



10th POSTGRADUATE
**Lymphoma
Conference**

T-cell engaging antibodies in DLBCL

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Rigshospitalet and University of Copenhagen, Denmark

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Hotel Monaco & Grand Canal

President:
P.L. Zinzani

Disclosures

- **Consultant/advisor:**

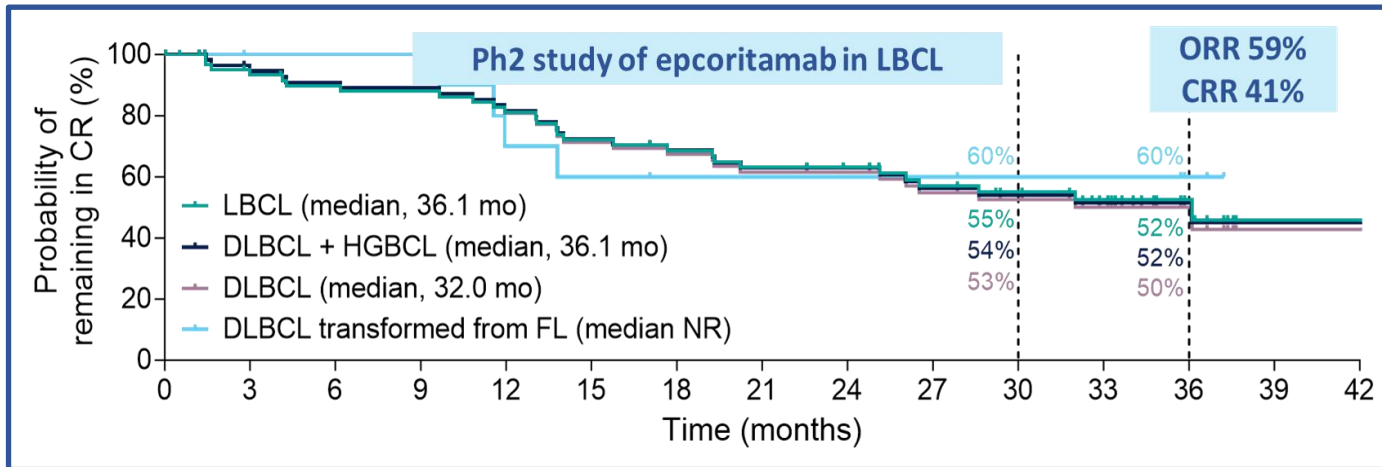
- AbbVie, AstraZeneca, Genmab, Johnson&Johnson, Merck, Roche, Takeda

- **Research support (institution):**

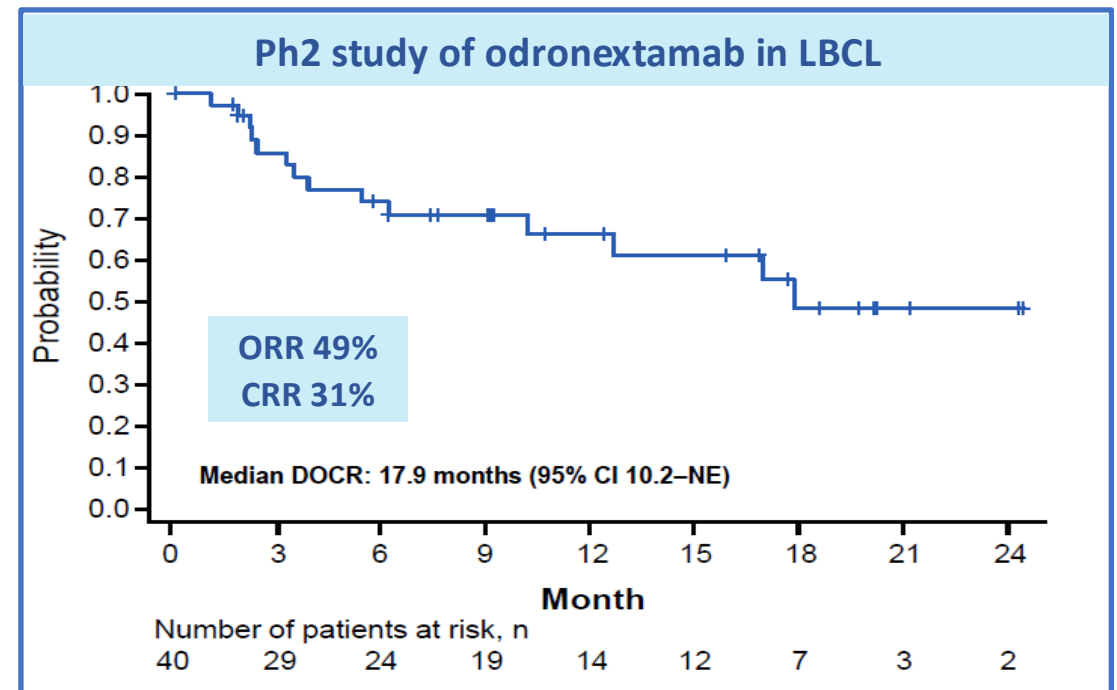
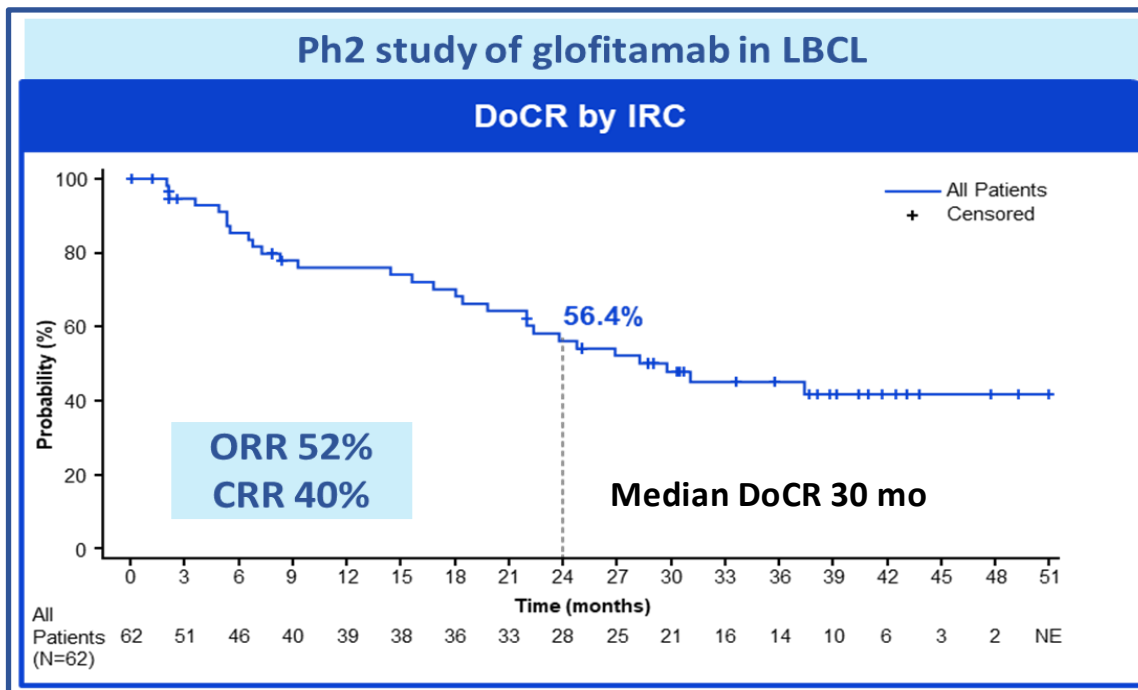
- AbbVie, Arvinas, AstraZeneca, Bristol Myers-Squibb, Celgene, Genentech, Genmab, Incyte, Johnson&Johnson, Merck, Novartis, Pfizer, Roche, Takeda

**CD20xCD3 bispecific antibodies
in R/R DLBCL**

Bispecific CD20xCD3 antibodies are approved in r/r LBCL

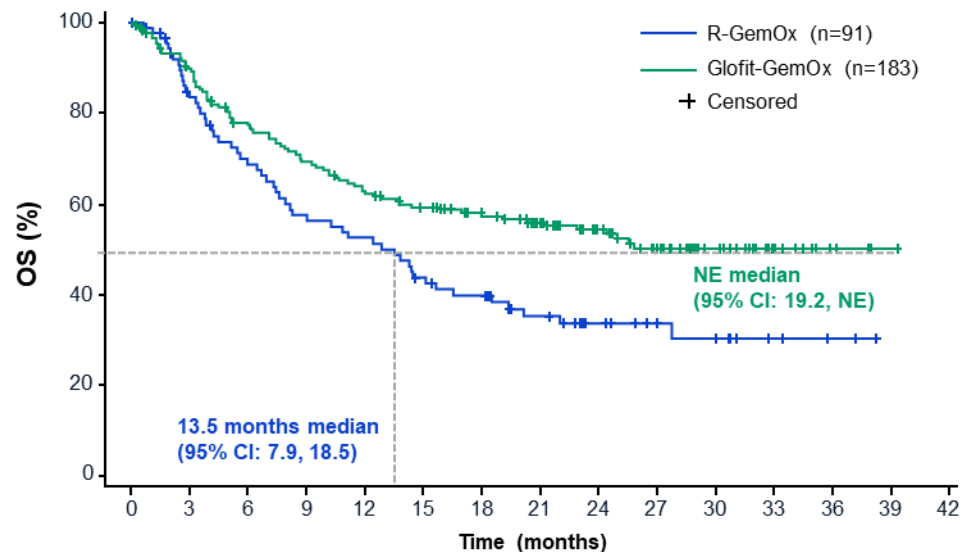


Ph2 study of mosunetuzumab in LBCL N=88	
CR rate, %	24 (15–34)
ORR, %	42 (32–53)
Median DOCR, months	NR (9.0–NE)
Median DOR, months	7.0 (4.2–NE)
Median PFS, months	3.2 (2.2–5.3)
Median OS, months	11.5 (9.0–16.4)

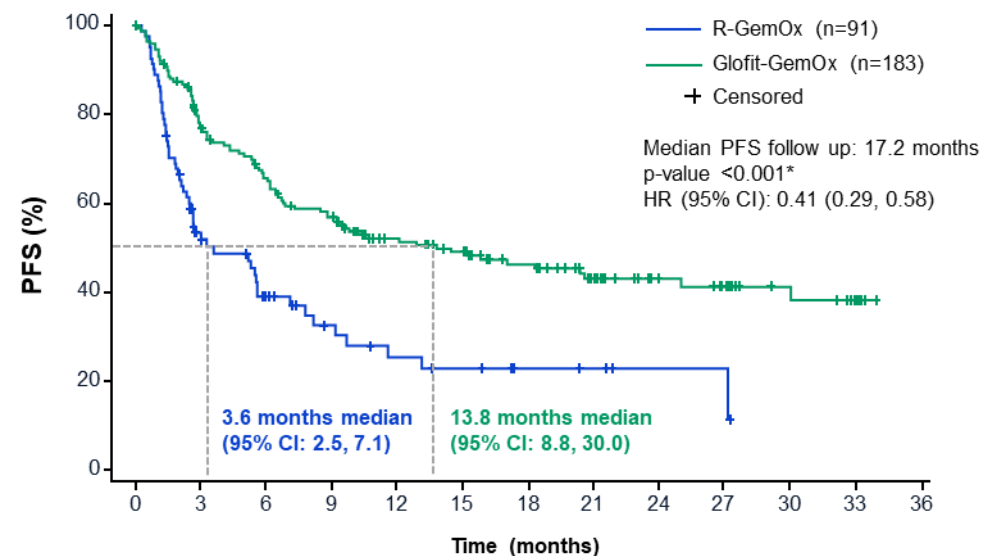


STARGLO: R-GemOx vs. Glofit-GemOx in r/r DLBCL

Overall survival with ~2 years of follow up



Progression-free survival with extended follow up

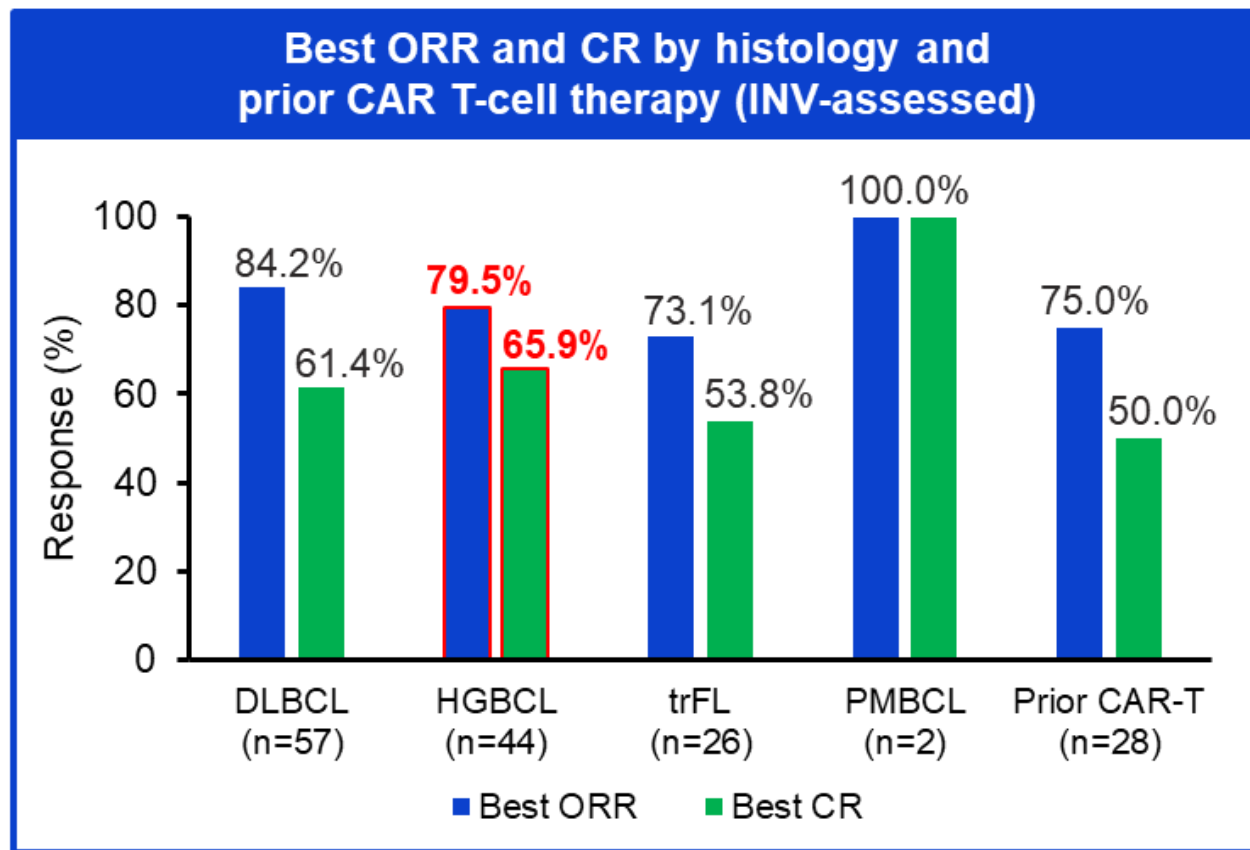


Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
2-year follow up analysis (median follow up: 24.7 months)		
OS, median (95% CI); months	13.5 (7.9, 18.5)	NE (19.2, NE)
HR (95% CI)	0.60 (0.42, 0.85)	
p-value*	0.003	
24-month OS, % (95% CI)	33.6 (22.9, 44.2)	54.4 (46.8, 62.0)

Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
PFS, median (95% CI); months	3.6 (2.5, 7.1)	13.8 (8.8, 30.0)
18-month PFS, % (95% CI)	23.0 (11.5, 34.4)	46.5 (38.5, 54.5)

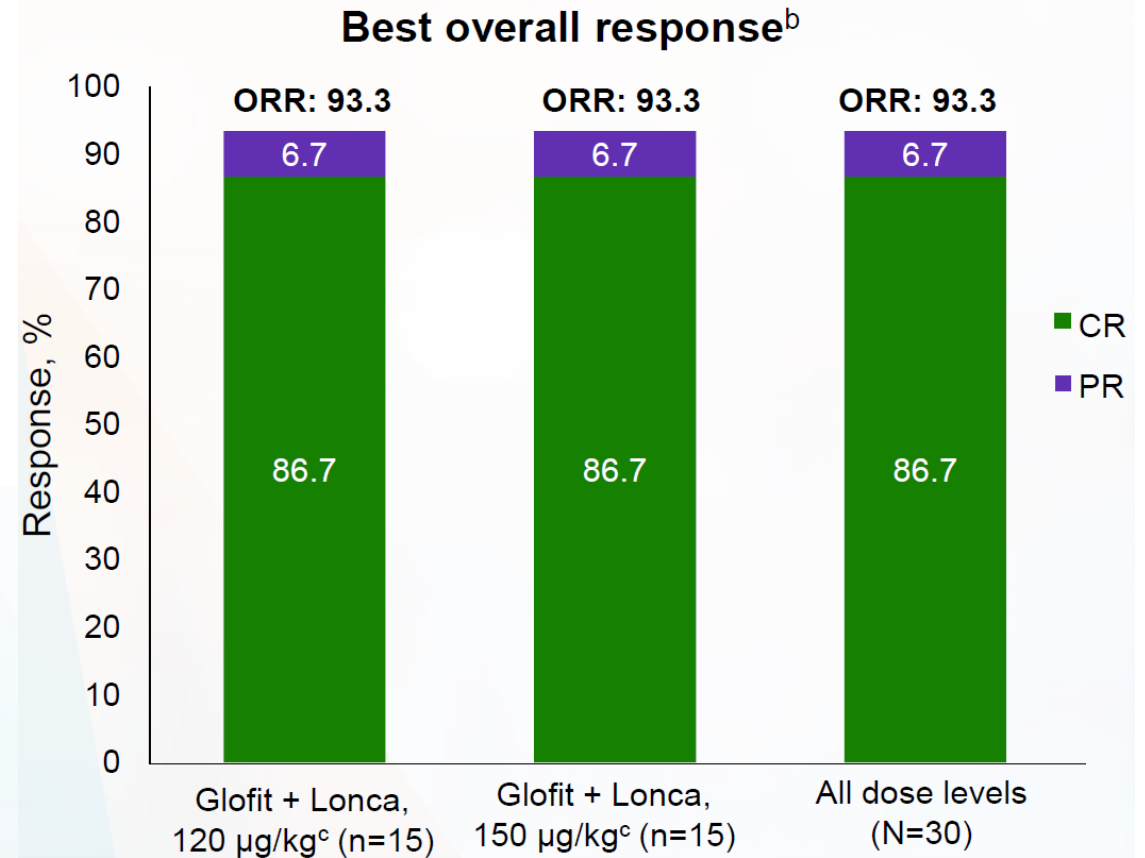
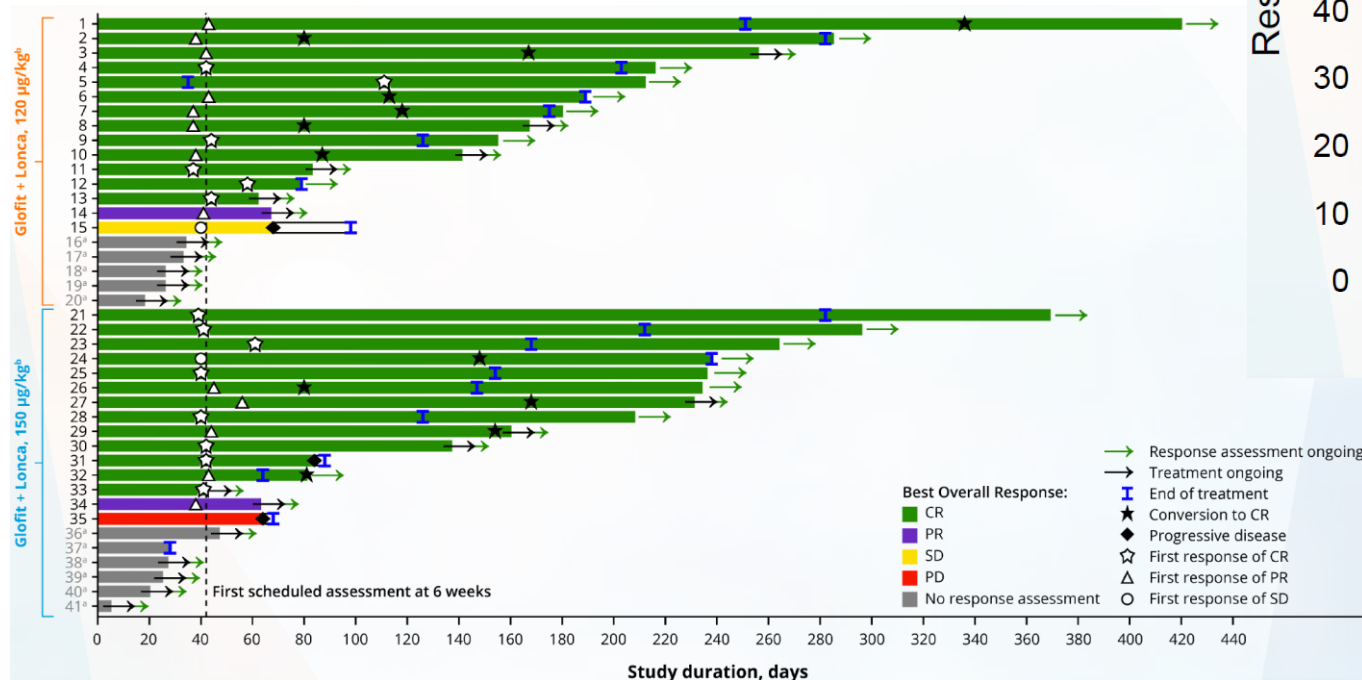
Glofitamab and Polatuzumab vedotin in r/r DLBCL

n (%) [95% CI]	By INV N=129	By IRC N=129
ORR	104 (80.6) [72.7–87.1]	101 (78.3) [70.2–85.1]
CR	80 (62.0) [53.1–70.4]	77 (59.7) [50.7–68.2]
PR	24 (18.6) [12.3–26.4]	24 (18.6) [12.3–26.4]
PD	16 (12.4) [7.3–19.4]	16 (12.4) [7.3–19.4]
DOR, median (months) [95% CI]	24.3 [15.0–37.8]	26.4 [10.9–44.3]



Impressive responses observed (66% CR) amongst patients with HGBCL

Glofitamab and Loncastuximab tesirine in r/r DLBCL

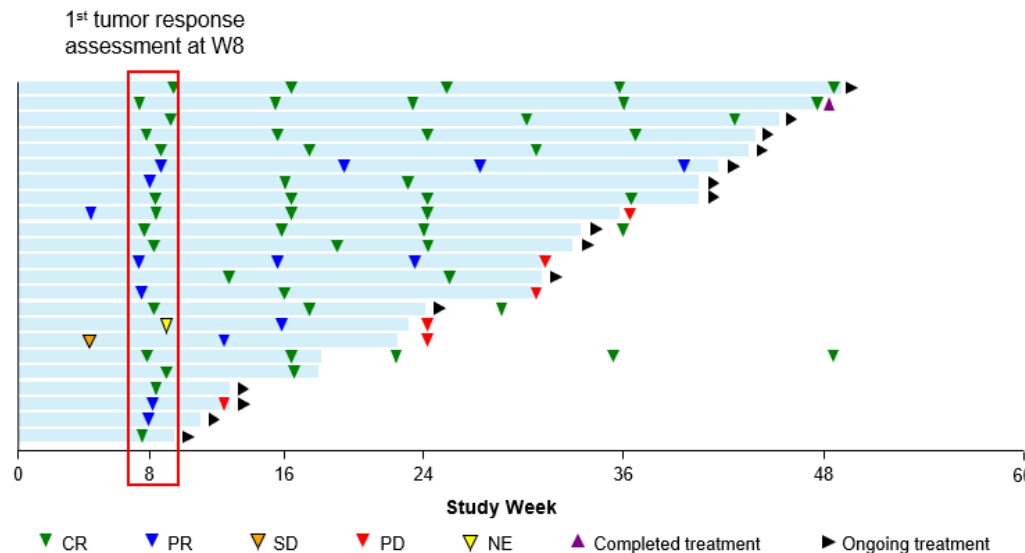


EPCORE NHL-5 arm 1: Phase Ib/II study of epcoritamab + R² in patients with R/R DLBCL

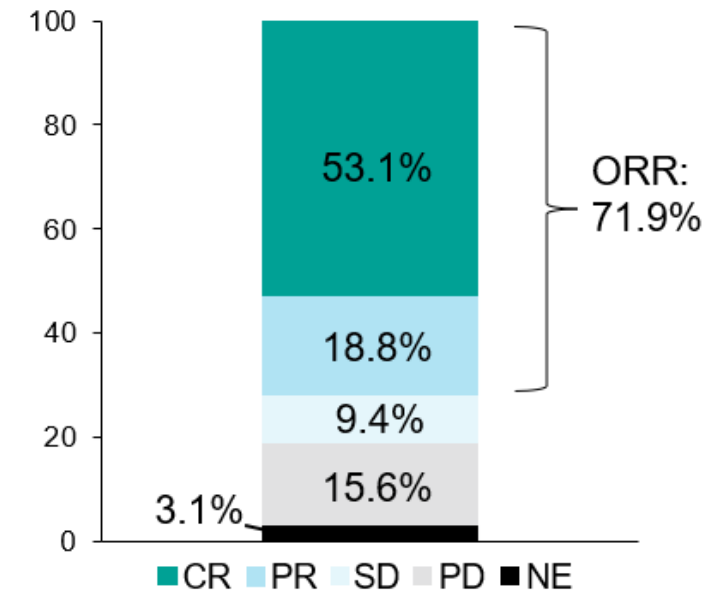
Key inclusion criteria: arm 1

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

	Total N=35
Median number of prior lines of anticancer therapy, n (range)	2 (1–4)
Prior systemic therapies, n (%)	
Prior CAR T therapy	8 (23)
Prior stem cell transplant	2 (6)
Refractory disease, n (%)	
Primary refractory	15 (43)
Refractory to ≥2 consecutive lines of anticancer therapy	8 (23)



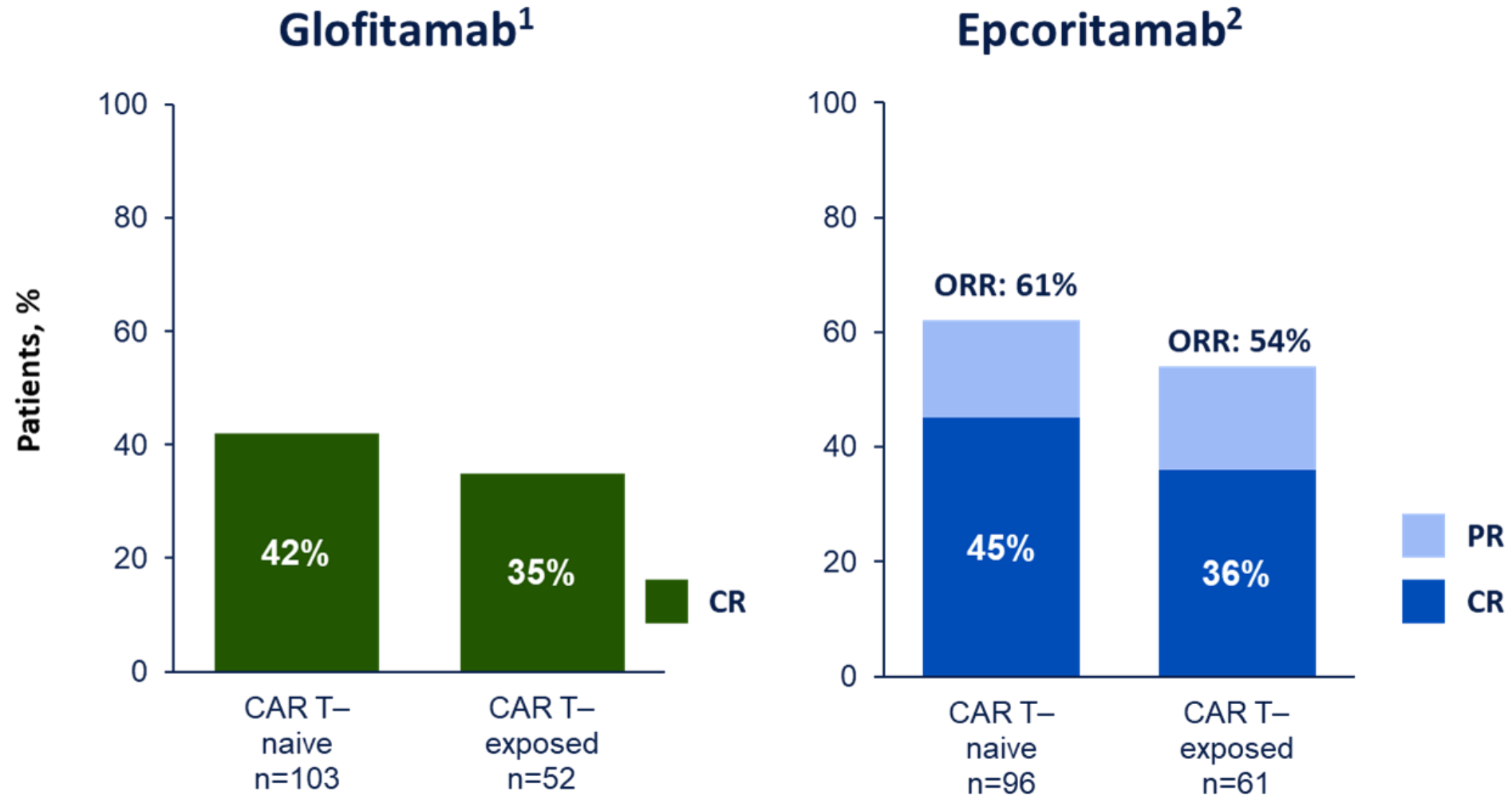
Best Overall Response^a (N=32)



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

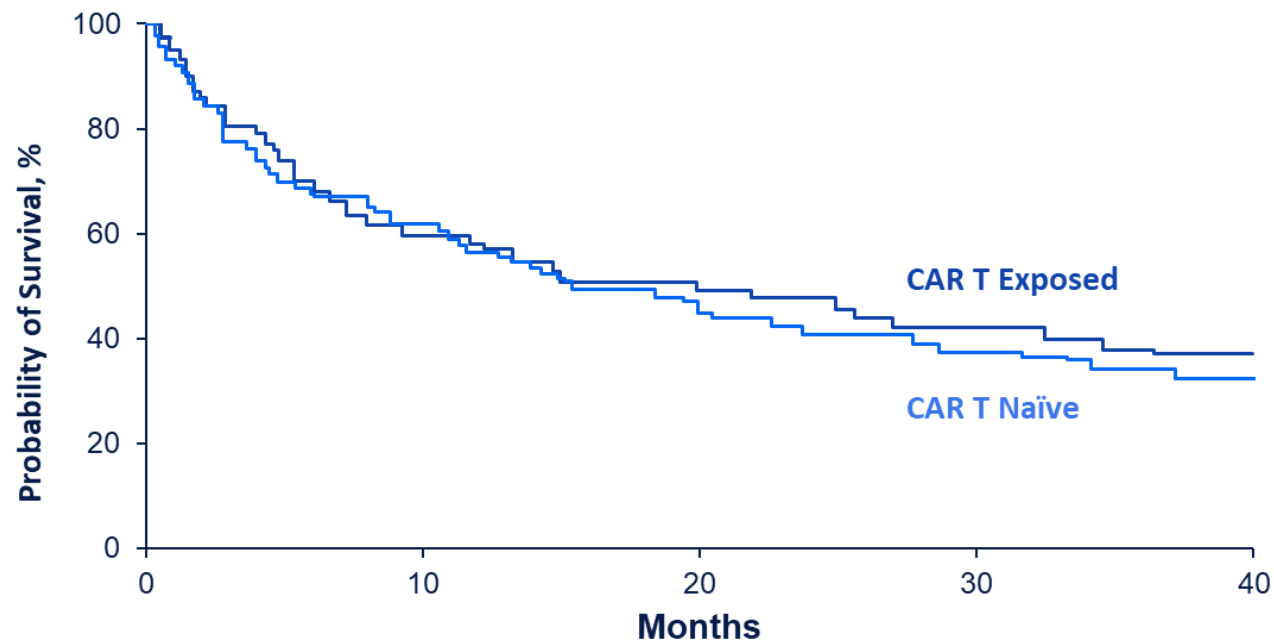
Sequencing CD20xCD3 bispecifics and CARTs

Phase II studies of glofitamab and epcoritamab in patients with R/R LBCL – CART exposed vs. CART naïve patients



Phase II dose expansion study of epcoritamab in patients with R/R LBCL – CART exposed vs. CART naïve patients

OS



No. at risk

	0	10	20	30	40
CAR T Exposed	61	34	28	22	2
CAR T Naïve	96	57	43	34	9

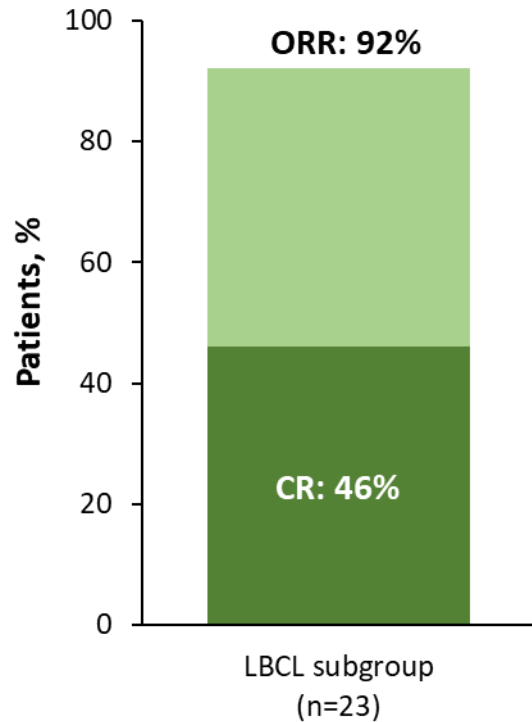
Best response, n (%)	CAR T Exposed N=61	CAR T Naïve n=96
ORR	33 (54)	59 (61)
CR	22 (36)	43 (45)
PR	11 (18)	16 (17)

Safety	Overall N=157
Most common TEAEs, ≥20%	
CRS	60%
Diarrhea	24%
Pyrexia	23%
Neutropenia	22%
Fatigue	22%
Injection-site reaction	21%

What about the efficacy of CART in patients previously exposed to bispecifics? Data from the DESCARTES registry:

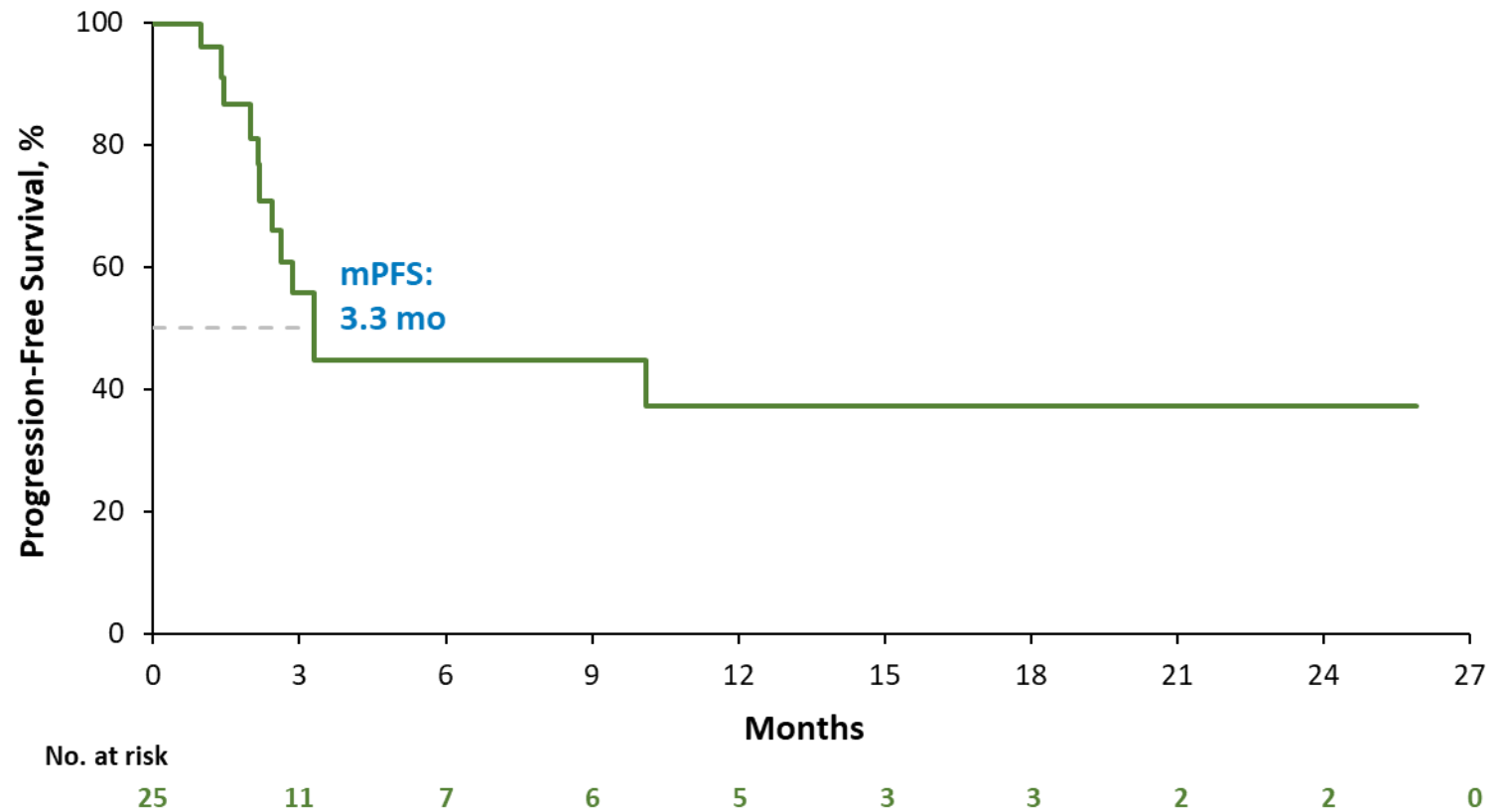
ORR: CAR T after BsAb in LBCL

Median follow-up = 12.3 months



PFS: CAR T after BsAb in LBCL

Median follow-up = 12.3 months



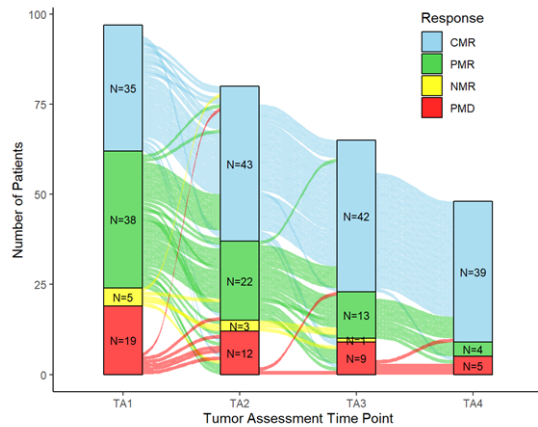
CD20xCD3 bispecifics and costimulation

Importance of costimulation

CD28 and 4-1BB costimulators show distinct clinical response kinetics

CD19-4-1BBL + glofitamab:

46% of complete metabolic responses (CMRs) achieved at a late assessment indicative of a gradual but persistent response.



CD19-CD28 + glofitamab:

88% of CMRs achieved rapidly, at first response assessment, indicating an immediate and robust response.

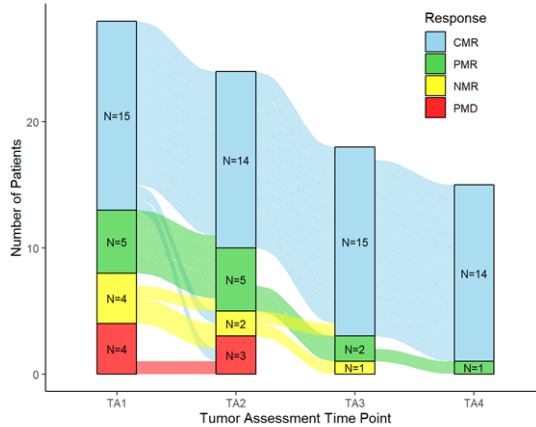


Figure 2. Evolution of response (per Lugano classification³) during the fixed-treatment period. First tumor assessment (TA) was performed on C3D1. NMR, no metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response.

CD19 costimulators reduce peripheral PD1+ memory T-cell expansion

	CD19-4-1BBL + glofitamab	CD19-CD28 + glofitamab
Cell type	CD8+ PD1+ Temra	CD8+ PD1+ effector memory
Timing	C5 (late effect)	C3/C4 (early effect)
Potential impact	↓ deep exhaustion ↑ long-term immune response	↓ early effector exhaustion ↑ effector response

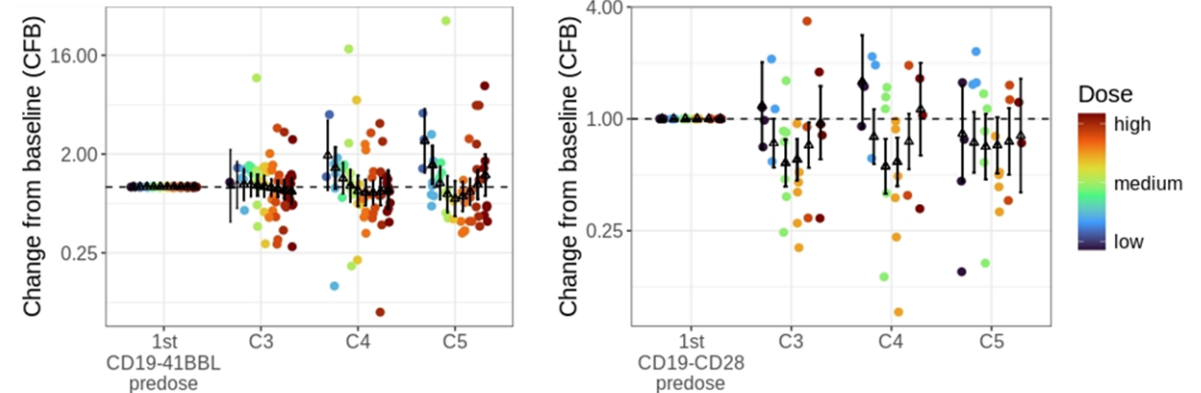
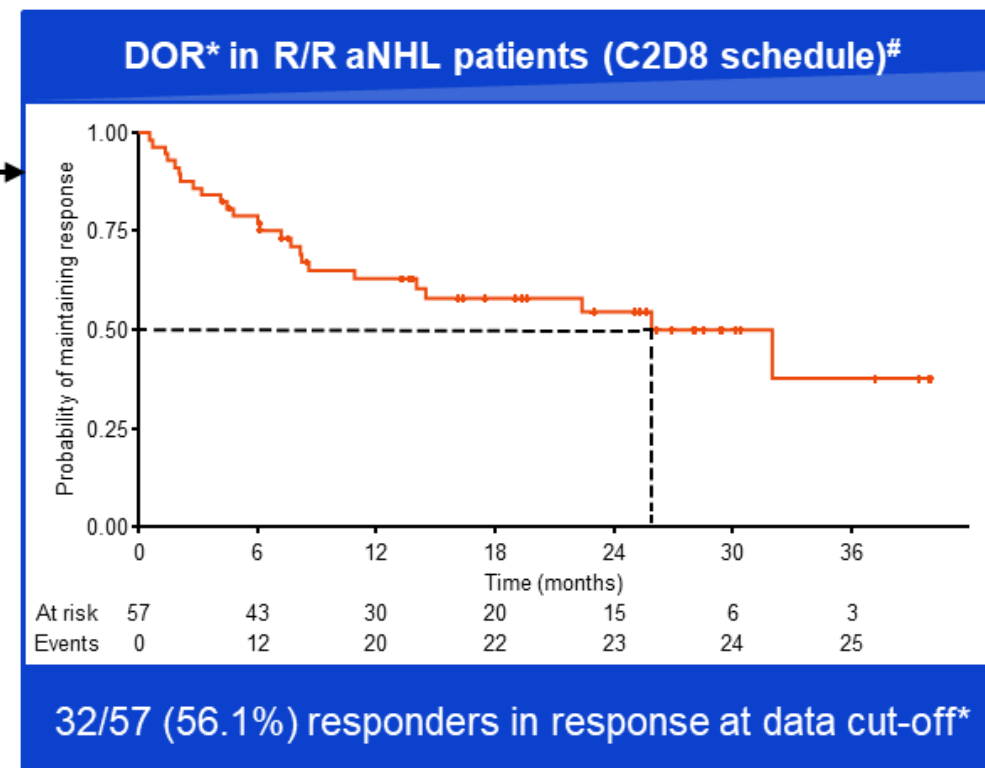


Figure 4. Dose-dependent effects of CD19-4-1BBL (left) and CD19-CD28 (right) on PD1+ memory T cells when combined with glofitamab. The fold changes at each indicated visit are measured relative to first CD19 costimulator predose (C2D8).

Glofitamab and Englumafusp alfa (CD19/4-1BBL)

n (%), C2D8 schedule	BOR	CMR	mDOR (95% CI)
R/R aNHL (n=83)*	57 (68.6)	47 (56.6)	25.9 months (7.2, NE)
3L+ (n=70)	47 (67.2)	37 (52.9)	14.3 months (8.2, 32.0)
2L (n=13)	10 (76.9)	10 (76.9)	NE (NE, NE)
Prior CAR-T (n=42)‡	27 (64.4)	20 (47.6)	14 months (6.1, NE)
No prior CAR-T (n=41)§	30 (73.2)	27 (65.9)	32 months (14.5, NE)



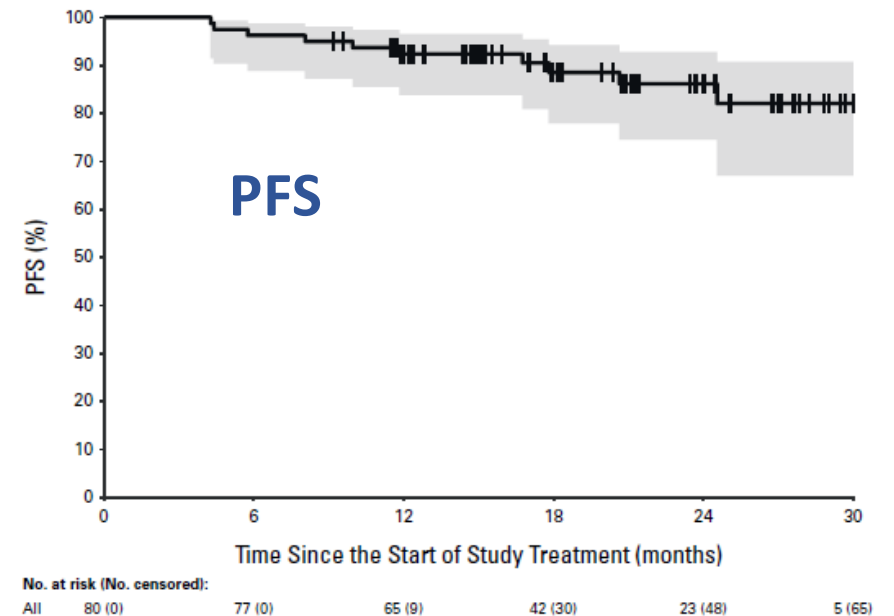
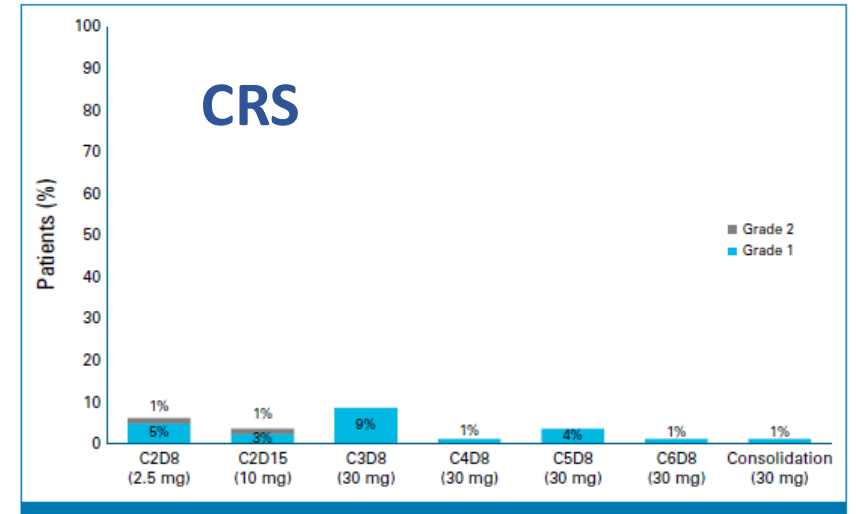
Early evidence of high efficacy in the 2L and no prior CAR-T subgroups

CD20xCD3 bispecifics in newly diagnosed DLBCL

COALITION study: R-CHOP or Pola-R-CHOP + glofitamab in 1st line treatment of DLBCL

- Newly diagnosed LBCL and age ≤ 65 years
- Min. 1 high-risk feature: IPI ≥ 3 , NCCN-IPI ≥ 4 , or double-hit
- All received 1 x R-CHOP, then randomized to
 - 5 x Glofit-R-CHOP (n = 40), or
 - 5 x Glofit-Pola-R-CHP (n = 40)
- Followed by two cycles of glofitamab consolidation

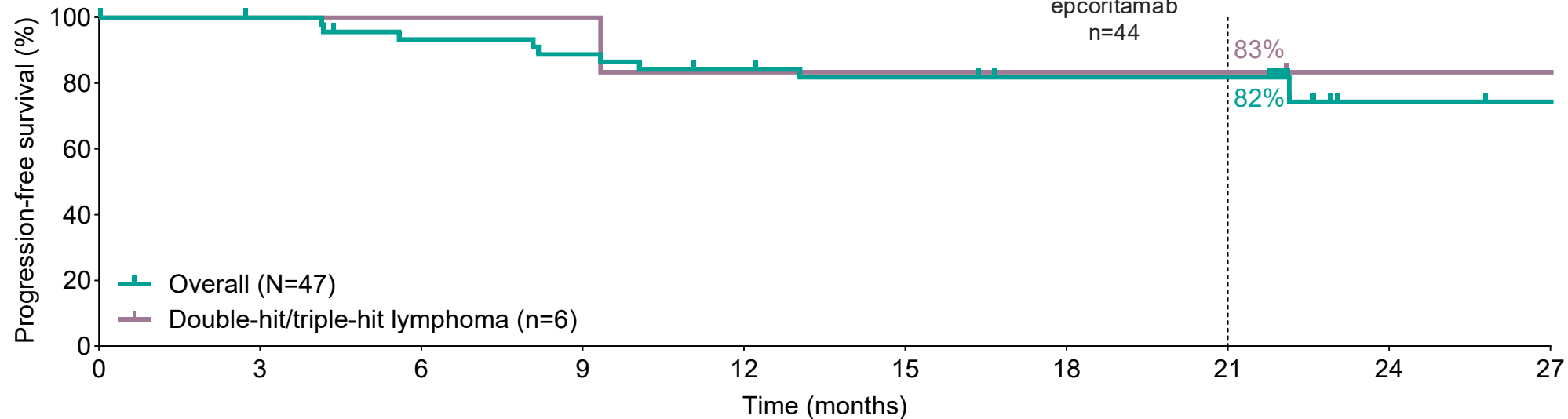
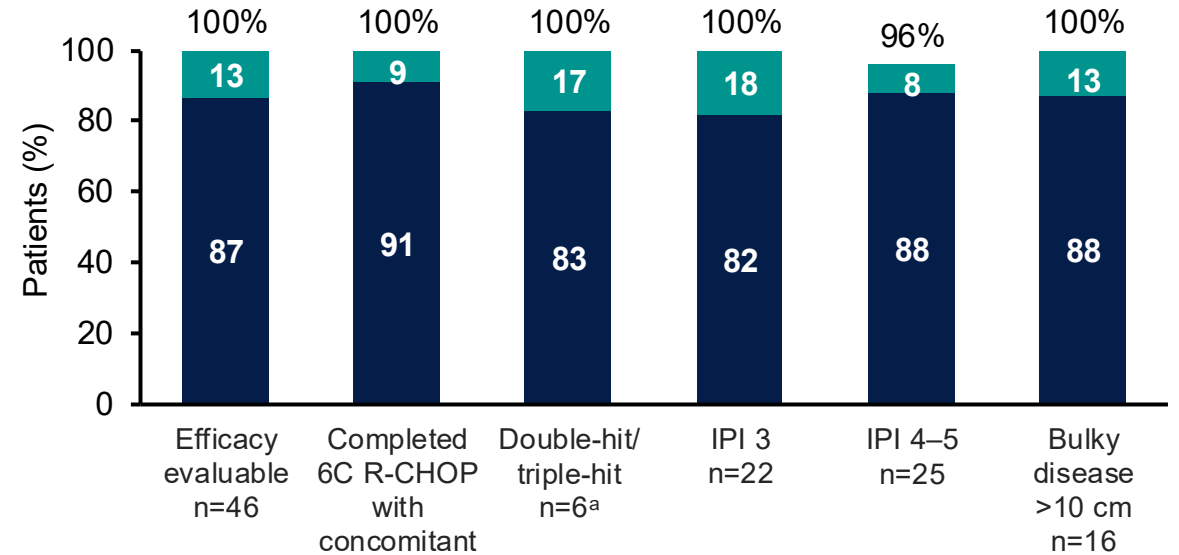
- ORR 100% in both arms
- CRR 98% in both arms
- Estimated 2-y PFS (20.7-month median FU):
 - 86% in the Glofit-R-CHOP arm
 - 92% in the Glofit-Pola-R-CHP arm



Epcoritamab + R-CHOP in high-risk DLBCL: EPCORE NHL-2 Arm 1

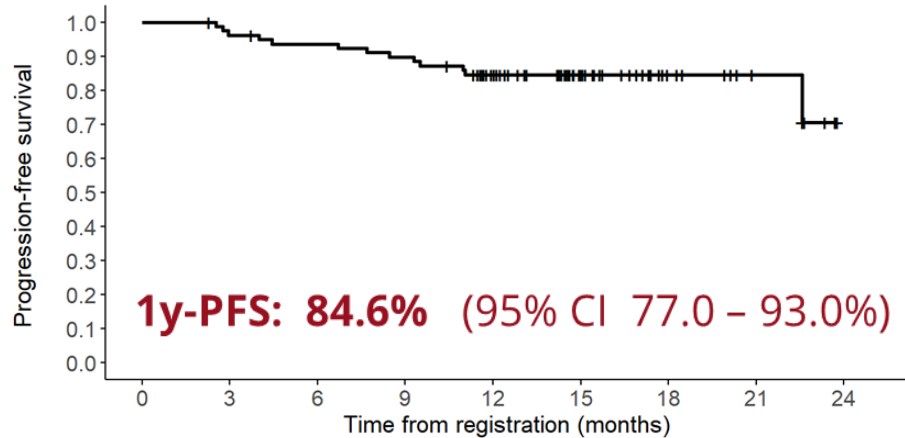
Key inclusion criteria

- Newly diagnosed CD20⁺ LBCL^a
- IPI score ≥ 3
- ECOG PS 0–2
- Adequate organ function



Phase II frontline chemolight R-pola-glo trial for elderly and medically unfit/frail patients with aggressive B-cell lymphoma

1-year Progression-free Survival (PFS)



RESULTS

Efficacy (n=20 evaluable):

- Median FU 15 month-1-year PFS 85% ; 1-year OS 90%
- After C2, C6 and EOT: ORR 96%, 94% and 90% (95% CI 89–99); CMR 58%, 75% and 81%
- Late conversions: 52% of early PR → CMR by C6; additional 40% converted during Glo consolidation, underscoring benefit of extended Glo exposure
- Alive at cut-off: 89% (71/80)
- Efficacy consistent across sGA risk groups; treatment mitigated adverse impact of IPI factors (e.g., LDH)

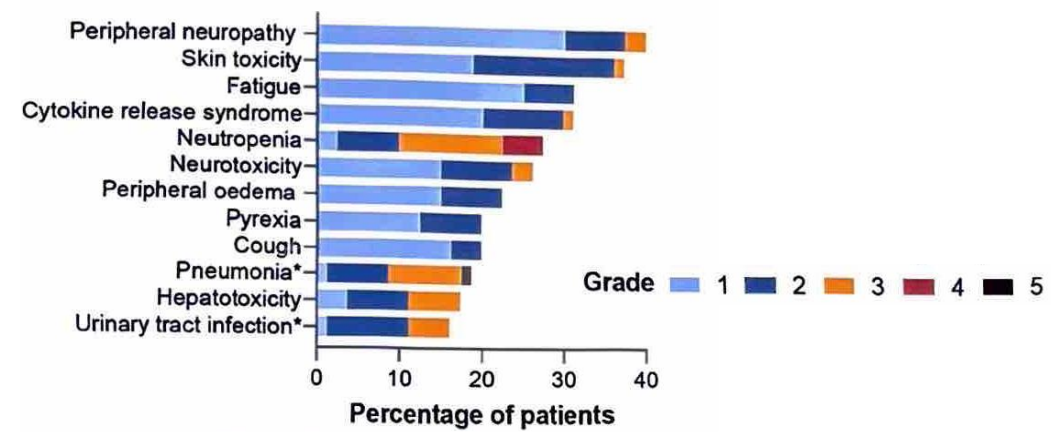
Safety:

- No grade 3–5 AEs in 34% (27/80)
- Infections grade 3–5: 26% (3 deaths: COVID 1, COVID+RSV 1, unknown 1)
- CRS: 31% (mostly early, low-grade; grade 3= 1; no grade 4/5; all resolved)
- ICANS: 4% (grade 2= 2; grade 3= 1)

CONCLUSIONS

- R-Pola-Glo delivers high and durable CMR with manageable safety in elderly/frail, medically unfit DLBCL
- 1-year survival metrics are favourable versus historical regimens for this population

Most common AE terms



**Other targets than CD20:
Surovatamig (CD19xCD3)**

Phase 1 study of surovatamig in r/r B-NHL: Focus on DLBCL

Key Eligibility Criteria

- Adults with R/R B-NHL
- CD19+ by flow cytometry or IHC
- ≥2 prior lines of therapy
- ≥1 measurable lesion
- No active CNS disease
- No leukemic presentation
- ECOG PS ≤2
- Prior anti-CD19 therapies, CAR T-cells, and anti-CD20 TCE allowed

Assessments

- Disease response: RECIL using PET-CT by ICR⁶
- CRS and ICANS: ASTCT criteria⁷
- AEs: CTCAE v5.0
- MRD: PhasED-Seq CLARITY assay in plasma ctDNA (approximately <1 part/million detection)

Endpoints

- | | |
|---------------------|--------------------|
| Primary | Secondary |
| Safety/tolerability | Antitumor activity |
| MTD/RP2D | |
| PK | |

106 patients with R/R DLBCL received at least 1 surovatamig dose of ≤0.08–25 mg

- Fixed-dose escalation (n=4), 1SUD (n=12), or 2SUD (n=90)

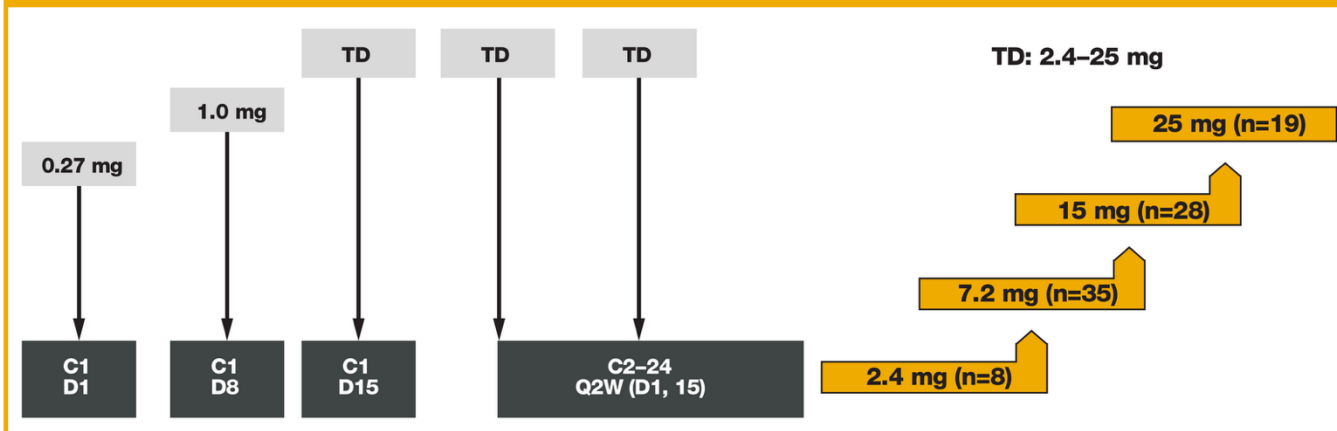
Median prior lines = 3 (2-13)

75% refractory to most recent LoT

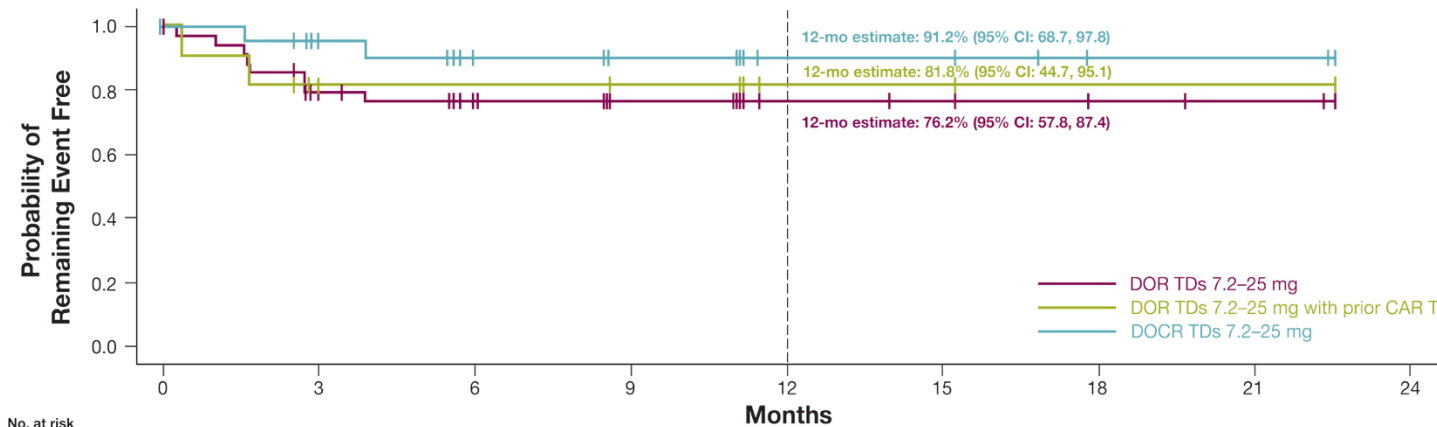
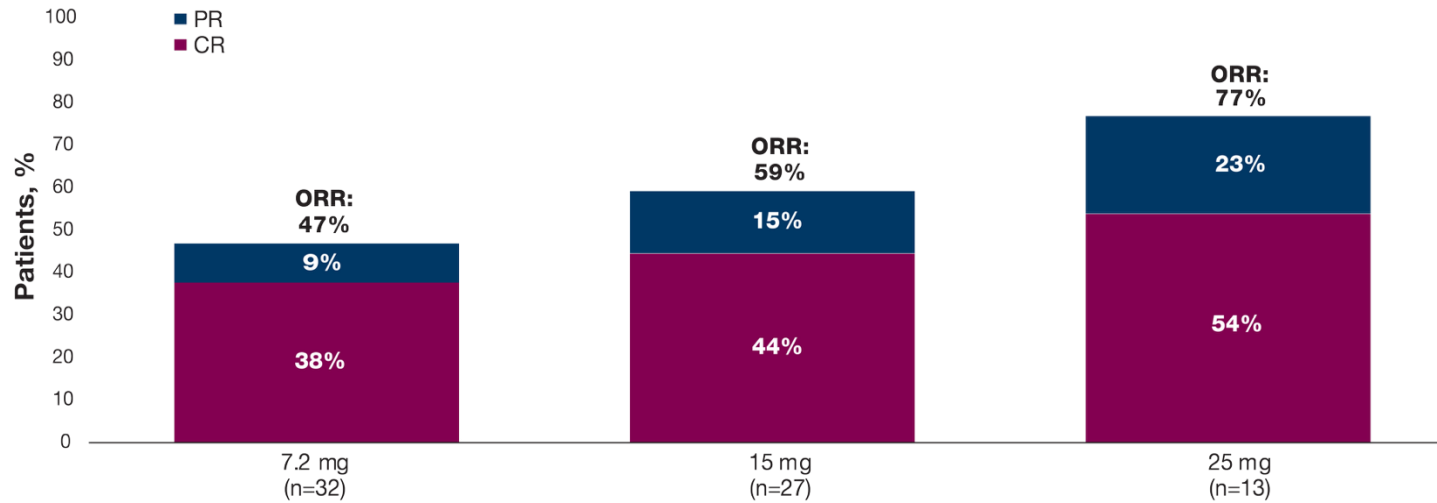
42% failing prior CD19 CART

15% failing prior CD20xCD3 bispecific

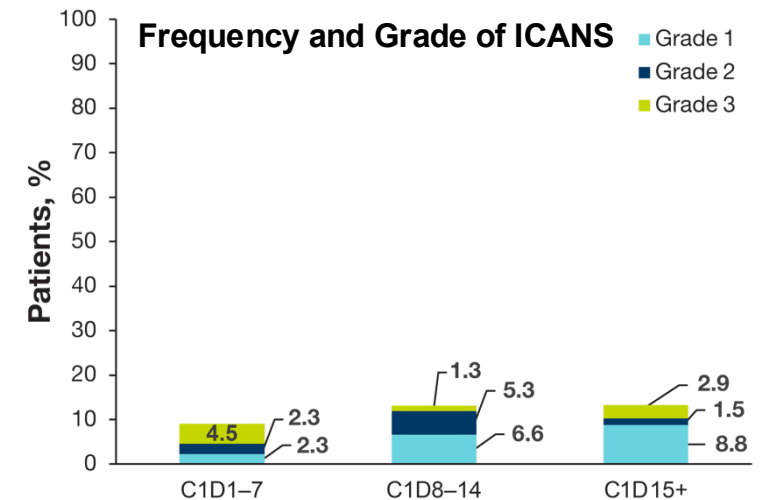
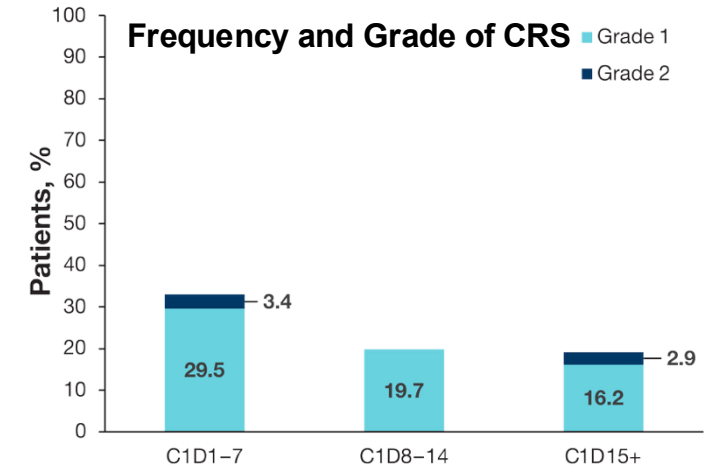
Double SUD (n=90)



Ph1 study of surovatamig: Efficacy and safety in r/r DLBCL



Time (Months)	0	3	6	9	12	15	18	21	24
DOR TDs 7.2-25 mg	41	23	15	11	6	5	3	2	0
DOR TDs 7.2-25 mg w/ prior CAR T	14	6	6	5	2	2	1	1	0
DOCR TDs 7.2-25 mg	31	19	13	10	5	5	2	2	0

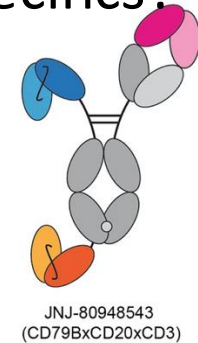


Summary

Where are the T-cell engagers going in DLBCL?

- Combinations with chemotherapy and ADCs
- Combinations with costimulatory molecules
- Other targets than CD20 (CD19, CD22, CD70, ROR1, BAFF-R, ...)
- Other effector cell targets than CD3 (CD16, CD8, ...)

- Trispecifics?



While the structure, the targets, and the strategies of the TCEs are being refined, the first generations are rapidly moving towards 1st line therapy:

- EPCORE DLBCL-2: Phase 3 trial of R-CHOP +/- **epcoritamab** in previously untreated LBCL (IPI 2-5)
- SKYGLO: Phase 3 study of Pola-R-CHP +/- **glofitamab** in previously untreated LBCL (IPI 2-5)



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