ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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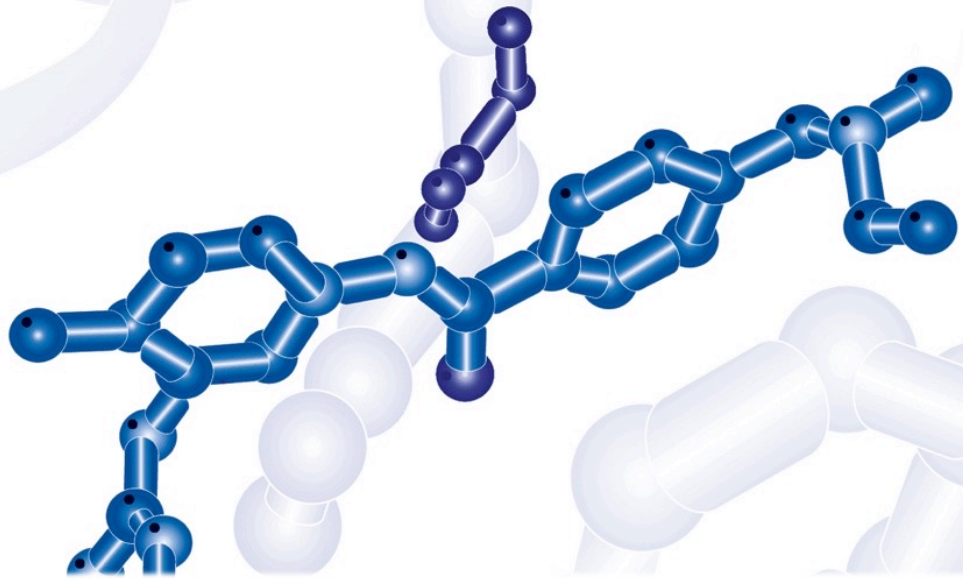

New Drugs in Hematology

President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
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Epcoritamab

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Disclosures of Lorenzo Falchi

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- **Advisory board:** AbbVie, Genentech, Genmab, ADC therapeutics, Johnson & Johnson, Regeneron, Chugai, Bristol Myers Squibb
- **Honoraria:** Roche, Genmab, AbbVie, Kite, Chugai
- **Travel Support:** Genmab, AbbVie, Roche, Kite, Chugai

Epcoritamab overview

SC-administered, bispecific CD3xCD20 Ab created using the technology platform via Fab-arm exchange of:

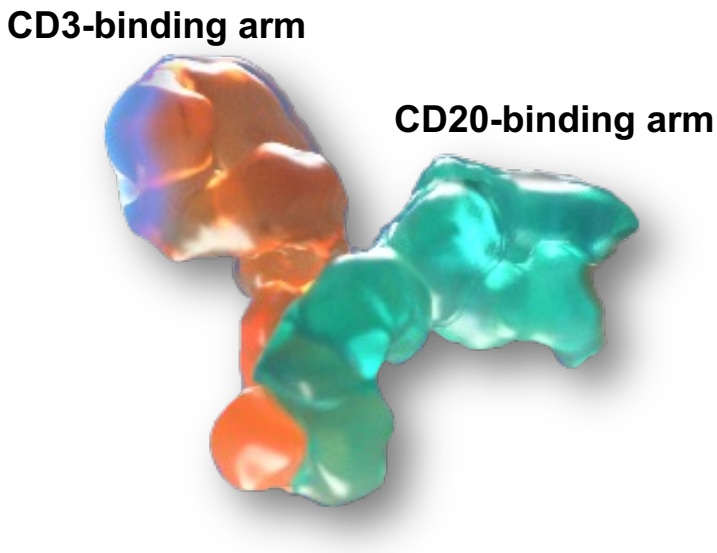
- Humanized CD3-specific IgG1
- Human CD20-specific IgG1

Retains normal FcRn binding for a long plasma half-life

Three point mutations were introduced to ensure:

- No Fcγ receptor binding to prevent ADCC or ADCP induction
- No T-cell activation without binding to CD20
- No C1q binding (no CDC induction)

SC administration leads to lower Cmax and lower levels of cytokines as compared to IV

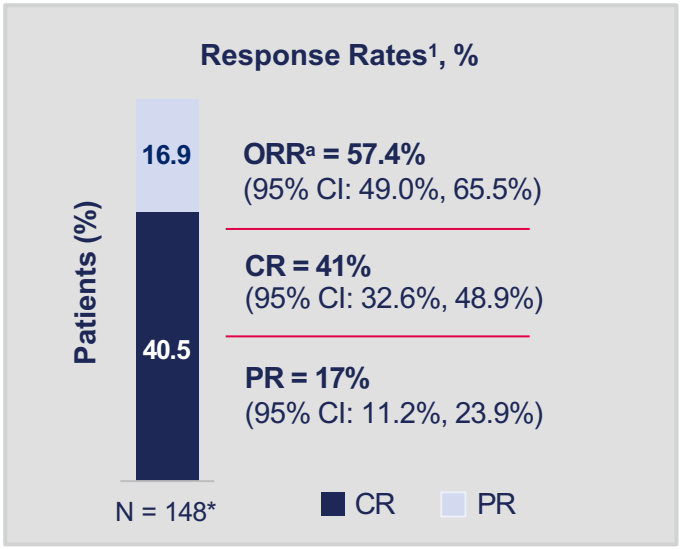


ADCP, antibody-dependent cellular phagocytosis; SC, subcutaneous.

Chavez et al. *Best Prac Res Clin Haematol*. 2018;31:135–146; Hiemstra et al. Poster PS1031 presented at EHA 2019; Labrijn et al. *PNAS*. 2013;110:5145–50; Labrijn et al. *Nat Protoc*. 2014;9:2450-2463; Mohammed et al. *J Blood Med*. 2019;10:71-84; Teeling JL et al. *Blood*. 2004;104:1793-1800.

Some lessons learned from epcoritamab monotherapy

EPCORE NHL-1 LBCL 49-Month Study Follow-Up: Efficacy summary



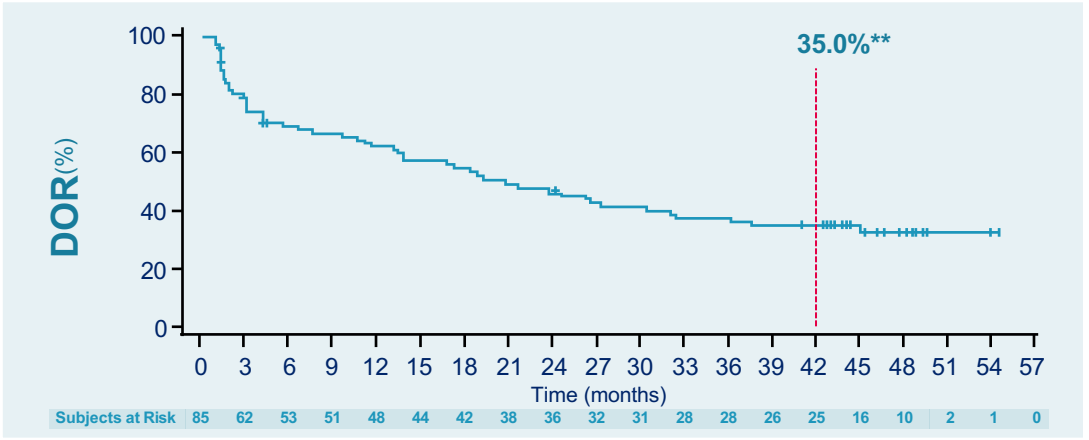
Safety

Observations were consistent with the known epcoritamab safety profile.

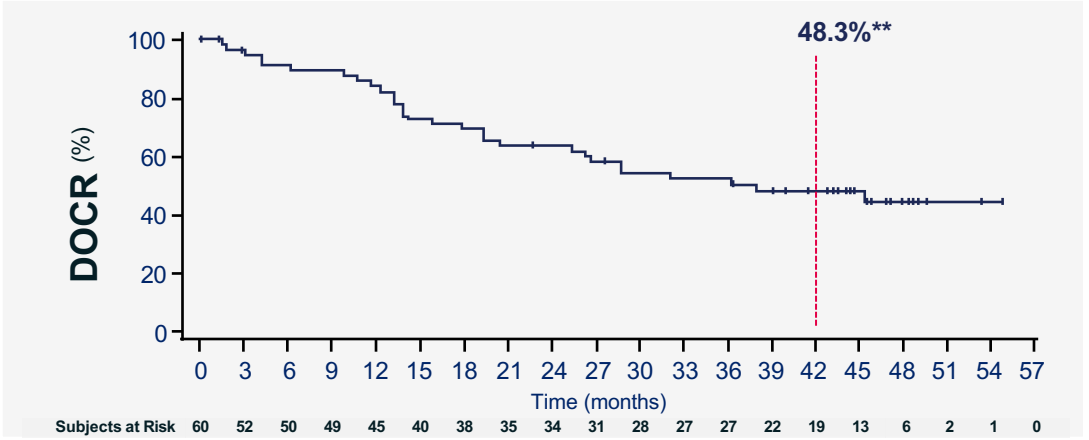
- **D/C due to AR: 7.6%[2]**
- **Serious infections: 33.1%[2]**
- **Serious infections ≥5%:[2]**
  - **COVID-19 events^ (17.2%)**
  - **Pneumonia (5.7%)**

Fatal infections occurred in 16 patients, of which 12 were COVID-19 events^.[1,2]

^COVID-19 events represent COVID-19 and/or COVID-19 pneumonia.



Median DOR†	20.8 months
95% CI	13.0, 32.0
Median follow-up[b]	46.2 months



Median DOCR†	37.7 months
95% CI	20.2, NR
Median follow-up[c]	44.1 months

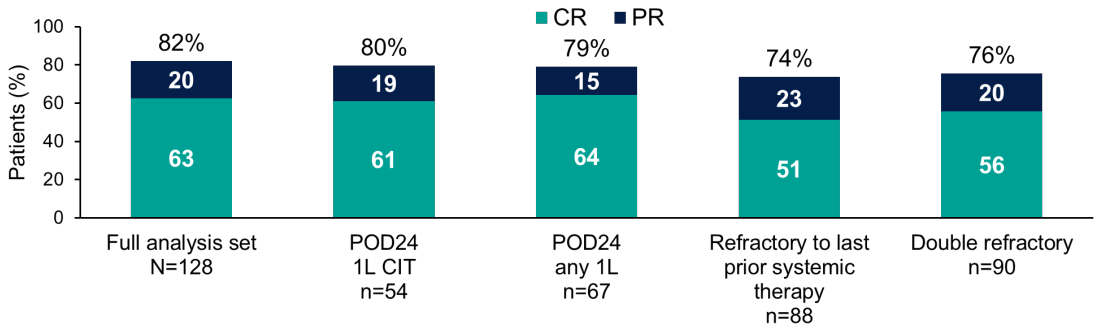
Data cutoff: May 2025. *Based on INV assessment. The efficacy population includes 148 patients with DLBCL, NOS, including DLBCL arising from indolent lymphoma, and HGBCL. **36- and 42-month landmark estimate of patients remaining in response (DOR) and in complete response (DOCR). †Based on Kaplan-Meier estimate. [a]Based on Lugano criteria. [b]Median follow-up for DOR: median time from documented response to event/censoring in patients achieving response. [c]Median follow-up for DOCR: Median time from documented response to event/censoring in patients achieving a CR.

Abbreviations: CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; DOCR, duration of complete response; HGBCL, high-grade B-cell lymphoma; INV, investigator; NHL, non-Hodgkin lymphoma; NR, not reached; ORR, objective response rate; PR, partial response.

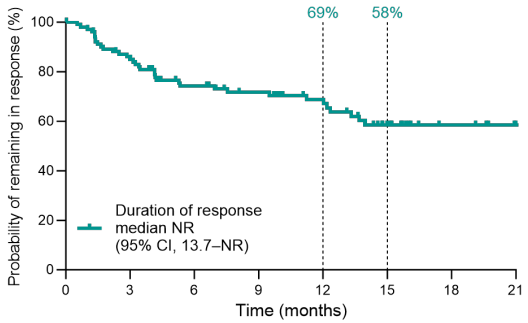
1. Karimi Y et al. ASH 2025. Poster 5513. 2. Data on File at Abbvie and Genmab. ABVRRTI81774.

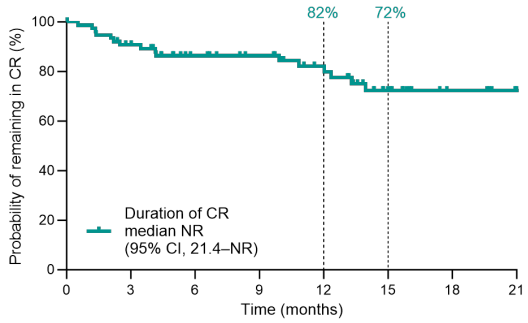
EPCORE NHL-1 FL cohort: Efficacy summary

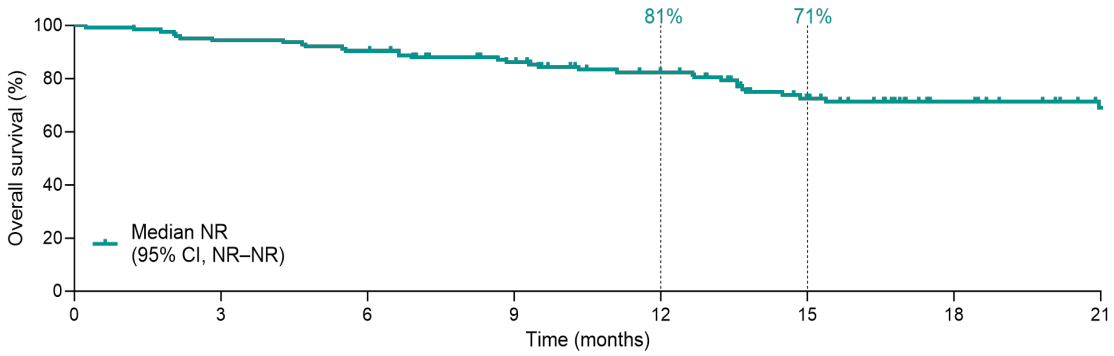
- Median follow-up 17.4 months
- Median n. prior lines of therapy: 3 (2-9)
- Double refractory: 70%



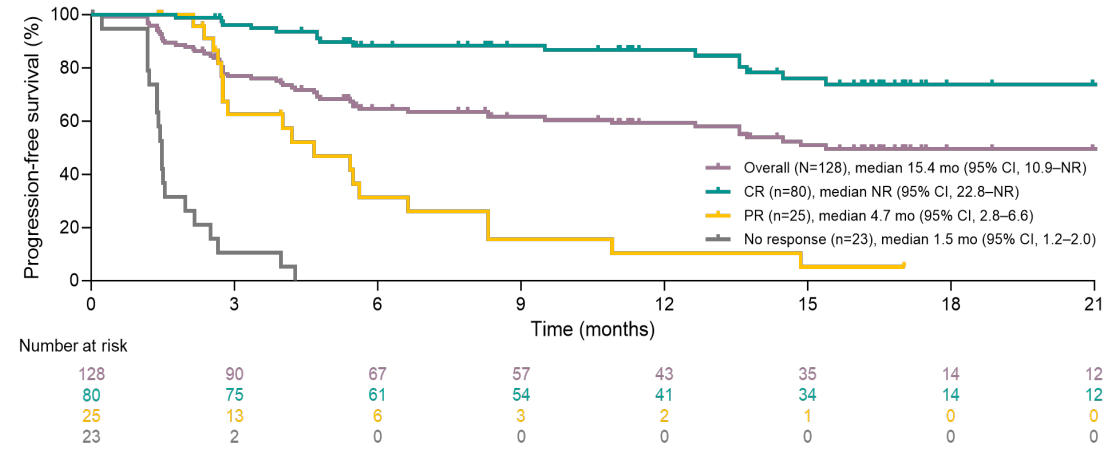
- Median time to response was 1.4 mo (range, 1.0–3.0)
- Median time to complete response was 1.5 mo (range, 1.2–11.1)
- Median time to next antilymphoma therapy was NR (range, 0.2+ to 30.0+)







Progression-Free Survival Median NR in Complete Responders



- Of 100 MRD-evaluable patients, MRD negativity was achieved in 68 patients and was associated with improved PFS and OS

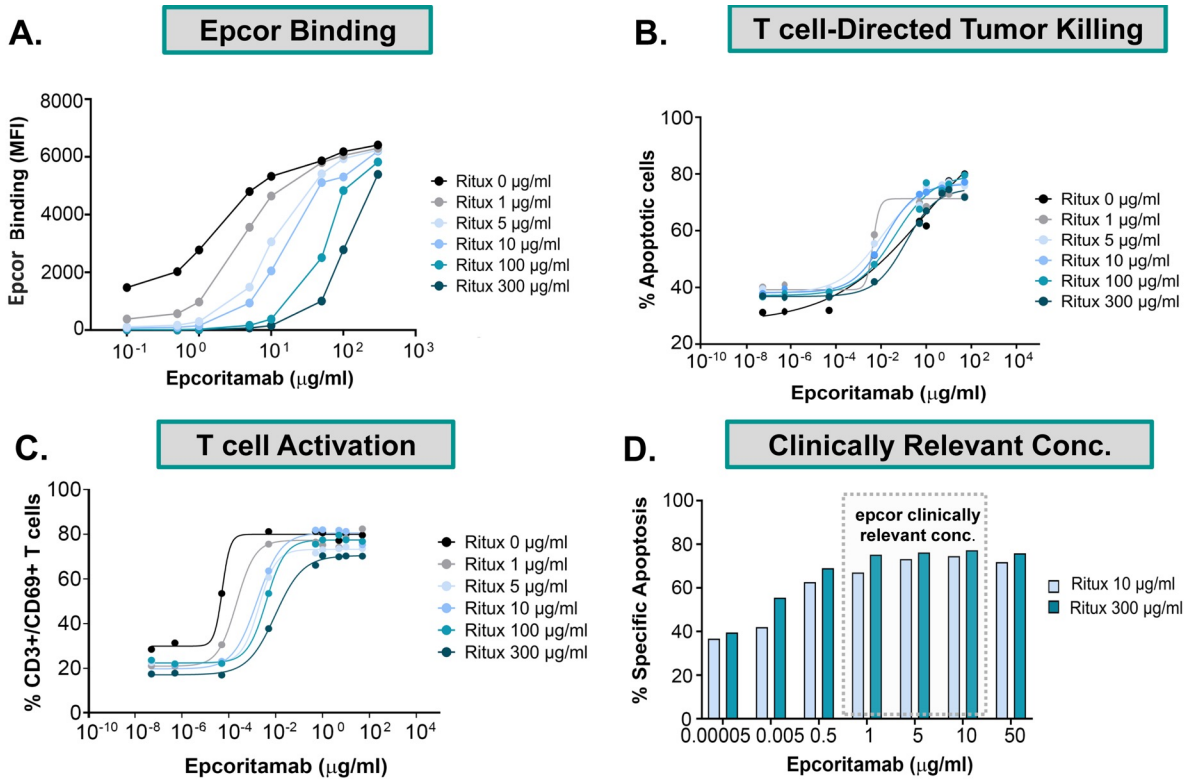
Linton et al. ASH 2023

Epcoritamab combinatorial strategies in DLBCL, FL

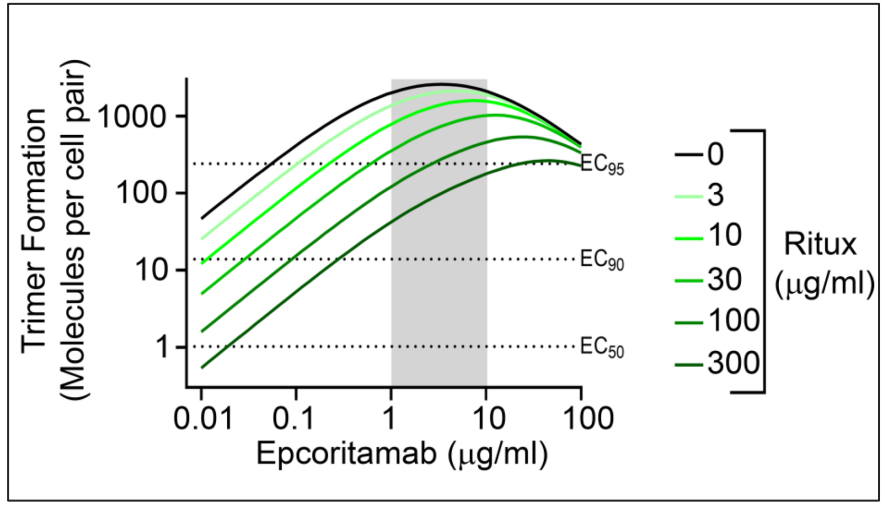
	Large B-cell lymphoma	Follicular lymphoma
1st line	• R-CHOP • R-CHP-polatuzumab • Epcoritamab-R-CHOP vs R-CHOP (EPCORE DLBCL-2) • Lenalidomide	• R-lenalidomide • Bendamustine • Epcoritamab+R2 vs R2 (EPCORE FL-2)
2nd line+	• R-DHAX/C • GemOx • Lenalidomide • Epcoritamab vs R-GemOx/ BR (EPCORE DLBCL-1)	• R-lenalidomide • Lenalidomide • Epcoritamab+R2 vs R2 (EPCORE FL-1)

Source: Citation

Rituximab exerts binding interference, but minimal effect on epcoritamab potency *in vitro*



Increasing concentrations of rituximab resulted in **(A)** a dose-dependent reduction of epcoritamab binding to Daudi cells but had **(B)** minimal impact on tumor cytotoxicity or **(C)** T cell activation (CD69 induction) at **(D)** epcoritamab and rituximab clinically relevant concentrations



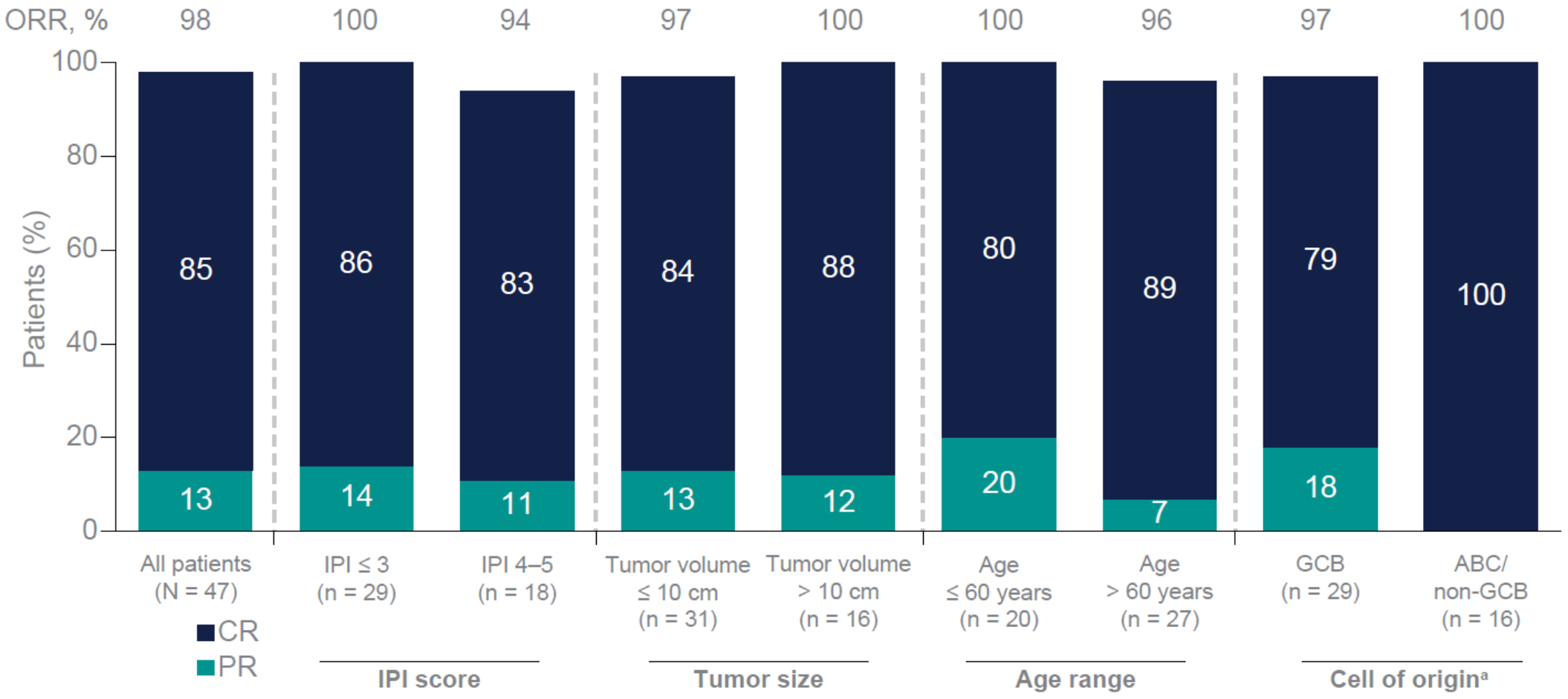
Epcoritamab-induced trimer formation in the presence of clinically relevant concentrations of rituximab remains above EC90 values across clinically relevant epcoritamab concentrations (grayed)

Epcor, epcoritamab; Ritux, rituximab; EC_{50}, effective concentration at 50% cell cytotoxicity.

Epling-Burnette et al. ASH 2022; Abstract 4182

Large B-cell lymphoma

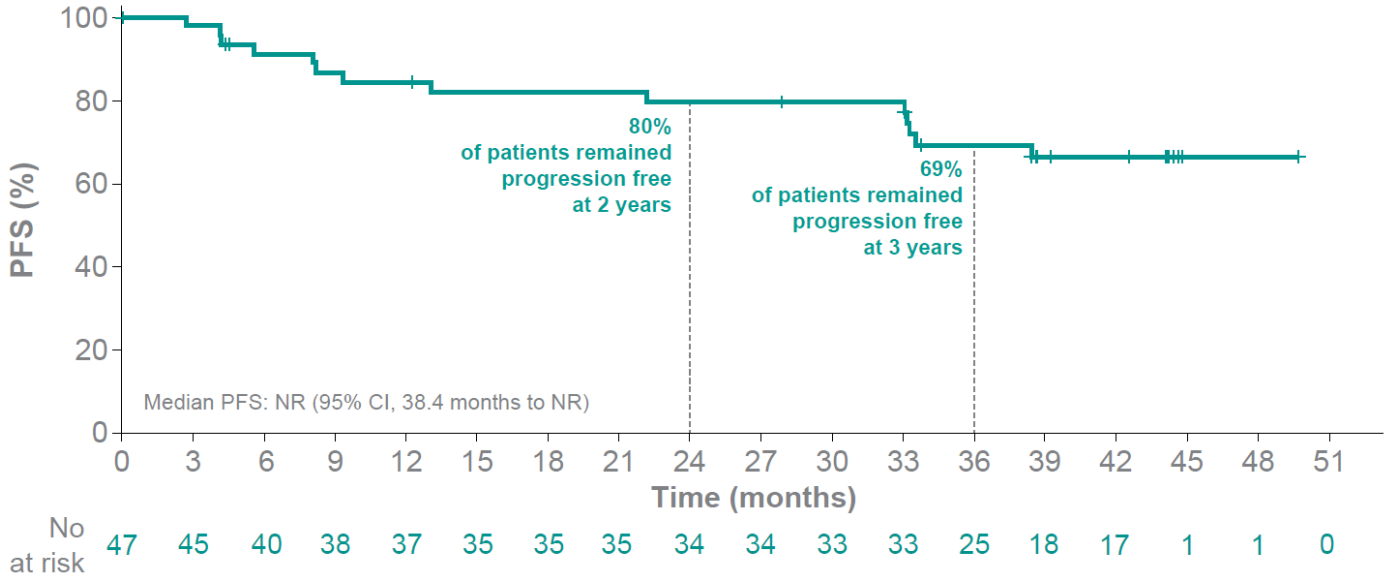
Epcoritamab + R-CHOP in 1L high-risk DLBCL: High CR Rates Across Clinically Relevant Subgroups

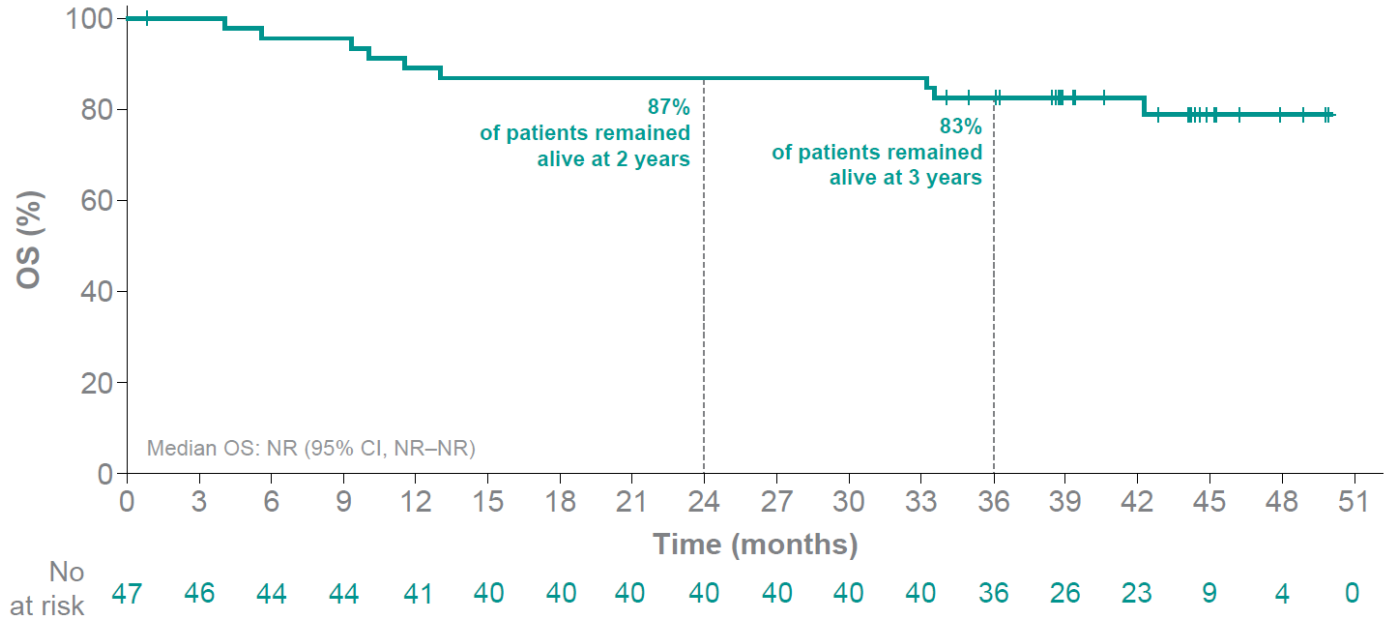


Data cutoff: Apr 9, 2025. Investigator assessment per Lugano criteria (Cheson BD, et al. *J Clin Oncol* 2014;32:3059–3068). One patient was NE. [a]Cell of origin was unknown for 2 patients.

Sustained PFS and OS Beyond 3 Years

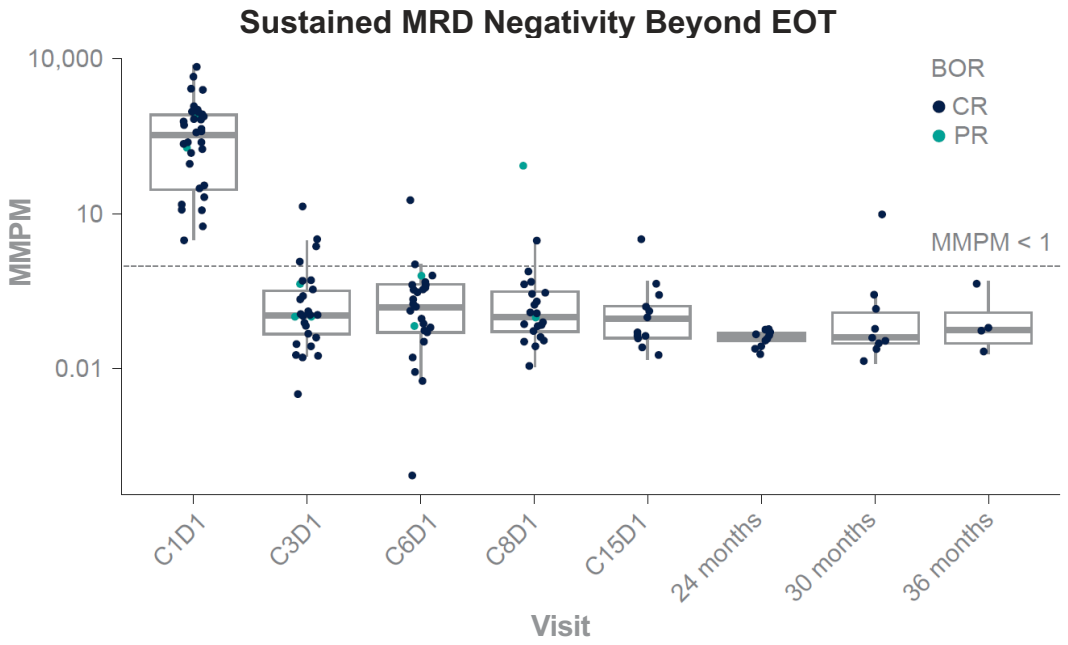
- Median PFS and median OS were NR in all clinically relevant subgroups, including IPI score (≤ 3 and 4–5), tumor size (≤ 10 and >10 cm), age (≤ 60 and > 60 years), and cell of origin (GCB and ABC/non-GCB)

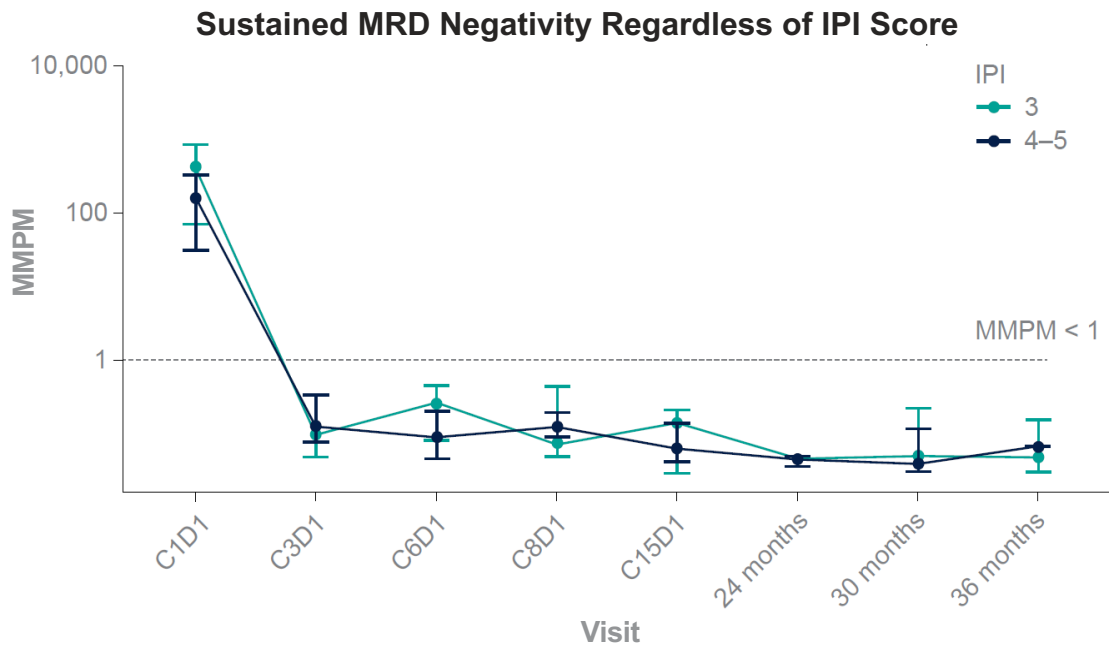




Data cutoff: Sep 21, 2025. Median follow-up for PFS: 44.1 months (95% CI, 38.6–44.2). Median follow-up for OS: 44.2 months (95% CI, 38.9–44.4).

Sustained MRD Negativity Beyond EOT Across Clinically Relevant Subgroups





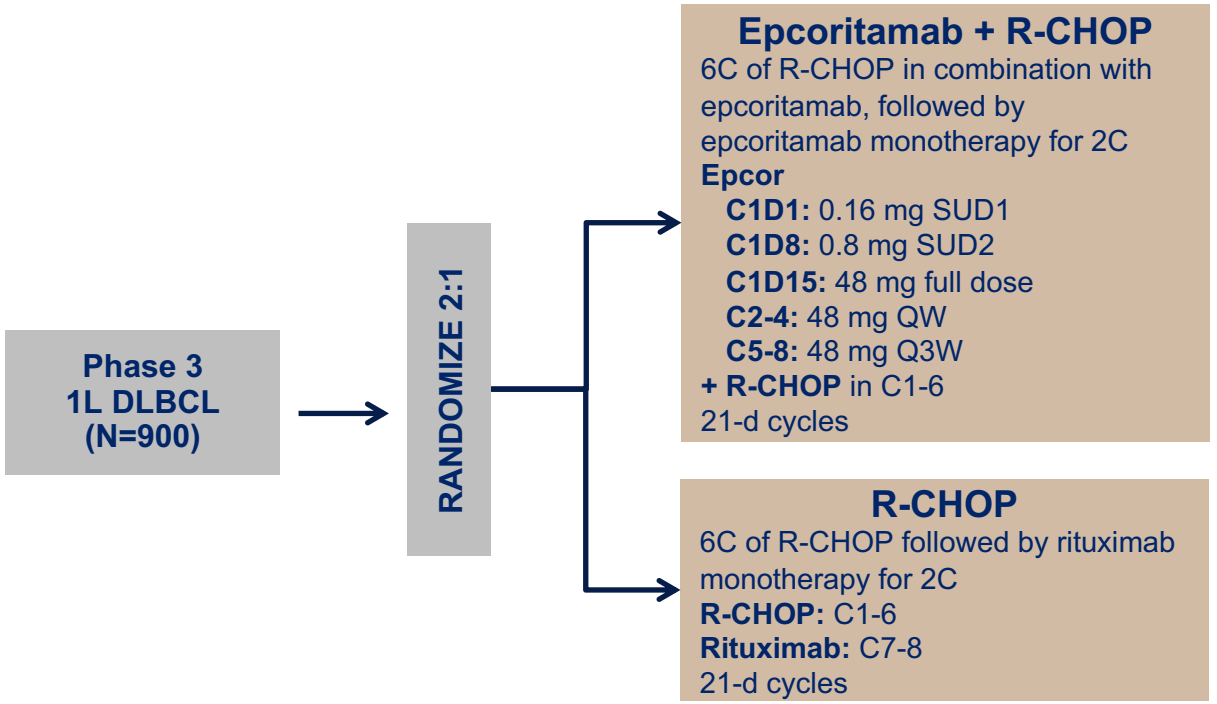
- At C3D1, 86% (25/29) of patients with available samples at that time point were MRD negative
  - The 4 complete responders who were still MRD positive at C3D1 subsequently converted to MRD negativity at later timepoints and achieved long-term responses
- MRD negativity was sustained through post-treatment follow-up in most complete responders with available samples
- Rapid and sustained reductions in ctDNA were observed in all clinically relevant subgroups, including IPI score (3 and 4–5), tumor size (≤ 10 vs and 10 cm), age (≤ 60 and > 60 years), or cell of origin (GCB and ABC/non-GCB)

Data cutoff: Apr 9, 2025. MRD analyses were performed with plasma ctDNA samples using the exploratory AVENIO Oncology Assay NHL Lymphoma test (Roche). The MRD-evaluable population included patients with a non-negative baseline and ≥ 1 on-treatment MRD result. MRD negativity was defined as < 1 MMPM. Error bars represent 25% and 75% quantiles. Analysis excluded the 2 patients with IPI score < 3 at screening. BOR, best overall response; EOT, end of treatment.

Epcoritamab + R-CHOP vs. R-CHOP in 1L DLBCL: The EPCORE DLBCL-2 Study

Key inclusion criteria

- Planned to receive treatment with R-CHOP per investigator determination
- Newly diagnosed, histologically confirmed CD20+ DLBCL (de novo or transformed, including: DLBCL-NOS, HGBCL with *MYC* and *BCL-2* and/or *BCL-6* rearrangement with DLBCL morphology, T-cell/histiocyte-rich LBCL, EBV+ DLBCL-NOS, FL Gr3b)
- IPI score of 2-5[a]
- ECOG PS of 0-2 prior to initiating R-CHOP treatment[b]
- Availability of archival (within 8 weeks) or fresh or paraffin embedded tissue at screening
- LVEF ≥50% at screening



Endpoints

Primary: PFS per Lugano by IRC for patients with an IPI of 3-5

Secondary[c]: PFS, EFS, CR, OS, MRD negativity

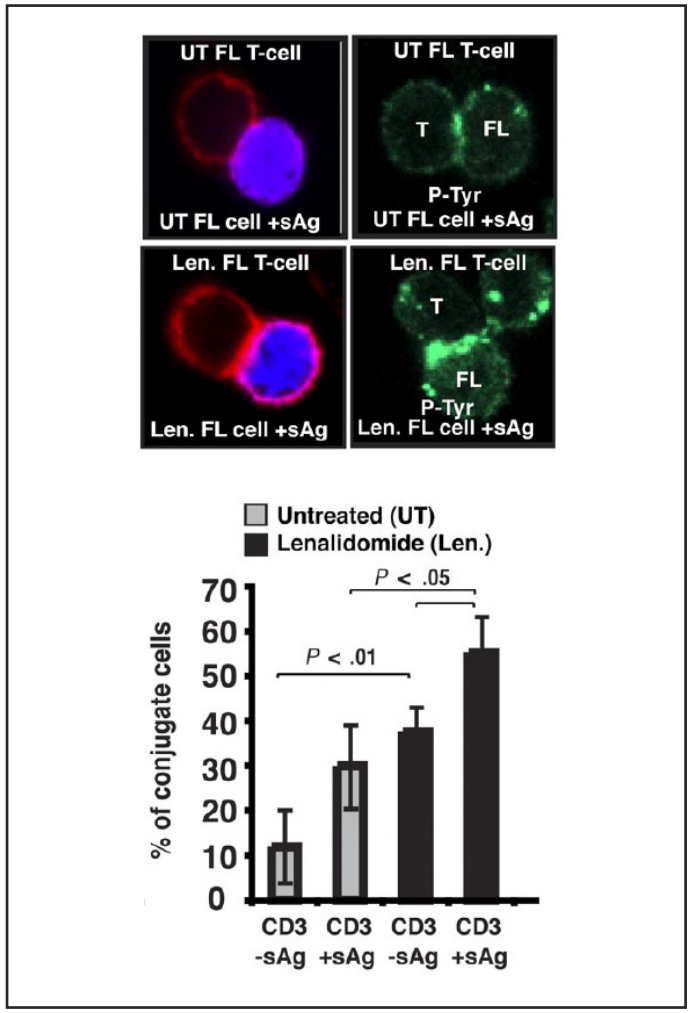
[a]The number of patients with IPI 2 will be capped at 30% of the overall sample size
[b]Note that participants with an initial ECOG PS ≥3 may be screened if pre-phase treatment is planned. Participants may be eligible if ECOG PS were to improve to 0-2 during pre-phase treatment
[c]PFS analyzed in all randomized patients. EFS, CR, OS, and MRD negativity analyzed for both patients with an IPI of 3-5 and all randomized patients

1L, first line; C, cycle; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBV+; Epstein-Barr virus positive; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; Epcor, epcoritamab; FL, follicular lymphoma; ; HGBCL, high grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; IRC, independent review committee; LVEF, left ventricular ejection fraction; MRD, minimum residual disease; MRI, magnetic resonance imaging; NOS, not otherwise specified; OS, overall survival; PET, PFS, progression-free survival; positron emission tomography; PS, performance status; QW, once weekly; Q#W, every # wk; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SUD, step-up dose.

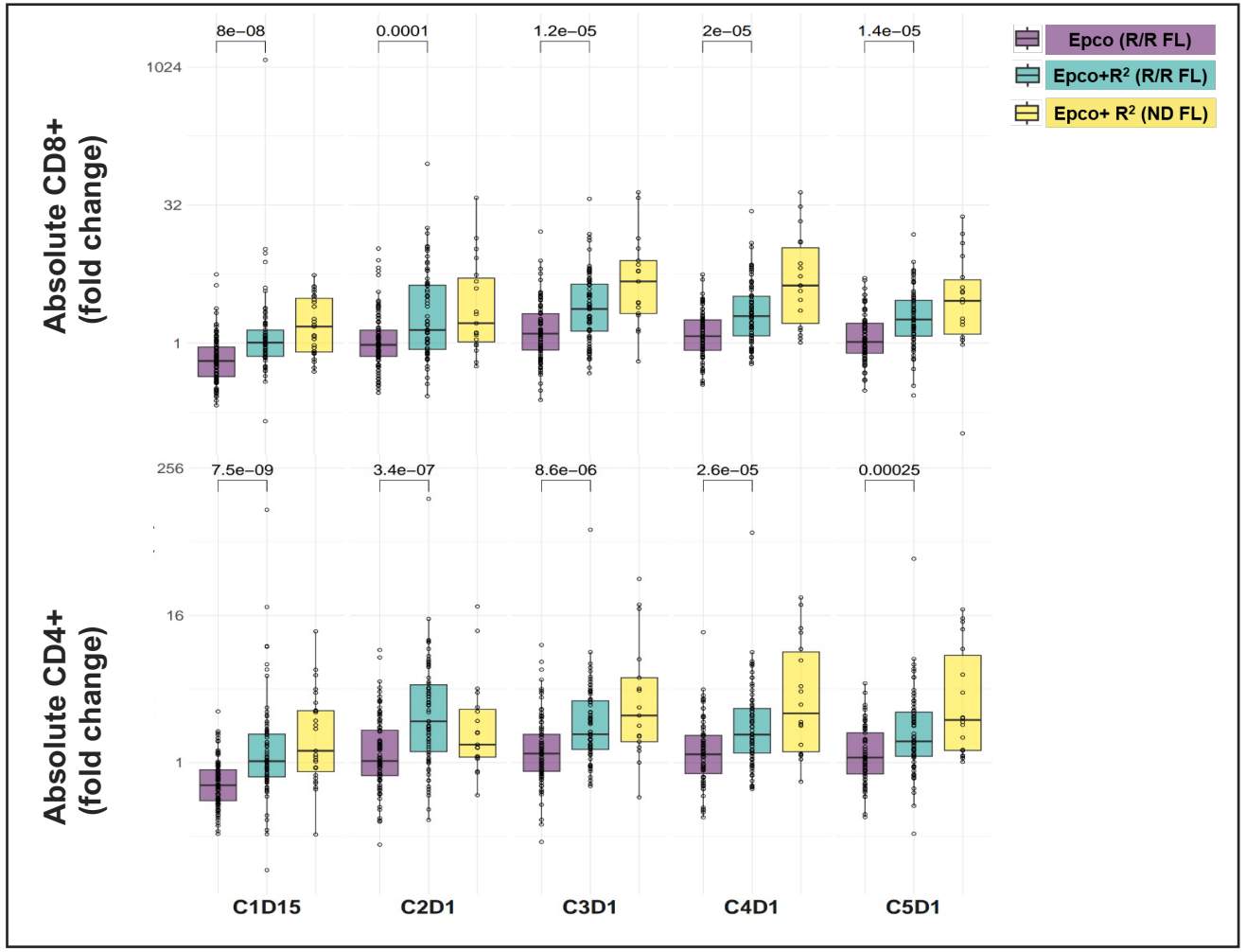
Follicular lymphoma

Lenalidomide as rational combination partner for epcoritamab

Len restores a dysfunctional T-cell-FL cell immune synapse *in vitro*



Len + epcor leads to significant increases in CD8+ and CD4+ cells vs. epcor alone (peripheral blood T-cell activation assay)



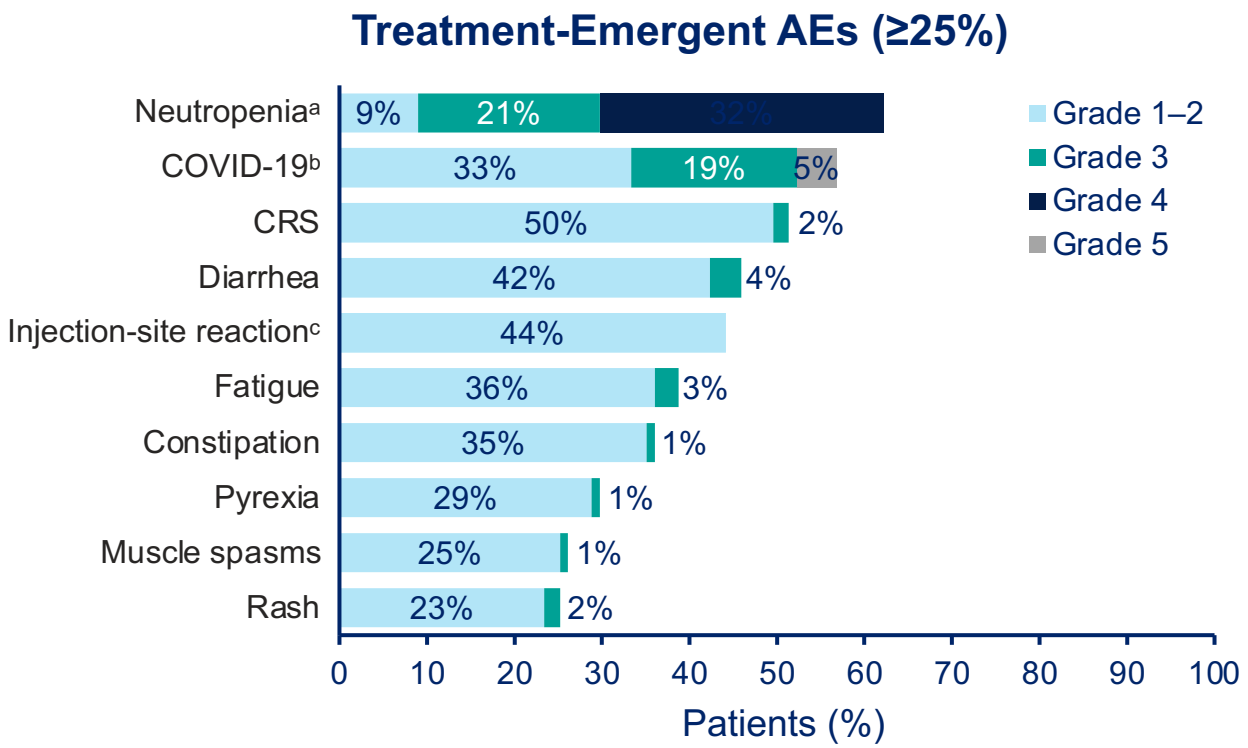
Ramsay et al. Blood 2009; Si et al. AACR 2024

Epcoritamab + R^2 Results in Deep Responses with a Manageable Safety Profile: 2-year follow-up

Best Response, n (%)[a]	N=111
Overall response	**107 (96)**
Complete response	**97 (87)**
Partial response	10 (9)
Progressive disease	2 (2)

MRD Negativity, n/n (%)	MRD Evaluable
MRD negativity at any time[b]	**66/75 (88)**
MRD negative and complete response[c]	63/68 (93)
MRD negativity in high-risk subgroups	
POD24 (1L CIT)	26/30 (87)
Primary refractory	25/28 (89)
Double refractory	23/27 (85)

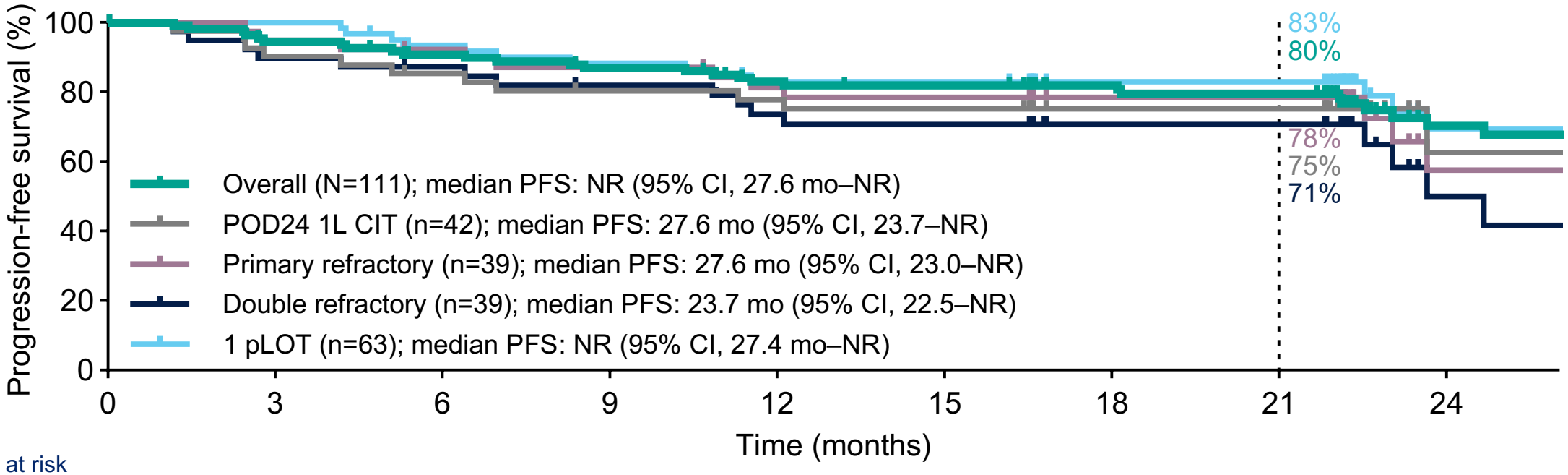
[a]Two patients were not evaluable for response. [b]MRD negative at any time point with an assay cutoff of 10^{-6} (PBMC assay; clonoSEQ). [c]One patient became MRD positive at a subsequent assessment (C5D1); patient later experienced radiographic PD.



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

Falchi et al. *Blood* (2024) 144 (Supplement 1): 342 and Blood, online, ahead of print

Progression-Free Survival and Duration of Response



Patients at risk									
Overall	111	102	95	90	82	80	68	66	29
POD24 1L CIT	42	37	34	31	30	29	21	21	5
Primary refractory	39	37	35	32	28	27	22	22	7
Double refractory	39	35	33	30	26	25	18	18	6
1 pLOT	63	61	55	52	45	45	38	38	13

PFS in MRD- vs. MRD+ patients: 86% vs 44% at 21 months*

Data cutoff: May 15, 2024. PFS is among the full analysis population. Median follow-up for PFS: 22.3 months.

Falchi et al. *Blood* (2024) 144 (Supplement 1): 342 and Blood, online, ahead of print

EPCORE FL-1: Phase 3, Global, Randomized, Open-Label Study

Key eligibility criteria

- Histologically confirmed CD20+ FL
- Grade 1-3a, Stage II-IV
- ≥ 1 prior treatment including anti-CD20 mAb plus an alkylating agent
- Met ≥ 1 GELF criterion

Randomization 1:1

Fixed-Duration: 12 Cycles (28-Day Cycles)

Epcoritamab (48 mg) plus R²

- **Epcoritamab** (3-SUD cycle 1: QW;[a,b] cycles 2–3, QW; cycles 4–12, Q4W)
- **Rituximab** (375 mg/m²), 5 cycles (cycle 1, QW; cycles 2–5, Q4W)
- **Lenalidomide** (20 mg), 12 cycles (cycle 1–12, QD, D1-21)

R²

- **Rituximab** (375 mg/m²), 5 cycles (cycle 1, QW; cycles 2–5, Q4W)
- **Lenalidomide** (20 mg), 12 cycles (cycle 1–12, QD, D1-21)

Stratification factors

- Disease status:
  - 2L: > or ≤ 2 years since last therapy
  - 3L+: > or < 6 months since last therapy
- Region: US/EU vs Rest of World

- **Dual primary endpoints: ORR per IRC and PFS per IRC**
- Key secondary endpoints: CR rate per IRC, OS, and MRD[c]
- Additional secondary endpoints: DOR, DOCR, TTNLT, safety, and PRO assessments

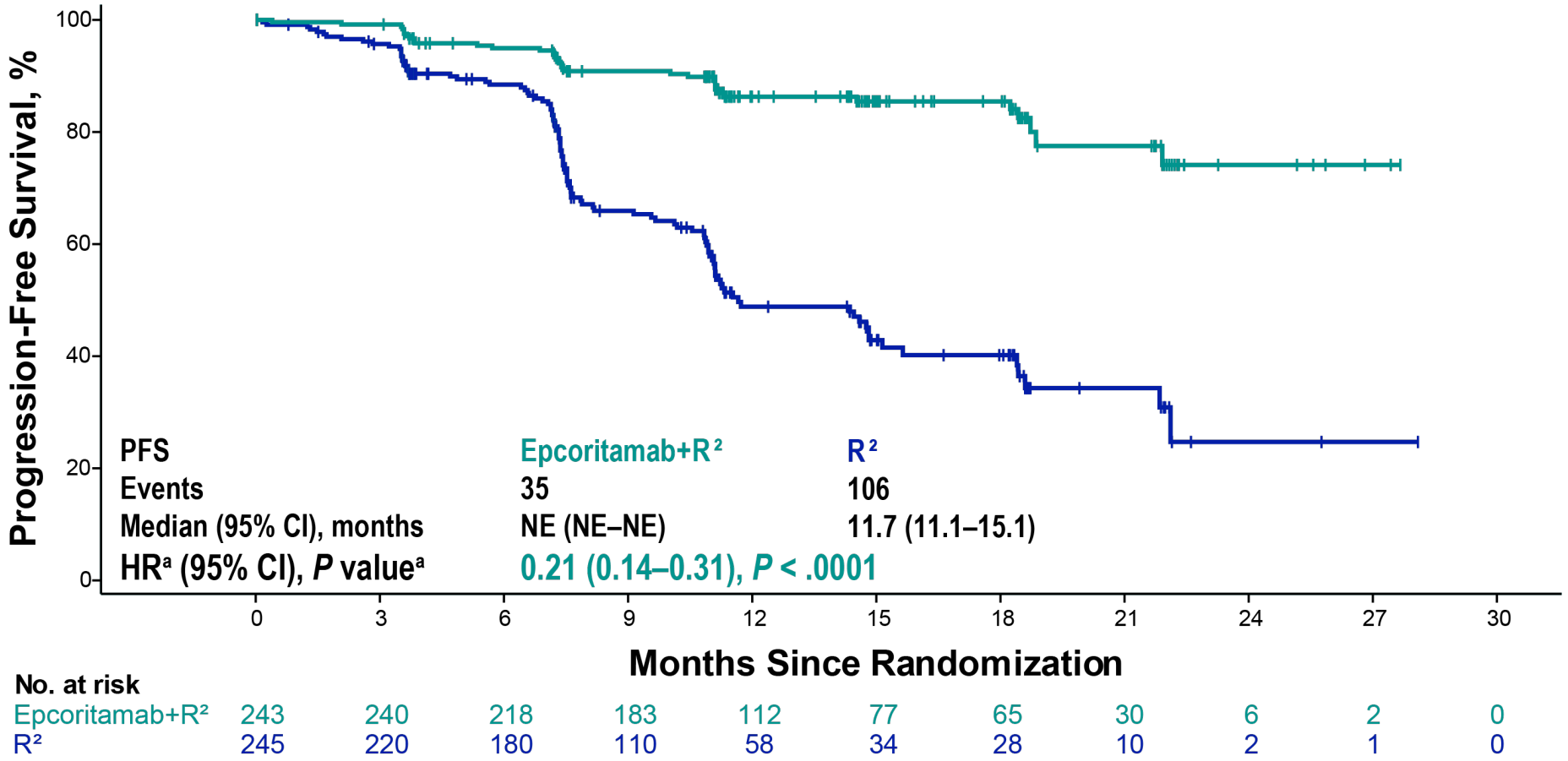
Data cutoff: May 24, 2025; median follow-up: 14.8 months[d]
Enrollment period: October 2022 - January 2025

[a]Two step-up dosing (SUD) regimens during cycle 1 to mitigate the risk of cytokine release syndrome: either a 2-SUD (0.16 mg on cycle 1 day 1, 0.8 mg on cycle 1 day 8), or 3-SUD (0.16 mg on cycle 1 day 1, 0.8 mg on cycle 1 day 8, 3 mg on cycle 1 day 15) regimen, followed by full dose 48 mg. The 3-SUD regimen was implemented after reduced CRS severity and incidence had been observed in the EPCORE NHL-1 FL trial (NCT03625037).[1] [b]The 24 mg epcoritamab plus R² arm was closed to enrollment based on the superior efficacy for the 48 mg dose from EPCORE NHL-2.[2] Only the data for the optimal dose explored (48 mg) are presented here. [c]Minimal residual disease data are forthcoming in a future analysis. [d]The data presented here are from the second planned interim analysis (May 24, 2025) after 78% Information Fraction for PFS had occurred.

1. Vose J, et al. *J Clin Oncol.* 2024;42(16_suppl):7015–7015. 2. Falchi L, et al. *Blood*. 2024;144(Supplement 1):342–342.

Falchi L, et al. *Lancet.* 2026 Jan 10;407(10524):161-173

Epcoritamab+R² Resulted in Superior PFS per IRC With 79% Risk Reduction



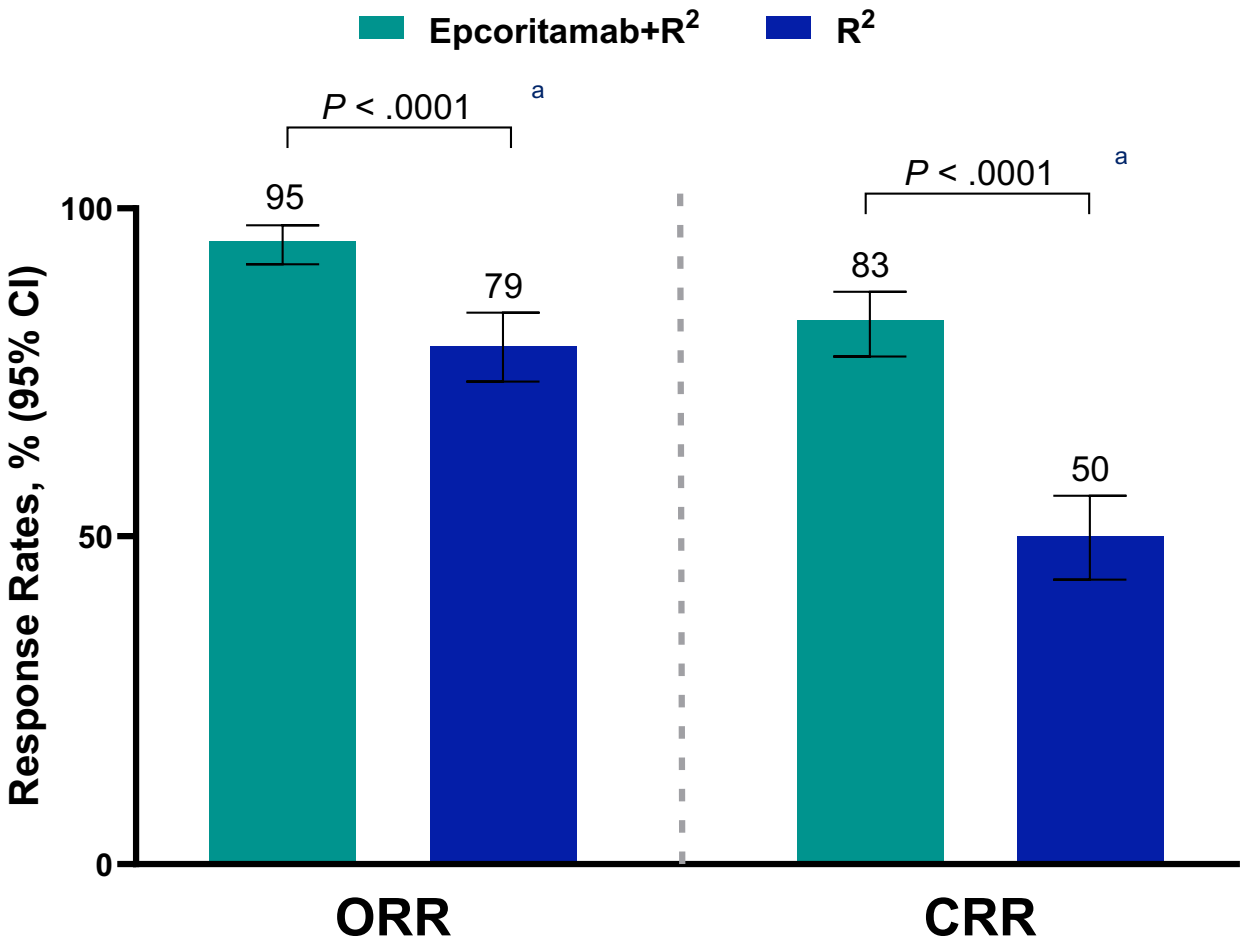
- Concordance rate was 94% for PFS between IRC and investigator assessment
- The estimated 16-month PFS was 85.5% (95% CI: 79.7, 89.7) for epcoritamab+R² and 40.2% (95% CI: 31.8, 48.4) for R²

Median follow-up for PFS: epcoritamab+R² (14.4m), R² (11.5m). The first planned interim analysis (January 10, 2025) achieved statistical significance on PFS, HR 0.21 (95% CI 0.13, 0.33) $P < 0.0001$, with a 1-sided significance level of 0.0023.

[a]Nominal *P* value is based on stratified log-rank test. Hazard ratio is estimated using stratified Cox proportional hazards model. This analysis was performed on the 78% information fraction.

Falchi L, et al. *Lancet.* 2026 Jan 10;407(10524):161-173

Epcoritamab+R^2 Resulted in Higher Response Rates Versus R^2



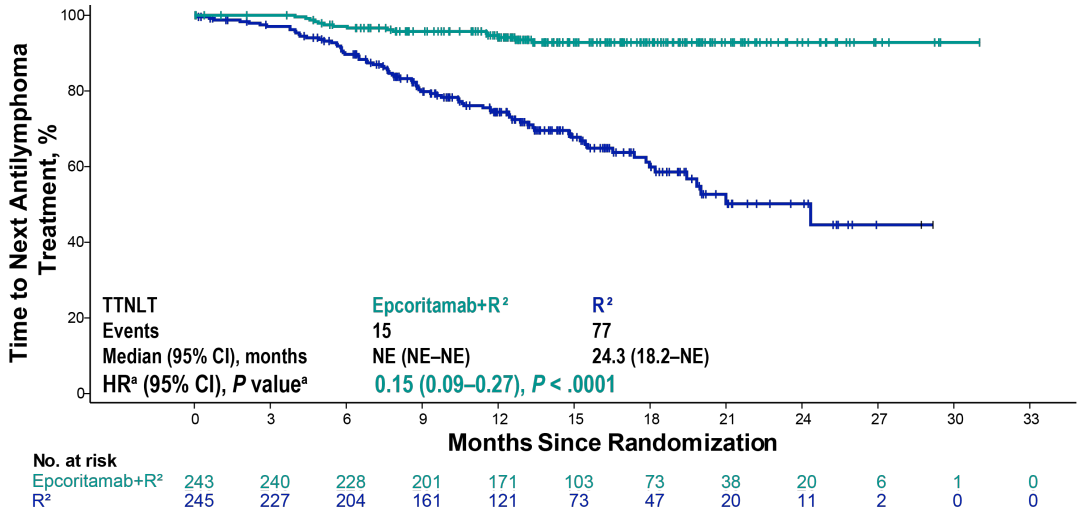
	Epcoritamab+R^2 (N = 243)	R^2 (N = 245)
ORR, n (%)	231 (95)	194 (79)
CRR, n (%)	201 (83)	122 (50)
PR, n (%)	30 (12)	72 (29)
SD, n (%)	1 (< 1)	17 (7)
PD, n (%)	7 (3)	16 (7)
NE,[b] n (%)	4 (2)	18 (7)

The first planned interim analysis (January 10, 2025) achieved statistical significance for ORR (N = 232; 95.7% vs 81.0%; *P* < 0.0001, with a 1-sided significance level of 0.005) and CR (74.5% vs 43.3%; *P* < 0.0001, with a 1-sided significance level of 0.025).
[a]Nominal *P* value by stratified Cochran-Mantel-Haenszel method. [b]Patients with no post-baseline disease assessment were also included.

Falchi L, et al. *Lancet.* 2026 Jan 10;407(10524):161-173

Epcoritamab+R^2 Extended Time to Next Treatment and Associated with Positive OS Trend

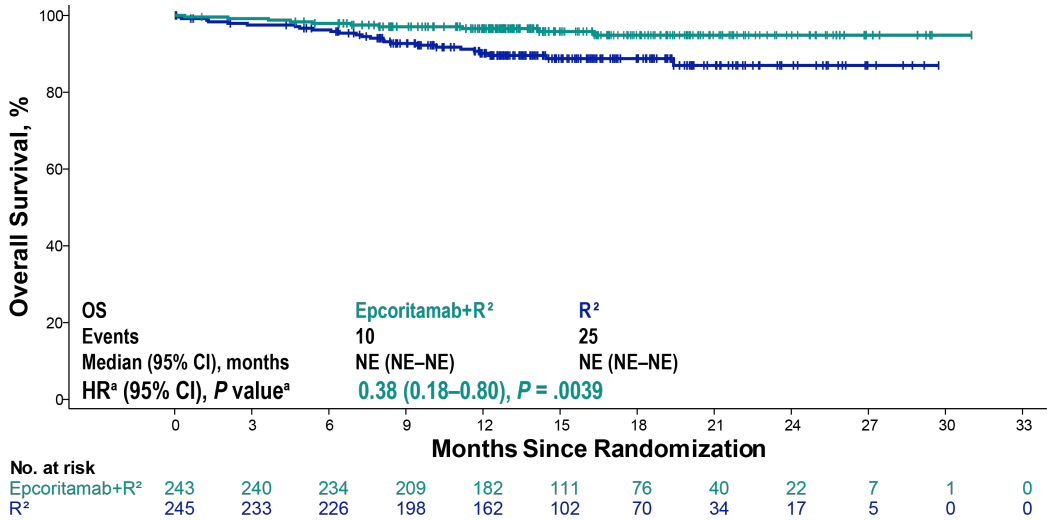
Time to next anti-lymphoma therapy



- At 16 months, 92.8% of patients treated with epcoritamab+R^2 remained free from new antilymphoma treatment compared with 64.9% of patients treated with R^2

Median follow-up for TTNLT: epcoritamab+R^2 (14.6m), R^2 (14.1m). TTNLT results are for descriptive purposes only. [a]Nominal *P* value is based on stratified log-rank test. Hazard ratio is estimated using stratified Cox proportional hazards model.

Overall survival



- The 16-month estimate for OS was 95.8% with epcoritamab+R^2 and 88.8% with R^2

Median follow-up for OS: epcoritamab+R^2 (14.8m), R^2 (14.6m). The OS data is based on the 24% (35/146 events) information fraction and has not yet reached statistical significance; additional analyses are forthcoming. [a]*P* value is based on stratified log-rank test with 1-sided significance level of 0.000005. Hazard ratio is estimated using stratified Cox proportional hazards model.

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Manageable AEs With No New Safety Signals

Adverse Event, n (%)	Epcoritamab+R^2 (N = 243)		R^2 (N = 238)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any adverse event	242 (100)	219 (90)	235 (99)	161 (68)
Serious adverse event	135 (56)	-	69 (29)	-
Adverse event leading to treatment discontinuation	46 (19)	-	29 (12)	-
Epcoritamab	21 (9)	-	-	-
Rituximab	7 (3)	-	12 (5)	-
Lenalidomide	45 (19)	-	29 (12)	-
Adverse event of clinical interest > 20%[a,b]				
Infections[c]	188 (77)	81 (33)	125 (53)	37 (16)
Neutropenia	180 (74)	167 (69)	123 (52)	100 (42)
Cytokine release syndrome	85 (35)	-	1 (< 1)	-
Anemia	68 (28)	19 (8)	41 (17)	11 (5)
Thrombocytopenia	67 (28)	23 (9)	44 (18)	15 (6)
Pyrexia	58 (24)	1 (< 1)	33 (14)	3 (1)
Rash	58 (24)	19 (8)	53 (22)	9 (4)
COVID-19	54 (22)	7 (3)	32 (13)	4 (2)

[a]Neutropenia, anemia, pyrexia, rash and COVID-19 are grouped terms comprising multiple clinically related Preferred Terms. [b]This includes the AESI of CRS. [c]Events were in the MedDRA system organ class "Infections and Infestations." No grade 5 infections were reported.

- Neutropenia was manageable and few patients discontinued any study drug (epcoritamab+R^2, 3%; R^2, 2%)
  - Incidence of febrile neutropenia: epcoritamab+R^2, 6%; R^2, 3%
- Infections were manageable and few patients discontinued any study drug (epcoritamab+R^2, 6%; R^2, 1%)
- Fatal adverse events were rare (epcoritamab+R^2, 2%; R^2, 4%)
- Despite higher rates of AEs in the epcoritamab+R^2 arm, most patients completed the prescribed regimen (median relative dose intensity ≥ 90% for epcoritamab+R^2)

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Epcoritamab-R² in 1L FL (EPCORE NHL-2, Arm 6): 2 year follow-up

Key inclusion criteria
- 1L CD20⁺ FL, G1-3a
- ECOG PS 0–2
- Measurable disease
- Adequate organ function

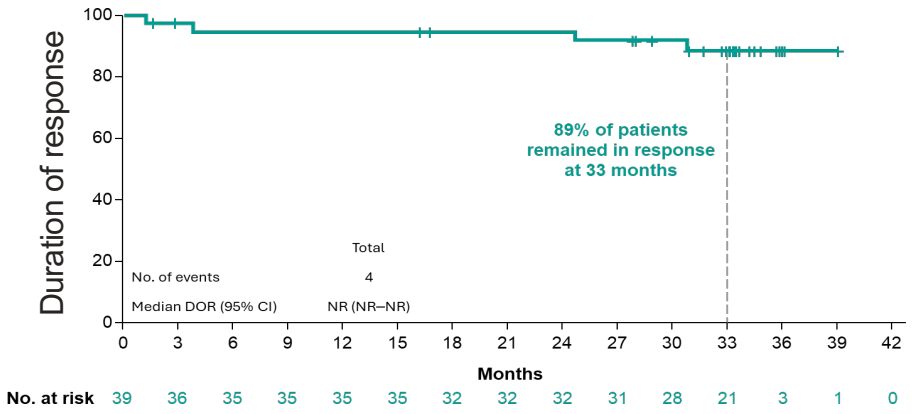
Arm 6 (1L FL) expansion, N=41

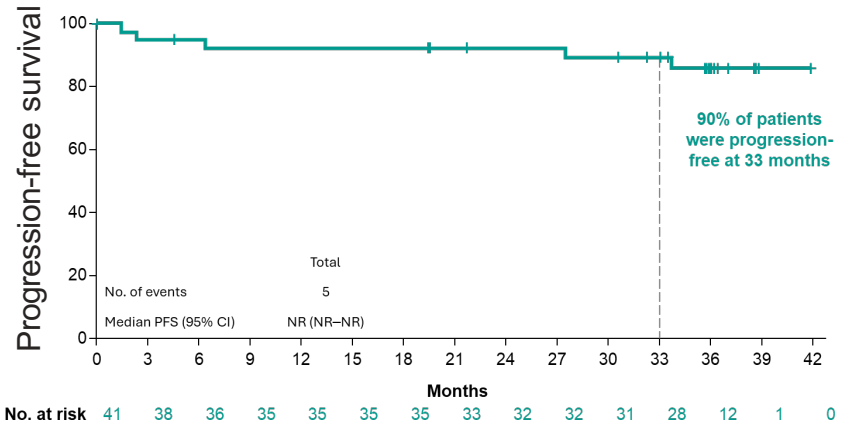
Epcoritamab (SC)	Rituximab (IV)	Lenalidomide (oral)
48 mg	**375 mg/m²**	**20 mg**
QW C1–2, Q4W C3+ (28 d/C)	QW C1, Q4W C2–6	QD for 21 d in C1–12
Treatment up to 2 y		

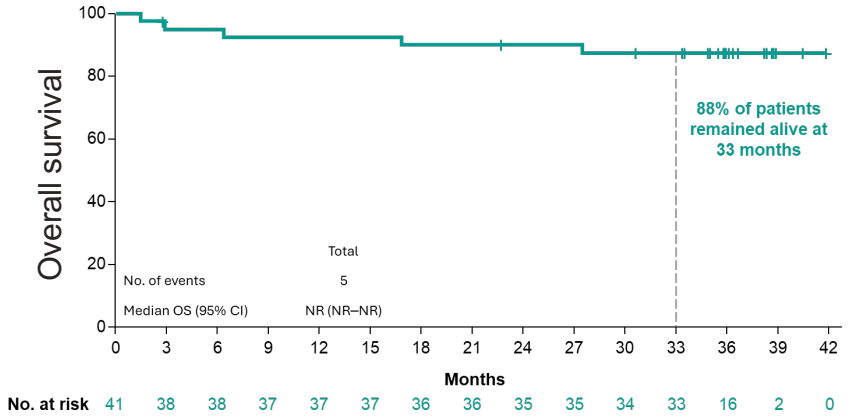
Median follow-up: 22.8 mo
Primary objective: Antitumor activity (ORR)
Key secondary endpoints: Safety, DOR, DOCR, PFS, OS

Responses

	Epcoritamab + R² N = 41
Overall response, n (%)	39 (95)
CR	36 (88)
PR	3 (7)
NE	2 (5)







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Epcoritamab combinations in B-NHL: Take-home messages

- **Epcoritamab is a potent, versatile CD3xCD20 BsAb**
  - SC administration and unique AE profile allow combinability
- **In FL:**
  - R^2 as a rational combination partner both in 2L+ and 1L
  - Phase 1/2 data promising (high ORR/CR; reproducible AE profile)
  - EPCORE FL-1 sets a standard and a new benchmark in 2L+
- **In DLBCL:**
  - Encouraging single-agent activity in 3L+
  - With R-CHOP/R-CHP-pola in 1L: high CR with MRD- rates; encouraging PFS
  - EPCORE DLBCL-2: 1L Phase 3 ongoing and data awaited

Memorial Sloan Kettering
Cancer Center