ASH 2024 Updates in Aggressive Lymphoma: Focus on Bi-specifics

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ASH Review

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Disclosures

Consulting Fees and Honoraria:

- AbbVie
- ADC
- Astra-Zeneca
- BeiGene
- Genentech
- Janssen
- Kite
- Novartis
- Pharmacyclics

Research Funding:

- Genentech

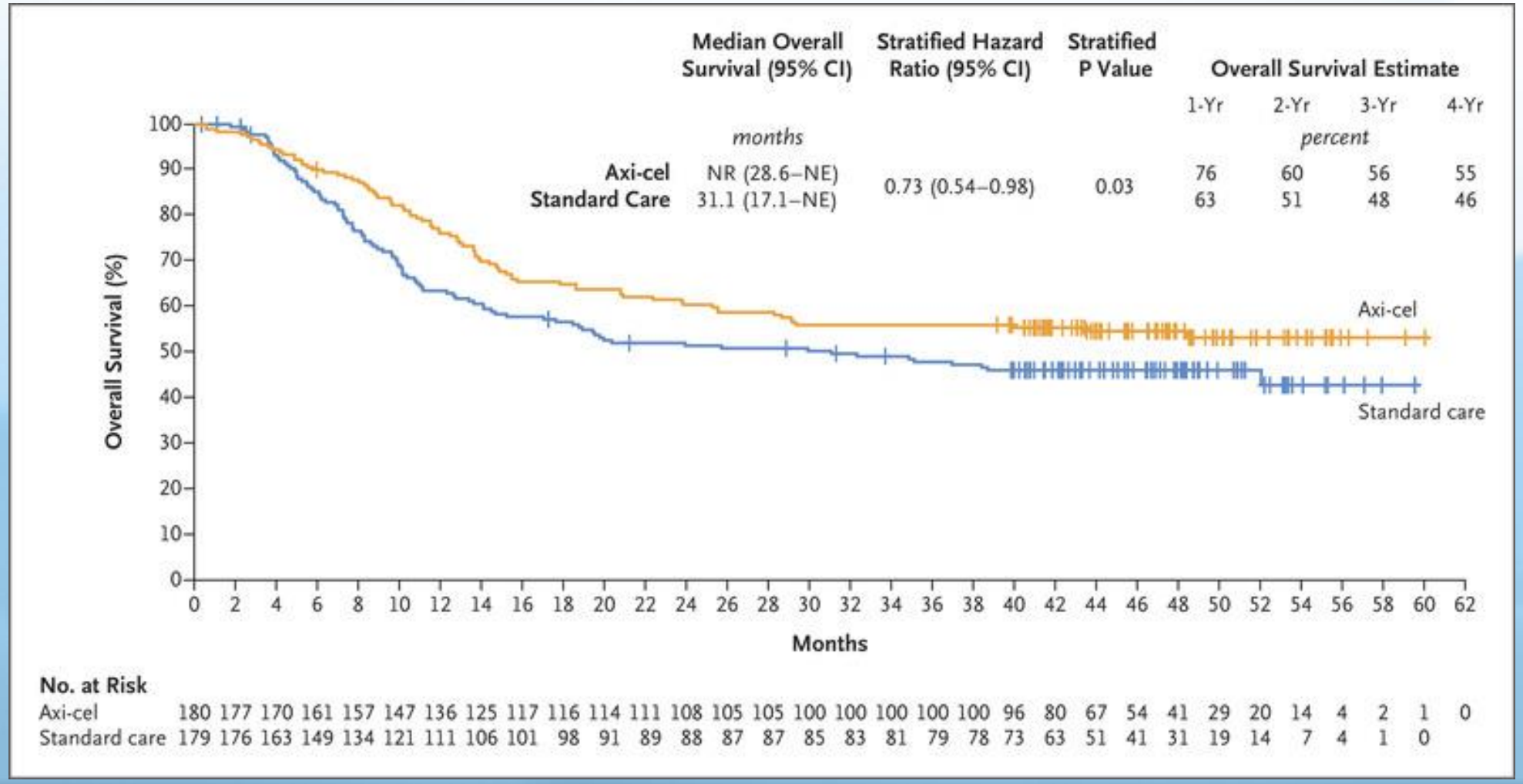
Travel:

- BMS

Agenda

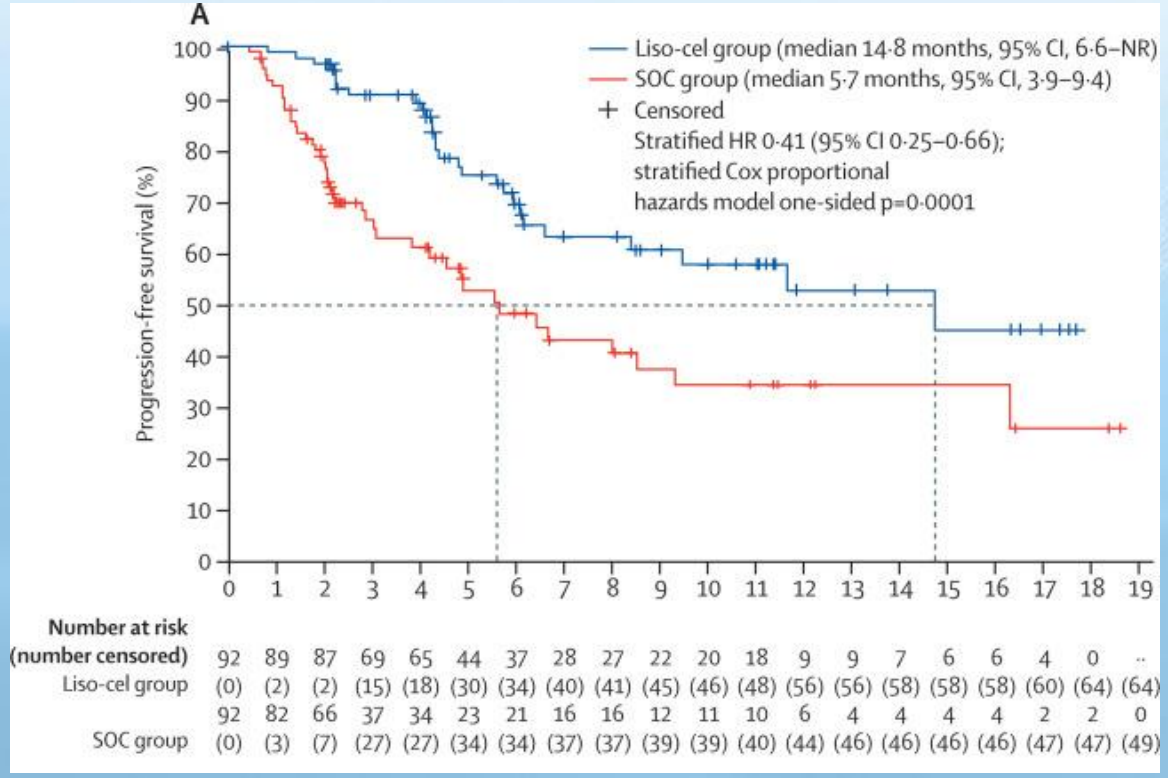
- Preamble: CAR-T remains standard of care for second line DLBCL
- Rationale and MOA of bi-specifics in R/R DLBCL
- Monotherapy data
- Bi-specifics + chemotherapy data
- Case examples

ZUMA-7: Axi-cel improves OS vs intent to transplant

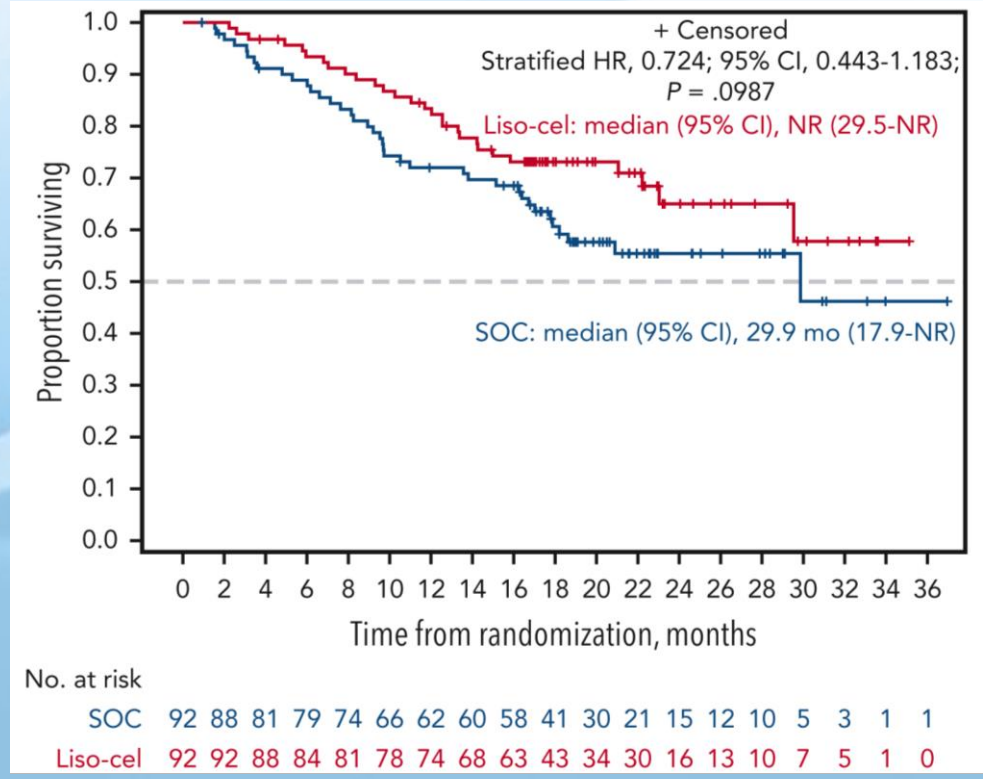


TRANSFORM: Liso-cel better than autoSCT

EFS



OS



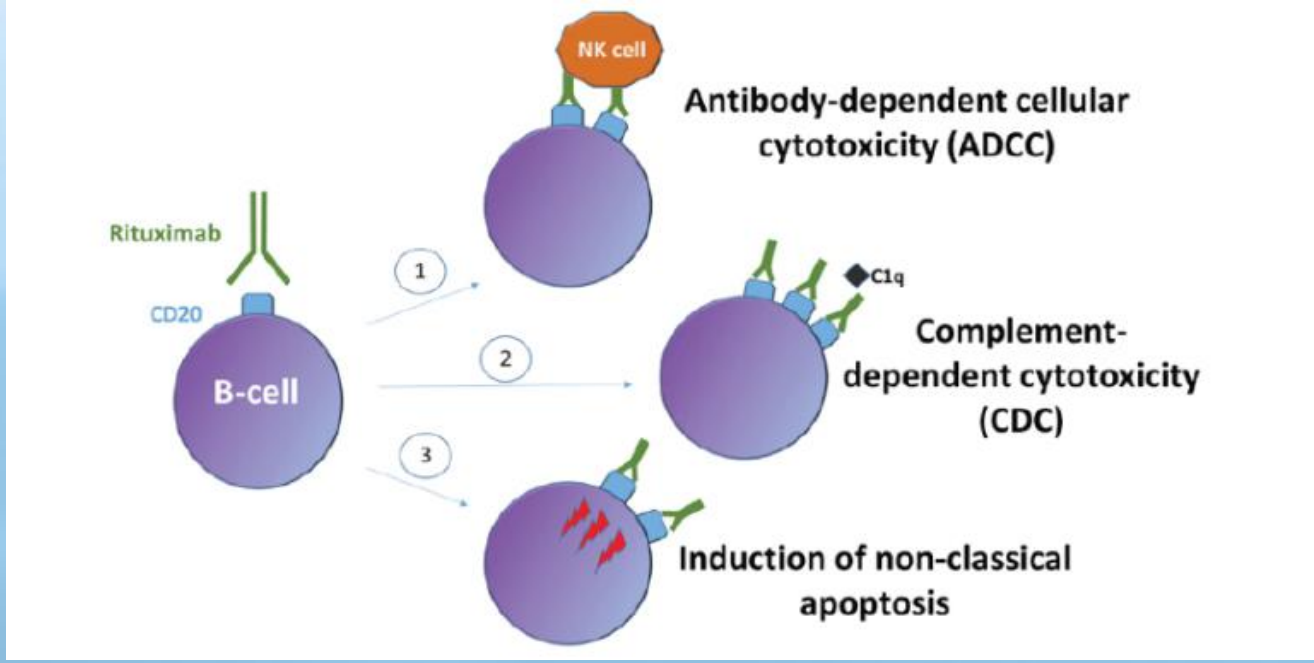
CAR-T is standard of care for R/R DLBCL in second line

However, challenges persist:

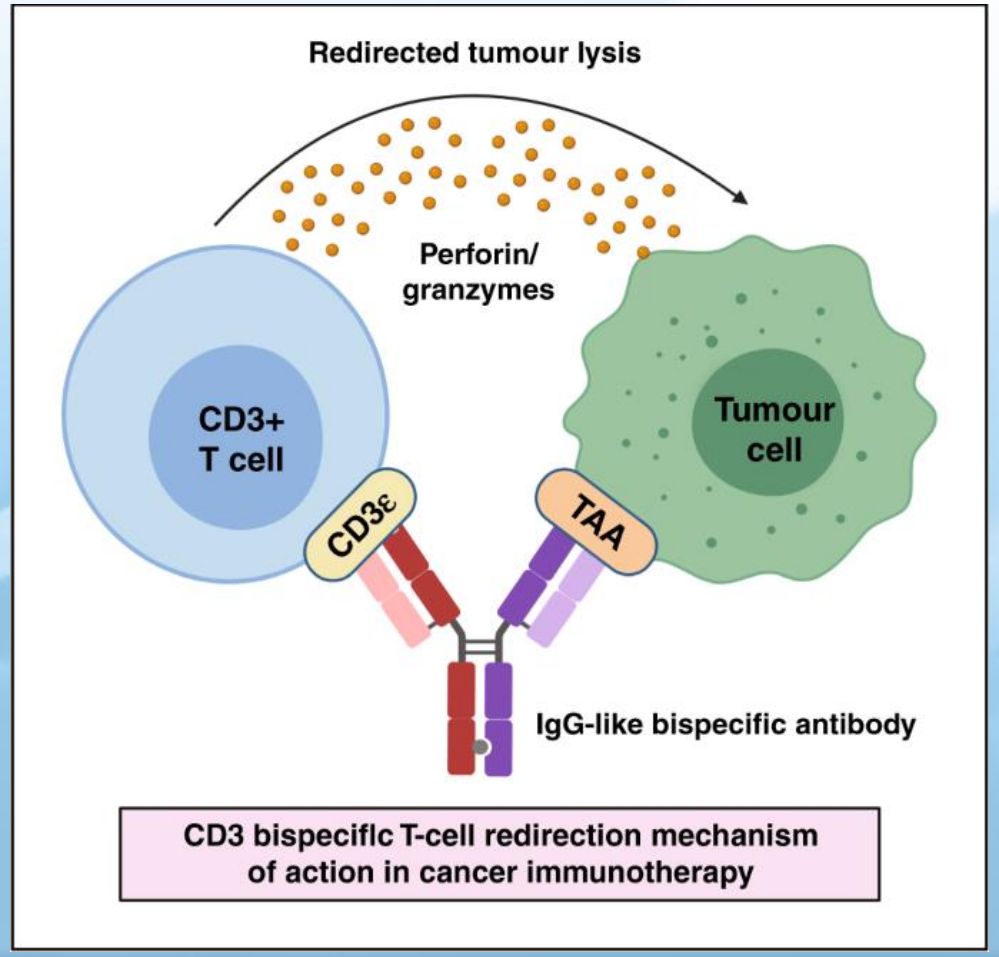
- Post CAR-T relapses?
- Delivery logistics of CAR-T
- Non-relapse mortality (mostly infections) ~6-8%

Bi-specific monotherapy in relapsed DLBCL

mAb therapy



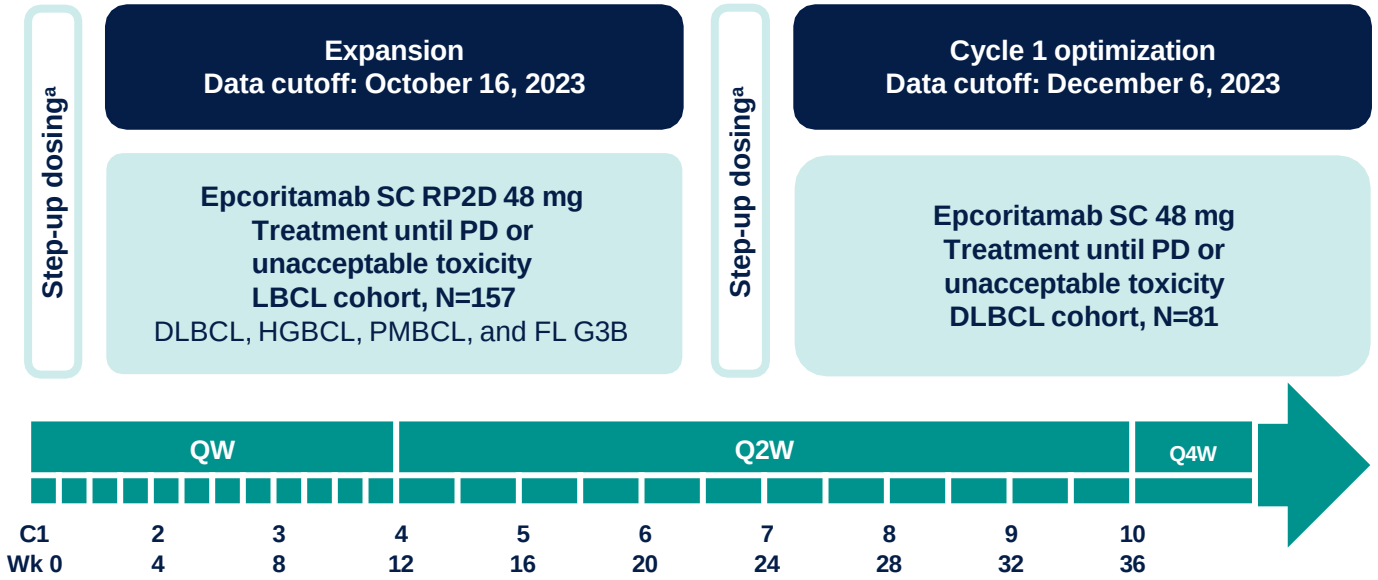
Bi-specific



Study Design: EPCORE® NHL-1

Key inclusion criteria:

- R/R CD20+ mature B-cell neoplasm
  - Optimization: DLBCL, NOS (de novo or transformed from FL)
- ECOG PS 0–2
- ≥2 prior lines of systemic antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed



Expansion

To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study

C1 optimization

Recommendations[b]: Dexamethasone 15 mg premedication[c]; administer 500 mL of isotonic IV fluids on the day of each dose prior to administration; hospitalization not required but patients must remain in close proximity to treatment facility for 24 h following first full dose

- For this follow-up analysis, efficacy was based on investigator assessment
- Time-to-event endpoints (ie, DOCR, PFS, OS) were analyzed by response using the Kaplan–Meier method
- Sensitivity analyses for PFS and OS were carried out based on an adjusted population excluding patients with COVID-19–related deaths on study
- Exploratory MRD analyses were performed using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA, USA) next-generation sequencing assay to evaluate ctDNA in plasma
- 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

CAR, chimeric antigen receptor; CT, computed tomography; ctDNA, circulating tumor DNA; D, day; DOCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; h, hour(s); MRI, magnetic resonance imaging; mo, month(s); OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SC, subcutaneous; SUD, step-up dose; wk, week(s). [a]SUD 1: priming, 0.16 mg; SUD 2: intermediate, 0.8 mg. Corticosteroid prophylaxis was used in cycle 1 to mitigate CRS. [b]Other recommendations include 2–3 L of fluid intake during the 24 h prior to and following each dose, holding antihypertensive medications for 24 h prior to each dose, and self-monitoring of temperature 3 times daily for 4 d following each dose. [c]On D1, D8, D15, and D22 and prophylaxis on D2–4, D9–11, D16–18, and D23–25. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

Baseline Characteristics and Prior Treatments

	LBCL N=157	LBCL Complete Responders, n=65
Median age (range), y	64 (20–83)	68 (20–83)
≥75 y, n (%)	29 (18)	15 (23)
ECOG PS, n (%)		
0	74 (47)	36 (55)
1	78 (50)	29 (45)
2	5 (3)	0
DLBCL,[a] n (%)	139 (89)	58 (89)
De novo, n/n (%)	97/139 (70)	39/58 (67)
Transformed, n/n (%)	40/139 (29)	19/58 (33)
Ann Arbor stage IV disease, n (%)	96 (61)	38 (58)
Median time from initial diagnosis to first dose, y	1.6	2.1
Median time from end of last therapy to first dose, mo	2.4	2.9
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)
≥3 prior lines of therapy, n (%)	110 (70)	47 (72)
Primary refractory[b] disease, n (%)	95 (61)	31 (48)
Refractory[b] to last systemic therapy, n (%)	130 (83)	48 (74)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	118 (75)	45 (69)
Prior ASCT, n (%)	31 (20)	15 (23)
Prior CAR T-cell therapy, n (%)	61 (39)	22 (34)

ASCT, autologous stem cell transplant; y, year(s). [a]Other disease types were FL G3B (n=5; CR, n=3), HGBCL (n=9; CR, n=2), and PMBCL (n=4; CR, n=2). DLBCL type was unknown in 2 patients. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within 6 mo of completion of therapy.

Long-Term Efficacy Outcomes

Deep and Durable Responses by Disease Subtype

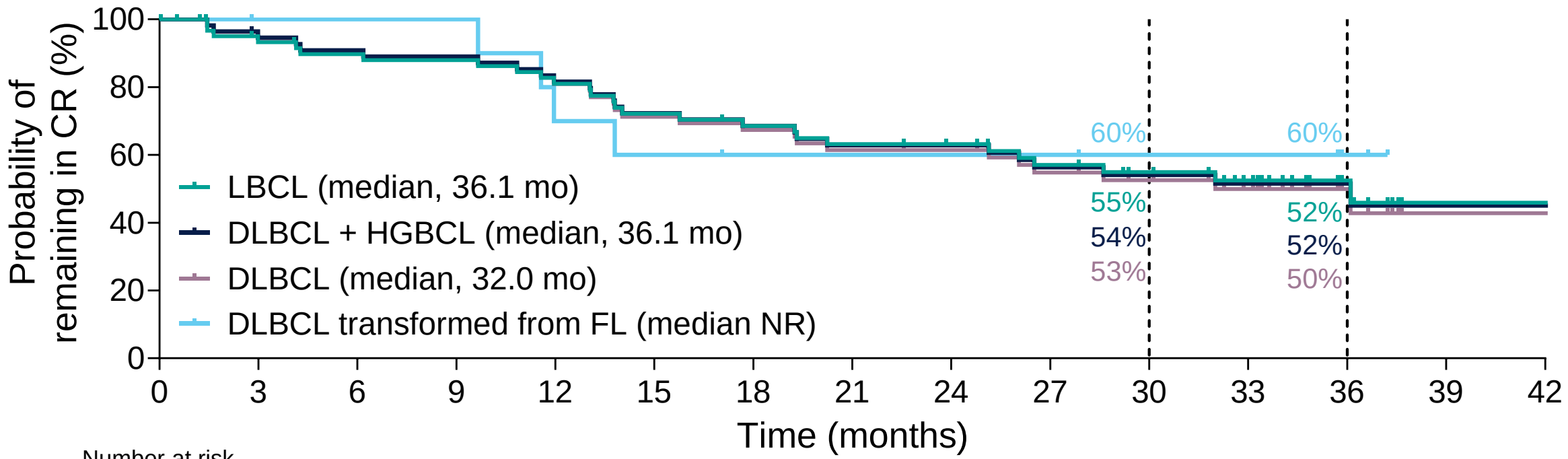
	LBCL N=157	DLBCL Transformed From FL n=32
ORR, n (%)	92 (59)	16 (50)
CR	65 (41)	14 (44)
PR	27 (17)	2 (6)
Median DOR, mo (95% CI)	20.8 (13.0–32.0)	NR (10.6–NR)
36-mo estimate, %	39	55

For patients in the DLBCL + HGBCL subgroup (n=148), ORR/CR rate was 57%/41% and median DOR was 20.8 mo (95% CI, 13.0–32.0) with a 36-mo estimate of 38%. For patients in the DLBCL subgroup (n=139), ORR/CR rate was 58%/42% and median DOR was 20.8 mo (95% CI, 13.4–32.0) with a 36-mo estimate of 38%.

CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; mo, months; LBCL, large B-cell lymphoma; mo, month; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response.

Vose JM, et al. ASH 2024. Poster 4480.

Durable Complete Responses



Number at risk

65	54	51	50	46	41	38	35	33	28	24	18	8	1	1
60	51	49	48	44	39	36	33	31	26	23	18	8	1	1
58	49	47	46	42	37	34	31	30	25	22	17	7	1	1
14	10	10	10	7	6	5	5	5	5	4	4	2	0	0

- Overall Median DOCR of 36.1 mo (95% CI, 20.2–NR)

CI, confidence interval; CR, complete response; DOCR, duration of complete response; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; mo, month(s); NR, not reached; PR, partial response.
Vose JM, et al. ASH 2024. Poster 4480.

Toxicities

	Expansion, N=157	C1 Optimization, N=81
CRS, n (%)[a]	80 (51)	30 (37)
G1	50 (32)	21 (26)
G2	25 (16)	8 (10)
G3	5 (3)	1 (1)
Treated with tocilizumab, n/n (%)[b]	23/80 (29)	13/30 (43)
Treated with corticosteroid, n/n (%)[b]	17/80 (21)	6/30 (20)
Leading to treatment discontinuation, n (%)	1 (1)	0
CRS resolution, n/n (%)[b]	78/80 (98)	30/30 (100)
Median time to resolution (range),[b] d	2 (1–27)	2 (1–15)

- Majority of CRS on the day 15 step-up dose
- 10 patients (6%) had ICANS; all events were G1–2 except one (G5)
- Most CRS events occurred following the first full dose

Infections on study:

- 46 patients (29%) had G≥3 serious infections
- 15 patients (10%) discontinued treatment due to infection

17 patients (11%) had fatal TEAEs

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

[a]Graded by Lee et al 2019 criteria.[1] [b]Among patients with CRS.

Study design

Pivotal single-arm Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

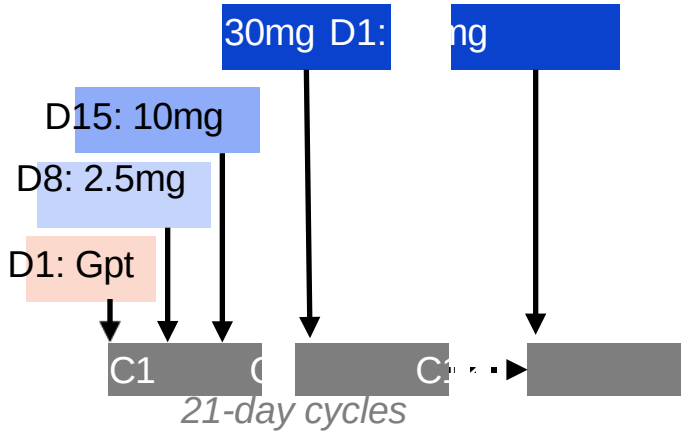
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

- Obinutuzumab IV pre-treatment (1000mg)
- C1 step-up dosing
- Monitoring after first glofitamab dose (2.5mg)



Endpoints

- **Primary:** CR (best response) rate by IRC*
- **Key secondary:** ORR,† DoR,† DoCR,† PFS, and OS

*By PET-CT (Lugano criteria)[1]; †By IRC and investigator. C, cycle; CRS, cytokine release syndrome; D, day; DoR, duration of response; DoCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; Gpt, obinutuzumab pre-treatment; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; IV, intravenous; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Baseline characteristics

n (%)*		All patients (N=154)†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I/II	35 (22.7)
	III/IV	116 (75.3)
NHL subtype	DLBCL	110 (71.4)
	trFL	28 (18.2)
	HGBCL	10 (6.5)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	19 (12.3)

n (%)*	All patients (N=154)†
Median no. of prior lines, n (range) 2 prior lines	3 (2–7)
≥3 prior lines	61 (39.6)
	93 (60.4)
Prior CAR-T	51 (33.1)
Refractory to prior CAR-T§	46 (29.9)
Prior ASCT	29 (18.8)
Refractory to any prior therapy	138 (89.6)
Refractory to last prior therapy	131 (85.1)
Refractory to first line of prior therapy	90 (58.4)
Refractory to any prior anti-CD20	128 (83.1)

The patient population was heavily pre-treated and highly refractory to prior therapy

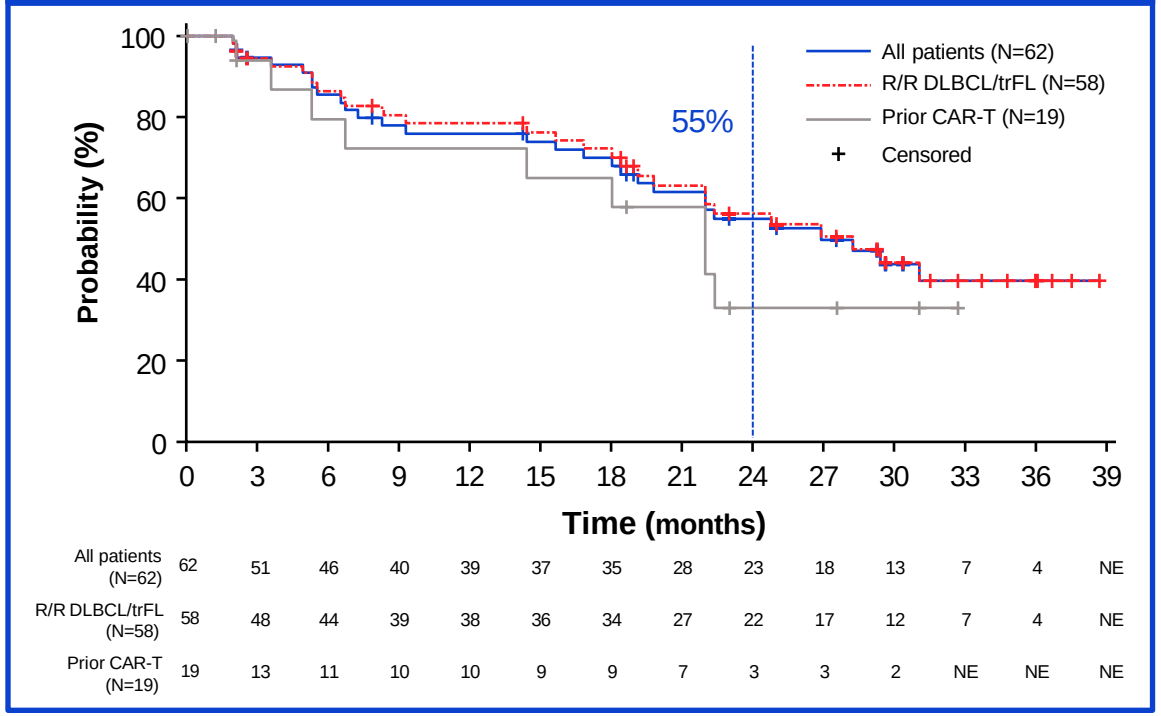
Clinical cut-off date: September 4, 2023. *Unless otherwise specified; †Safety-evaluable population (all treated patients; one patient enrolled in the intent-to-treat population did not receive any study drug and was excluded from the safety-evaluable population); ‡ECOG PS 2, n=1 (0.6%); one patient had an ECOG PS of 1 at enrolment, but deteriorated before the receipt of study treatment;[1] §Patients who had no response or relapsed within 6 months. ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; NHL, non-Hodgkin lymphoma; trFL, transformed follicular lymphoma.

1. Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Response rates and DoCR

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)†
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

DoCR by IRC



- Median time on study: 32.1 months (range: 0–43)

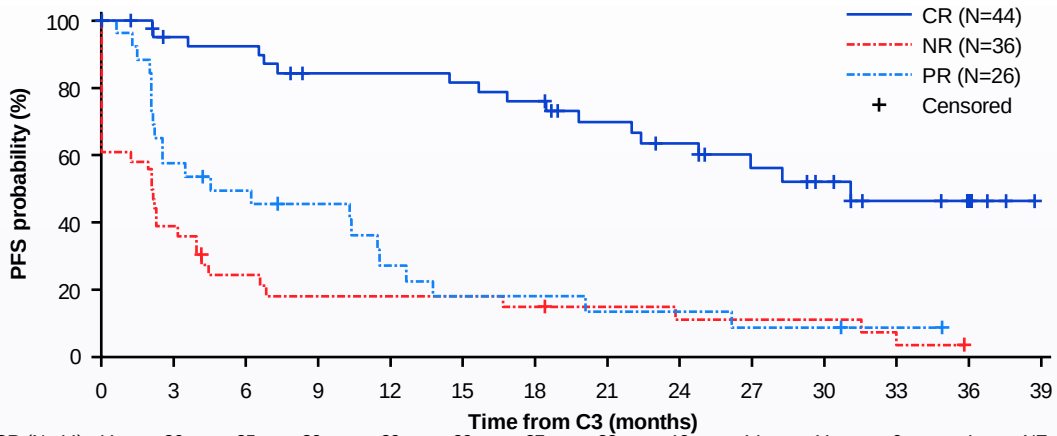
With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); †Patients in this subgroup had similar baseline characteristics to the overall population; ‡Primary efficacy population reported in the glofitamab USPI, all patients received at least one dose of glofitamab. CI, confidence interval; NE, not estimable; NR, not reached; USPI, United States prescribing information.

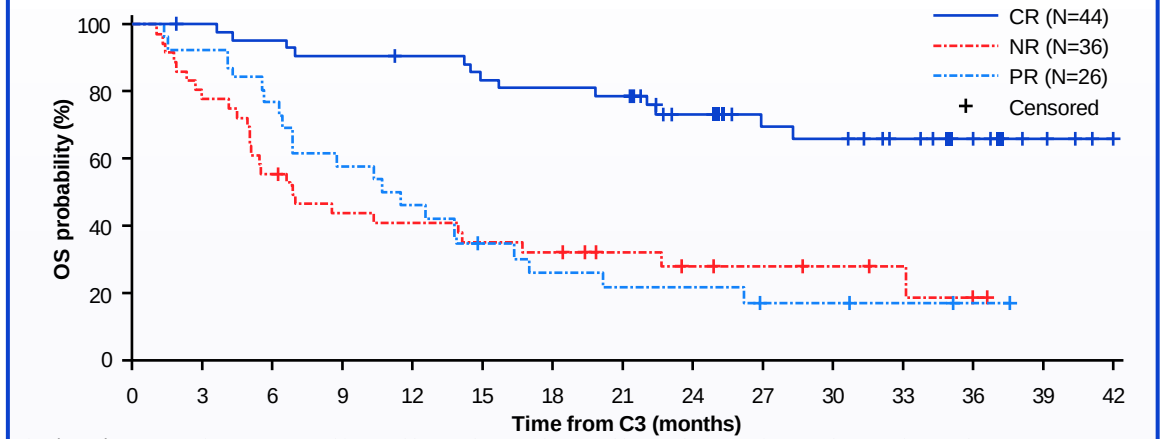
1. COLUMVI USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf.

Landmark analysis by response at Cycle 3

PFS



OS



Landmark PFS from C3 in patients with CR at C3*	N=44
Median PFS, months (95% CI)	31.1 (22.4–NE)
24-month PFS rate, % (95% CI)	63.5 (47.5–79.6)

Landmark OS from C3 in patients with CR at C3*	N=44
Median OS, months (95% CI)	NE (NE)
24-month OS rate, % (95% CI)	73.4 (59.9–87.0)

A high proportion of patients with a CR at C3 remained progression-free and alive after 24 months

*KM estimates. NR, no response.

Safety summary

- **CRS* remained the most common AE**
  - CRS occurred in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon
- **The incidence of AEs and SAEs was stable compared with earlier analyses[1,2]**
  - No new AEs were reported, including ICANS, CRS, infections, or Grade 5 AEs

N (%)	N=154
AE Glofitamab-related	152 (99) 140 (91)
Grade ≥3 AE Glofitamab-related	100 (65) 69 (45)
SAE Glofitamab-related	75 (49) 46 (30)
Grade 5 (fatal) AE Glofitamab-related	11 (7) 0
AE leading to treatment discontinuation Glofitamab-related	14 (9) 5 (3)
AE leading to dose modification/interruption of glofitamab Glofitamab-related	29 (19) 16 (10)

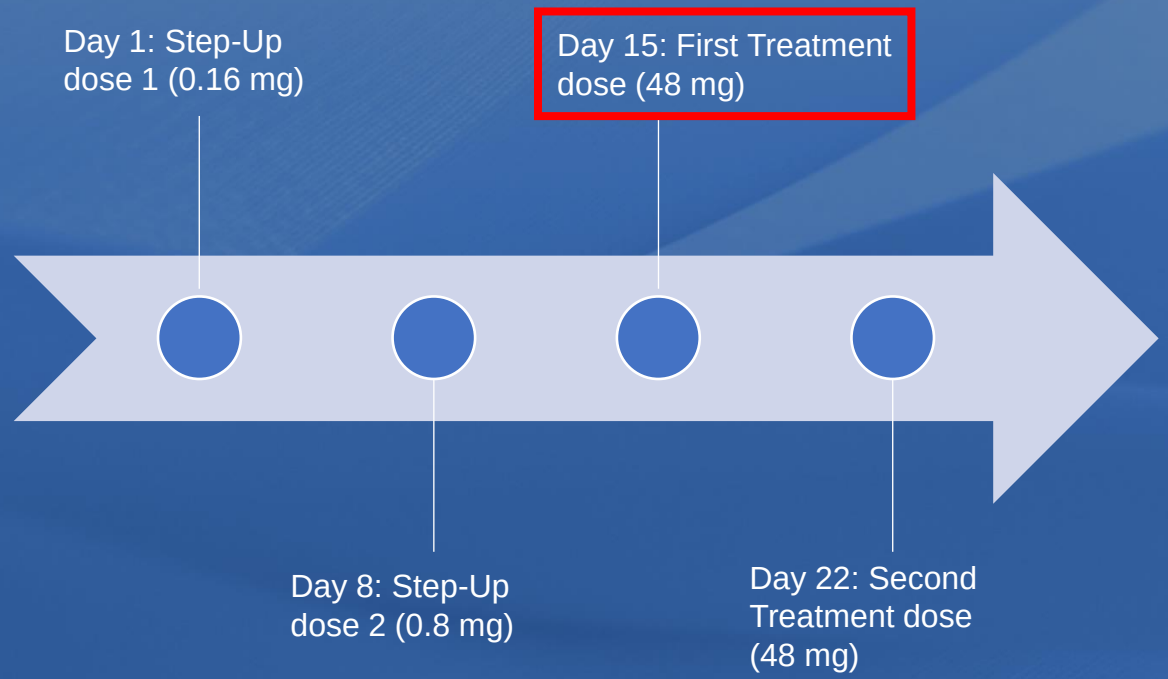
The safety profile was consistent with previous analyses, with no new AEs reported[1,2]

*By ASTCT grade. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy criteria; ICANS, immune effector cell-associated neurotoxicity syndrome; SAE, serious adverse event.

1. Dickinson M, et al. N Engl J Med 2022;387:2220–31;
2. Dickinson M, et al. ICML 2023; Oral 095.

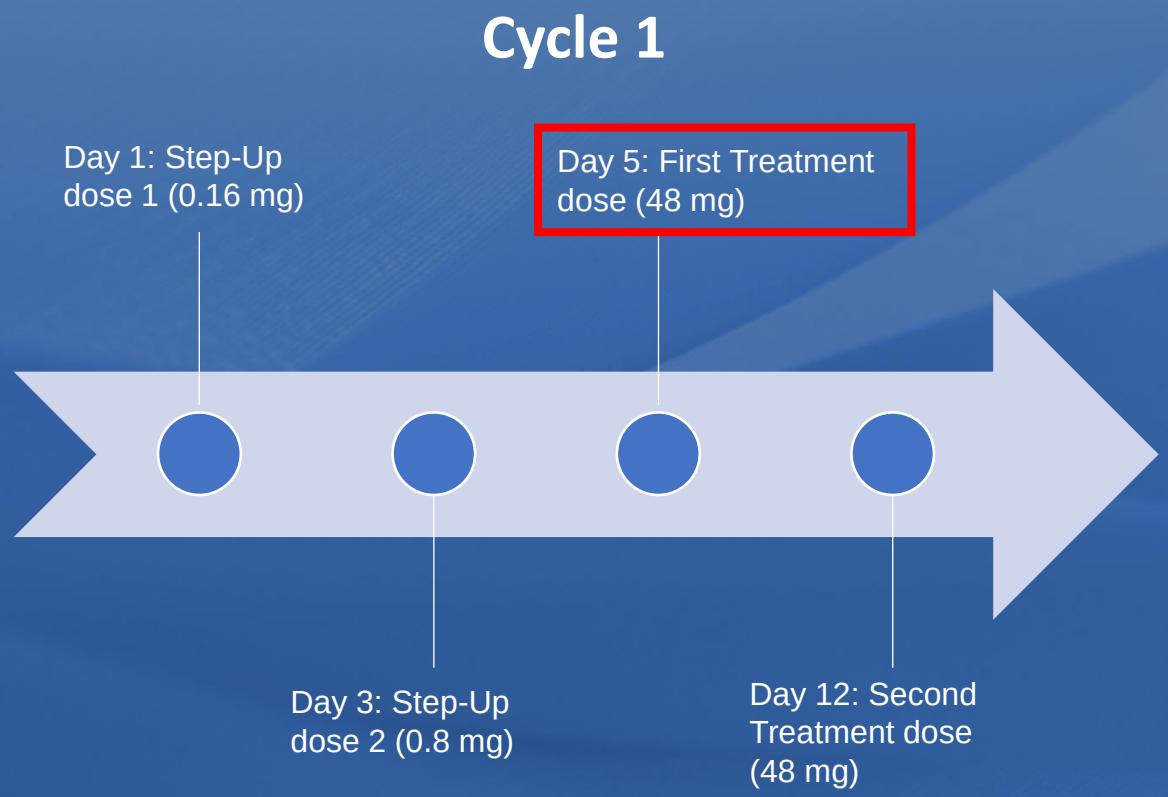
Epcoritamab Step-Up Dosing

Cycle 1



- Dexamethasone administered Days 1-4, 8-11, 15-18, and 22-25

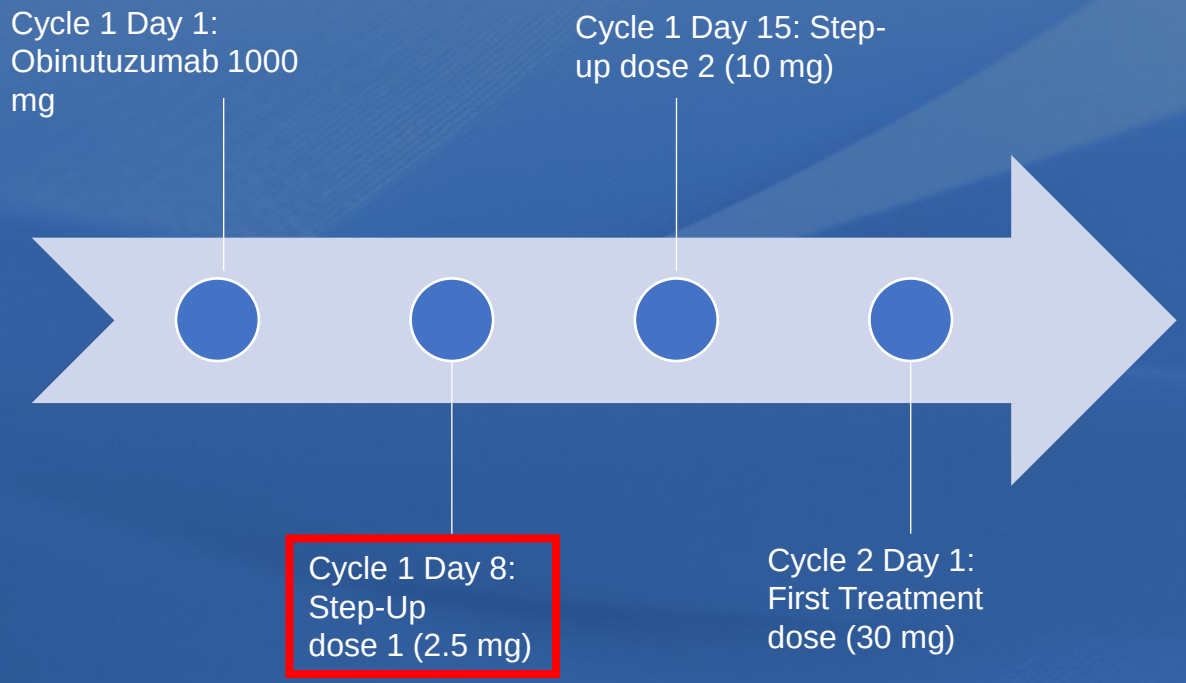
Rapid Epcoritamab Step-Up Dosing



- Dexamethasone administered Days 1-7 and Days 12-15
- Standard weekly dosing is resumed with Cycle 2

Glofitamab Step-Up Dosing

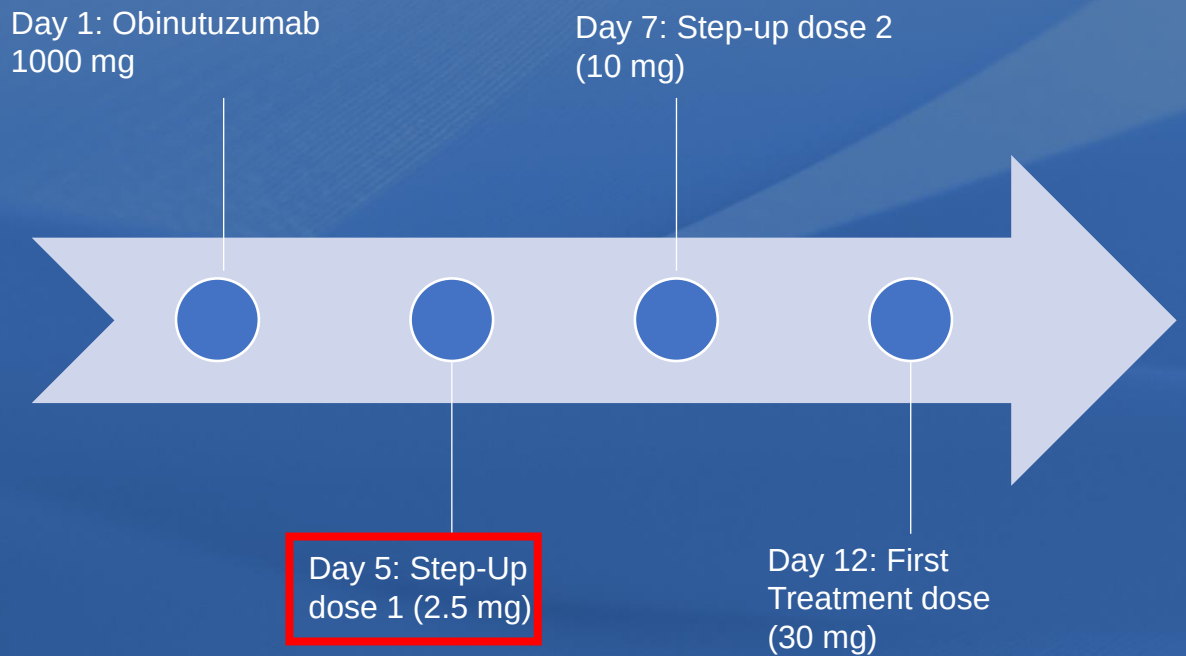
Cycle 1 and 2 (21 Days)



- Dexamethasone administered prior to each dose in Cycles 1-3
- Can consider dexamethasone 12, 24, and 48 hours after each dose in cycle 1

Rapid Glofitamab Step-Up Dosing

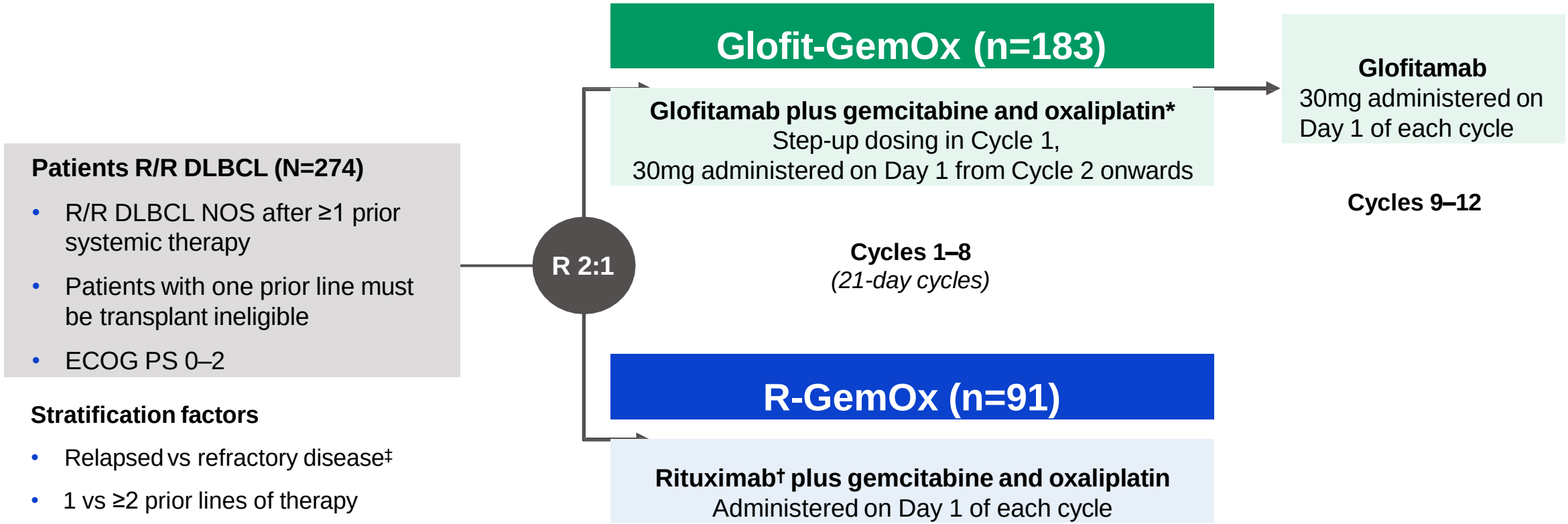
Cycle 1 (18 Days)



- Dexamethasone administered prior to each dose in Cycles 1-3
- Can consider dexamethasone 12, 24, and 48 hours after each dose in cycle 1

Bi-specific + chemoimmunotherapy in relapsed DLBCL

STARGLO: randomized Phase III trial in ASCT-ineligible patients with R/R DLBCL



*Gemcitabine 1000mg/m^2 and oxaliplatin 100mg/m^2. In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m^2. ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. ASCT, autologous stem cell transplant; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; NOS, not otherwise specified; R 2:1, patients randomized in a 2:1 ratio.

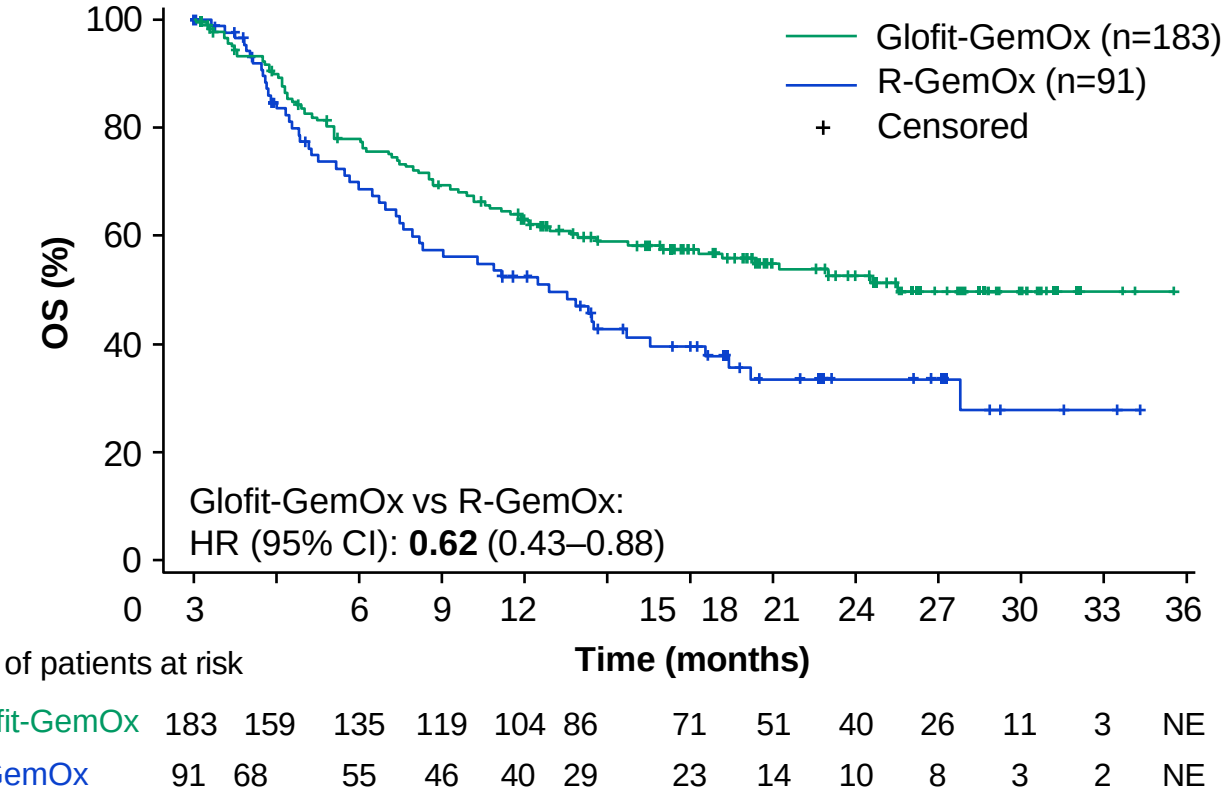
Baseline characteristics

n (%), unless otherwise stated		R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years	Median (range)	68.0 (20–84)	68.0 (22–88)
	≥65 years	56 (61.5)	116 (63.4)
Sex	Male	53 (58.2)	105 (57.4)
Race	Asian	51 (56.0)	86 (47.0)
	Black or African American	1 (1.1)	2 (1.1)
	White	33 (36.3)	82 (44.8)
	Unknown	6 (6.6)	13 (7.1)
ECOG PS	0	44 (50.0)	72 (40.0)
	1	36 (40.9)	89 (49.4)
	2	8 (9.1)	19 (10.6)
Ann Arbor stage	I–II	20 (22.0)	60 (32.8)
	III–IV	70 (76.9)	123 (67.2)
Number of prior lines of therapy	1	57 (62.6)	115 (62.8)
	≥2	34 (37.4)	68 (37.2)
Primary refractory	Yes	47 (51.6)	106 (57.9)
R/R to last prior therapy	Relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Bulky disease (≥10cm)	Present	14 (15.4)	23 (12.6)
Cell of origin at initial diagnosis	GCB	29 (31.9)	60 (32.8)
	Non-GCB (including ABC)	50 (54.9)	103 (56.3)
	Unknown	12 (13.2)	20 (10.9)
Prior CAR T-cell therapy	Received	8 (8.8)	13 (7.1)

ABC, activated B-cell-like; CAR, chimeric antigen receptor; GCB, germinal center B-cell-like.

Primary endpoint: overall survival

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

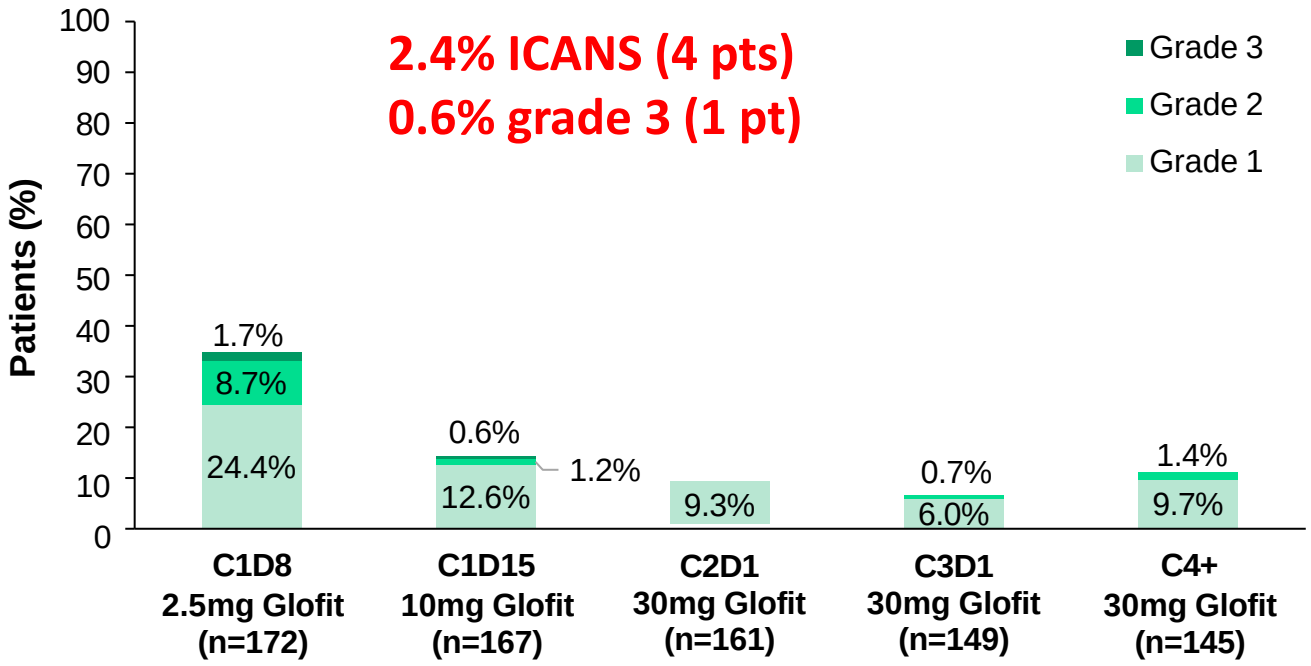
Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** vs R-GemOx

24-month OS not reported at the primary analysis as data were not sufficiently mature.
*p-value is alpha controlled at the primary analysis and descriptive at updated analysis. CI, confidence interval; HR, hazard ratio; NE, not evaluable.

Cytokine release syndrome

n (%) of patients with ≥1 CRS AE*	Glofit-GemOx (Glofit exposed) n=172
Any grade†	76 (44.2)
Grade 1	54 (31.4)
Grade 2	18 (10.5)
Grade 3	4 (2.3)‡
Median time to CRS onset, hours (range)	
2.5mg glofitamab (C1D8)	13.5 (4.4–134.9)
10mg glofitamab (C1D15)	32.4 (7.4–564.3)
Median CRS duration, hours (range)	
2.5mg glofitamab (C1D8)	22.7 (0.0–168.0)
10mg glofitamab (C1D15)	24.0 (0.0–248.5)
Tocilizumab for CRS management, n / n (%)	28 / 76 (36.8)
Corticosteroids for CRS management, n / n (%)	39 / 76 (51.3)

CRS by cycle and grade in the updated analysis



CRS mainly occurred in C1 and was predominantly low grade

Dexamethasone premedication was mandated to prevent/mitigate CRS prior to step-up doses and prior to at least two 30mg doses of glofitamab, until no additional CRS was observed.
*Unless otherwise specified. †No Grade 4 or 5 CRS events were reported. ‡One patient had a Grade 3 CRS event confounded by a concurrent Grade 5 Septic Shock that required multiple pressors.

Subcutaneous Epcoritamab + GemOx in Patients With Relapsed or Refractory DLBCL: Updated Results From EPCORE NHL-2

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Presented at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, IL (Poster number: 7037)

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Study Design: EPCORE® NHL-2 Arm 5

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab SC + GemOx in adults with R/R DLBCL ineligible for ASCT

Key inclusion criteria

- R/R CD20+ DLBCL[a]
  - DLBCL, NOS
  - "Double-" or "triple-hit" DLBCL
  - FL grade 3B
  - T-cell/histiocyte-rich DLBCL
- Eligible for GemOx
- Ineligible for ASCT or prior ASCT failure
- ECOG PS 0–2
- FDG-avid disease by PET
- Adequate organ function

Data cutoff: December 15, 2023
Median follow-up (range): 13.2 mo (1.0+ to 34.6)

Treatment regimen: Concomitant epcoritamab SC 48 mg + GemOx

	Agent	C1	C2	C3	C4	C5–9	C10+ until progression[c]
	Epcoritamab SC 48 mg[b]	QW	QW	QW	Q2W	Q2W	Q4W
GemOx	Gemcitabine 1000 mg/m^2 IV	Q2W					
GemOx	Oxaliplatin 100 mg/m^2 IV						

- **Primary objective:** Assess antitumor activity
- **Key secondary endpoints:** DOR, DOCR, TTR, PFS, OS, TEAEs

Cycles are 28 d. C, cycle; CT, computed tomography; d, day(s); DOCR, duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; FL, follicular lymphoma; IV, intravenous; NOS, not otherwise specified; PET, positron emission tomography; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SC, subcutaneous; SUD, step-up dose; TEAE, treatment-emergent adverse event; TTR, time to response; wk, week(s). [a]De novo or histologically transformed from FL or nodal marginal zone lymphoma based on World Health Organization 2016 classification. [b]SUD 1: priming, 0.16 mg; SUD 2: intermediate, 0.8 mg. [c]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. ClinicalTrials.gov: NCT04663347. EudraCT: 2020-000845-15.

Baseline Characteristics and Prior Treatments

Demographics	N=103
Median age (range), y	72 (20–87)
≥75 y, n (%)	36 (35)
Male, n (%)	57 (55)

Disease Characteristics and Prior Treatments	N=103
ECOG PS, n (%)	
0	33 (32)
1	57 (55)
2	13 (13)
IPI, n (%)	
<3	38 (37)
≥3	65 (63)
Bulky disease,[a] n (%)	
>10 cm	20 (19)
DLBCL type,[b] n (%)	
De novo	75 (73)
Transformed	24 (23)
DH/TH by local assessment,[c] n (%)	15 (15)
DH/TH by central lab,[c] n (%)	6 (6)

Disease Characteristics and Prior Treatments	N=103
Ann Arbor stage, n (%)	
I/II	22 (21)
III	18 (17)
IV	63 (61)
Median time from initial diagnosis to first dose (range), mo	13 (0.6–178)
Median time from end of last therapy to first dose (range), mo	5 (0.6–99)
Median prior lines of therapy (range)	2 (1–6)
Prior lines of therapy, n (%)	
1	39 (38)
2	27 (26)
≥3	37 (36)
Primary refractory[d] disease, n (%)	54 (52)
Refractory[d] to last systemic therapy, n (%)	72 (70)
Refractory[d] to ≥2 consecutive lines of therapy, n (%)	38 (37)
Prior ASCT, n (%)	10 (10)
Relapsed ≤12 mo after ASCT, n/n (%)	5/10 (50)
Prior CAR T therapy, n (%)	29 (28)

CAR T therapy, chimeric antigen receptor T-cell therapy; DH, double-hit; IPI, International Prognostic Index; IRC, independent review committee; TH, triple-hit; y, year(s). [a]Bulky disease per IRC assessment; 12 patients had bulky disease >10 cm per investigator assessment. [b]De novo versus transformed status of 4 patients was missing. [c]DH/TH status not assessed in 45 patients. [d]Refractory disease is defined as disease that either progressed during therapy or progressed within 6 mo of completion of therapy.

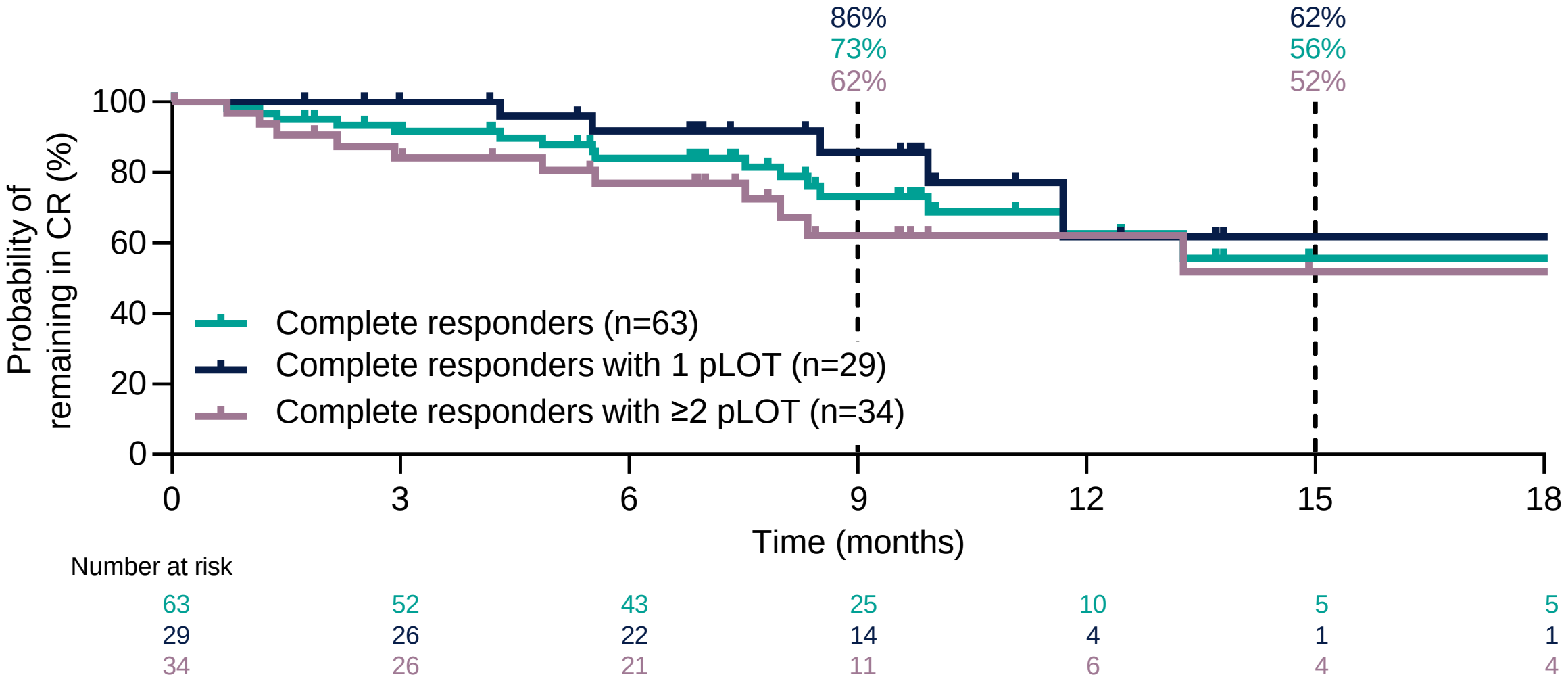
Responses Occurred Early and Rates Were High

Best Overall Response	Investigator Assessment N=103[a]	IRC Assessment N=103[b]
Overall response rate, n (%)	82 (80)	88 (85)
Complete response	60 (58)	63 (61)
Partial response	22 (21)	25 (24)
Median time to response (range), mo	1.5 (0.9–11.1)	1.5 (0.9–3.0)
Median time to complete response (range), mo	1.7 (1.3–10.7)	2.6 (1.3–22.1)

[a]Five patients were not evaluable for response per investigator. [b]Four patients were not evaluable for response per IRC.

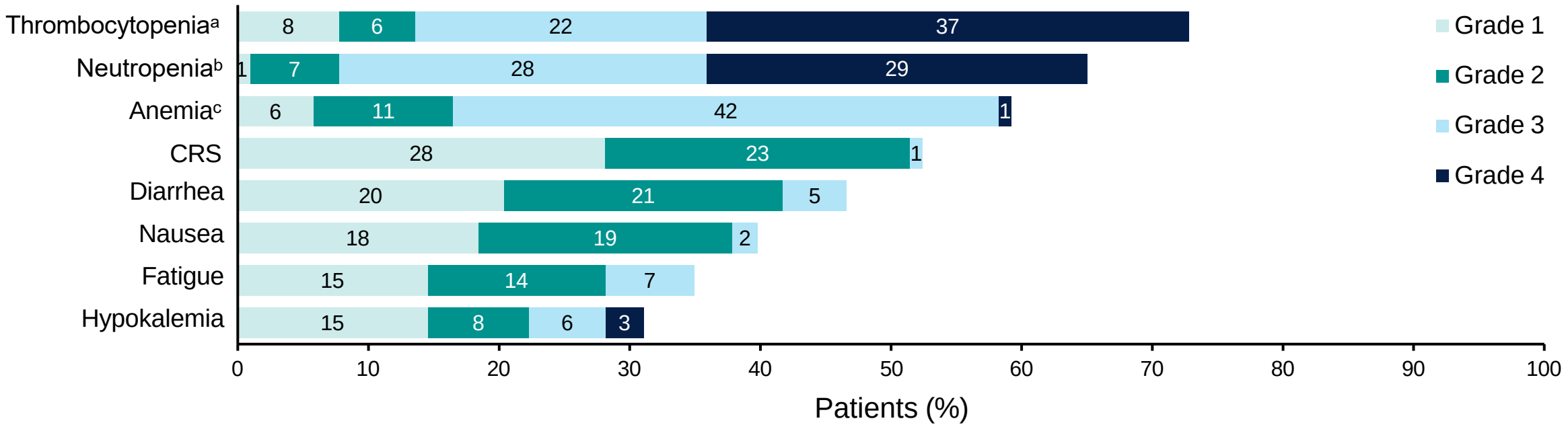
- High concordance (90%) between investigator and IRC assessment
- By IRC assessment, median duration of response among complete responders was 25.4 mo (range, 2.2 to 31.9+)

Complete Responses Were Durable



Kaplan–Meier estimates per IRC assessment.

Common (>30%) Treatment-Emergent Adverse Events



- 7 patients experienced febrile neutropenia
- ICANS was reported in 3 patients (grade 1–3, n=1 each); all events resolved and 1 patient discontinued treatment due to ICANS
- No clinical tumor lysis syndrome
- 13 patients had grade 5 TEAEs
  - 5 events were related to COVID-19; all patients had ≥1 risk factor for severe COVID, and 3 of the 5 patients with grade 5 COVID had CR
- One discontinuation to proceed with allogeneic stem cell transplant

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; SMQ, standardized MedDRA queries. [a]Combined term includes hematopoietic thrombocytopenia using SMQ narrow search. [b]Combined term includes neutropenia and decreased neutrophil count. [c]Combined term includes anemia, decreased hematocrit, decreased hemoglobin, decreased red blood cell count, and decreased serum ferritin.

Epcoritamab + R-DHAX/C in Transplant-Eligible Patients (Pts) With High-Risk Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)

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Presented at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, IL (Poster number: 7032)

Genmab

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Study Design: EPCORE® NHL-2 Arm 4

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R-DHAX/C in adults with R/R DLBCL who are eligible for transplant

Key inclusion criteria

- R/R CD20+ DLBCL
  - DLBCL, NOS
  - "Double-hit" or "triple-hit" DLBCL[a]
  - FL grade 3B
  - T-cell/ histiocyte-rich DLBCL
- Eligible for R-DHAX/C and HDT-ASCT
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: January 31, 2024
Median follow-up: 27.7 mo

Dose escalation, n=8

Step-up dosing[b]

Epcoritamab (SC)
24 mg (n=3) or 48 mg (n=5)
QW C1–4,
Q2W C5–9,
Q4W C10+*

+ R-DHAX/C
C1–3

Primary objectives: DLTs/Safety and tolerability
Key secondary objective: Antitumor activity

Expansion, n=21

Step-up dosing[b]

Epcoritamab (SC)
48 mg
QW C1–4,
Q2W C5–9,
Q4W C10+*

+ R-DHAX/C
C1–3

Primary endpoint: ORR per Lugano criteria[c]
***Epcoritamab treatment until HDT-ASCT or PD (whichever is earlier)**

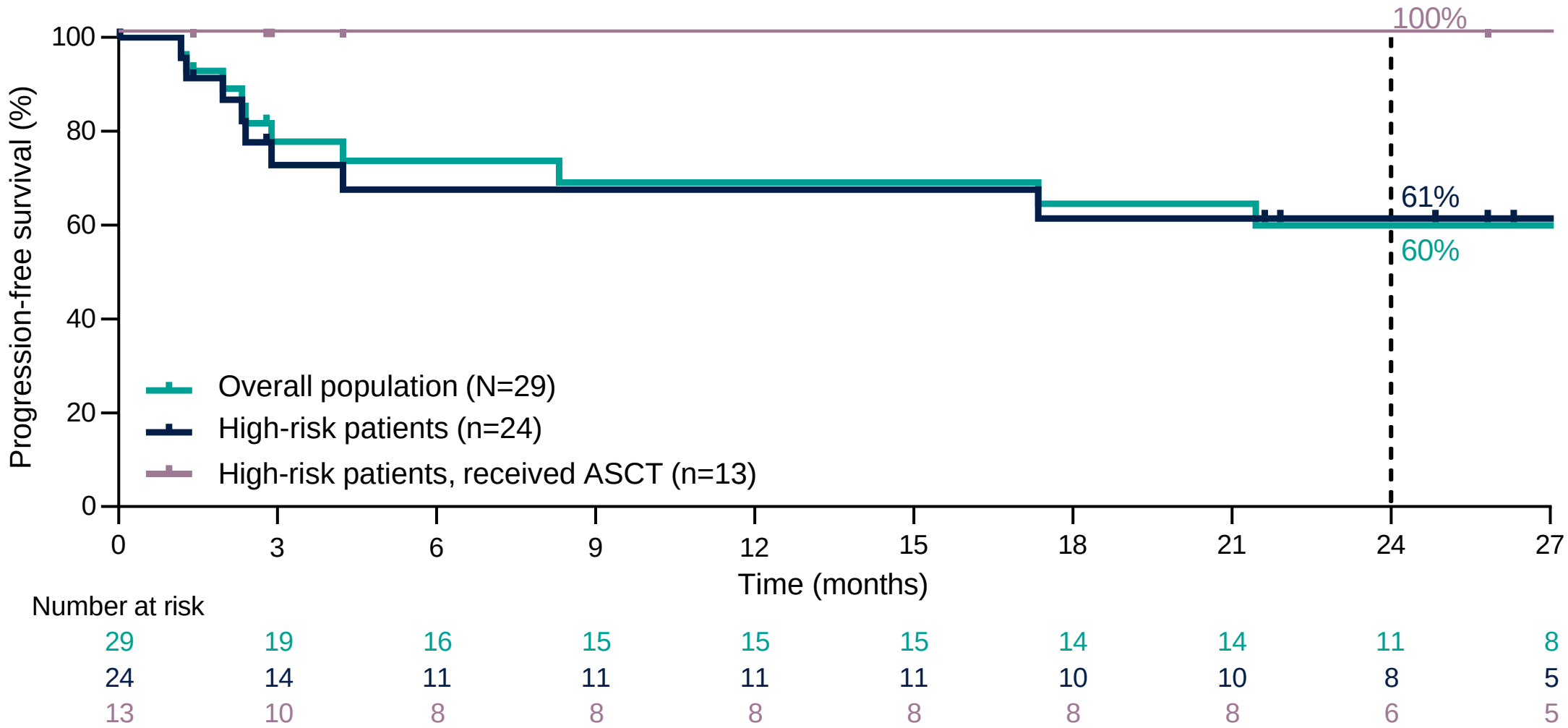
R-DHAX/C regimen in C1–3, 21 d each: rituximab 375 mg/m^2 IV Q3W; dexamethasone 40 mg/d IV or orally on D1–4; cytarabine 2 g/m^2 IV repeated after 12 h Q3W; carboplatin AUC = 5 mg/mL x min (Calvert formula) or oxaliplatin 100 mg/m^2 IV Q3W. Cycle 4 was 21 d. Cycles 5+ were 28 d. C, cycle; CT, computed tomography; d, day(s); DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; h, hour(s); HGBCL, high-grade B-cell lymphoma; IV, intravenous; min, minute(s); mo, month(s); MRI, magnetic resonance imaging; NOS, not otherwise specified; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PS, performance status; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; SUD, step-up dose; wk, week(s). [a]Classified as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations. [b]SUD 1: 0.16 mg; SUD 2: 0.8 mg. Corticosteroid prophylaxis was used in C1 to mitigate CRS. [c]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until PD. ClinicalTrials.gov: NCT04663347. EudraCT: 2020-000845-15.

Baseline Characteristics and Prior Treatments

Characteristic	N=29
Median age, y (range)	58 (28–75)
Male, n (%)	24 (83)
Ann Arbor stage, n (%)	
II–III	9 (31)
IV	20 (69)
Transformed from indolent lymphoma, n (%)	11 (38)
ECOG PS, n (%)	
0	11 (38)
1	18 (62)
Median time from diagnosis to first dose, mo (range)	10.8 (0.3–54.1)
Median number of prior lines of therapy (range)	1 (1–3)
Prior CAR T therapy, n (%)	3 (10)
Primary refractory[a] disease, n (%)	18 (62)
Progressed within 12 mo of initial therapy, n (%)	24 (83)
Relapsed[b] after last line of therapy, n (%)	12 (41)

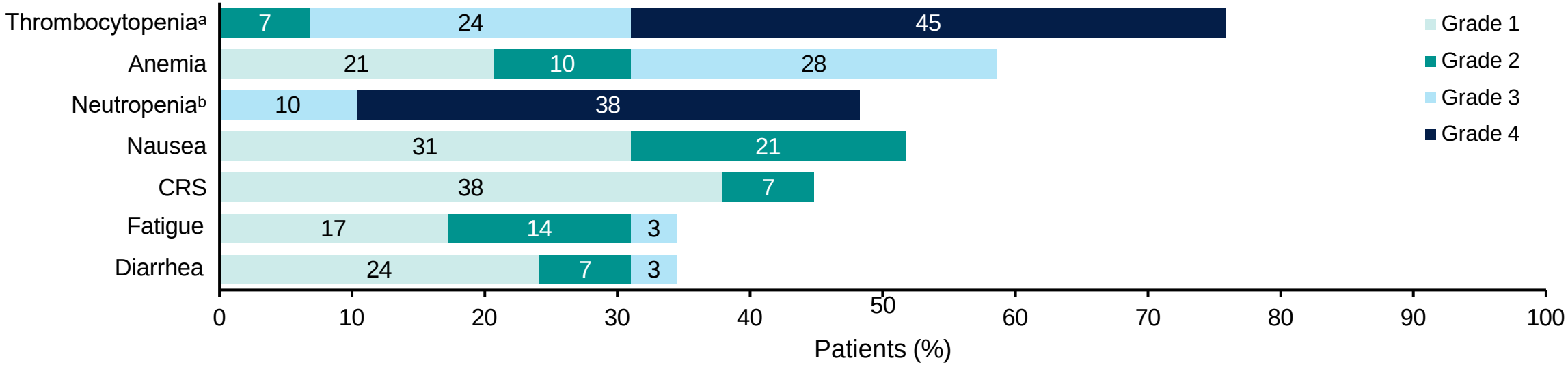
y, years. [a]Refractory indicates no response or disease progression within 6 mo after therapy. [b]Relapsed indicates disease progression >6 mo after therapy.

High Rate of PFS in High-Risk Patients Who Received ASCT



High risk indicates patients with primary refractory disease or who relapsed within 12 months of initial therapy. Kaplan–Meier estimates of patients remaining progression free are shown.
PFS, progression-free survival.

Common (>30%) Treatment-Emergent Adverse Events



- Febrile neutropenia was reported in 5 patients (17%; all G3)
- 11 patients had TEAEs that led to R-DHAX/C dose modification; 3 patients discontinued R-DHAX/C due to TEAEs
  - TEAEs that led to discontinuation of R-DHAX/C were anemia, decreased neutrophil count, decreased platelet count, and streptococcal endocarditis (n=1), Guillain-Barré syndrome (n=1), and lower respiratory tract infection, pneumonia, and thrombocytopenia (n=1)
- 13 (45%) patients had CRS and all were G1 or G2 events
- 1 patient had ICANS (G2), with confusional state as a symptom
  - ICANS resolved; the patient discontinued epcoritamab treatment
- No patients experienced CTLS and there were no fatal TEAEs

CRS, cytokine release syndrome; CTLS, clinical tumor lysis syndrome; G, grade; TEAE, treatment-emergent adverse event. [a]Combined term includes thrombocytopenia and decreased platelet count. [b]Combined term includes neutropenia and decreased neutrophil count.

Bispecific Antibodies in R/R DLBCL

	Glofitamab[1]	Epcoritamab[2]
Patients	N = 127 aNHL Prior CAR T = 51 (33%)	N = 157 Prior CAR T = 61 (39%)
ORR	aNHL 52% Prior CAR T NR	DLBCL 63% Prior CAR T 54%
CR	aNHL 39% Prior CAR T 35%	DLBCL 39% Prior CAR T 34%
CRS	50.3% (any grade) 3.5% ≥Gr 3	50% (any grade) 3% Gr 3
Neurotoxicity	5.3% ICANS-like 1.2% Gr 3	3% Gr 1 3% Gr 3
Route of Administration	IV	SQ
Steroid PPx	Pre-dose only mandated steroids	100mg prednisone or 15mg dexamethasone days 1-4
Duration	12 cycles = 36 weeks	Indefinite
Dosing Schedule	Obinutuzumab for single dose, then weekly glofitamab for 3 weeks, then every 3 weeks cycles 3-12	Weekly cycles 1-3 Twice per week cycles 4-9 Monthly cycles 10+

1. Hutchings M, et al. *J Clin Oncol.* 2021;39(18):1959-1970;
2. Thieblemont C, et al. *J Clin Oncol.* 2023;41(12):2238-2247.

Bispecific Monotherapy in R/R DLBCL: How I discuss with patients

	Glofitamab[1]	Epcoritamab[2]
Patients, Toxicity and Efficacy	The same!	The same!
Route of Administration	IV	SQ
Steroid PPx	Pre-dose only mandated steroids	100mg prednisone or 15mg dexamethasone days 1-4 after each injection
Duration	12 cycles = 36 weeks	Indefinite
Dosing Schedule	Obinutuzumab for single dose, then weekly glofitamab for 3 weeks, then every 3 weeks cycles 3-12	Weekly cycles 1-3 Twice per week cycles 4-9 Monthly cycles 10+

1. Hutchings M, et al. *J Clin Oncol.* 2021;39(18):1959-1970;
2. Thieblemont C, et al. *J Clin Oncol.* 2023;41(12):2238-2247.

Bi-specific + chemo in relapsed DLBCL

	Glofit + GemOx	Epco + GemOx	Epco + DHAC/X
Median Age	68yo	72yo	58yo
Prior Therapy	63% only 1L 7% prior CAR-T	38% only 1L 28% prior CAR-T	>50% only 1L 3% prior CAR-T
Efficacy	12.1 mos median PFS OS benefit over R-GemOx	Durable CRs reported	60% 2yr PFS
CRS	44% any grade 2.3% grade 3	52% CRS 1% grade 3	45% any grade 0% grade 3
ICANS	2.4% any grade 0.6% grade 3	2.9% any grade 1% grade 3	3.5% any grade No grade 3
Treatment related mortality	**8.3%**	**12.6%**	**0%**

Case #1

- 36yo very fit young man
- Primary refractory DLBCL (did not achieve CR with primary therapy):
  - Did not respond to R-ICE delivered by local oncologist
  - CAR-T with CR at day 30, PD at day 90
- Now disease rapidly progressing, with significant post CAR-T cytopenias preventing clinical trial enrollment
- Has matched sibling donor
- **Rapid uptitration glofitamab or epcoritamab**
  - Need rapid response with plan for consolidation with alloSCT
  - Can consider adding GemOx or DHAOx

Case #2

- 68yo very fit man
- Multiply relapsed DLBCL:
  - Prior autoSCT
  - Prior CAR-T
- Stage IV CKD with Cr 2.6; baseline cytopenias
- Due to renal insufficiency, not candidate for clinical trials or allogeneic stem cell transplant
- **Epcoritamab**
  - Indefinite therapy
  - Would not add chemotherapy given age, heavily pre-treated disease with cytopenias, prior receipt of platinum based chemo

Case #3

- 76yo actively smoking, unfit male
- Multiply relapsed DLBCL originally diagnosed in 2004:
  - Prior autologous transplant
  - 7 prior lines of therapy over prolonged period
- Borderline candidate for CAR-T due to age, smoking, cardiovascular history
  - Decides not interested in CAR-T
- Lives 90 minutes from KC and no ability to get bi-specifics locally
- **Glofitamab**
  - Every 3 week dosing
  - Time-limited therapy
  - No chemotherapy due to age, prior therapy history, active smoking

Case #4

- 60yo fit male
- Relapsed DLBCL:
  - Relapsed 15 mos after completion of R-CHOP
  - Insurance mandates he receive CAR-T or transplant out of state
- Now with progressive disease with obstructive jaundice from peri-portal node
  - Peri-portal node is his only site of disease at relapse
- **Glofitamab (rapid) + GemOx:**
  - Enables CAR-T indication after therapy
  - Not clearly chemo-refractory and fit
  - ?XRT to peri-portal node?

Case #5

- 74yo male, ambulatory with some co-morbidities (PS 2)
- Lives 2 hours from KC with his elderly wife
- Relapsed transformed DLBCL from MZL with secondary CNS involvement:
  - CSF cleared with R-ICE x 2 and IT chemotherapy
  - Not a candidate for CAR-T due to frailty
- **Glofitamab + zanubrutinib**
  - Published data in CNS
  - Distance from center
  - Zanubrutinib has CNS penetration and underlying MZL

Take Home Points

- CAR-T remains the standard of care for R/R DLBCL
- Bi-specific monotherapy associated with durable responses and relatively high non-relapse mortality among more heavily pre-treated patients
- Glofitamab and epcoritamab have similar efficacy and toxicity profiles, but differ in:
  - Dosing schedule, route, and duration
  - Steroid prophylaxis
    - Please only use the dexamethasone optimization with epcoritamab!
- Bi-specifics + chemo improve response rates, but add toxicity
  - Longer follow up required to see if CRs are durable