manageable and consistent with previous reports
  - Most common (≥30%) TEAEs were CRS (70%; with 2SUD), injection site reaction (42%), COVID-19 (36%), and fatigue (30%)
  - Among 18 fatal TEAEs, most frequently (≥2 patients) reported were COVID-19 (n=8) and pseudomonal sepsis (n=2)
- In the C1 OPT cohort, the safety profile was generally consistent with previous disclosures with improved CRS rates and severity over the pooled EXP cohort and no new safety signals
  - TEAEs led to treatment discontinuation in 12% of patients (1% COVID-19)
  - One (1%) fatal TEAE occurred (viral respiratory tract infection)
  - CRS and ICANS remained unchanged from prior disclosures
    - All CRS events (in 49% [42/86] of patients) were low grade and resolved
    - No ICANS events were reported

CRS Events in the C1 OPT Cohort

	C1 OPT (N=86)
Patients with ≥1 CRS event, n (%)	42 (49)
Grade 1	39 (45)
Fever	39 (45)
Grade 2	8 (9)
Fever	8 (9)
Hypotension	6 (7)
Hypoxia	2 (2)
Tocilizumab treatment, n (%)	11 (26)
CRS leading to epcoritamab discontinuation, n (%)	0
Median time to first CRS onset, days (range)	23 (1–52)
CRS resolution, n (%)	42 (100)
Median time to resolution, days (range)	2 (1–14)

Data cutoff: December 2024. CRS dynamics from the previous data cut are presented in Linton KM, et al. *Lancet Haematol* 2024;11(8):e593-e605. In the population based on the FDA-approved indication of epcoritamab (N=127), 99% had a TEAE, 73% had a grade ≥3 TEAE, 14% had a fatal TEAE, 28% had a TEAE leading to treatment discontinuation, 66% had CRS, and 6% had ICANS.

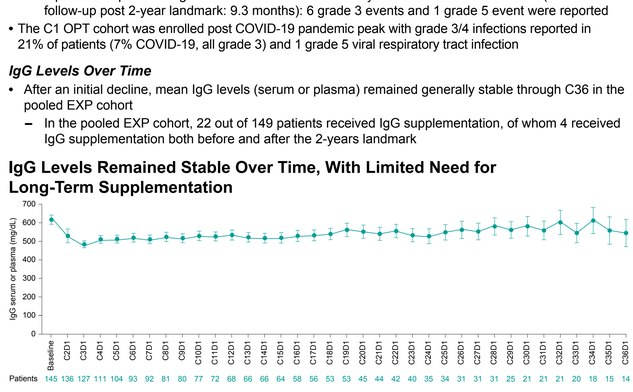
Infections

- The pooled EXP cohort was enrolled during the COVID-19 pandemic with grade 3/4 infections reported in 35% of patients (18% COVID-19) and grade 5 infections in 7% of patients (5% COVID-19)
  - 5 patients experienced grade ≥3 infections more than 2 years after treatment initiation (median follow-up post 2-year landmark: 9.3 months): 6 grade 3 events and 1 grade 5 event were reported
- The C1 OPT cohort was enrolled post COVID-19 pandemic peak with grade 3/4 infections reported in 21% of patients (7% COVID-19, all grade 3) and 1 grade 5 viral respiratory tract infection

IgG Levels Over Time

- After an initial decline, mean IgG levels (serum or plasma) remained generally stable through C36 in the pooled EXP cohort
  - In the pooled EXP cohort, 22 out of 149 patients received IgG supplementation, of whom 4 received IgG supplementation both before and after the 2-years landmark

IgG Levels Remained Stable Over Time, With Limited Need for Long-Term Supplementation



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