Bispecific antibodies in B-cell lymphomas: Running towards first line without dropping the ball

UNIVERSITY OF COPENHAGEN

Hematology Grand Rounds

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Disclosures

- **Consultant/advisor:**
  - AbbVie, AstraZeneca, Genmab, Johnson&Johnson, Merck, Roche, Takeda
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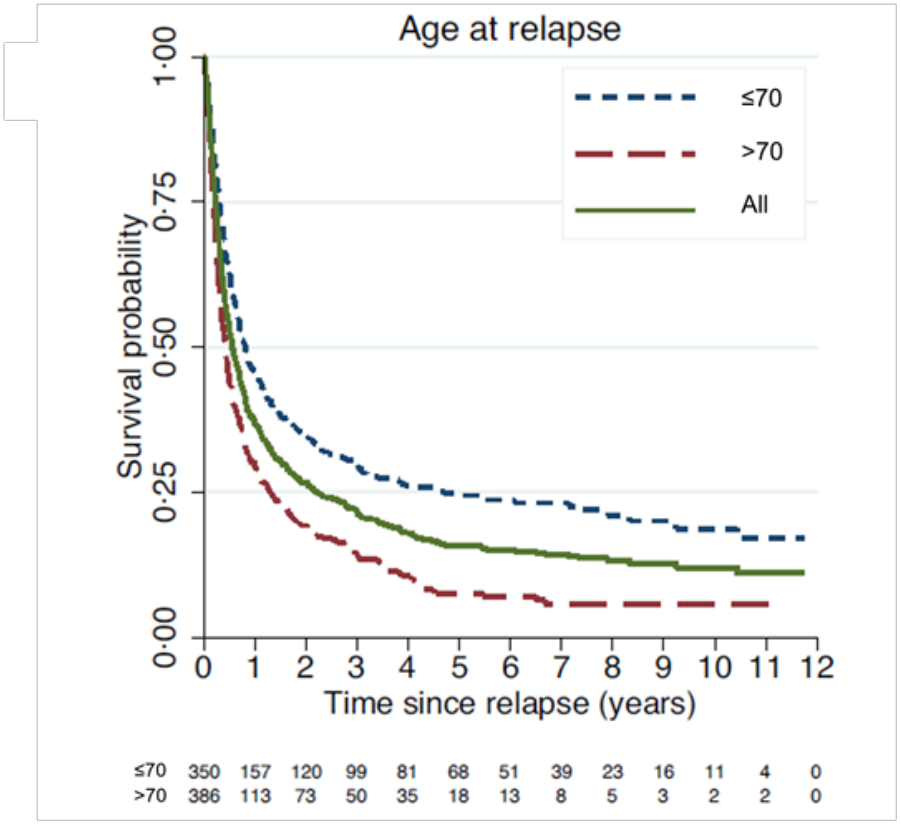
Outcomes for patients with r/r DLBCL are poor

OS in patients with R/R DLBCL (N=736)[1]



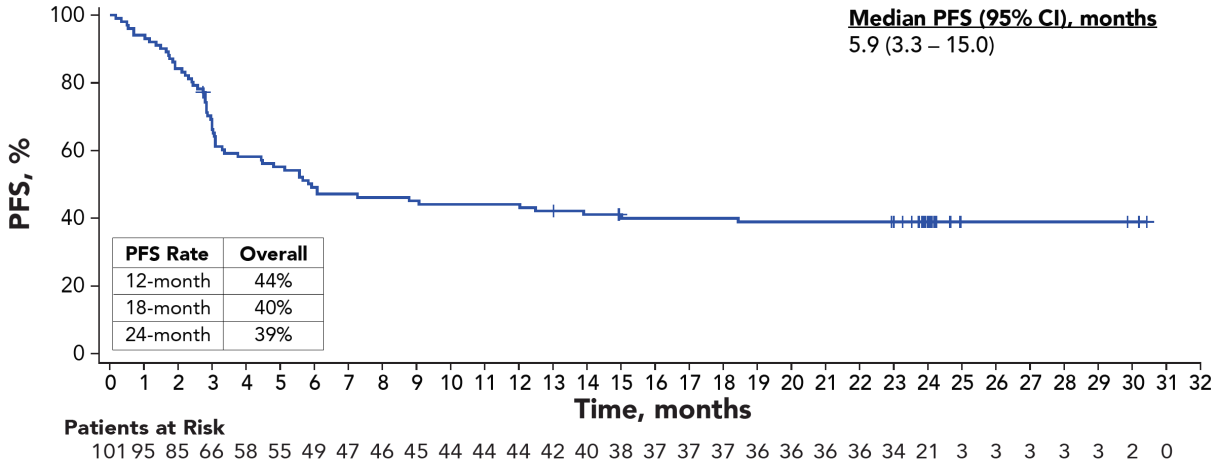
- In a recent analysis of a large population-based cohort of 736 patients with R/R DLBCL treated in Sweden during the period 2007–2018[1]
  - Overall outcomes were poor with a median OS of 6.6 months[1]
- Poor outcomes are observed in patients with treatment failure after R-CHOP, particularly in:
  - Patients with refractory disease[2]
  - Patients who are not candidates for or who have relapsed following HD-ASCT[3]
- CAR T-cell therapy is an option for patients with R/R DLBCL, but its use may be limited by potentially severe toxicities and logistical challenges[4,5]

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; HD-ASCT, high-dose therapy and autologous stem cell transplantation; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

1. Harrysson S, et al. Br J Haematol 2022;198:267–77.
2. Sehn L & Salles G. NEJM 2021;384:842–58.
3. Ayers EC, et al. Clin Lymphoma Myeloma Leuk 2020;20:661–67.
4. Fujiwara Y, et al. Pharmaceuticals 2022;15:207.
5. Roschewski M, et al. NEJM 2022;386:7.

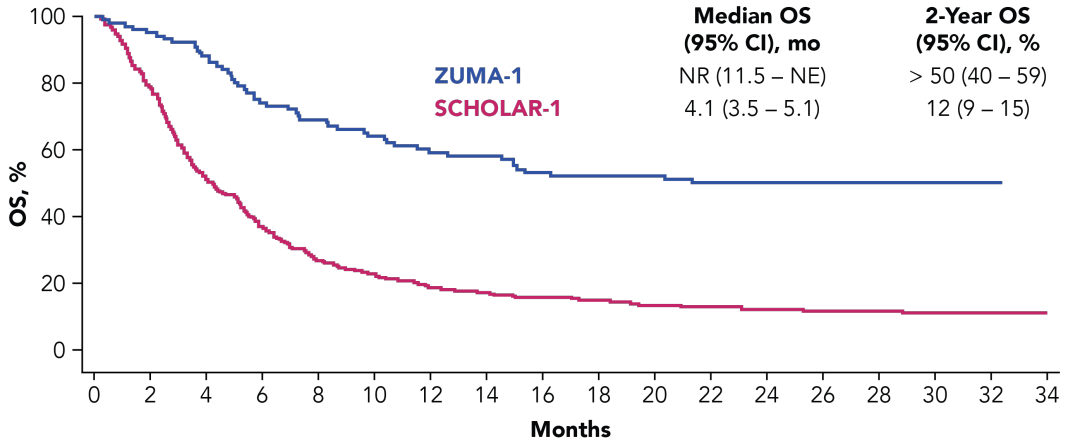
ZUMA-1: Phase 1-2 study of Axicabtagene Ciloleucel in r/r DLBCL

PFS: 39% progression-free at 27.1 mo



N= 145
70% with ≥ 3 prior therapies
65% refractory to most recent therapy

Standardized OS Comparison: ZUMA-1 vs. SCHOLAR-1



Similar results were seen in:

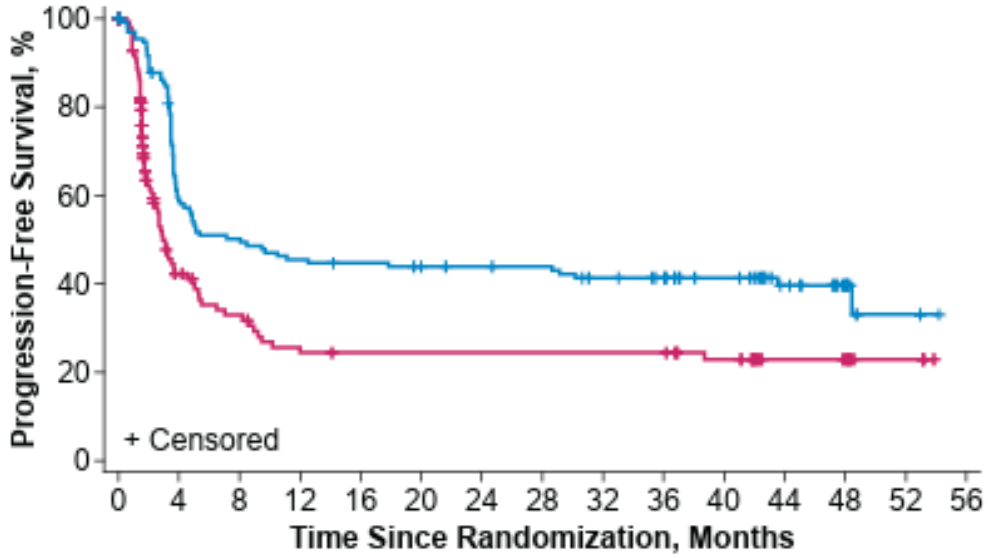
TRANSCEND[2] (Lisocabtagene maraleucel in r/r DLBCL with ≥ 3 prior therapies
JULIET[3] (Tisagenlecleucel in r/r DLBCL with ≥ 3 prior therapies)

1. Neelapu S, et al. N Eng J Med 2017;377(26):2531-2544.
2. Abramson JS, et al. Lancet 2020; 396(10254): 839-852.
3. Schuster SJ, et al. N Engl J Med 2019; 380(1):45-56.

ZUMA-7: PFS in primary refractory vs. early relapsed patients

Primary Refractory

	Median PFS, Months (95% CI)	PFS at 48 Months, % (95% CI)	Unstratified HR (95% CI)
Axi-cel (n=133)	8.0 (4.0-30.2)	39.6 (30.8-48.3)	0.528 (0.384-0.725)
SOC (n=131)	2.9 (2.3-5.0)	22.9 (14.7-32.1)	

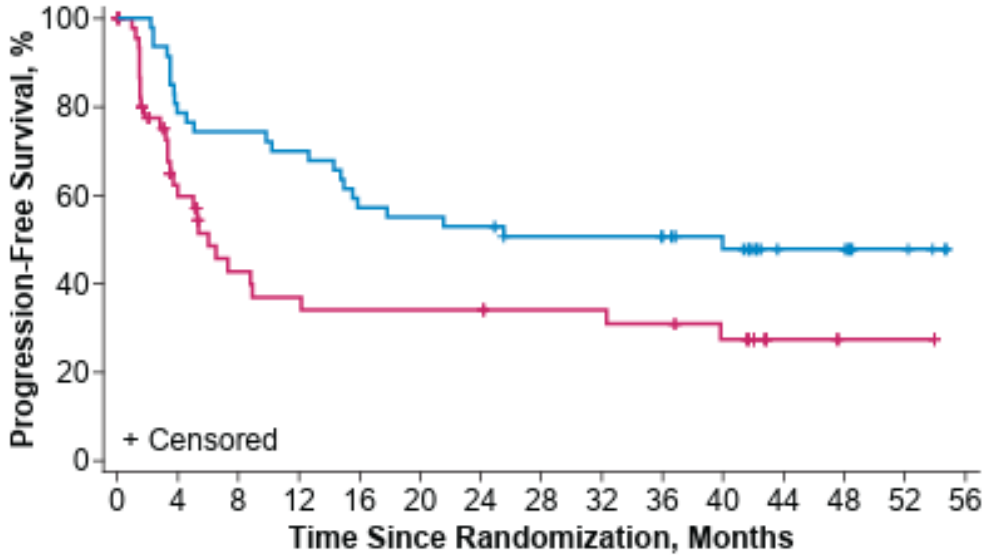


No. at Risk

Axi-cel	133	75	64	58	56	53	52	51	46	43	35	23	13	3	0
SOC	131	38	28	20	19	19	19	19	19	19	15	8	7	3	0

Early Relapsed

	Median PFS, Months (95% CI)	PFS at 48 Months, % (95% CI)	Unstratified HR (95% CI)
Axi-cel (n=47)	40.0 (14.7-NE)	48.1 (33.1-61.7)	0.496 (0.286-0.861)
SOC (n=48)	6.0 (3.4-12.1)	27.9 (14.4-43.1)	



No. at Risk

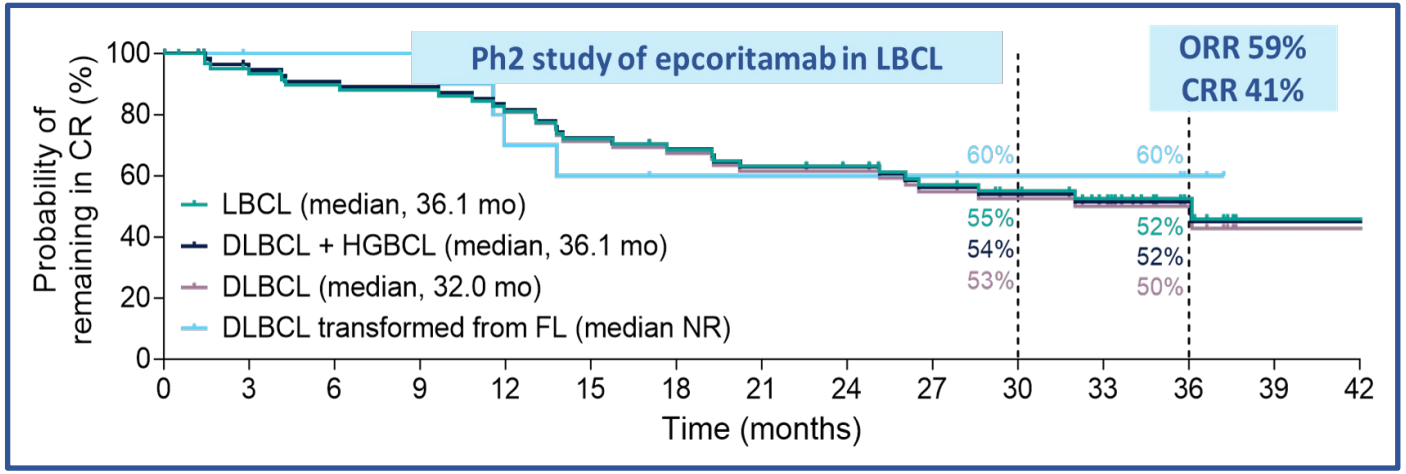
Axi-cel	47	37	35	33	27	26	25	22	22	20	17	9	9	4	0
SOC	48	23	15	13	12	12	12	11	11	10	8	2	1	1	0

- **PFS was improved with axi-cel versus SOC in primary refractory and in early relapsed LBCL**

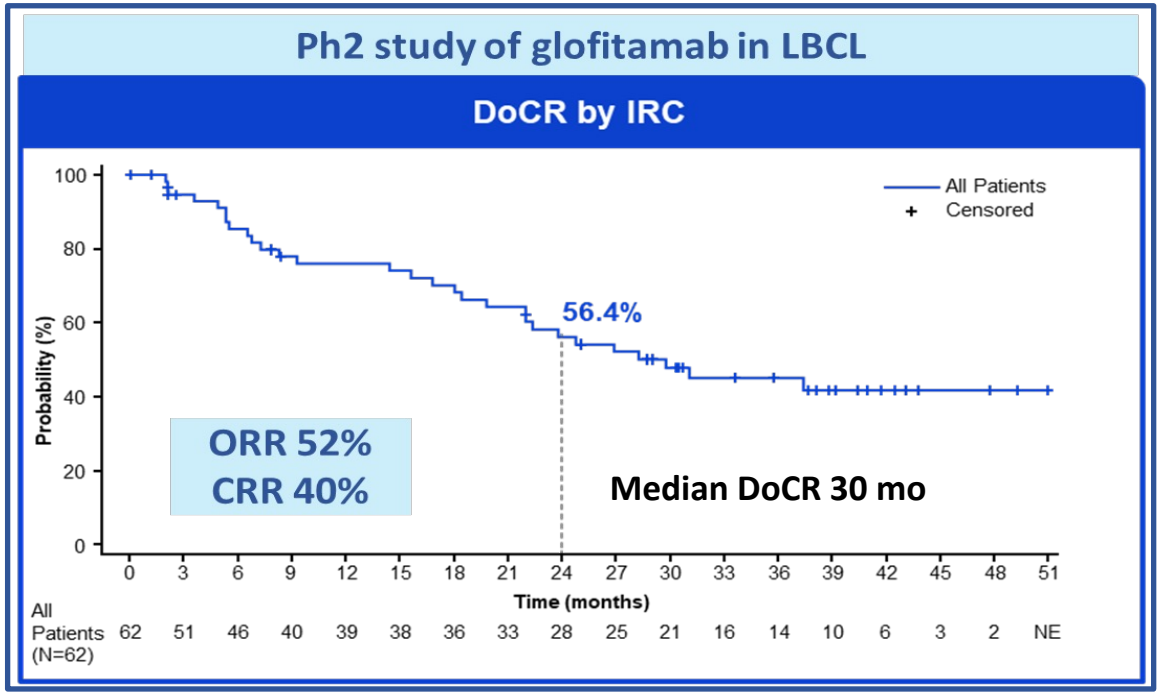
Westin et al. Tandem TCT 2025 (Abstract 244; poster presentation)

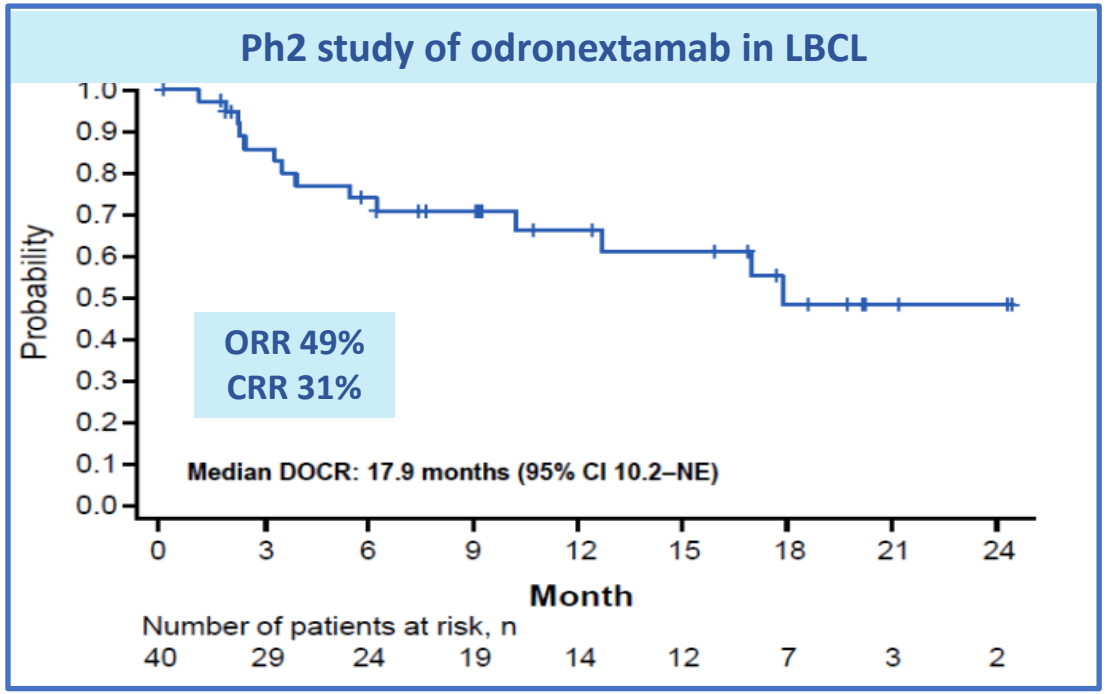
CD20xCD3 bispecific antibodies in R/R DLBCL

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)

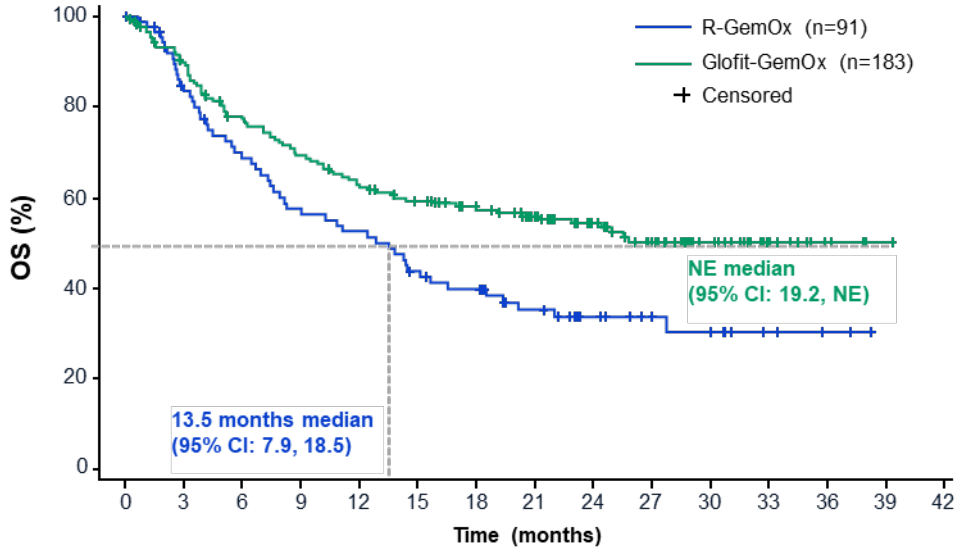




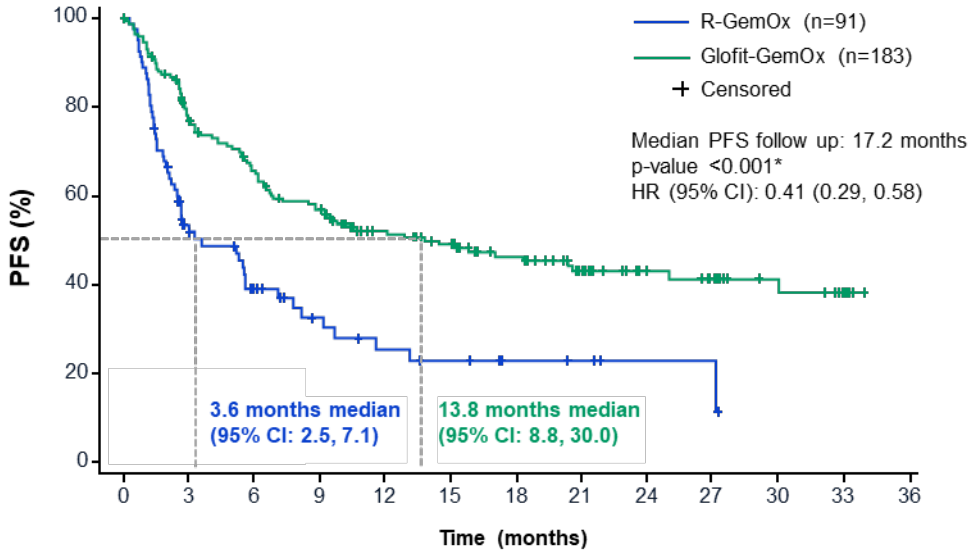
1. Vose JM, et al. ASH 2024. 2. Bartlett NL, et al. Blood Adv 2023;7(17):4926-4935. 3. Dickinson M, et al. ASH 2024. 4. Poon M, et al. ICML 2023, abstract #93.

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)

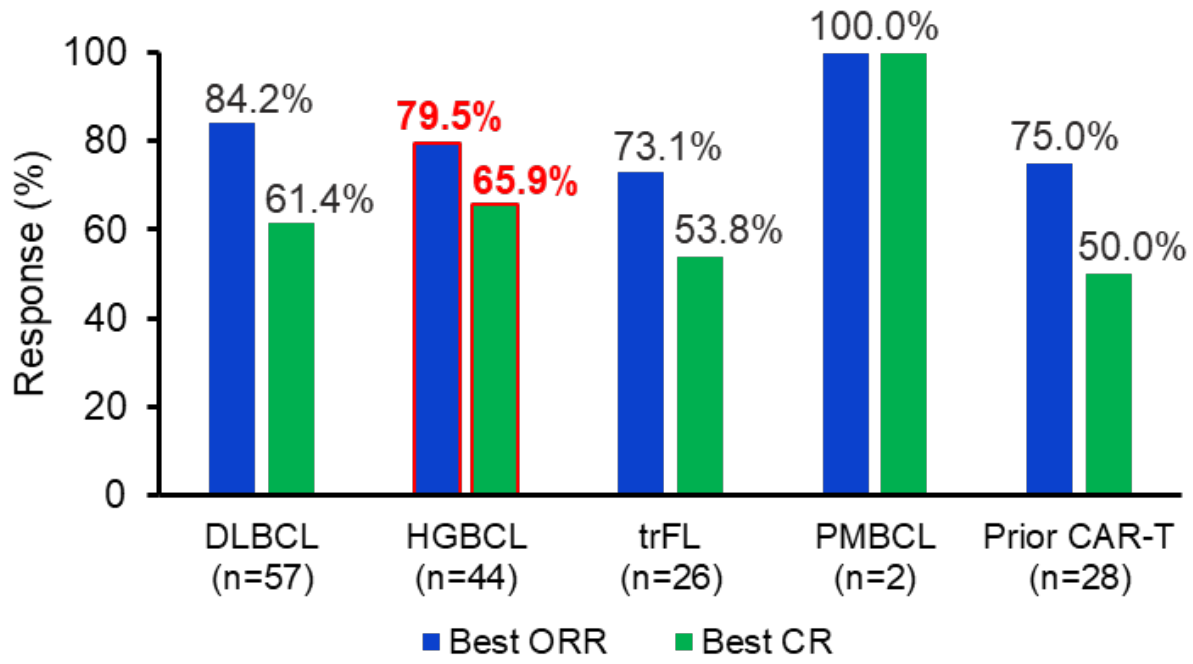
Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
PFS, median (95% CI); months	**3.6** (2.5, 7.1)	**13.8** (8.8, 30.0)
18-month PFS, % (95% CI)	**23.0** (11.5, 34.4)	**46.5** (38.5, 54.5)

Abramson J, et al. ASCO 2025. Abstract 7015.
Gregory G, et al. EHA 2025. Abstract PS1909.

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]

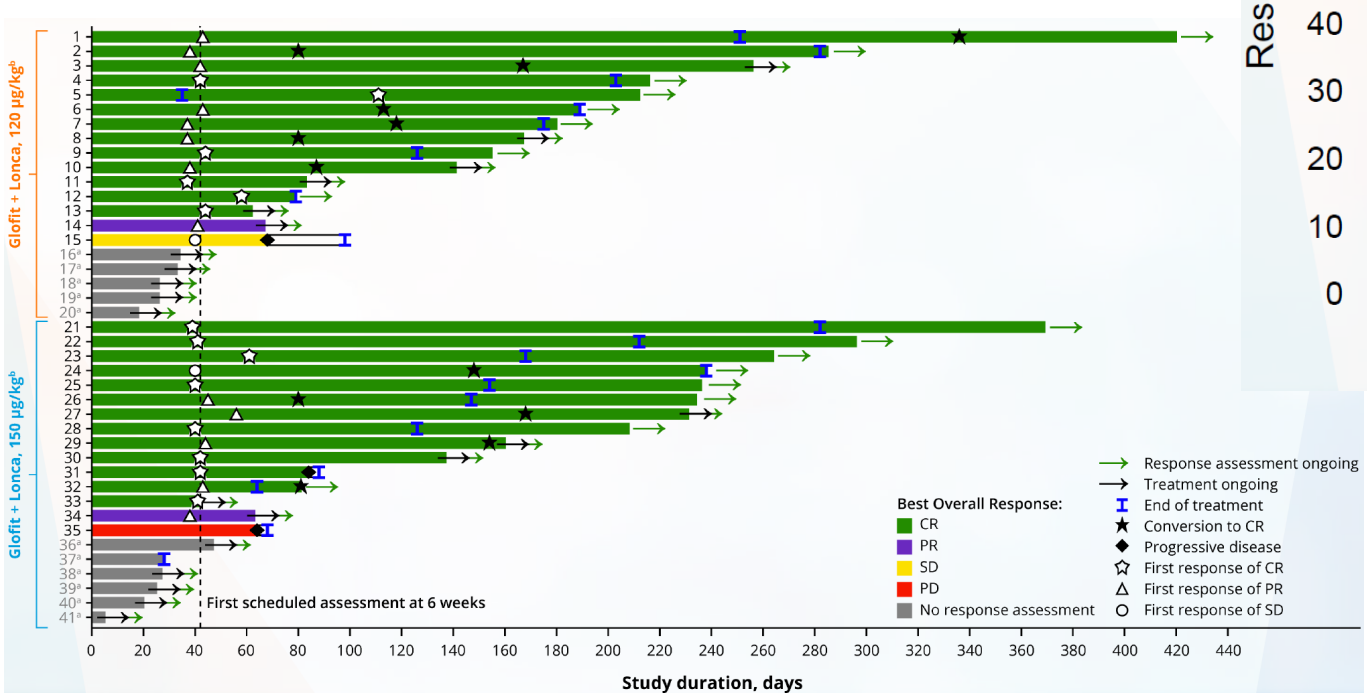
Best ORR and CR by histology and prior CAR T-cell therapy (INV-assessed)

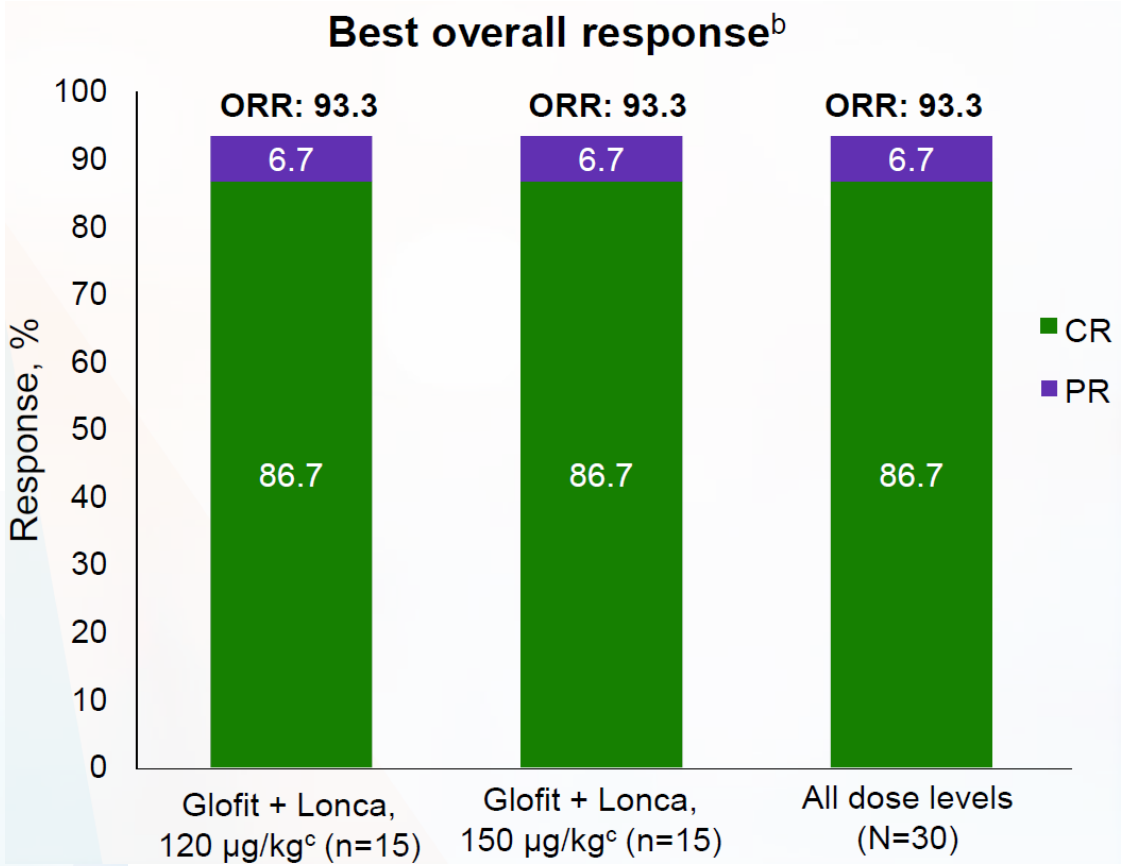


Impressive responses observed (**66% CR**) amongst patients with HGBCL

Hutchings M, et al. J Clin Oncol. 2025 Oct 20:JCO2500992. doi: 10.1200/JCO-25-00992. Online ahead of print.

Glofitamab and Loncastuximab tesirine in r/r DLBCL





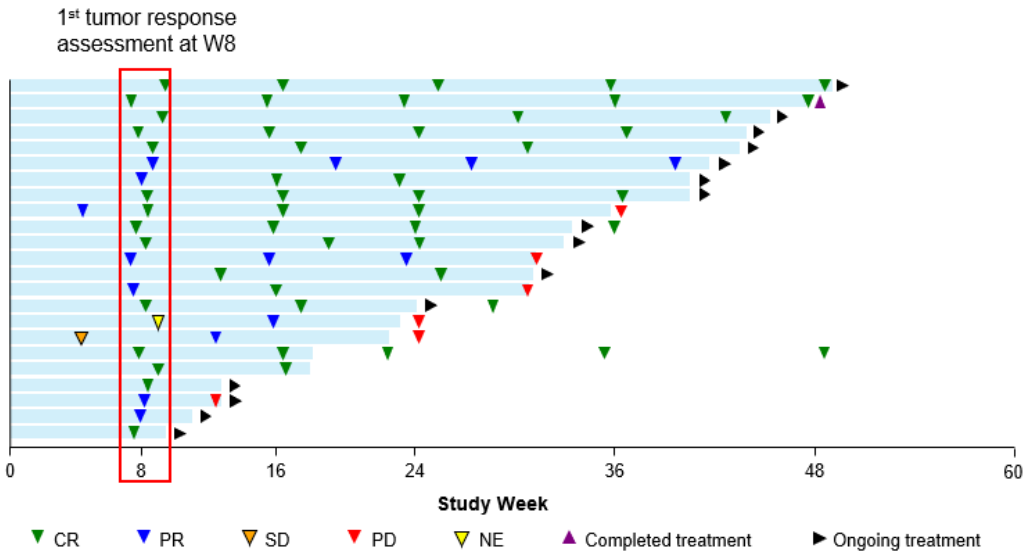
Alderuccio JP, et al. EHA and ICML 2025.

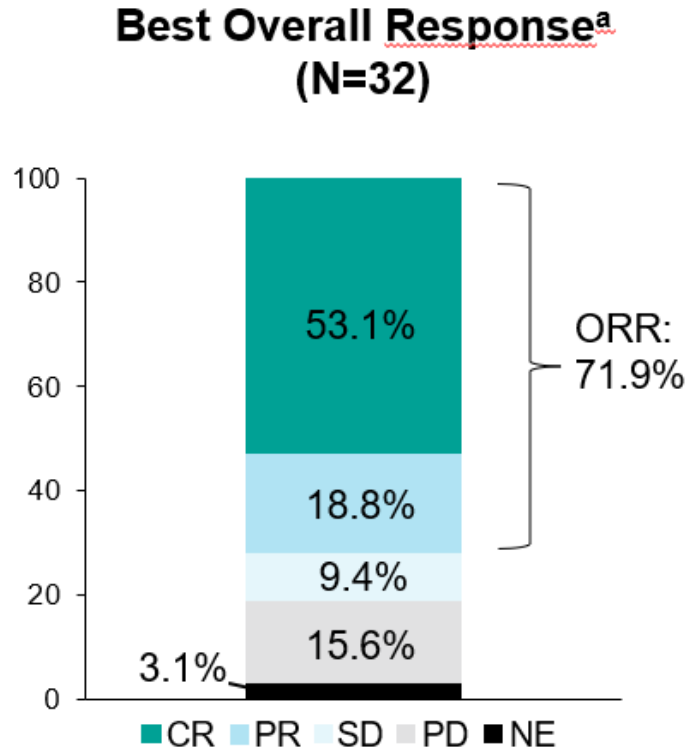
EPCORE NHL-5 arm 1:
Phase Ib/II study of epcoritamab + R^2 in patients with R/R DLBCL

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)



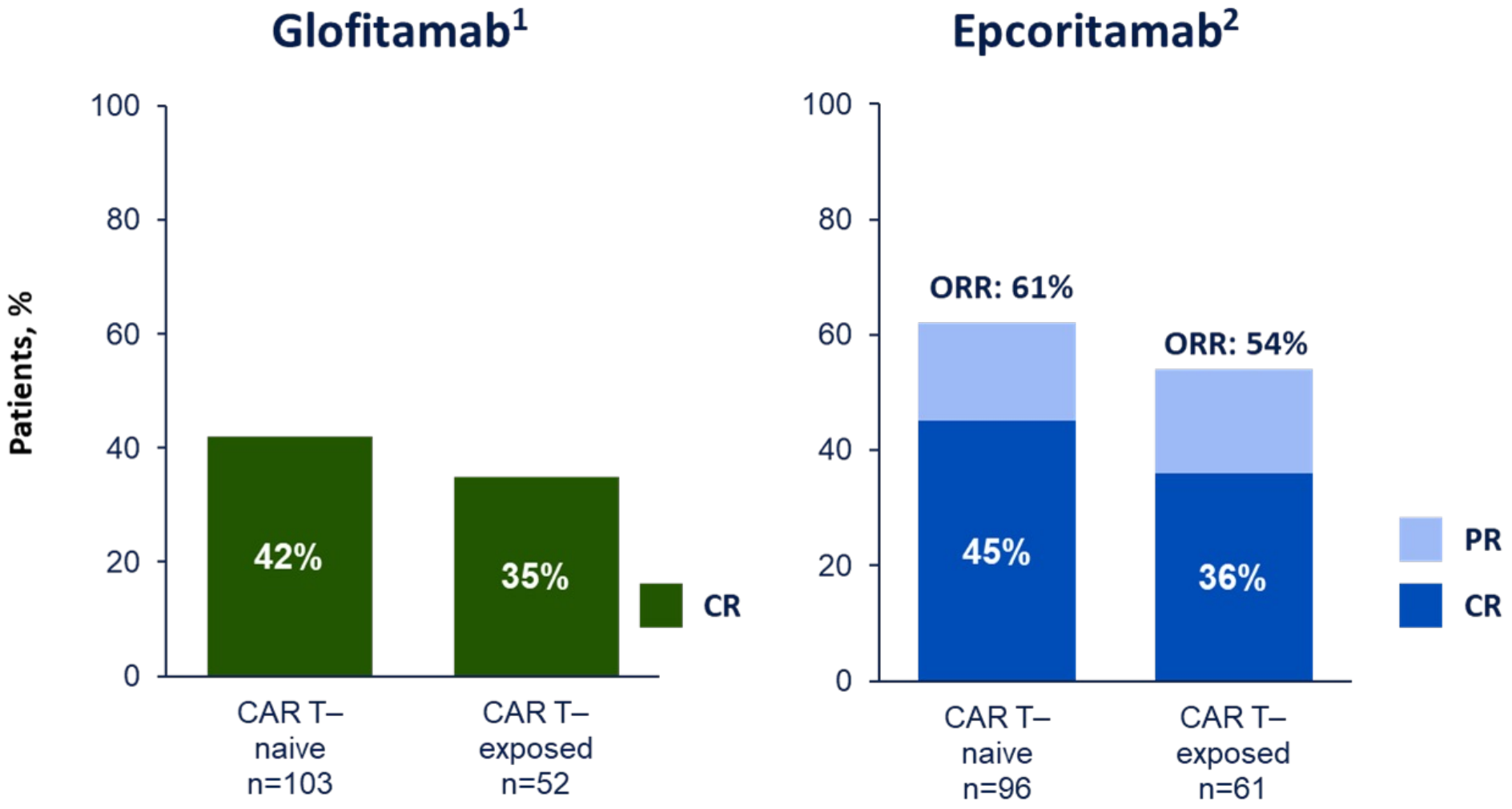


Data cutoff: Oct 6, 2023
Median follow-up: 8.2 mo

Avivi I J, et al. ASH 2023, abstract #438.

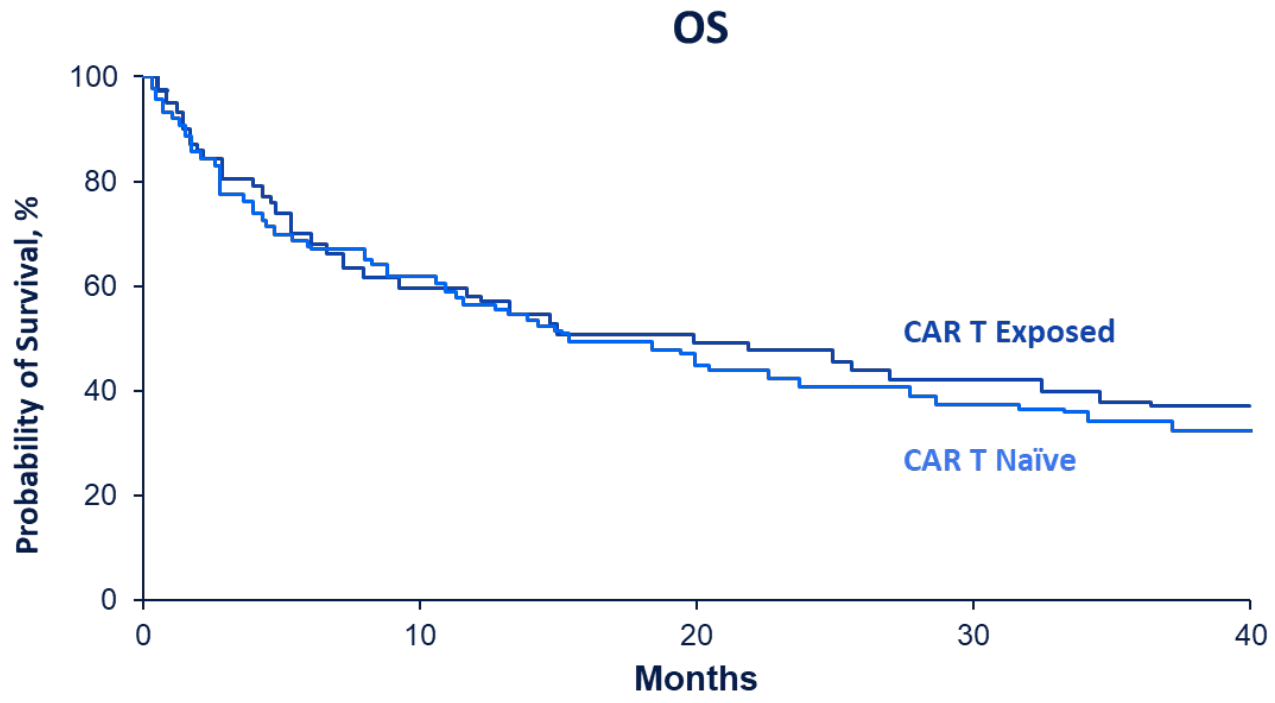
Sequencing CD20xCD3 bispecifics and CARTs

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



1. Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-2231. 2. Karimi Y, et al. Oral 1737. ASH. Dec 7-10, 2024.

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



No. at risk

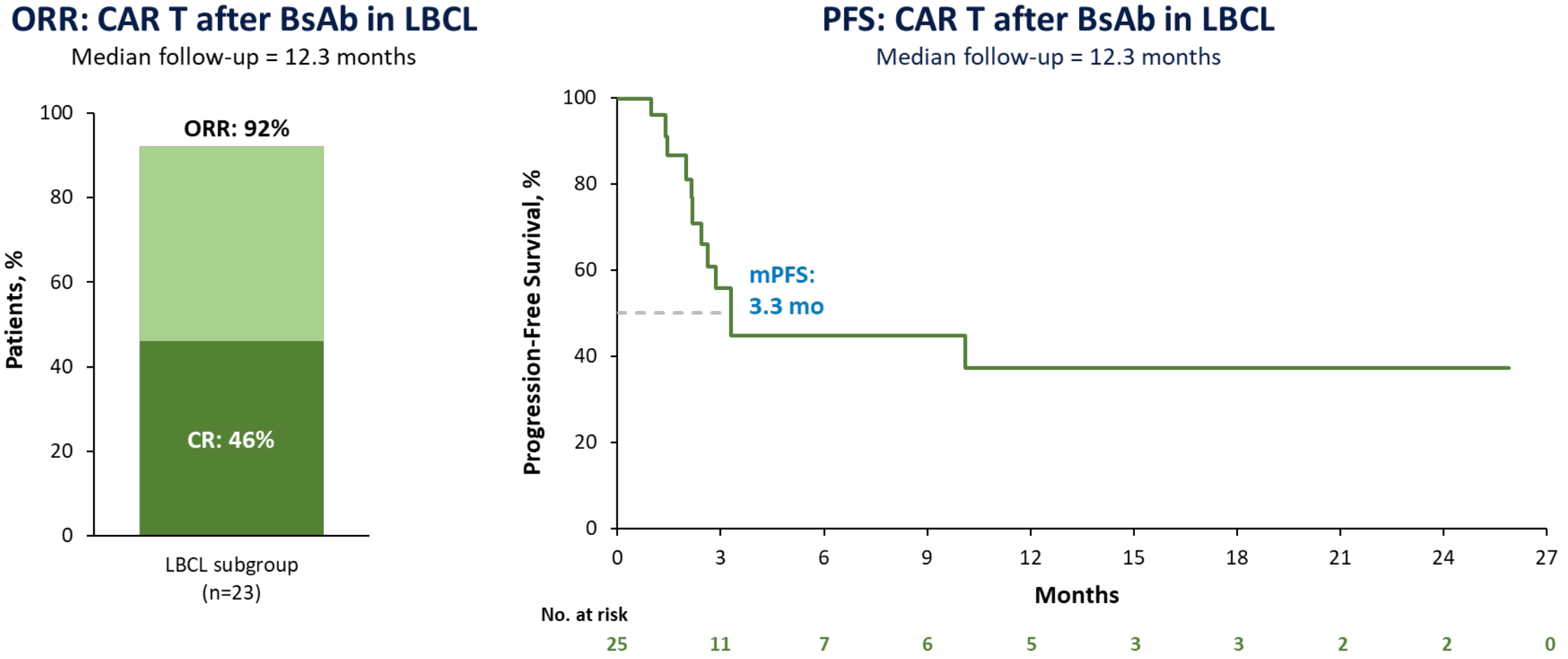
CAR T Exposed	61	34	28	22	2
CAR T Naïve	96	57	43	34	9

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%

Karimi Y, et al. Oral 1737. ASH. Dec 7-10, 2024.

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



Crochet G, et al. Blood 2024; 144(3): 334-338.

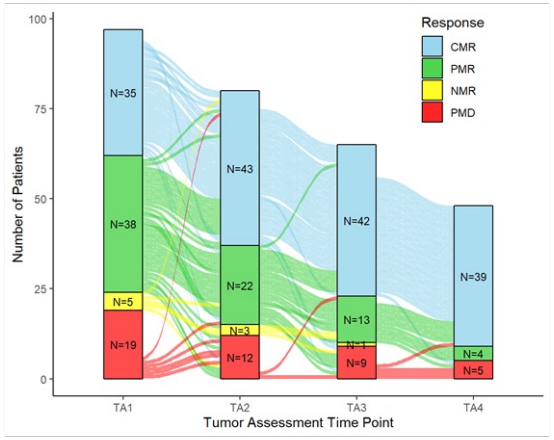
CD20xCD3 bispecifics and costimulation

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.

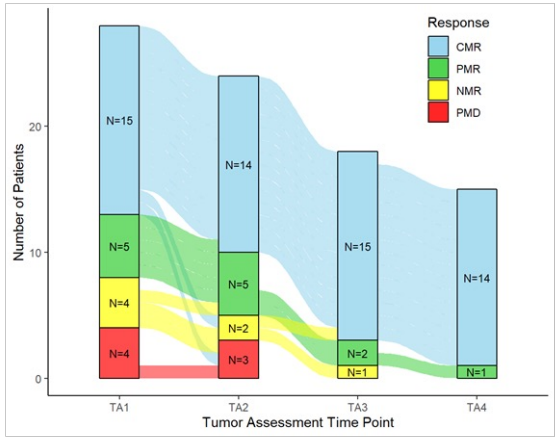


Figure 2. Evolution of response (per Lugano classification[3]) during the fixed-treatment period. First tumor assessment (TA) was performed on C3D1. NMR, no metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response.

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

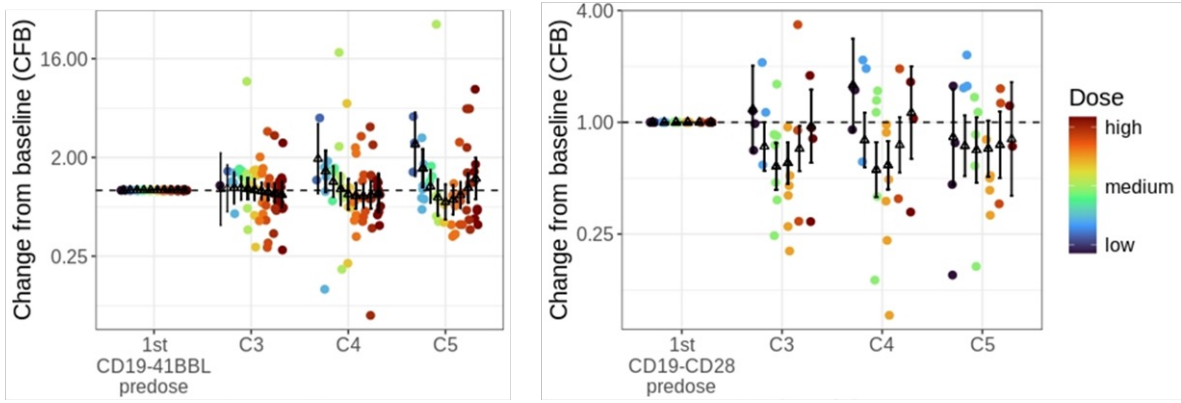


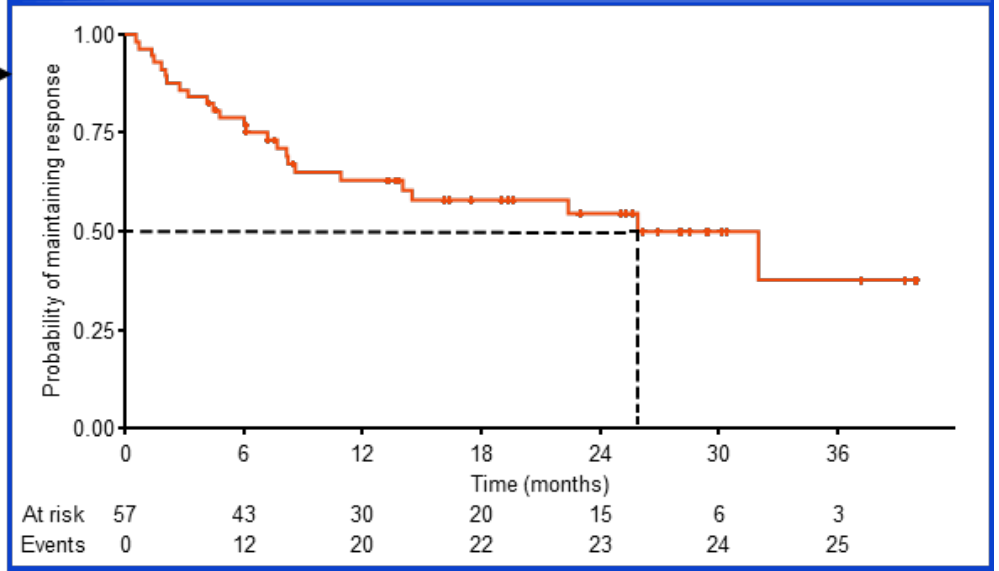
Figure 4. Dose-dependent effects of CD19-4-1BBL (left) and CD19-CD28 (right) on PD1+ memory T cells when combined with glofitamab. The fold changes at each indicated visit are measured relative to first CD19 costimulator predose (C2D8).

Korfi K, et al. AACR 2025

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)**

DOR* in R/R aNHL patients (C2D8 schedule)#



32/57 (56.1%) responders in response at data cut-off*

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

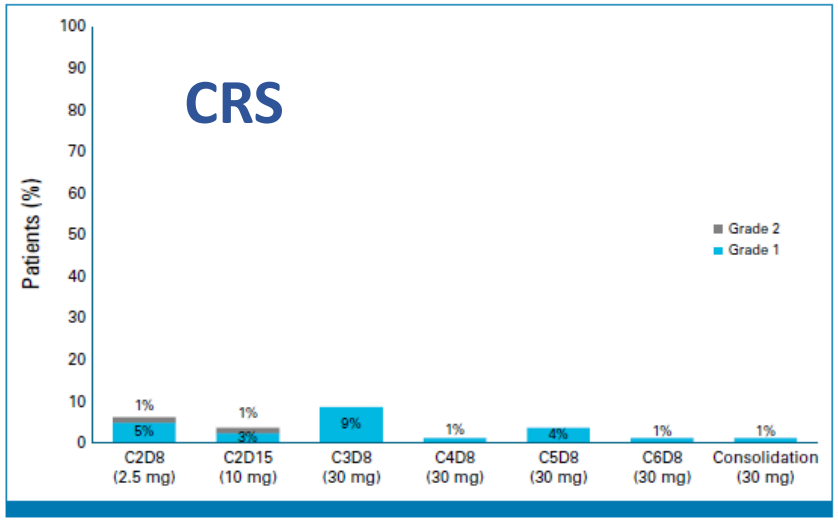
Hutchings M, et al. ASH 2024 (Abstract #990)

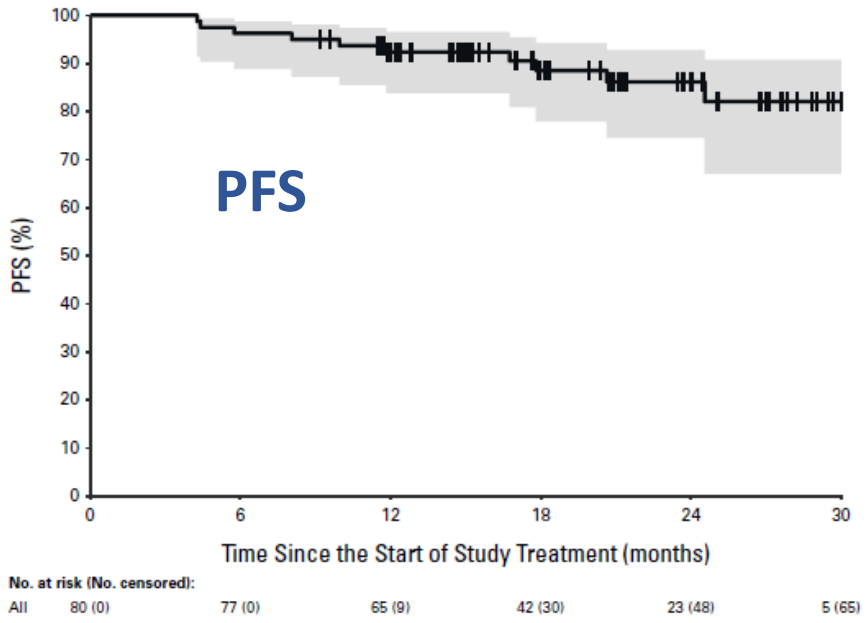
CD20xCD3 bispecifics in newly diagnosed DLBCL

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



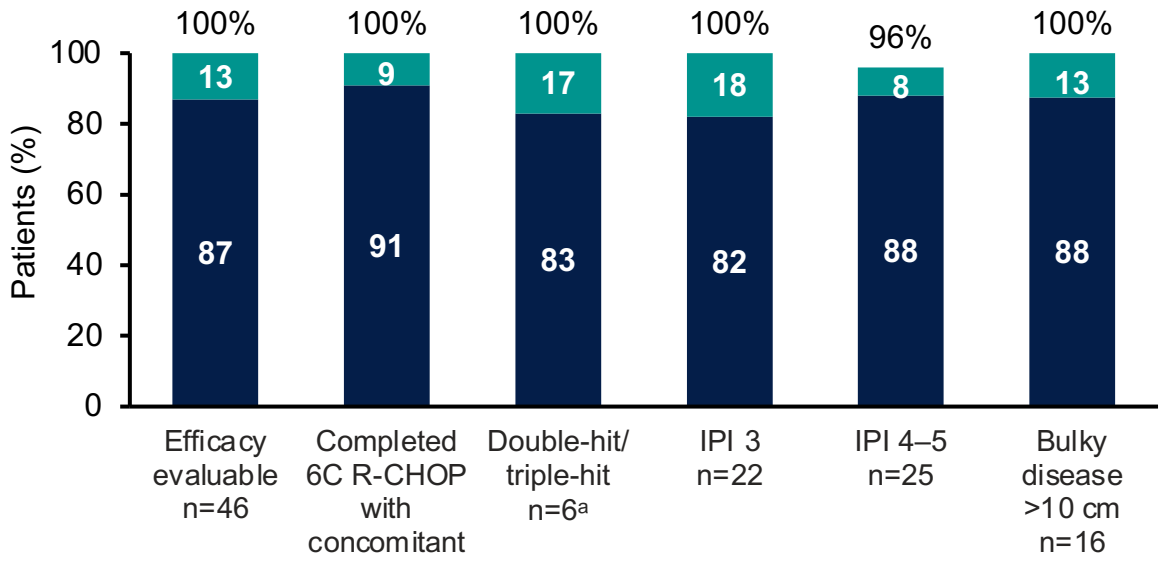


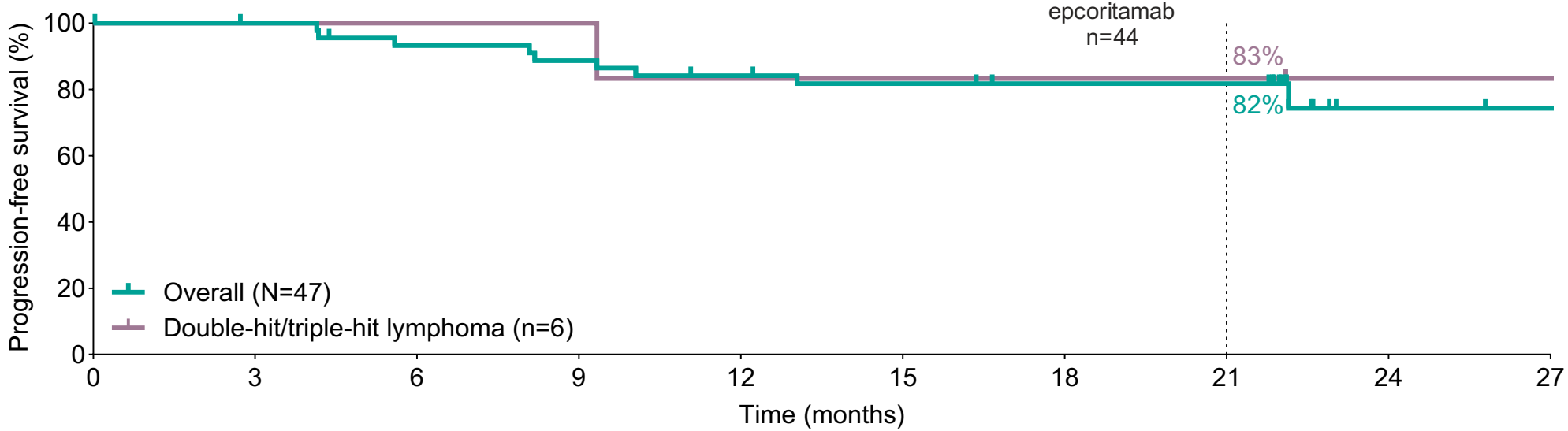
Minson A, et al. J Clin Oncol 2025, 43: 2595-2605.

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





Falchi et al. ASH 2024

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

B. Chapuy, R. Wurm-Kuczera, R. Michael, M. Wang, P. Pichler, A. Huster, A. Kerkhoff, M. Panny, R. Schroers, A. Ossami Saidy, F. Müller, F. Damm, M. Orlinger, P. Staber, C. Schwaenen, L. Wohn, C. Schmitt, M. Hoffmann, M. Hänel, J. Düll, S. Heyn, S. Mayer, T. Weber, P. Reimer, N. Rotter, U. Schnetzke, B. von Tresckow, G. Kammerer, J. Rasvina, B. Lehner, T. Mika, D. Böckle, C. Leng, A.L. Illert, B. Altmann, B. Friedrichs, E.Willenbacher, D. Mougiakakos, C. Pott, S. Al-Batran, A. Rosenwald, D. Hellwig, S. Dietrich, B. Glass, G. Lenz, U. Keller, M. Ziepert, T. Melchardt, R. Greil

BACKGROUND

- Triplet Rituximab + Polatuzumab vedotin + Glofitamab (R-Pola-Glo) may deliver deep responses while avoiding classical chemo intensity
- First planned primary analysis reported

OBJECTIVE

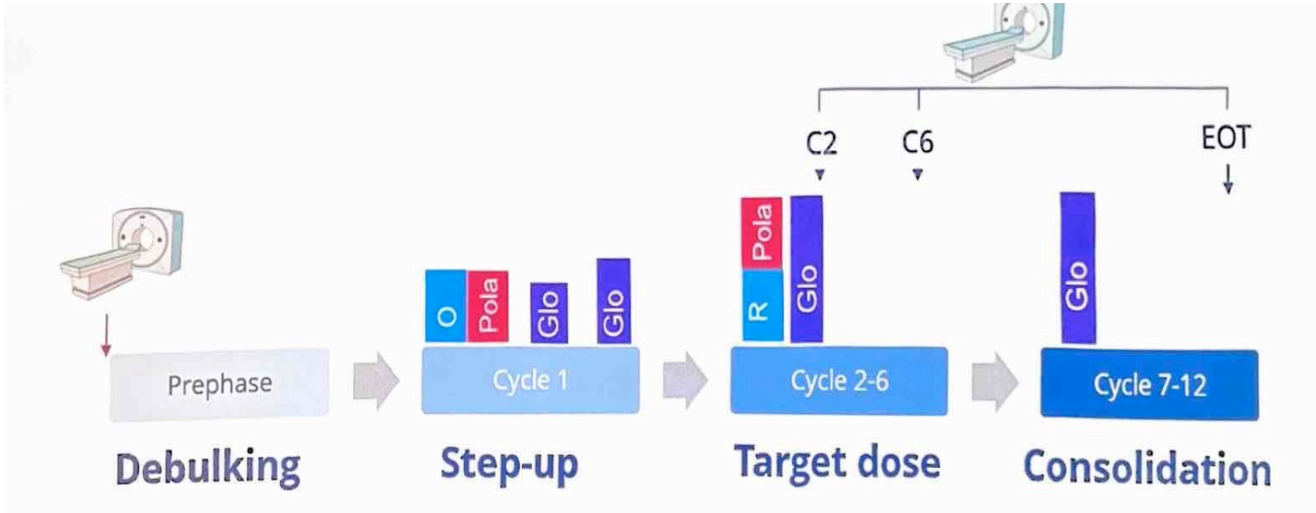
- Primary: 1-year PFS
- Secondary: EFS, OS, Feasibility, Toxicity

METHODS

- **Design**: multicenter, single-arm phase II
- **Treatment schema**: steroid pre-phase; 12 q3w cycles
  - **C1:** Obinutuzumab + Pola + SU Glo (2.5/10 mg)
  - **C2–C6:** R + Pola + Glo 30 mg
  - **C7–C12:** Glo consolidation (30 mg)
- **Assessments**: PET/CT Lugano after C2, C6, EOT; safety

POPULATION

- **N=80;** untreated DLBCL pts ineligible for full-dose R-CHOP; median age 80 (66–92); 19% >85yo; 91% unfit/frail by sGA; 63% stage III/IV; 63% elevated LDH; 28% ECOG 2; 64% IPI 3–5
- **Treatment completion**: 80% (64/80) completed therapy as planned



Therapy adherence and AEs

Cohort (N=80)	
Completed treatment as planned	80% (64/80)
AE, no grade 3–5 in any cycle	34% (27/80)
AE, grade 5	4% (3/80)

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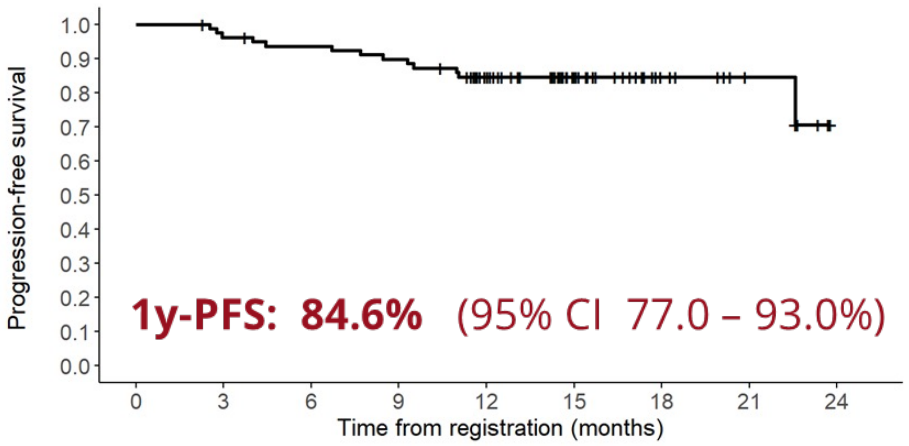
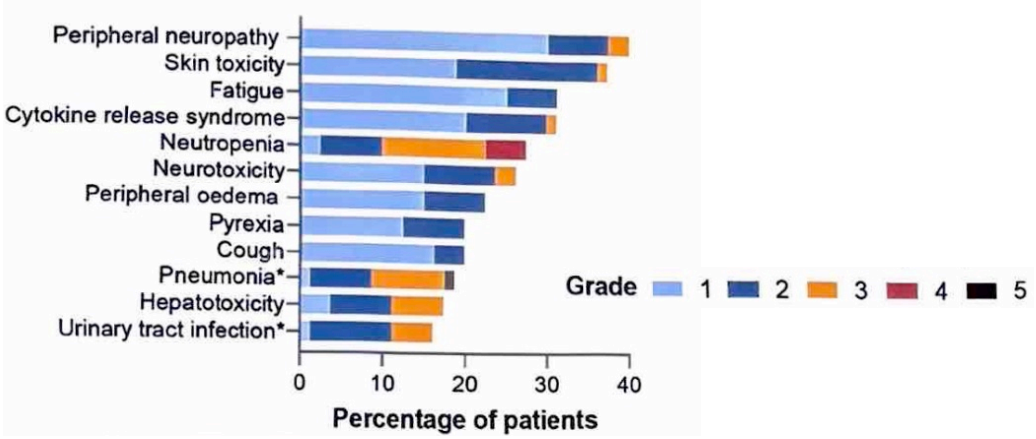
Phase II frontline chemolight R-pola-glo trial for elderly and medically unfit/frail patients with aggressive B-cell lymphoma

1-year Progression-free Survival (PFS)



Most common AE terms



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

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NKOTB: 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

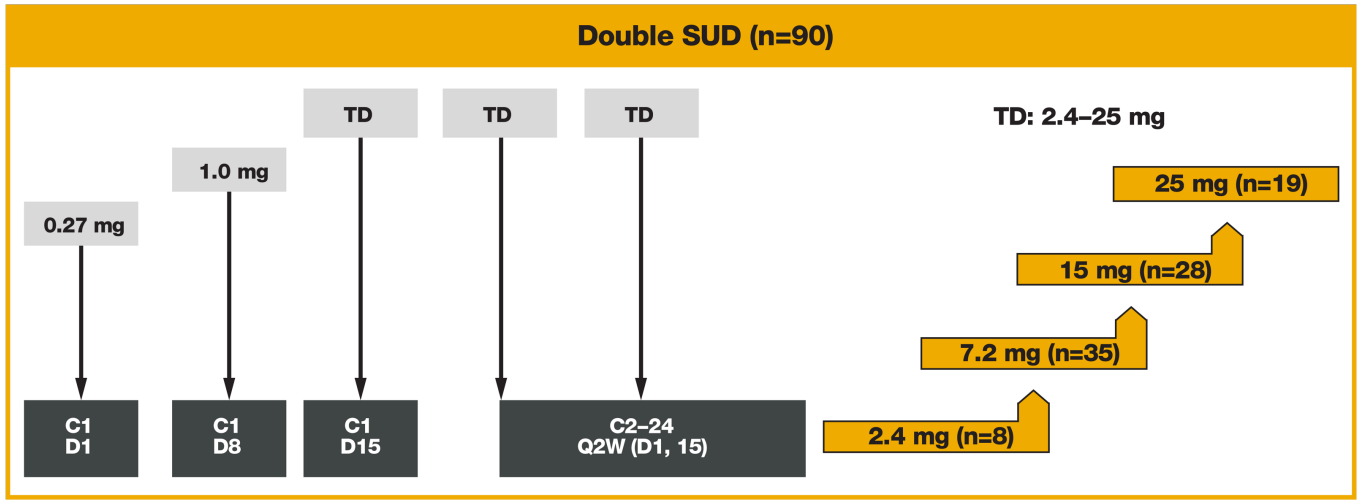
Assessments

- Disease response: RECIL using PET-CT by ICR[6]
- CRS and ICANS: ASTCT criteria[7]
- AEs: CTCAE v5.0
- MRD: PhasED-Seq CLARITY assay in plasma ctDNA (approximately <1 part/million detection

Endpoints

Primary
Safety/tolerability
MTD/RP2D
PK

Secondary
Antitumor activity



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

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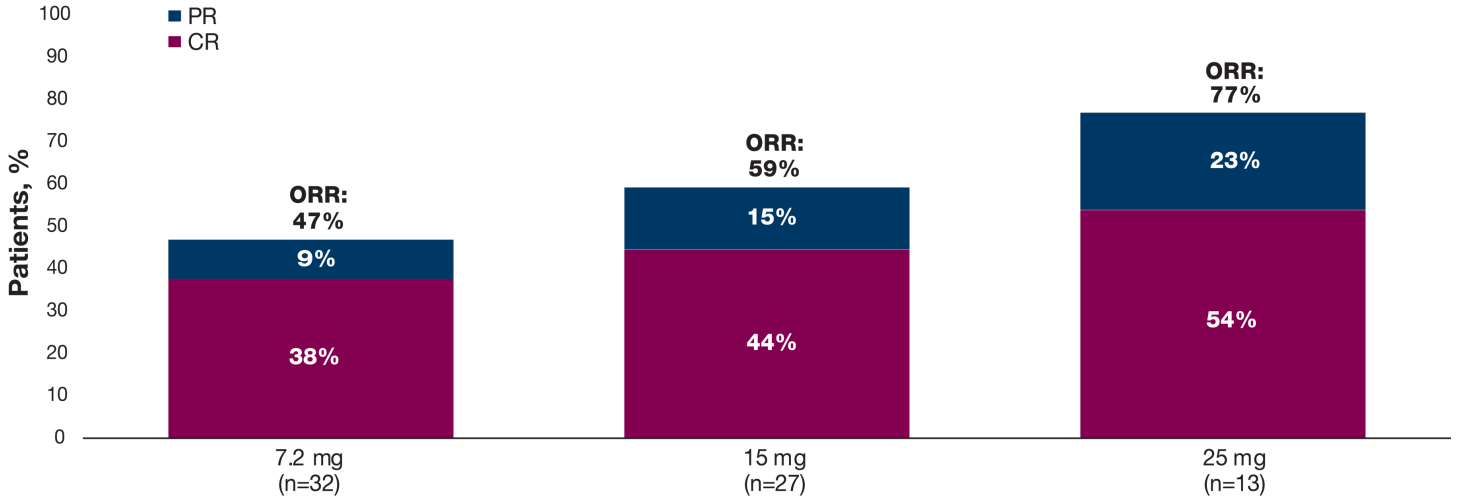
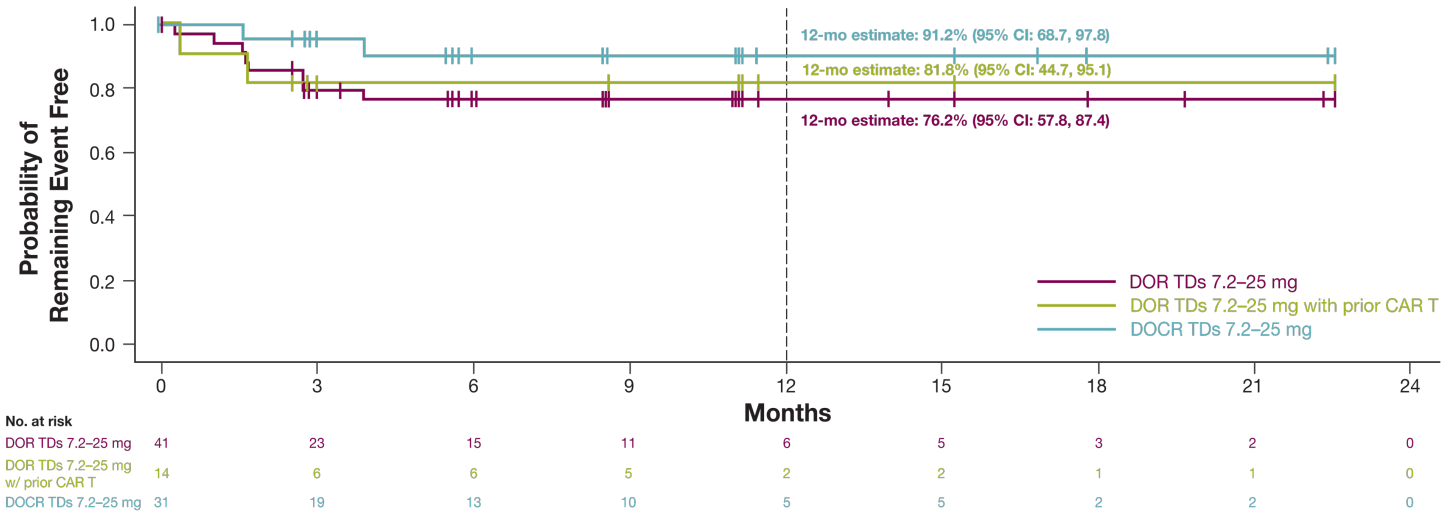
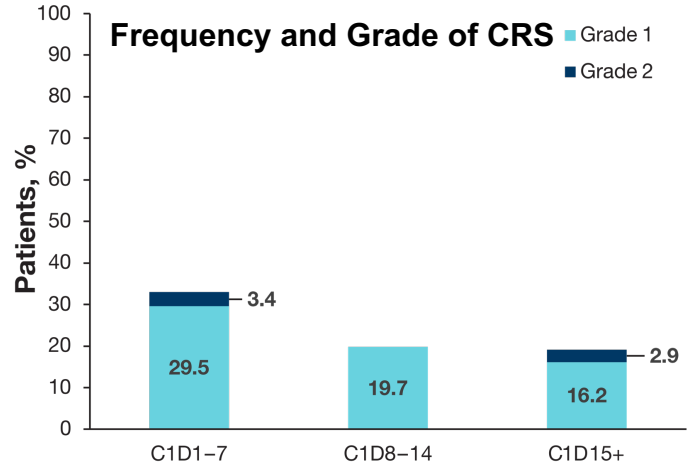
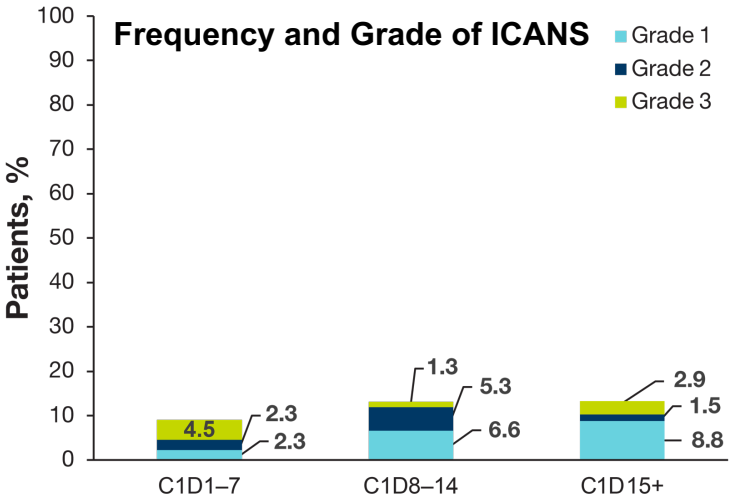
Ph1 study of surovatamig: Efficacy and safety in r/r DLBCL









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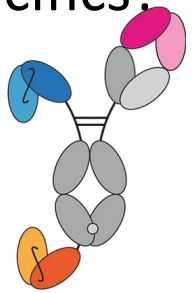
Summary

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?



JNJ-80948543
(CD79BxCD20xCD3)

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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