Charles University
1st Faculty of Medicine

General Hospital

The evolving landscape in R/R DLBCL

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Unmet challenges in high risk hematological malignancies

CLSG KLS
Czech Lymphoma Study Group
Kooperativní Lymfomová Skupina

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Disclosures

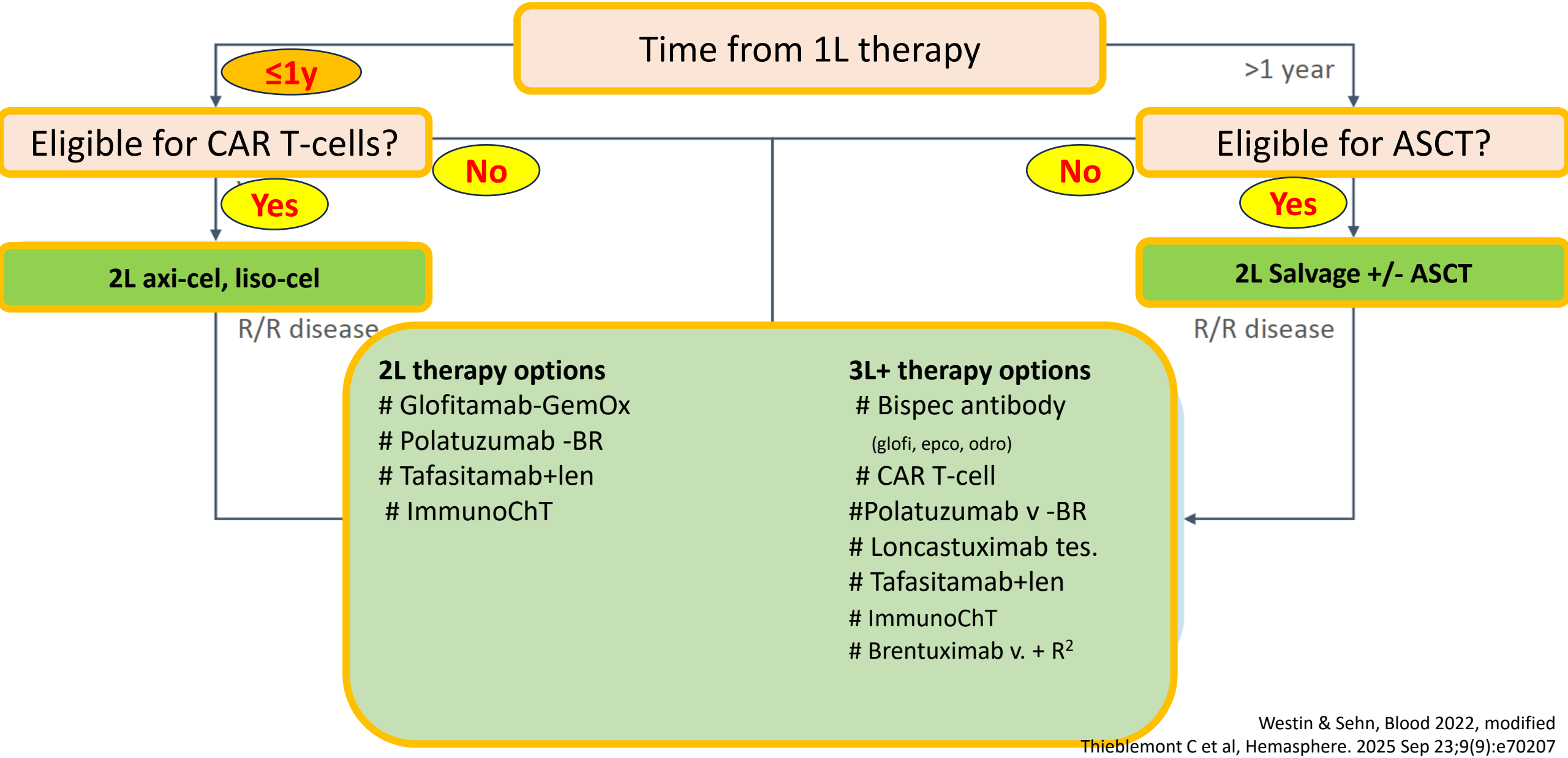
Disclosure of affiliations

Roche (Advisory board, research support, honoraria)
Takeda (Advisory board, honoraria)
Gilead (Advisory board, honoraria)
Abbvie (Advisory board, honoraria)
Caribou (Advisory board, honoraria)
GenMab (Advisory board, honoraria)
BMS (Advisory board, honoraria)
Janssen (Advisory board, honoraria)
Morphosys (Advisory board)
SOBI (Advisory board, honoraria)
Autolus (Advisory board, honoraria)
Novartis (Advisory board)

Outline

- Current suquencing
- CAR T-cell
- ADC
- Bispecific antibodies
- Combinations
- Other options and challenges

How to proceed? Sequence



Westin & Sehn, Blood 2022, modified
Thieblemont C et al, Hemasphere. 2025 Sep 23;9(9):e70207

Outline

- Current suquencing
- CAR T-cell
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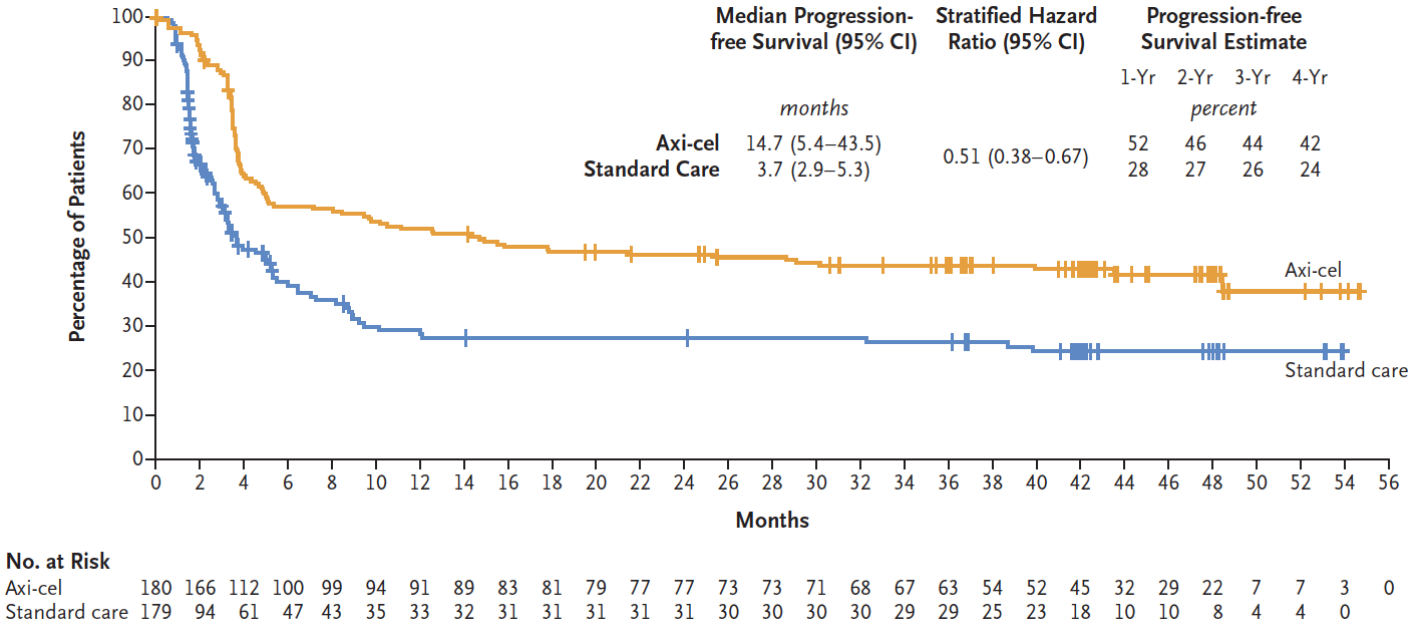
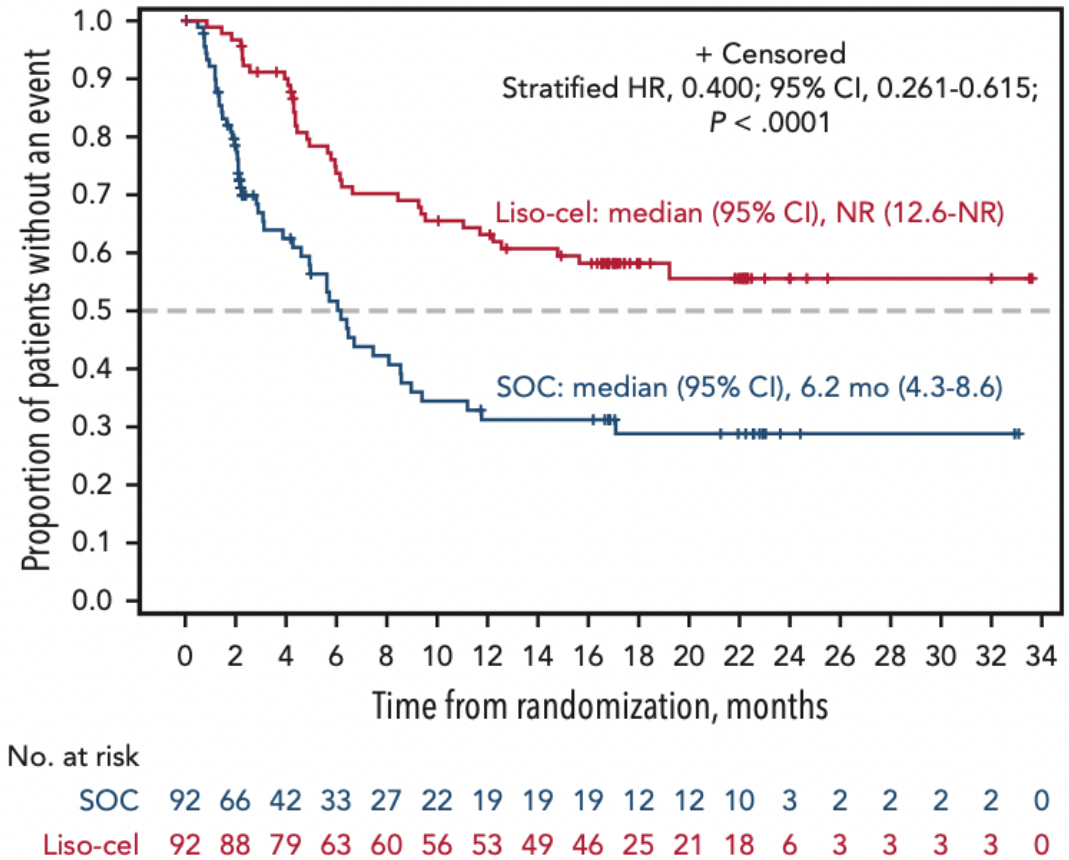
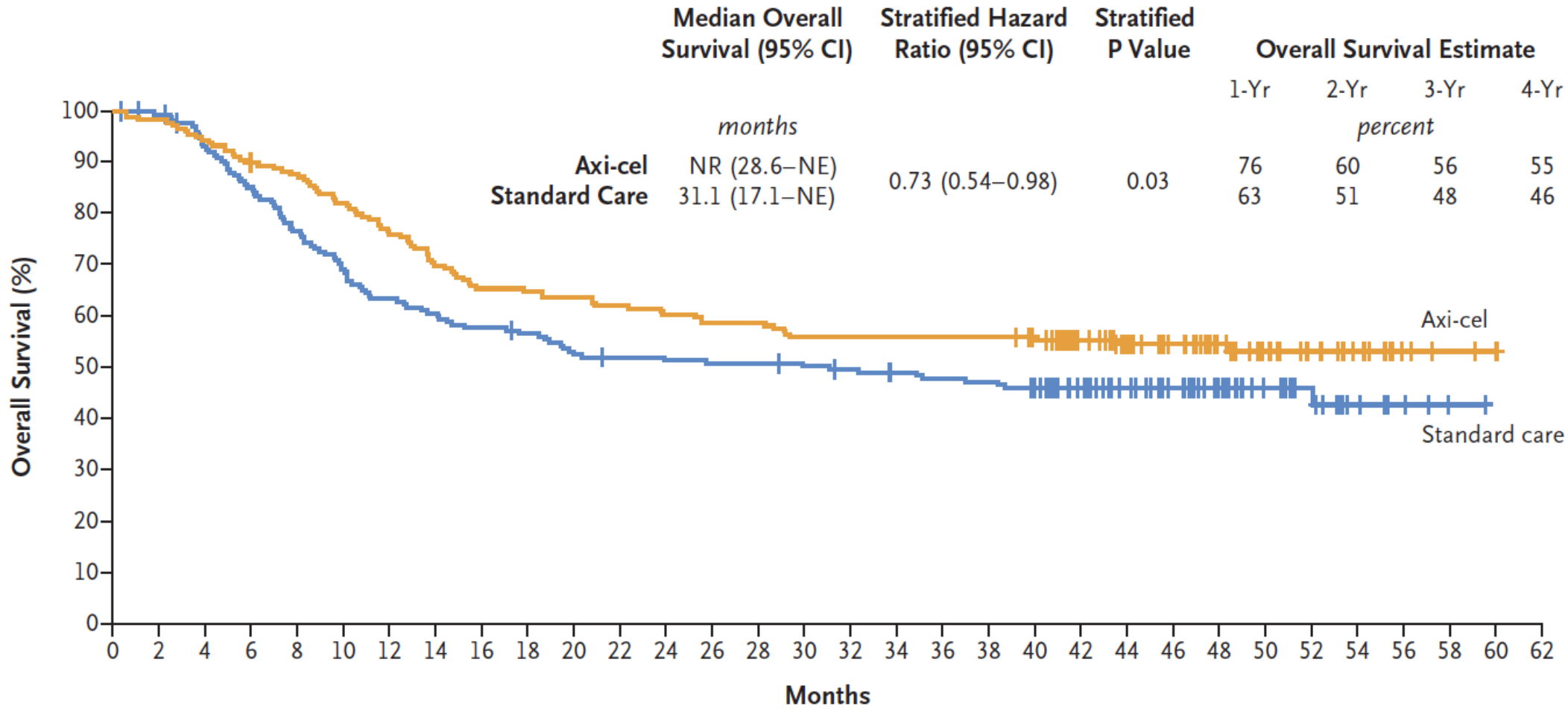
PFS: Axi-cel (Zuma-7) a Liso-cel (Transform) L2 ≤12m





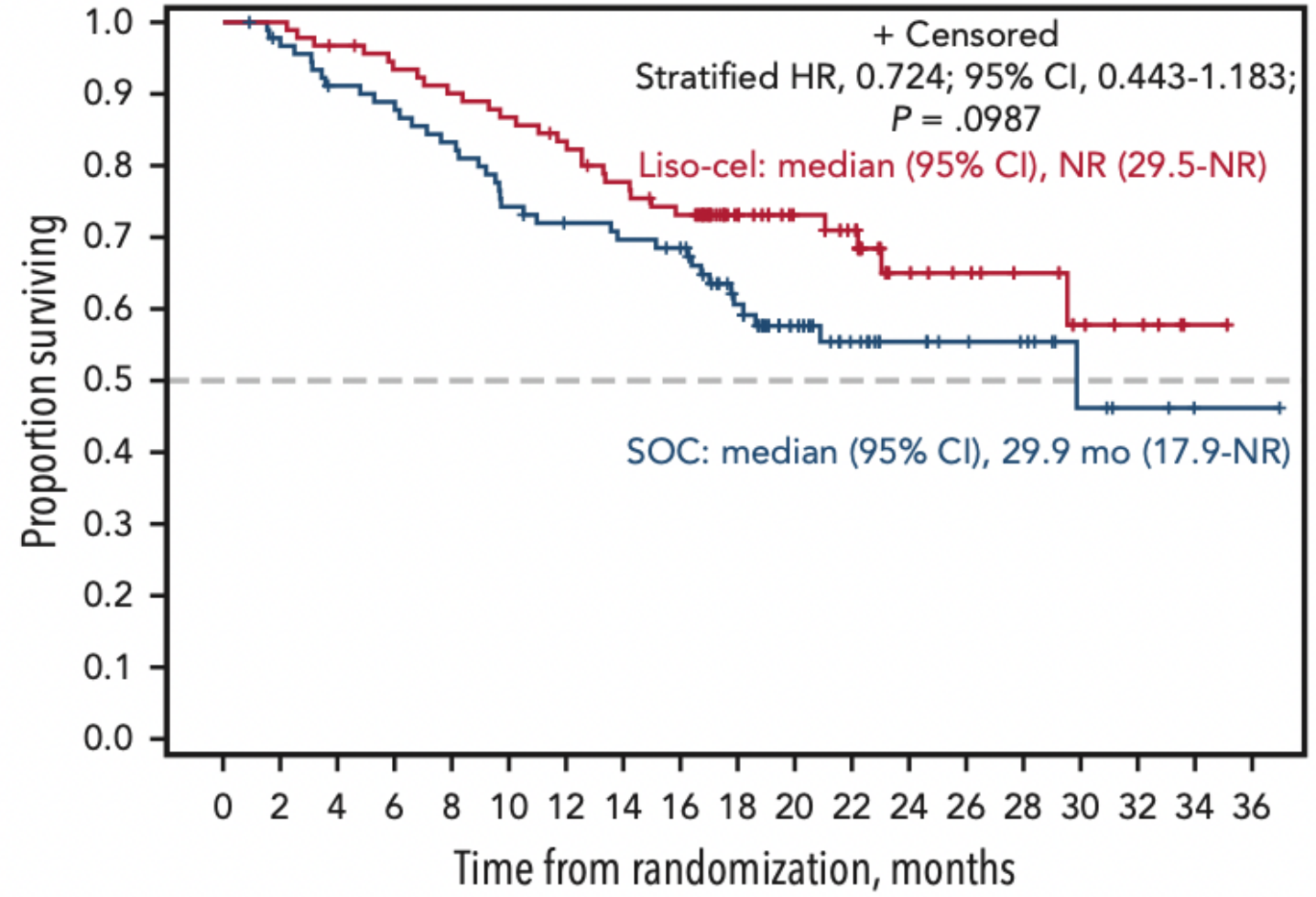
Westin J et al, NEJM 2023
Abramson J et al, Blood 2023

Zuma-7: L2 – Overall Survival Benefit



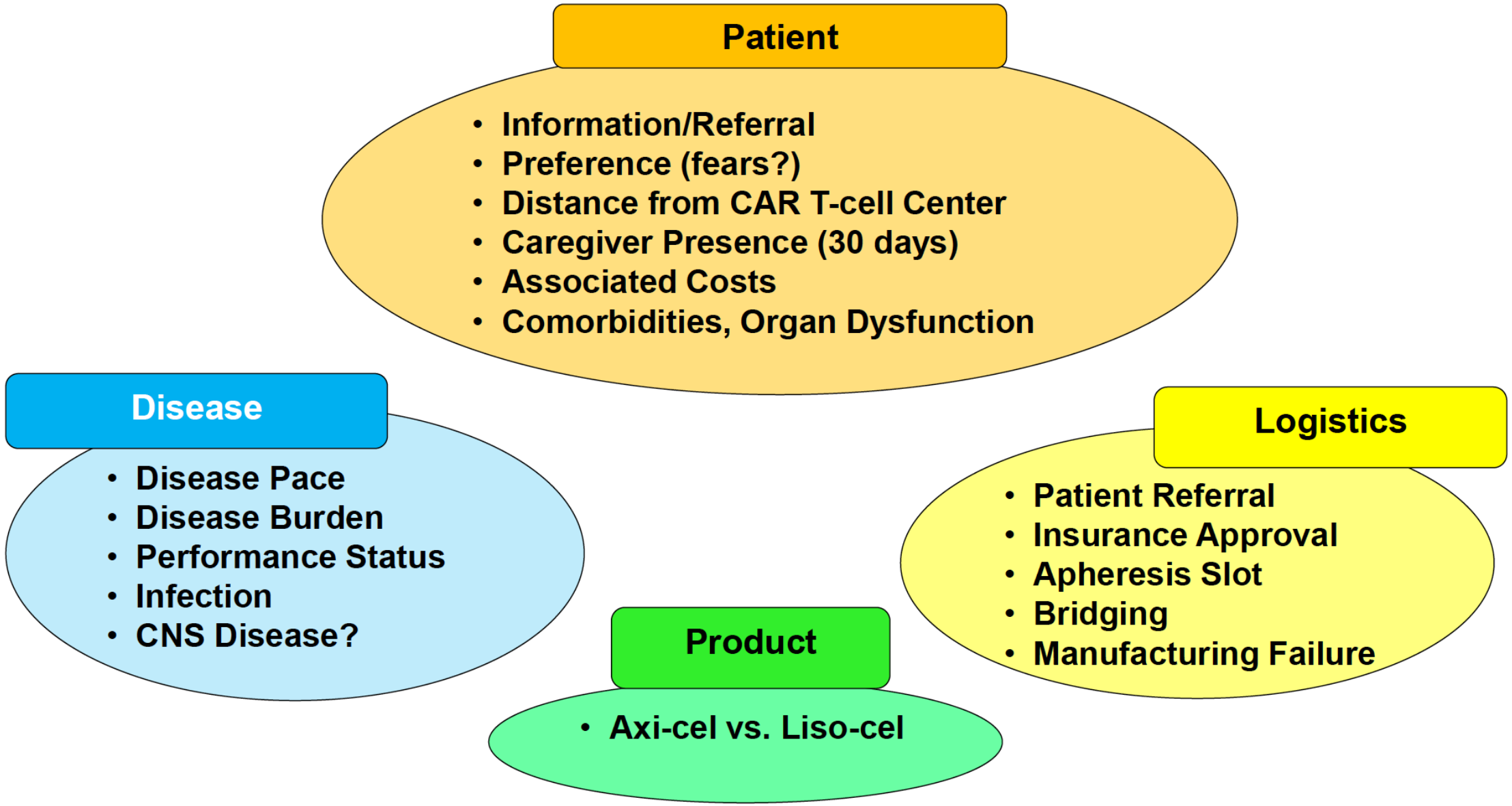
Westin J et al, NEJM 2023

Transform: L2 – Trend to Overall Survival Benefit



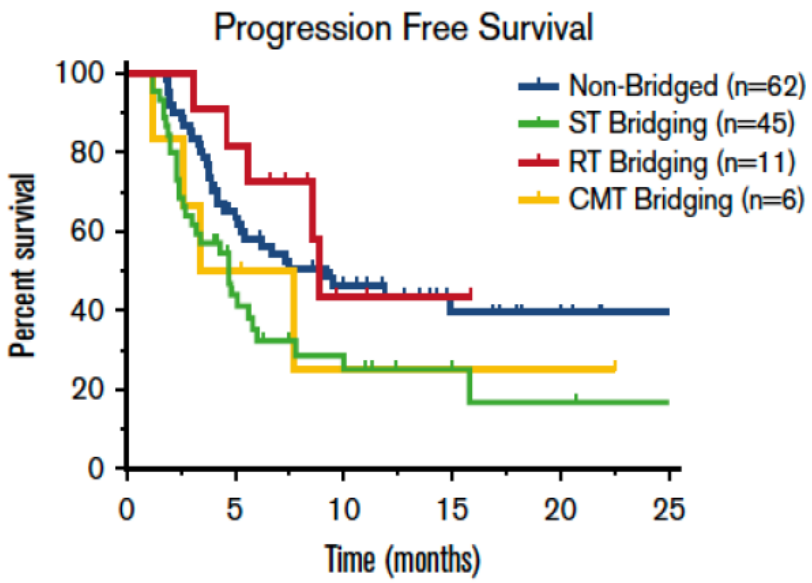
Abramson J, Blood 2023

Questions for CAR T-cell



Courtesy of Giles Salles

BridgingTherapy: are Bridging Strategies all Equal?



Chemotherapy	- R-GemOx, R-DHAox, R-GDI - R-CHOP, R-EPOCH - Pola-BR
ADC	- Polatuzumab Vedotin - Loncastuximab
Immuno	- Tafa-Len - R2 - CD3xCD20 BsAb
Targeted	- Ibru - Len
Other	- Steroids - Radiation - .. None

Increased risk of CAR T-cell toxicities?

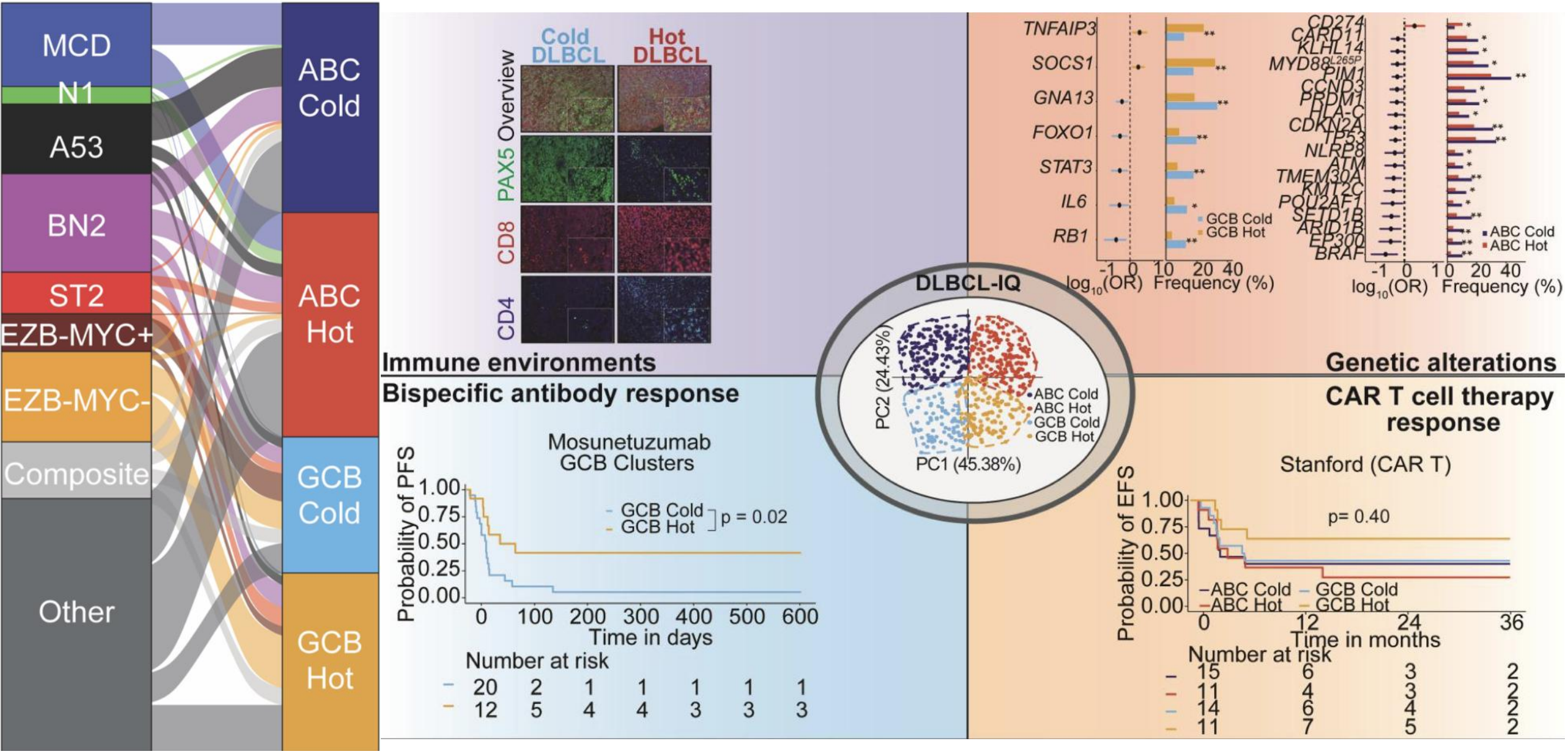
Risk of CD19 Ag masking orloss?

Influence in CAR T-cell efficacy?

Feasibility?

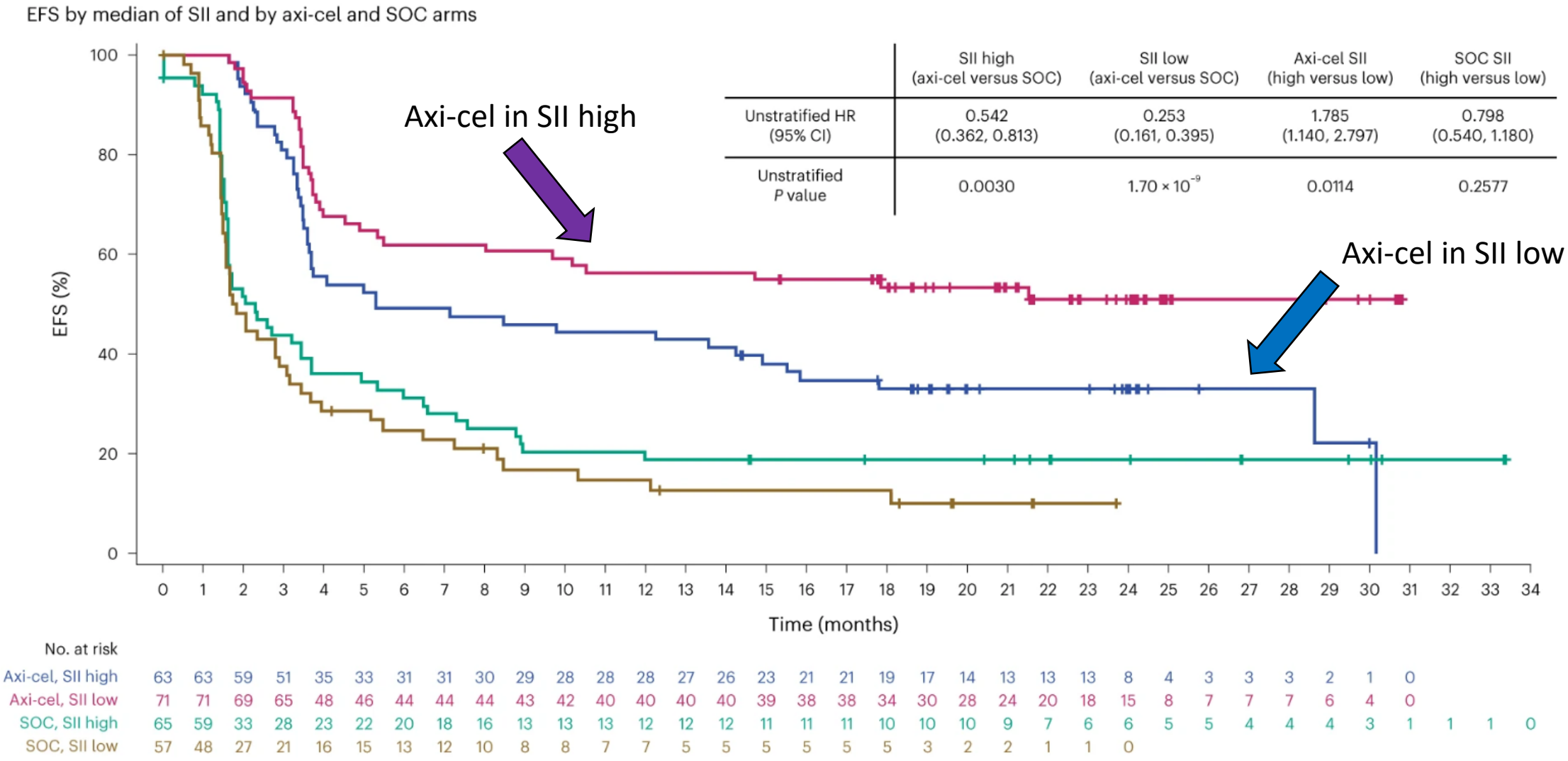
Pinnixet al., Blood 2020

Integrative genomic analysis of DLBCL identifies immune environments associated with T-cell engaging therapy



Tumuluru S et al, Blood. 2025 Jan 27:. Online ahead of print.

Response to axicel according to TME subtype



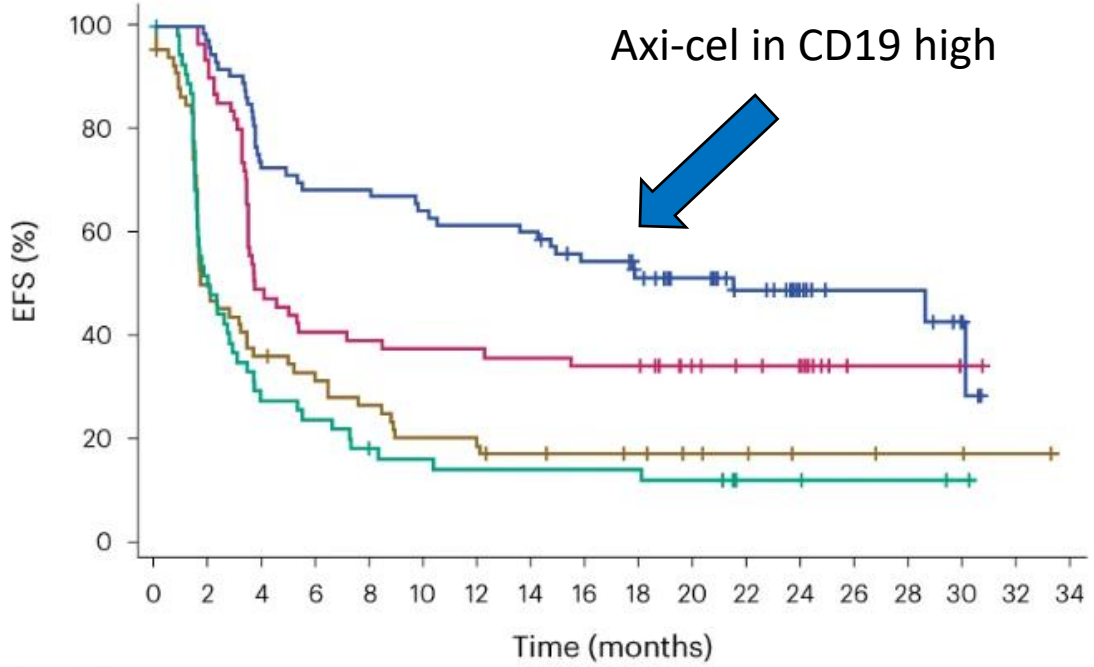
	SII high (axi-cel versus SOC)	SII low (axi-cel versus SOC)	Axi-cel SII (high versus low)	SOC SII (high versus low)
Unstratified HR (95% CI)	0.542 (0.362, 0.813)	0.253 (0.161, 0.395)	1.785 (1.140, 2.797)	0.798 (0.540, 1.180)
Unstratified *P* value	0.0030	1.70×10^{-9}	0.0114	0.2577

Frederick Locke et al. Impact of tumor microenvironment on efficacy of anti-CD19 CAR T cell therapy or chemotherapy and transplant in large B cell lymphoma. Nat Med. 2024 Feb;30(2):507-518. doi: 10.1038/s41591-023-02754-1. Epub 2024 Jan 17.

Higher CD19 gene and protein expression predict improved EFS after axi-cel

a EFS by median of CD19 gene expression and by axi-cel and SOC arms

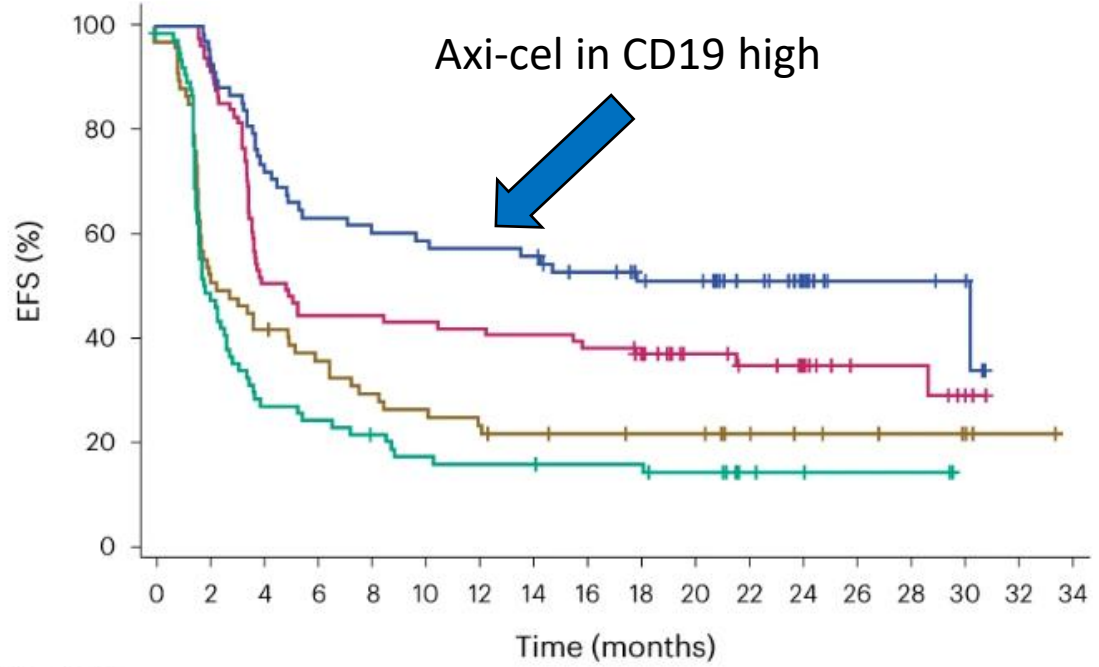
	CD19 gene high (axi-cel versus SOC)	CD19 gene low (axi-cel versus SOC)	Axi-cel CD19 gene (high versus low)	SOC CD19 gene (high versus low)
Unstratified HR (95% CI)	0.269 (0.174, 0.416)	0.517 (0.343, 0.780)	0.579 (0.371, 0.905)	1.126 (0.761, 1.667)
Unstratified *P* value	3.85×10^{-9}	0.0017	0.0165	0.5526



No. at risk																	
Axi-cel, CD19 gene high	73	71	53	50	50	47	45	44	38	32	27	20	13	8	8	4	
Axi-cel, CD19 gene low	61	57	30	25	24	23	23	22	21	21	15	13	10	2	2	1	
SOC, CD19 gene high	55	27	15	13	9	8	7	7	7	7	6	3	3	2	2	1	
SOC, CD19 gene low	67	33	24	20	17	13	12	10	9	8	6	5	3	3	2	2	1	0

b EFS by median of baseline CD19 protein expression (H-score as assessed by IHC) and by axi-cel and SOC arms

	CD19 high by IHC (axi-cel versus SOC)	CD19 low by IHC (axi-cel versus SOC)	Axi-cel CD19 (high versus low)	SOC CD19 (high versus low)
Unstratified HR (95% CI)	0.283 (0.184, 0.433)	0.572 (0.390, 0.840)	0.627 (0.407, 0.966)	1.254 (0.868, 1.812)
Unstratified *P* value	6.92×10^{-9}	0.0044	0.0341	0.2284



No. at risk																	
Axi-cel, CD19 high	68	66	50	43	42	40	39	38	33	29	28	21	14	6	6	4	
Axi-cel, CD19 low	81	76	41	36	36	35	34	33	31	28	18	15	10	6	6	2	
SOC, CD19 high	77	36	20	18	15	12	11	11	10	10	8	4	3	2	2	0	
SOC, CD19 low	67	36	28	23	19	17	15	13	12	11	11	8	6	5	4	3	1	0

Locke F et al.. Nat Med. 2024 Feb;30(2):507-518.

Novel CAR T-cell

- Rapcabtagene autoleucel
- Zamcabtagen autoleucel
- GLPG 5101
- huCART19-41BB-IL18
- KTE-363
- Cermacabtagene autoleucel
- CAR NK-cell

Rapcabtagene Autoluecel

- Rapid manufacturing platform to preserve T-cell stemness
- Expansion comparable to tisa-cel at a 25-fold lower dose
- Phase II trial of rapcabtagene autoleucel for R/R DLBCL

Baseline Characteristic	N=63
Median age, yr (range)	64 (26-81)
Median prior treatment	2 (2-6)
Refractory to prior line, %	59
Elevated LDH, %	43
Double hit, %	25

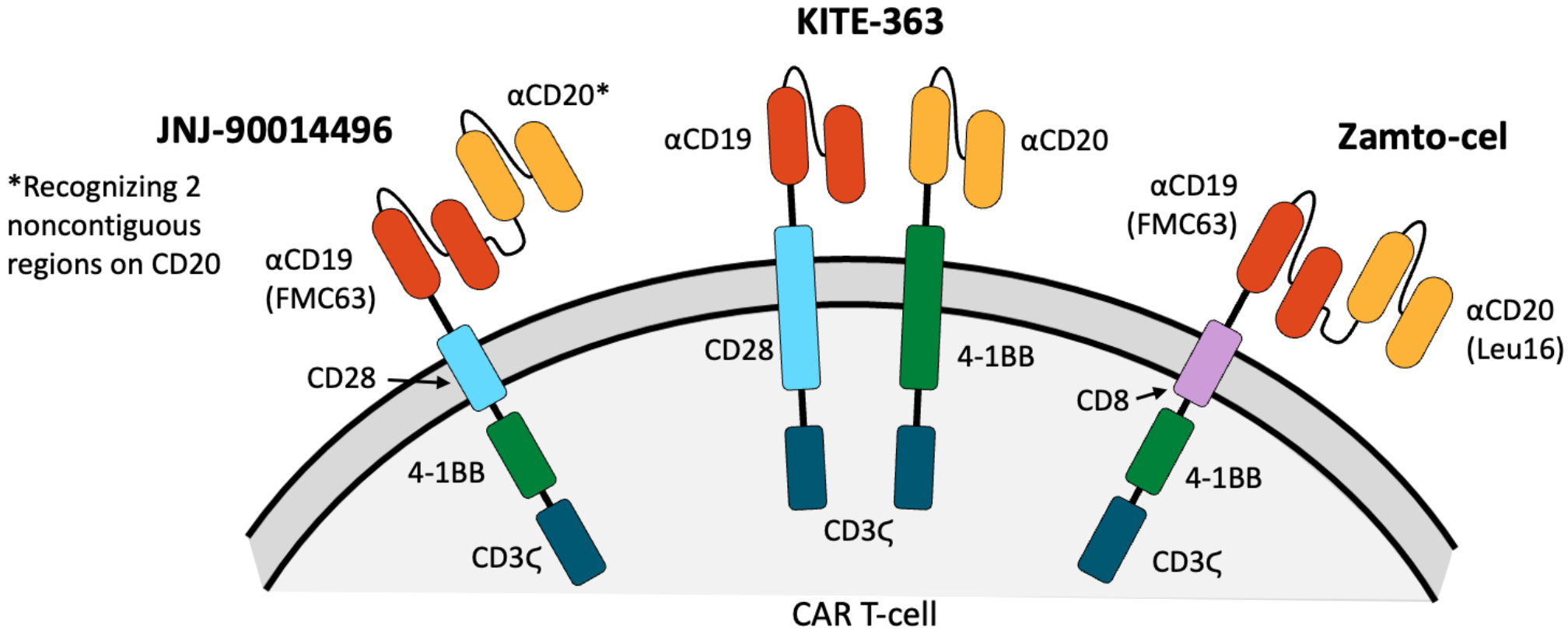
Efficacy	N=60
Overall response, %	88
Complete response, %	65
Median DoR, mo	15
Median PFS, mo	12

Safety	N=63
CRS, %	
• Any grade	43
• Grade ≥3	6
ICANS, %	
• Any grade	6
• Grade ≥3	3
Grade ≥3 infection, %	27

Barba, ASH 2024 (#439), Reidell, ASH 2024 (#67)

Dual-Target CAR T-cell

- Potentially improved efficacy vs single-target CAR T-cell therapy
- May prevent resistance due to antigen escape

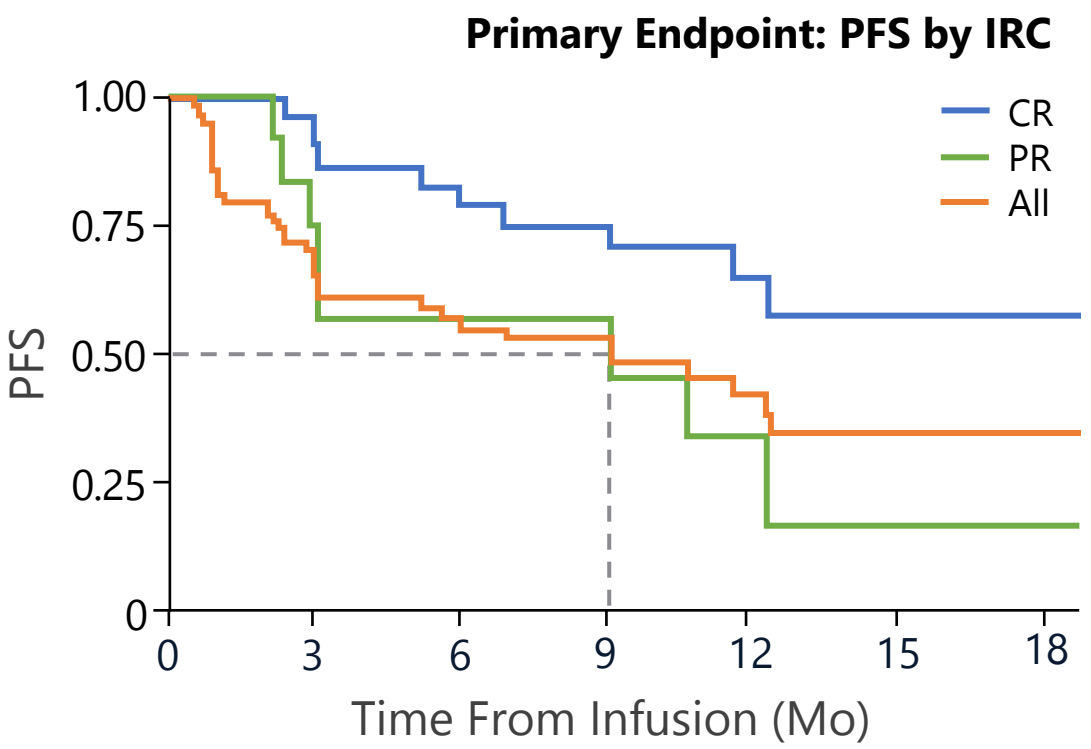


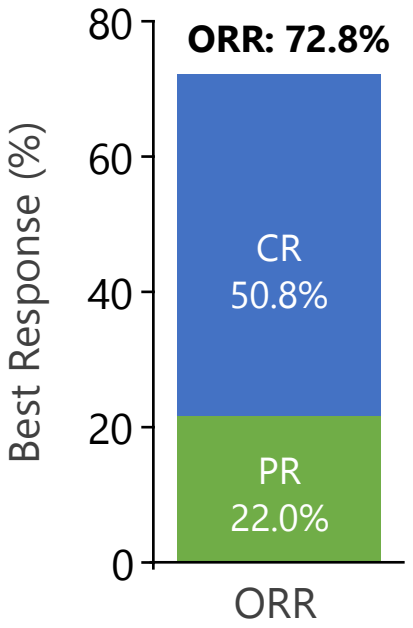
Zamtocabtagene Autoleucel

- Anti-CD19/CD20 CAR T-cell therapy with 14-day vein-to-vein time
- DAILY II: phase II study in patients with R/R DLBCL after ≥2 prior lines of treatment

Baseline characteristics	N = 59
Median age, yr (range)	63 (25-85)
Elevated LDH, %	53
IPI 3-5, %	52
2 prior lines of therapy, % ≥3 prior lines of therapy, %	75 25
Prior ASCT, %	25

Antigen loss at progression	n = 27
CD19	2
CD20	2
CD19 & CD20	1



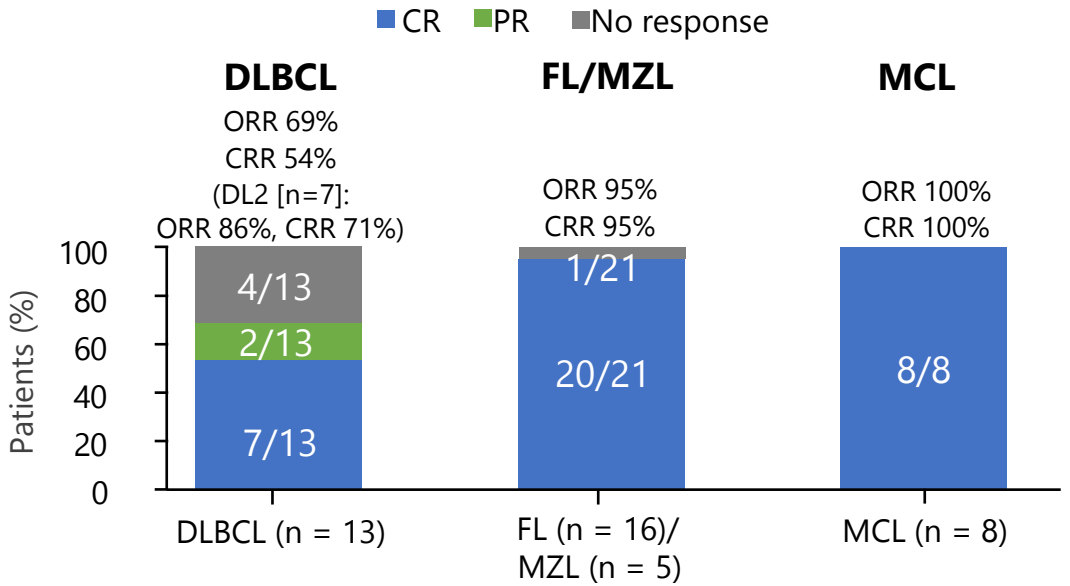


Shah. ASH 2024. Abstr 105. Shah. ICML 2025. Abstr 43.

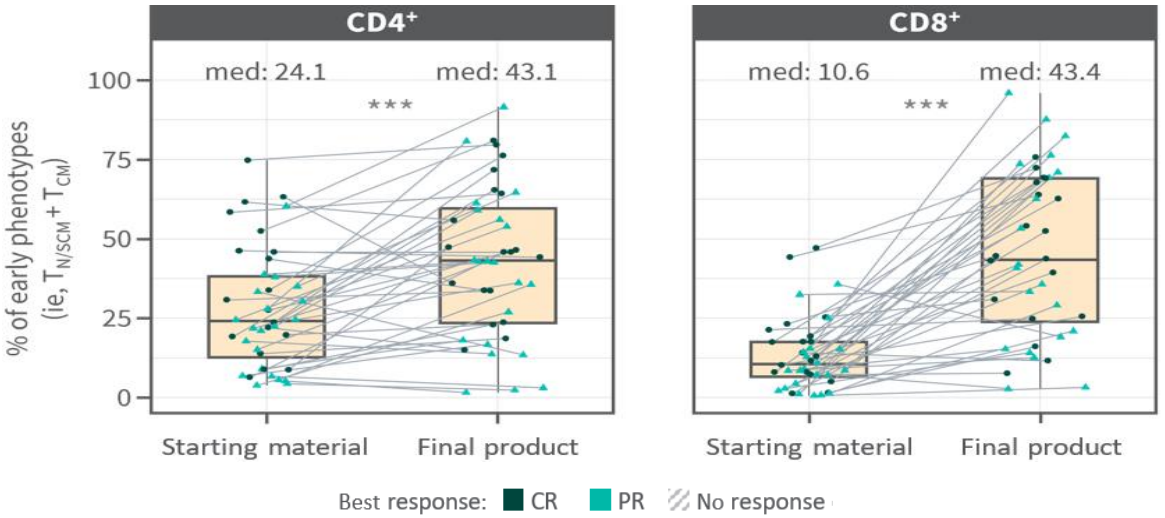
GLPG5101

- A fresh stem-like, early memory phenotype anti-CD19/CD20 CAR T-cell therapy with 7-day vein-to-vein time
- ATALANTA-1: phase I/II trial in patients with R/R B-NHL

Baseline characteristics	Phase I n = 20	Phase II n = 25
Median age, yr (range)	66.5 (25-78)	67 (40-81)
DLBCL, % MCL, % FL/MZL, %	65 15 15/5	0 30 64/16
High risk (M/FL) IPI, %	42	56
Median prior therapies (range)	2.5 (1-7)	3 (2-11)



Majority of responses ongoing at median 3.3 mo

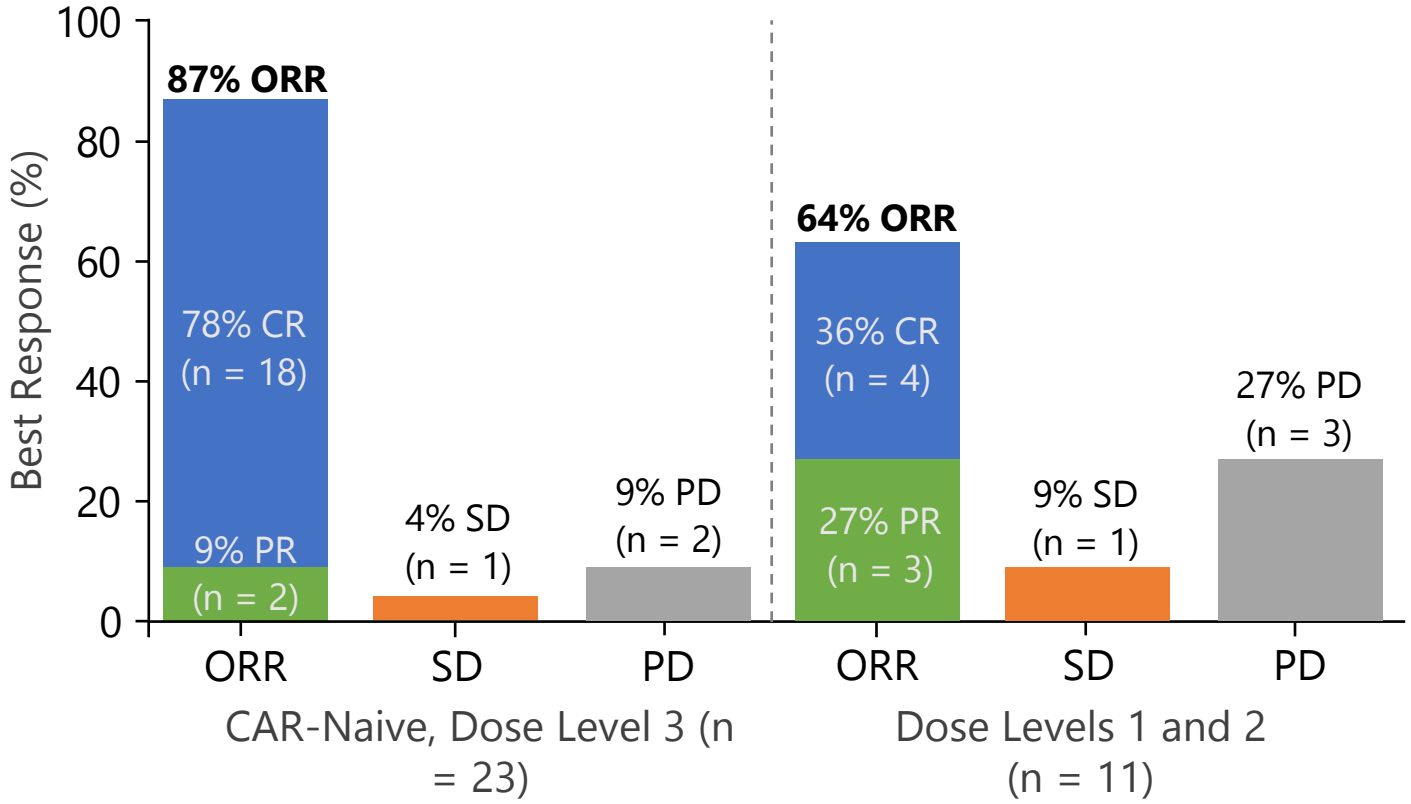


Kersten. ASH 2024. Abstr 93

Kite-363

- A bicistronic, lentiviral-encoded, autologous anti-CD19/CD20 CAR t-cell therapy
- Phase I trial in patients with R/R BCL

Baseline characteristics	N = 37
Median age, yr (range)	62 (25-83)
IPI 3-4, %	44
1 prior line of therapy (primary refractory) , % ≥2 prior lines of therapy, %	46 54
Prior anti-CD19 CAR, %	19

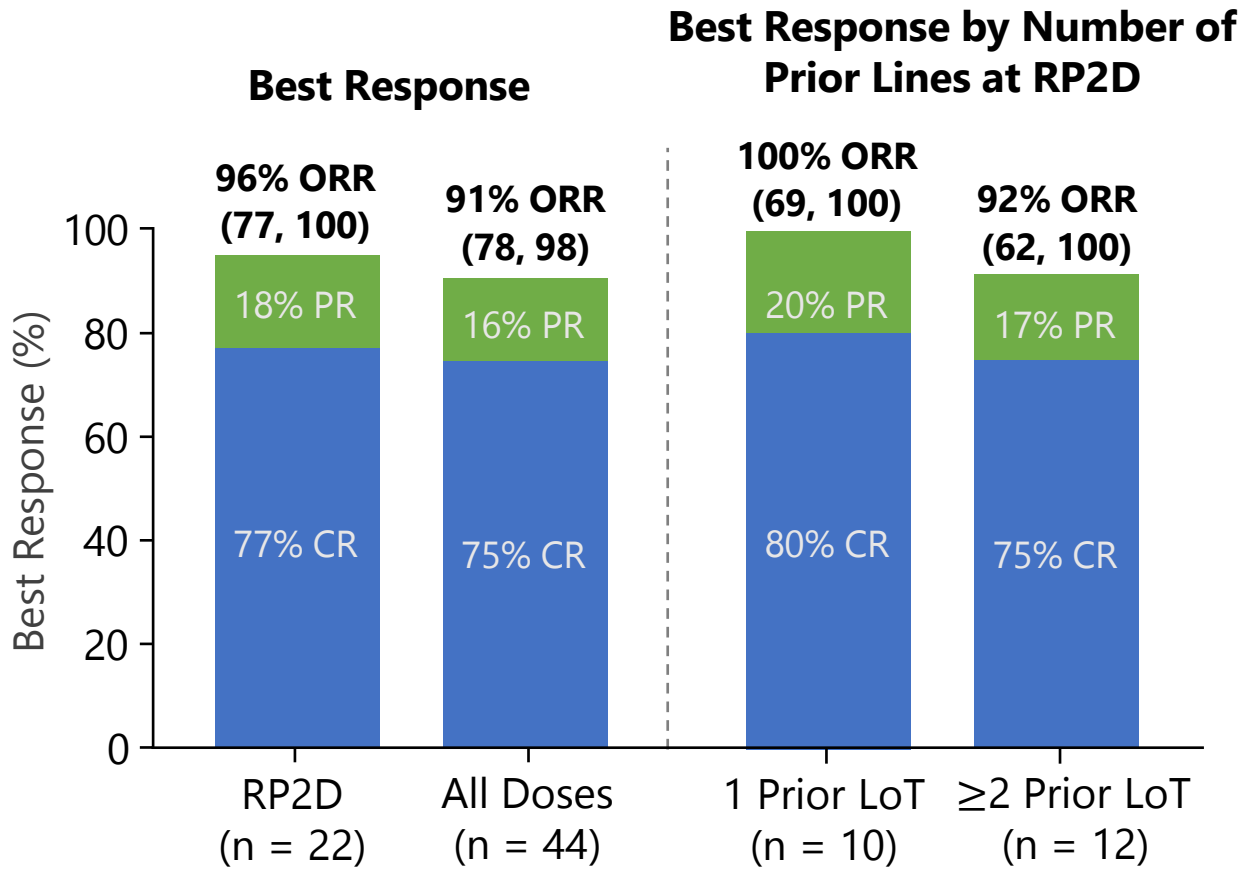


Dahiya. ASCO 2025. Abstr 7003. et al. Proc ICML 2025, and ASCO Abs. 7003

Prizloncabtagene Autoleucel (JNJ-90014496)

- Bispecific anti-CD19/CD20 CAR
- Phase Ib study in R/R LBCL

Baseline characteristics	All (N = 51)	RP2D (n = 25)
Median age, yr (range)	72 (39–87)	72 (40–87)
Primary refractory, %	57	56
Elevated LDH, %	35	36
Median prior lines of therapy (range)	1 (1–3)	1 (1–3)
Prior anti-CD20 BsAb, %	10	20
Prior anti-CD19 BsAb, %	4	8

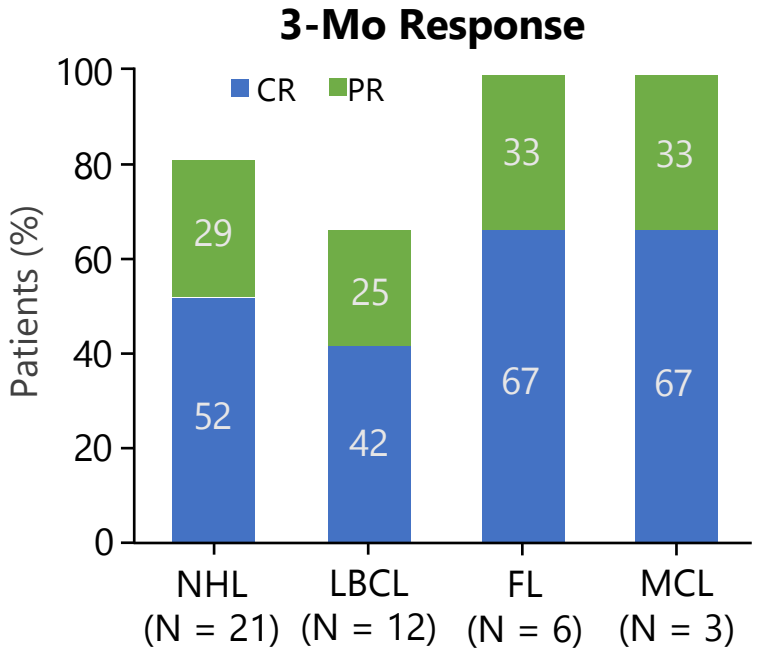


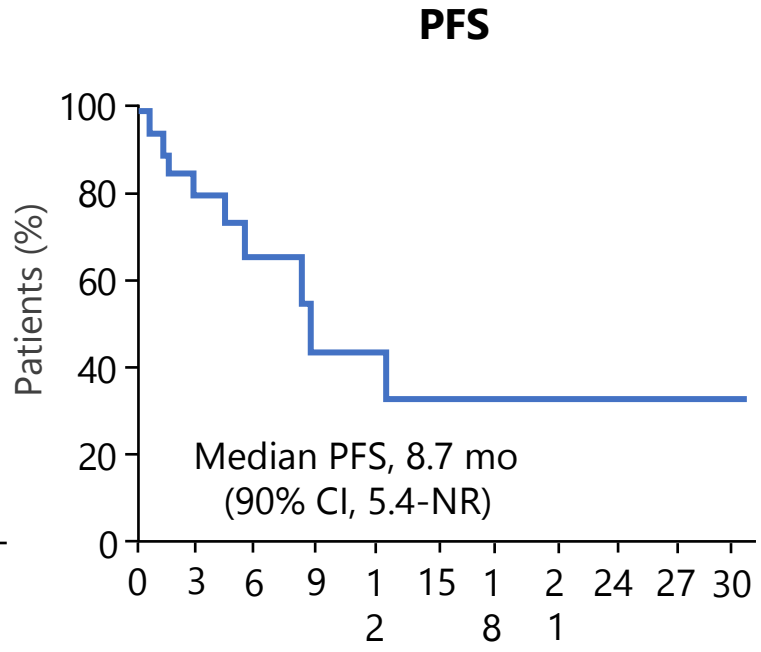
Patel. EHA 2025. Abstr S239.

huCART19-41BB-IL18

- Enhanced (armored) CAR-T cell that secretes IL-18; 3 day manufacturing time
- Phase I trial of huCART19-IL18 in patients with R/R lymphoma with previous anti-CD19 CAR T-cell therapy

Baseline characteristics	N = 21
Median age, yr (range)	64 (47-74)
DLBCL, % FL, % MCL, %	57 29 14
Median prior tx (range)	7 (4-14)
Prior CD28/4-1BB CAR, %	50/50



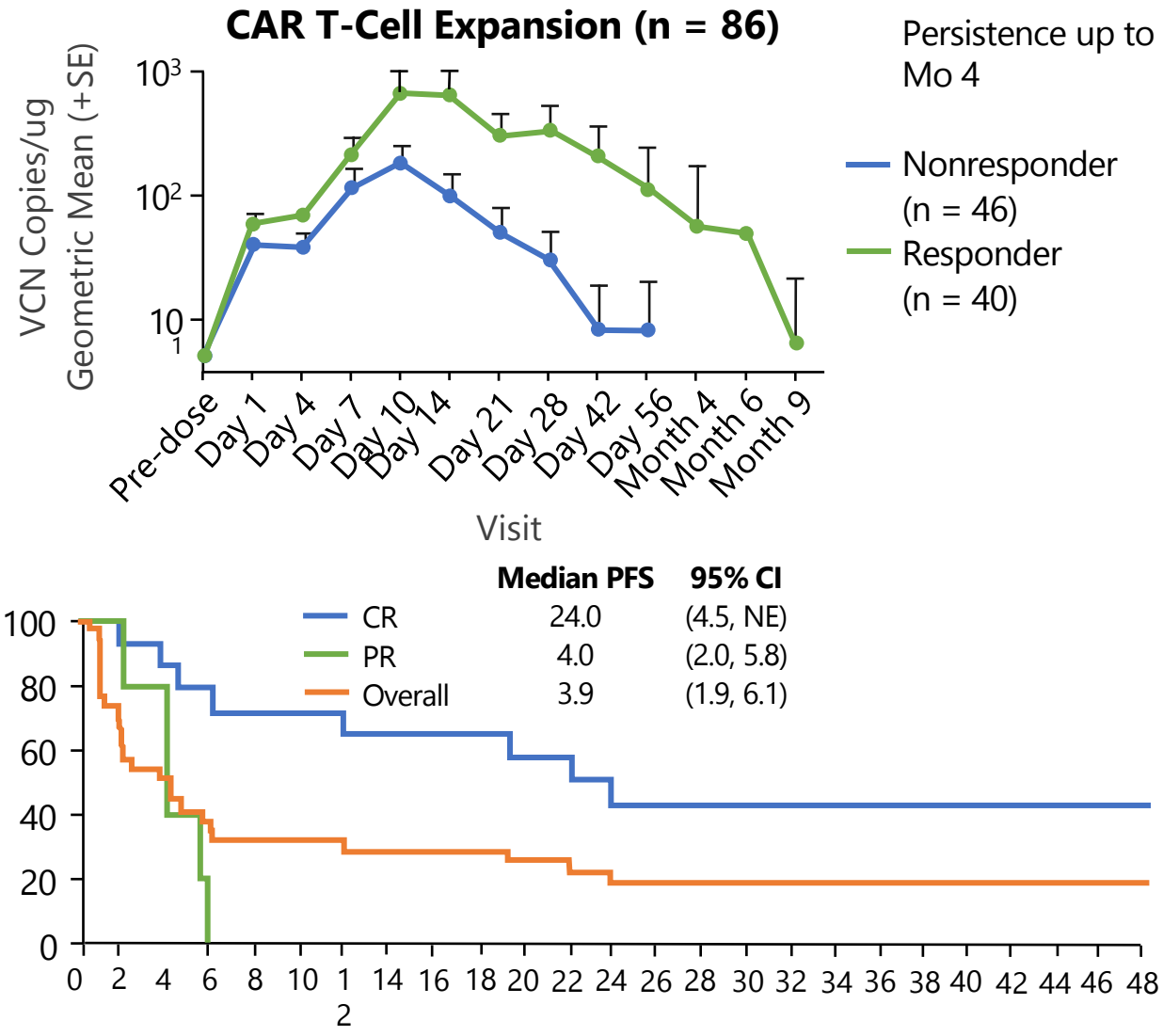


Svoboda. NEJM. 2025;392:1824.

Cemacabtagene Ansegedleucel

- Allogeneic CD19 CAR T-cell therapy
- Phase I/II trial in patients with R/R LBCL

Outcome, n (%)	All (N = 33)	Phase 2 Dose (n = 12)
ORR	19 (58)	8 (67)
CRR	14 (42)	7 (58)
6 mo CRR	10 (30)	5 (42)
12 mo CRR	8 (24)	4 (33)



Locke. JCO. 2025;43:1695.

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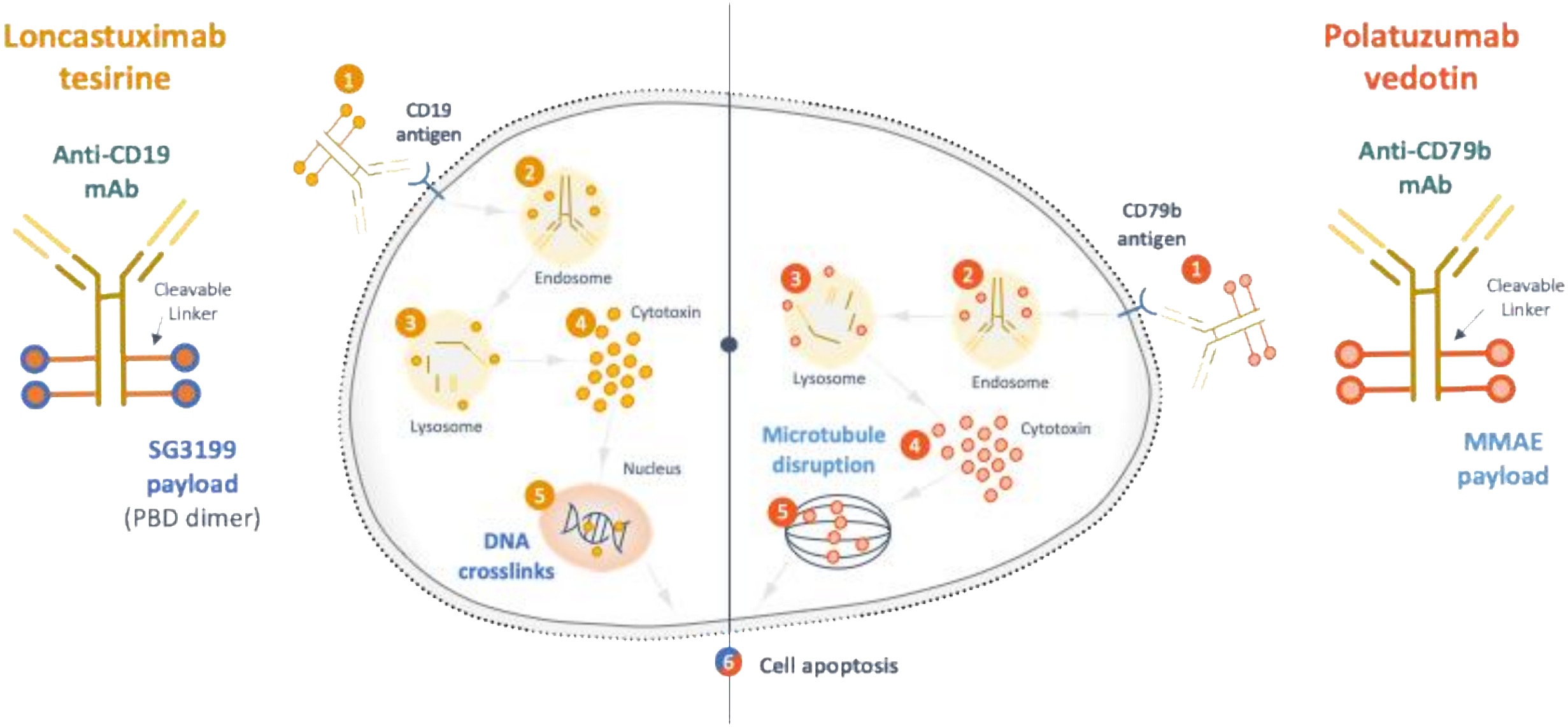
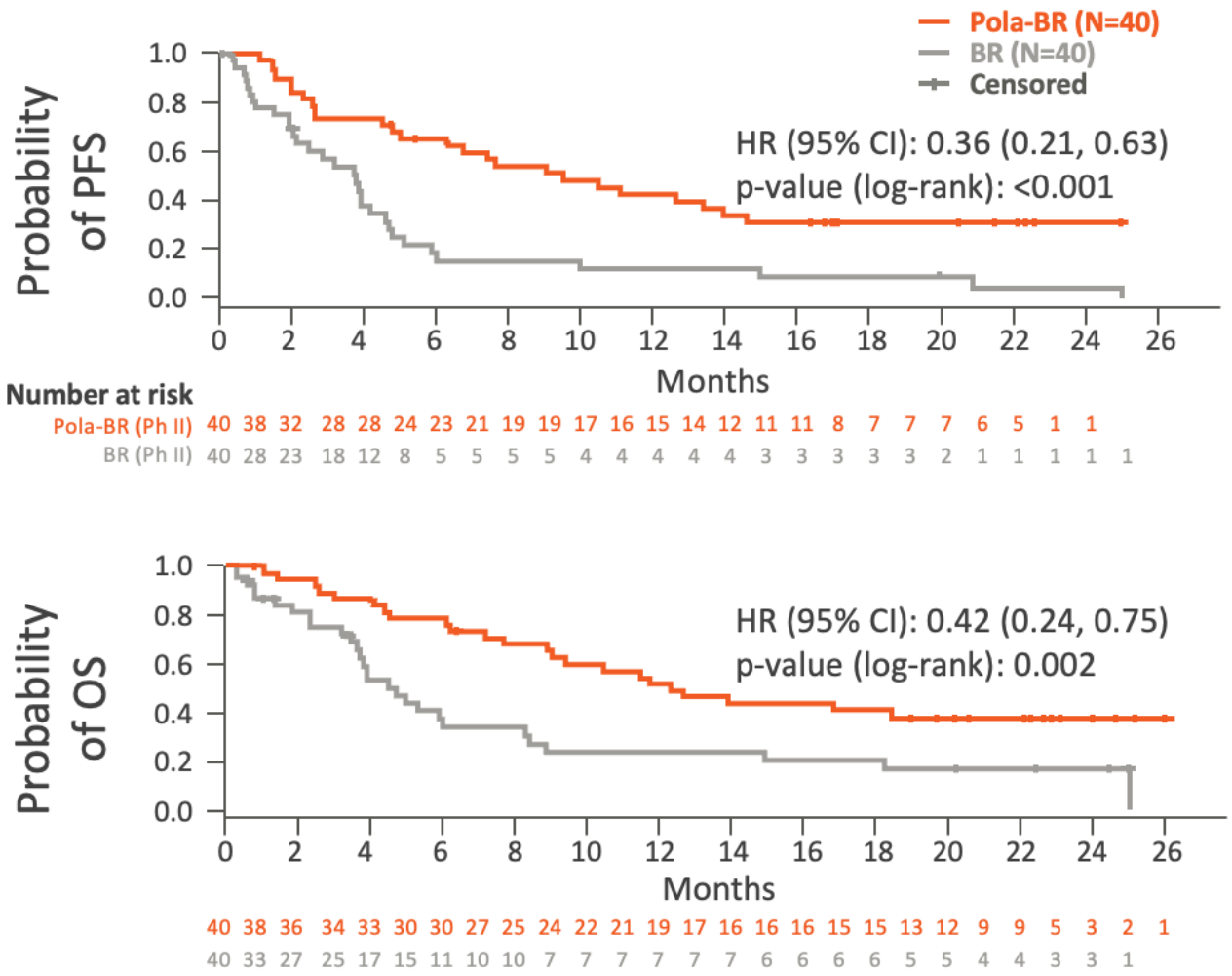
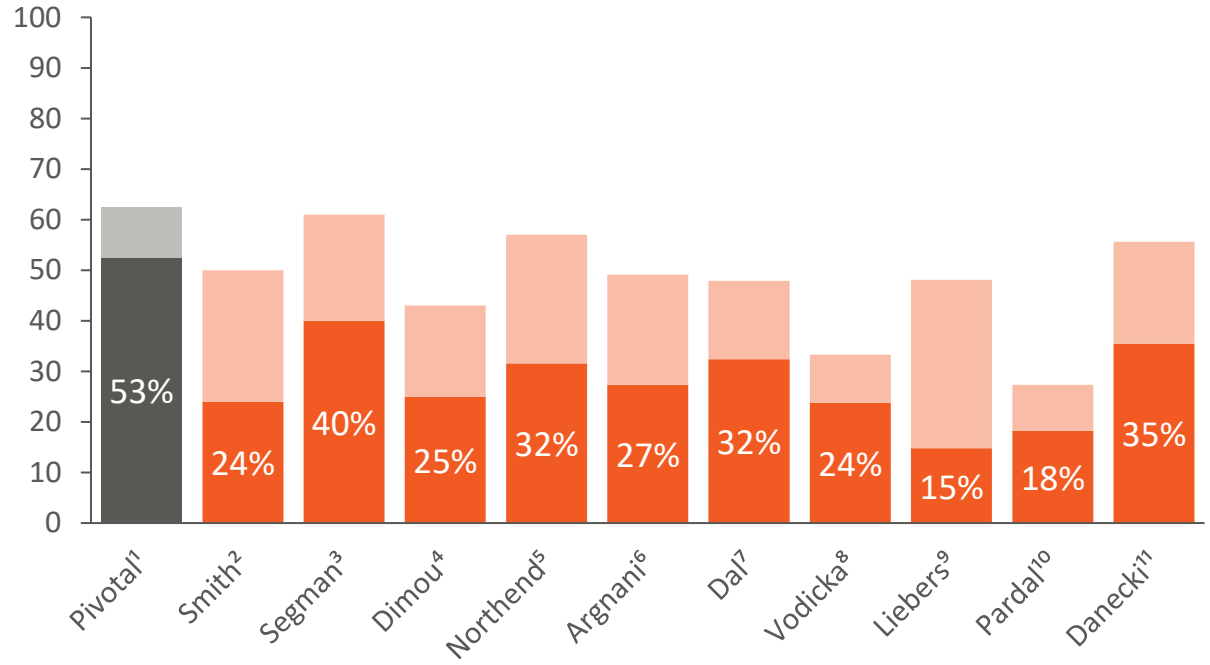
Mechanism of Action of ADC



1. Alderuccio et al. Blood Rev 2022
2. Joubert et al. Pharmaceuticals (Basel) 2020.

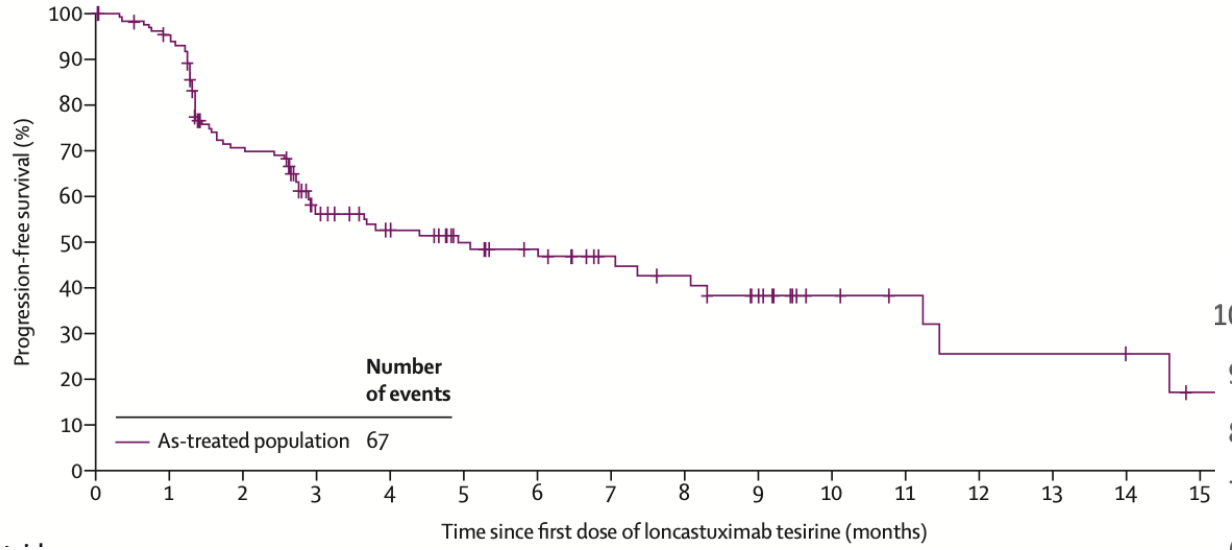
Polatuzumab vedotin + BR

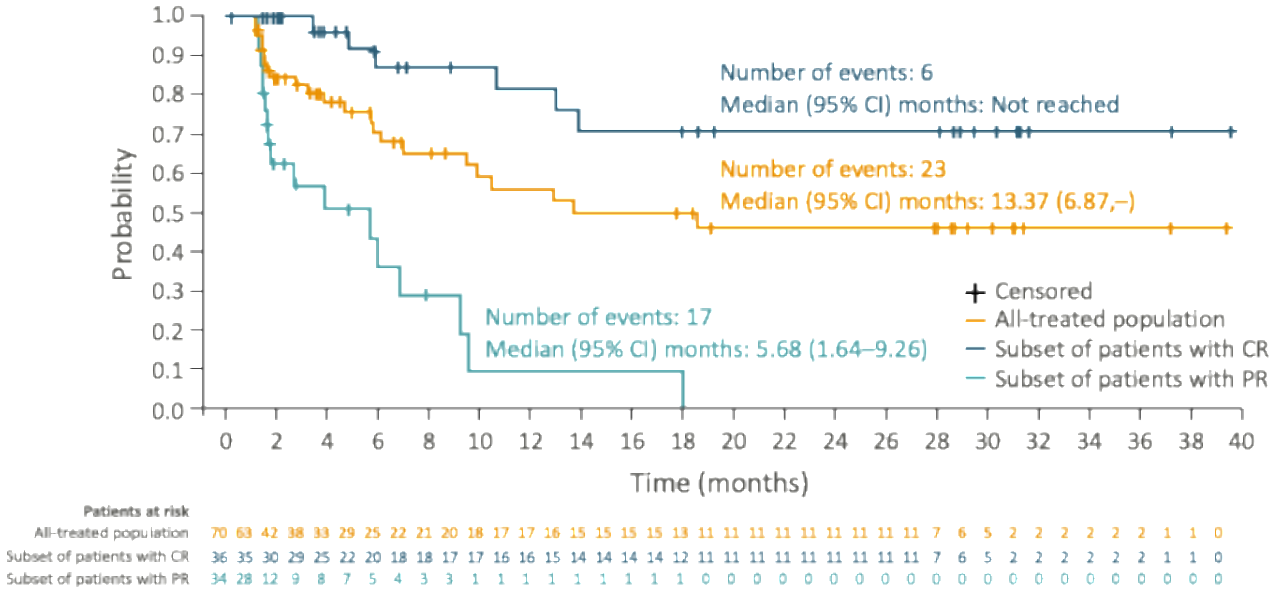


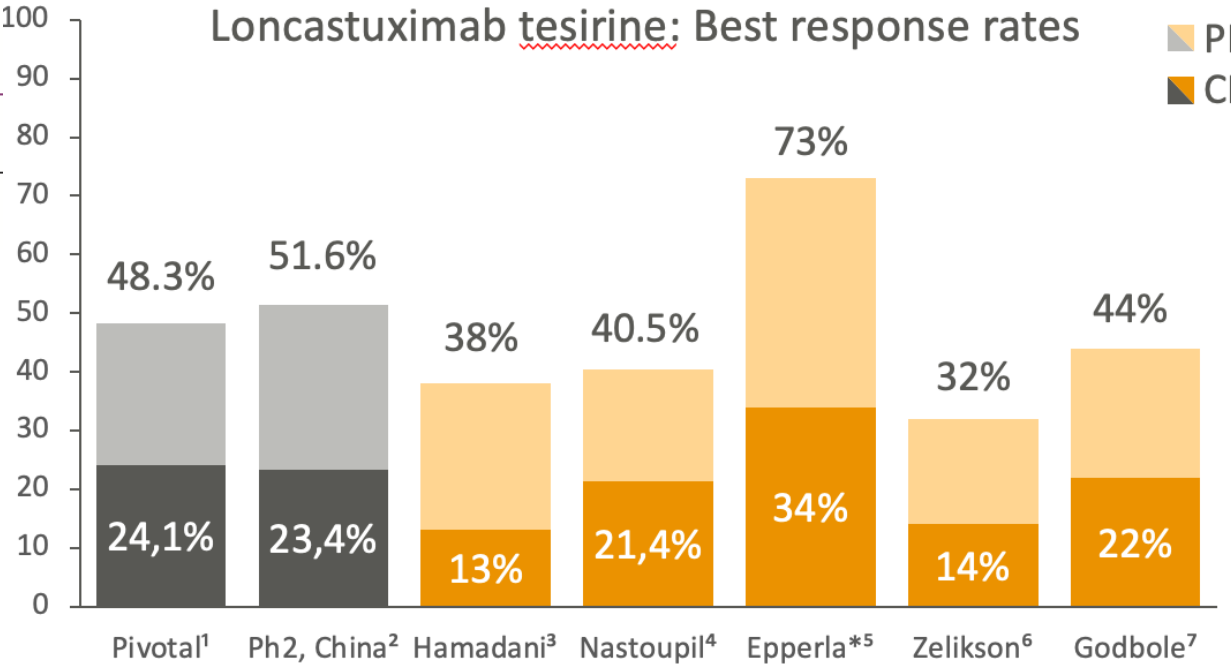


[1]Sehn et al. JCO 2019, Blood Adv 2022, 2. Smith et al. Clin Lymphoma Myeloma Leuk 2021 3. Segman et al. Leuk Lymphoma 2021 4. Dimou et al. Hematol Oncol 2021 5. Northend et al. Blood Adv 2022 6. Argnani et al. Hemasphere 2022 7. Dal et al. Ann Hematol 2023 8. Vodicka et al. Eur J Haematol 2022 9. Liebers et al. Blood Adv 2021 10. Pardal et al. EHA 2024; Abstract #PB3006 11. Danecki et al. EHA 2024; Abstract #P1182.

Loncastuximab tesirine

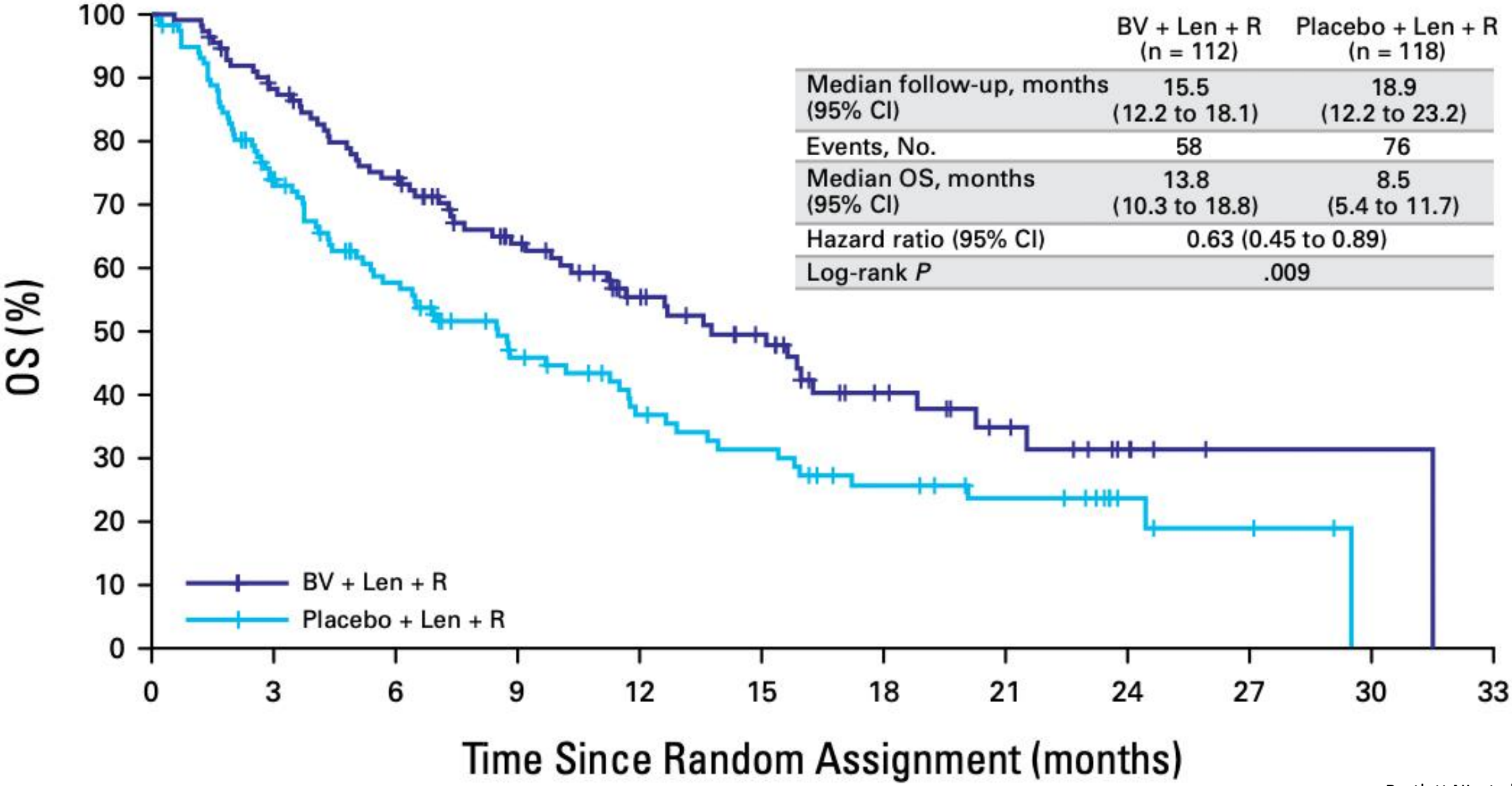






1. Caimi et al. *Lancet Oncol* 2021 2. Lin et al. *Haematologica* 2025 3. Hamadani et al. *eJHaem* 2024 4. Nastoupil et al. *Clin Lymphoma Myeloma Leuk* 2024 5. Epperla et al. *Blood Cancer J* 2024 6. Zelikson et al. *Haematologica* 2025 7. Godbole et al. *Blood* 2024.

ECHELON-3: Brentuximab vedotin + R^2 in R/R LBCL



	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
Median follow-up, months (95% CI)	15.5 (12.2 to 18.1)	18.9 (12.2 to 23.2)
Events, No.	58	76
Median OS, months (95% CI)	13.8 (10.3 to 18.8)	8.5 (5.4 to 11.7)
Hazard ratio (95% CI)	0.63 (0.45 to 0.89)	
Log-rank *P*	.009	

Bartlett NL et al, JCO 2025

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- Current suquencing
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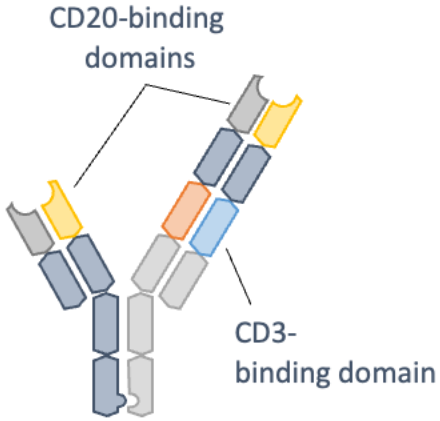
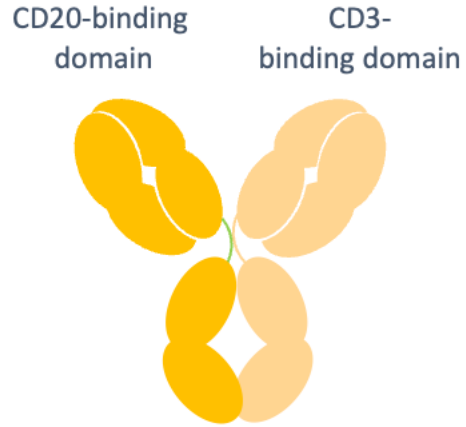
Mechanism of Action of Bispecific Antibodies

Fully humanised mouse IgG1-based bispecific antibodies which target CD20 and CD3[1–3]

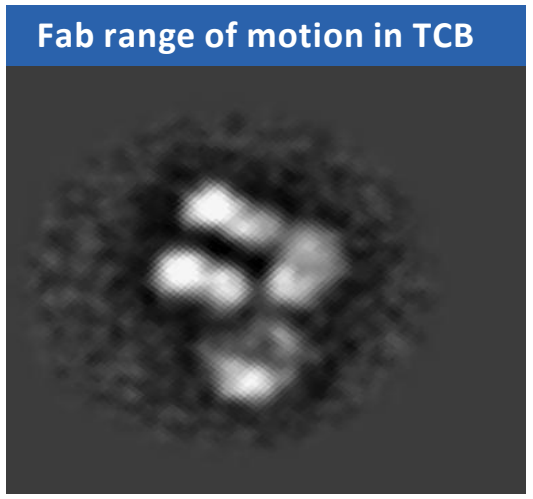
Glofitamab[1,2]



Epcoritamab[3]

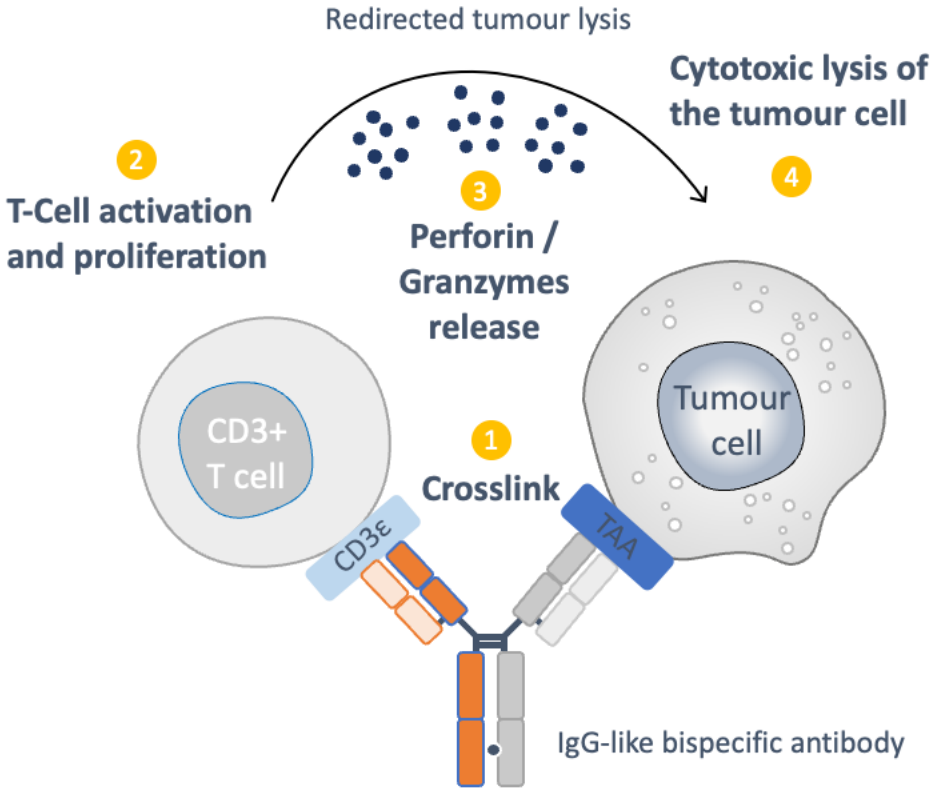


Fab range of motion in TCB



6

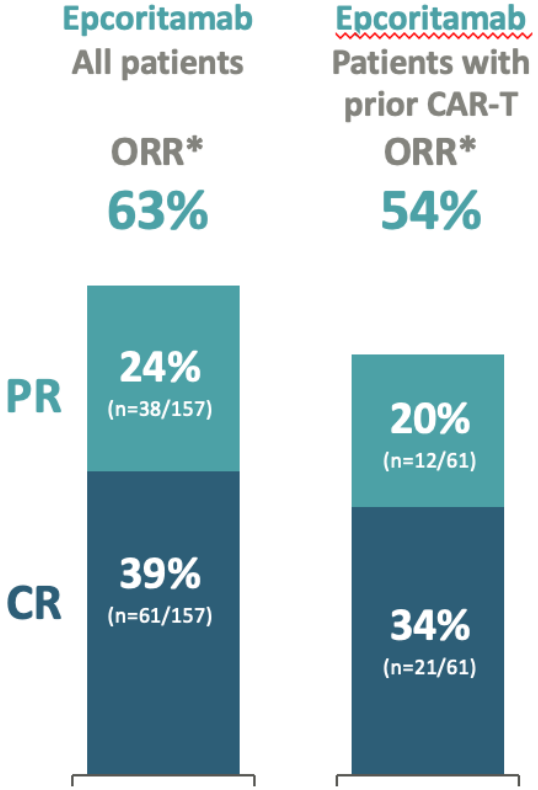
CD3 bispecific T-cell redirection mechanism of action in cancer immunotherapy[4,5]

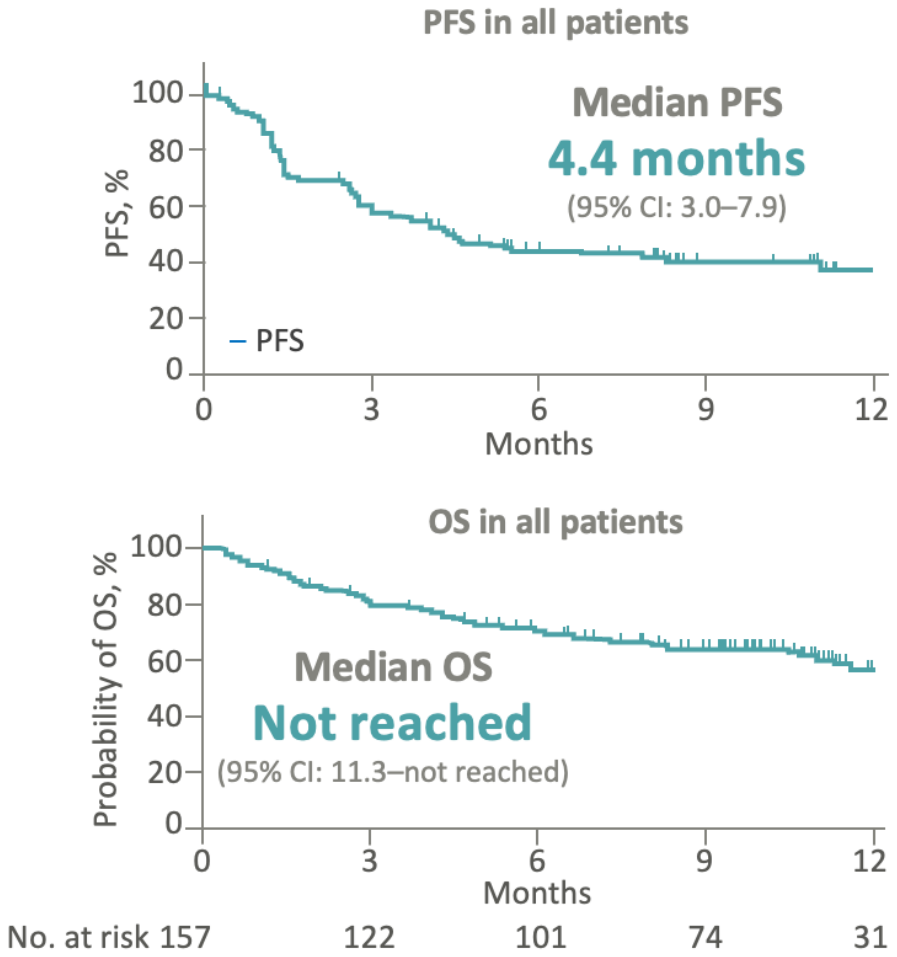


1. Lussanna et al. *J Clin Oncol* 2021 2. Columvi SmPC December 2024 3. Engelberts et al. *EBioMedicine* 2020 4. Zhou et al. *Biomarker Res* 2021 5. Singh et al. *Br J Cancer* 2021. 6. Courtesy by Pablo Umana

Epcoritamab in 3rd line + (EPCORE NHL-1 (Phase 2)

Baseline characteristics, n (%)	All patients (N=157)
Median (range) age, years	64 (20–83)
Male, sex	94 (60)
ECOG performance status 0/1	74 (47) / 78 (50)
Ann Arbor Stage III/IV†	21 (13) / 97 (62)
Nr. of previous lines (median, range)	3 (2–11)
Nr. of previous lines	
2 previous lines	46 (29)
3 previous lines	50 (32)
≥4 previous lines	61 (39)
Prior ASCT	31 (20)
Prior CAR T-cell therapy	61 (39)
Refractory to last prior therapy	130 (83)
Primary refractory	96 (61)
Refractory to CAR T-cell therapy, No./n (%)	46/61 (75)
DLBCL histology	139 (88.5)

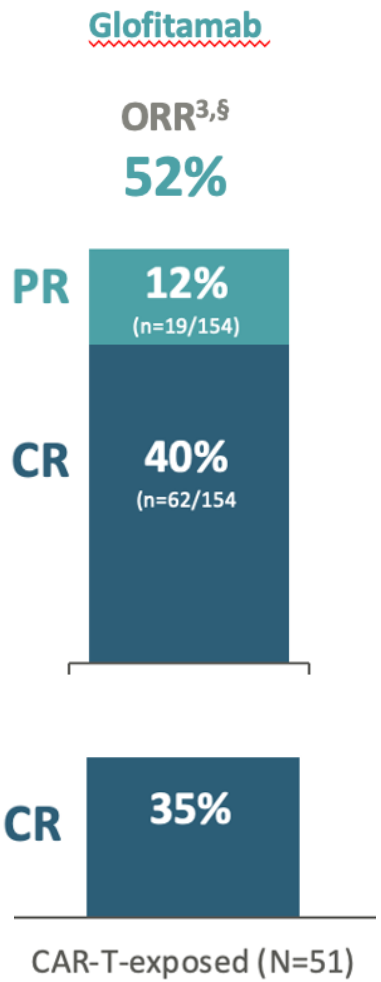


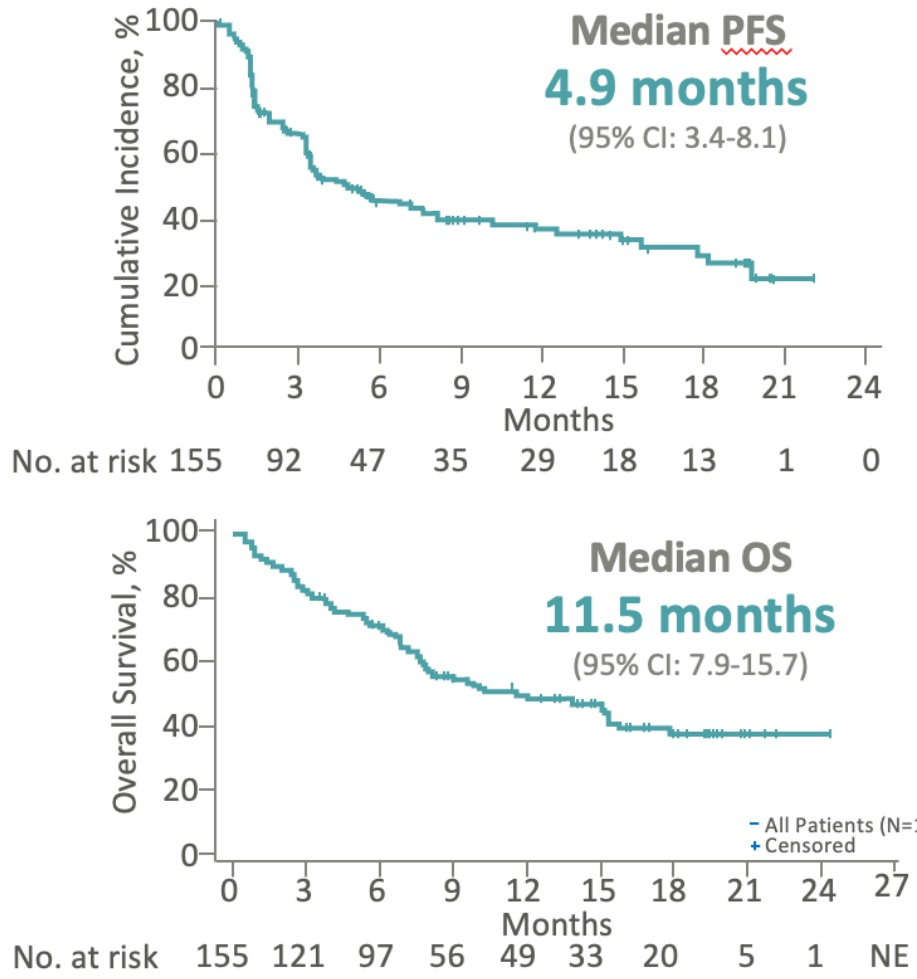


1. Thieblemont et al. *J Clin Oncol* 2022 **2.** Thieblemont et al. *J Clin Oncol* 2022 (Suppl.).

Glofitamab in 3rd line + (NP30179-Phase 1/2)

Baseline characteristics, n (%)	All patients (N=154)
Median (range) age, years	66 (21–90)
Male, sex	100 (65)
ECOG performance status 0/1	69 (45) / 84 (55)
Ann Arbor Stage III/IV†	31 (20) / 85 (55)
Bulky disease	
>6 cm	64 (42)
>10 cm	18 (12)
Nr. of previous lines (median, range)	3 (2–7)
Nr. of previous lines	
Only 2 previous lines	62 (40)
≥3 previous lines	92 (60)
Prior ASCT	28 (18)
Refractory to last prior therapy	132 (86)
Primary refractory‡	90 (58)
DLBCL histology	110 (71)



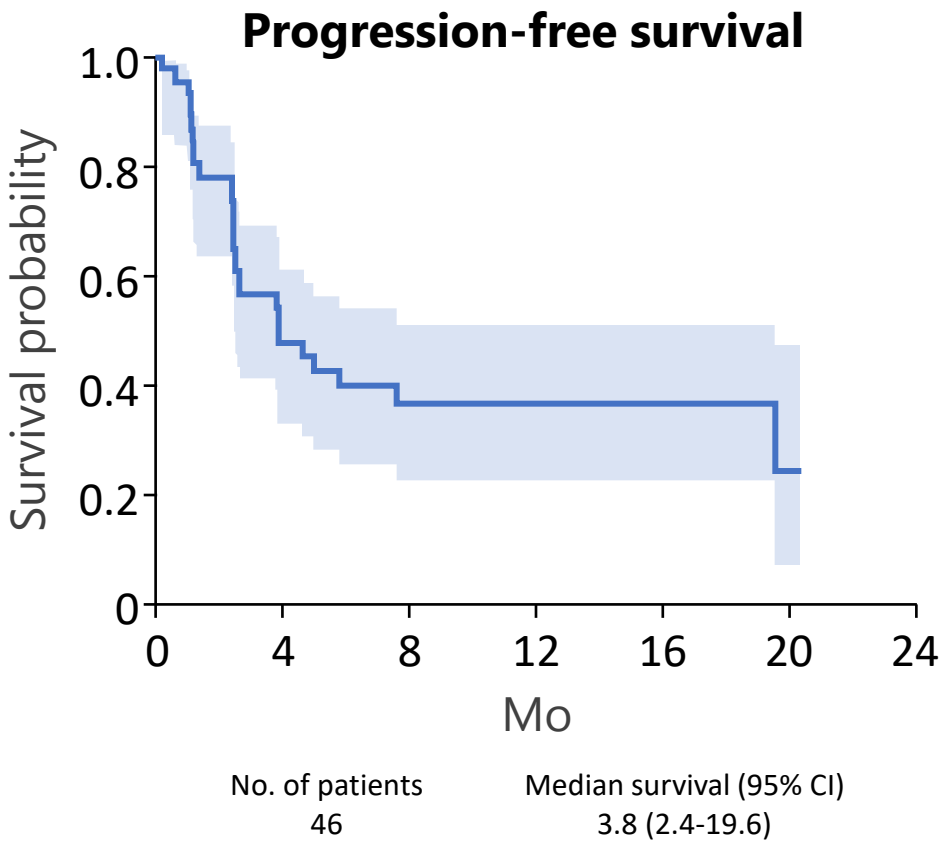


1. Dickinson et al. *N Engl J Med* 2022 **2.** Dickinson et al. *N Engl J Med* 2022 (Suppl.) **3.** Dickinson et al. ASH 2024; Oral presentation #865.

Glofitamab Following CAR T-Cell Therapy Failure in DLBCL

- LYSA: phase II study of glofitamab for patients with R/R DLBCL that had progressed/relapsed starting 1 mo after CAR-T cell therapy

Baseline Characteristics	N = 46
Mean age, yr	60
Elevated LDH, %	78%
Median prior tx (range)	3 (2-5)
Prior SCT, %	17
Refractory to last tx, %	33
Median time from CAR, mo (range)	4 (1-16)



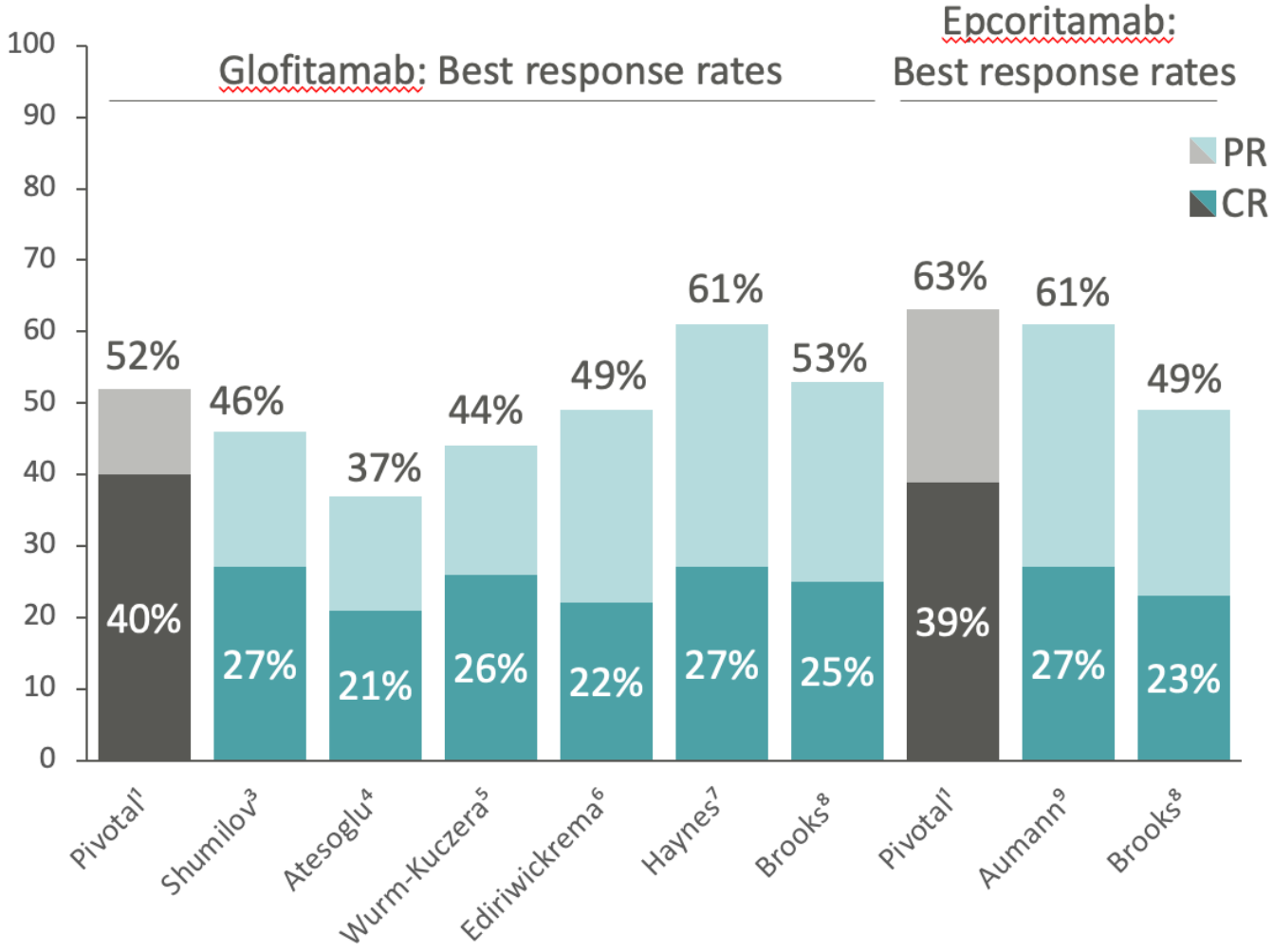
Best Response	
ORR, %	76
CRR, %	46
Median DOR, mo	20
Median DoCR, mo	NE

AESI	
CRS (gr 2), %	9
ICANS (gr 2), %	2
Tumor flare (gr 2), %	9

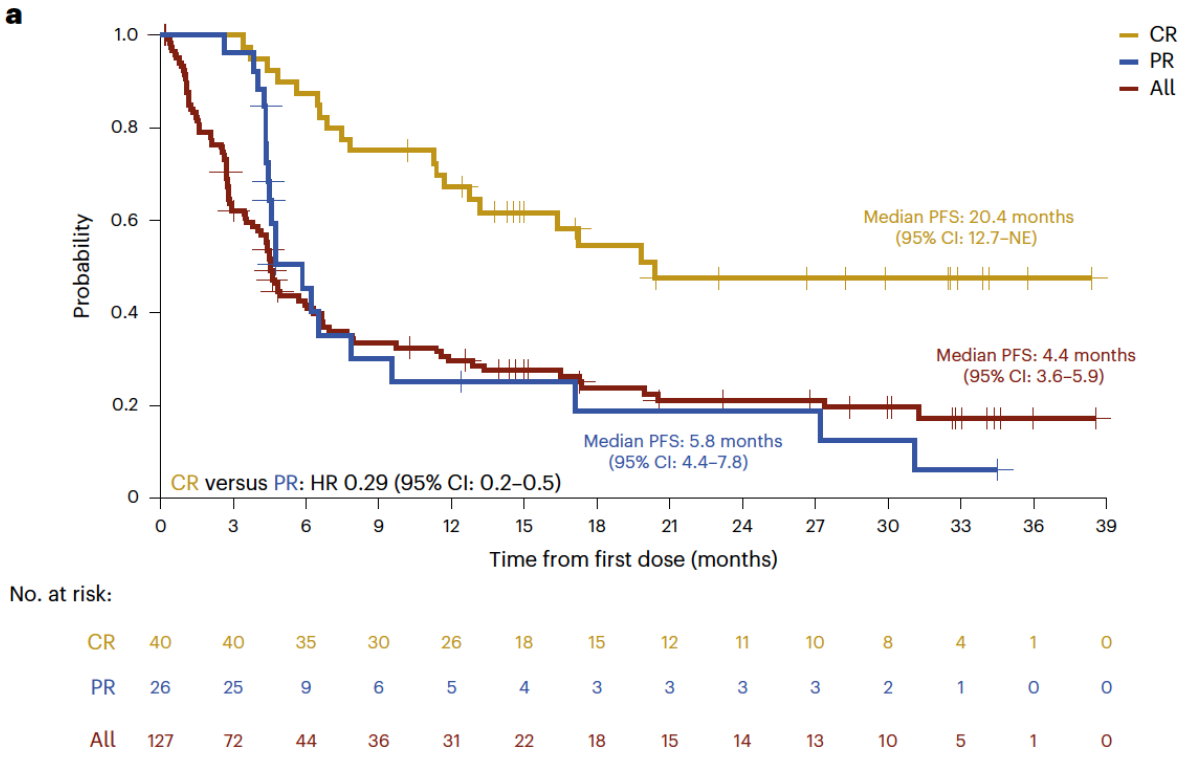
Cartron. Nat Cancer. 2025;6:1173.

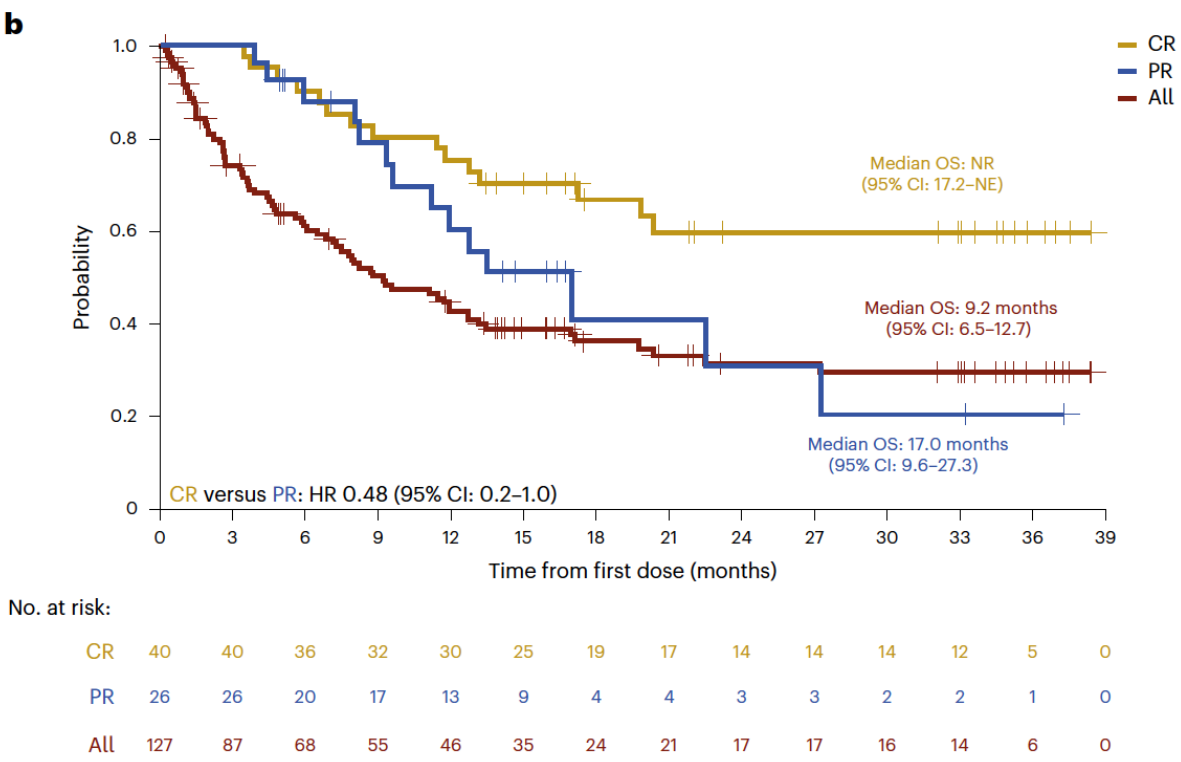
Bispecific Antibodies in the RW

	Pivotal studies[1,2]	RWE[3–9]
ge range, years	20–90	19–94
COG PS ≥2, %	0–3	9–40
ange of prior LoT, n	2–≥4	1–14
efractory to last therapy, %	83–86	54–84
rior CAR-T, %	33–39	60–71
nPFS, months	4.4–4.9	3.0–10.8
nOS, months	11.5–Not reached	5.7–Not reached



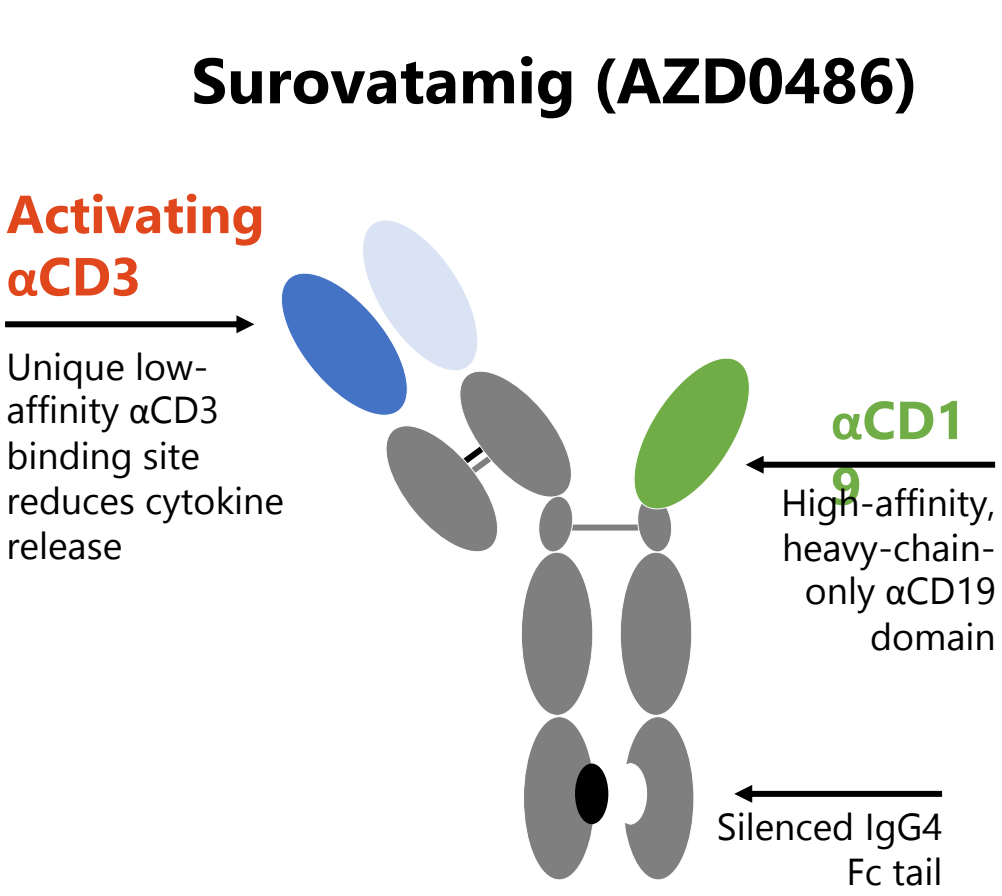
Odronextamab in 3+ line





Kim et al, Nat Cancer. 2025 Mar;6(3):528-539.

Surovatamig (AZD0486): Novel CD19 x CD3 Bispecific Antibody



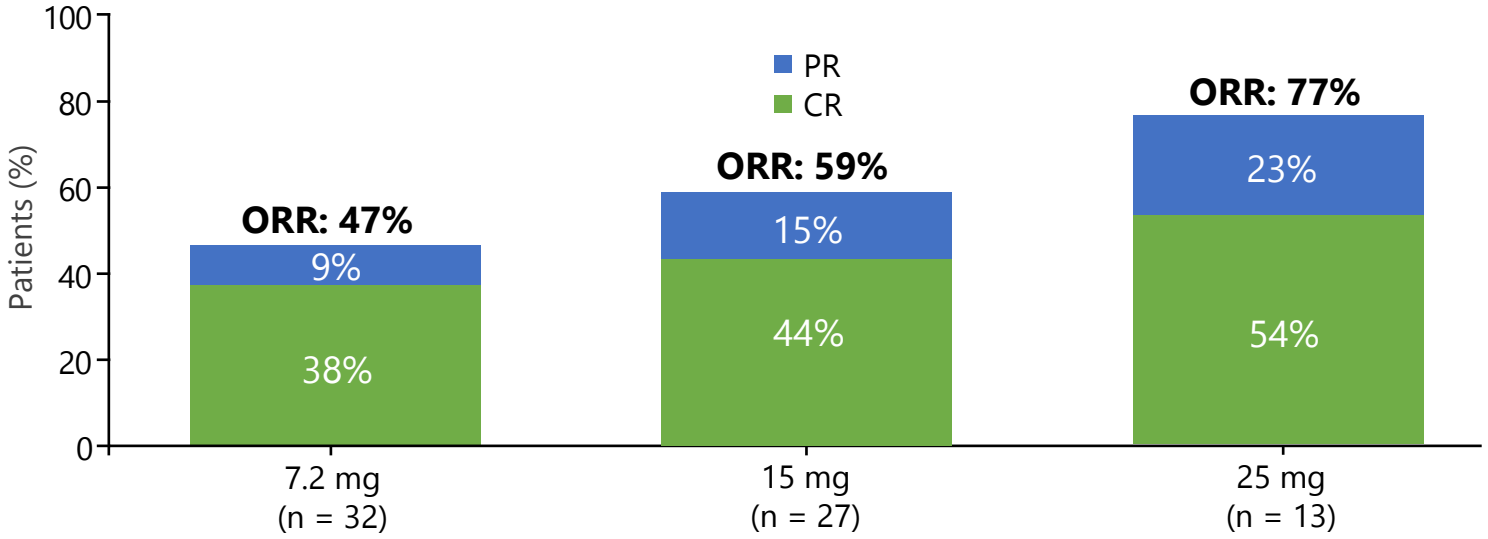
- Fully human CD3 x CD19 IgG4 bispecific T-cell engager
- Key design features:
  - Low-affinity αCD3 reduces cytokine release
  - Silenced Fc tail prolongs half-life and prevents nonspecific binding/ ADCC

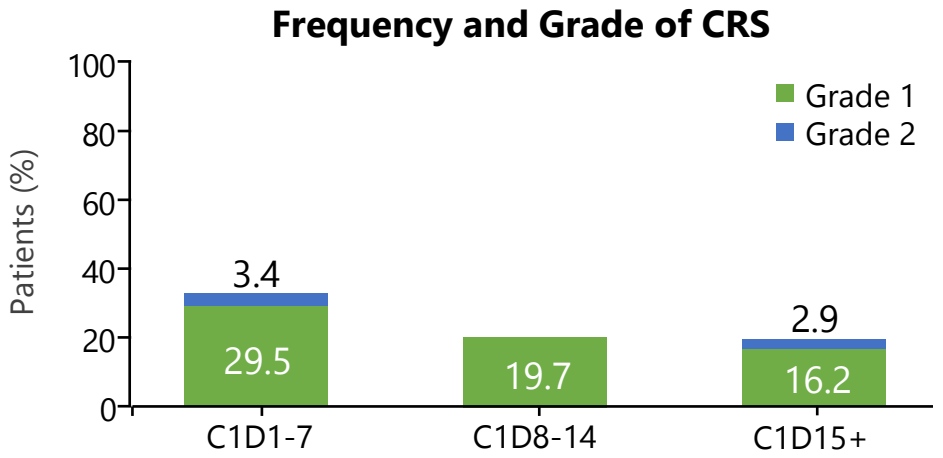
Gaballa. ASH 2024. Abstr 868.

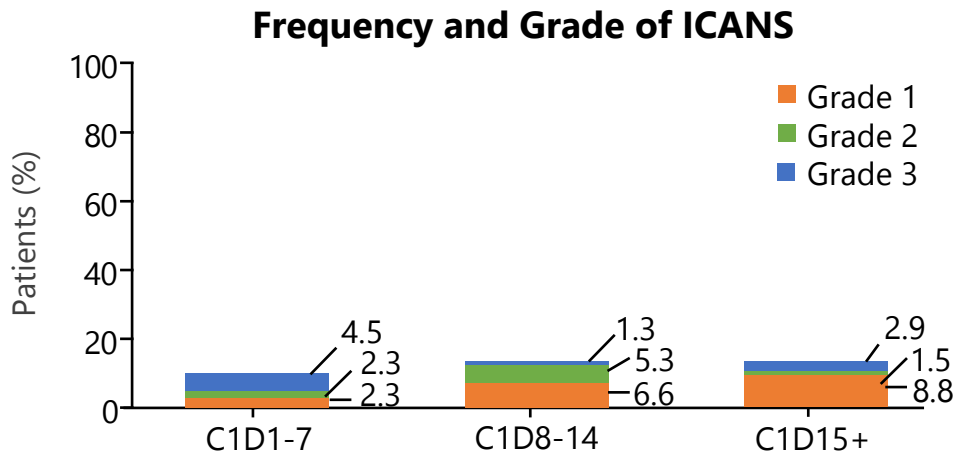
Surovatamig for R/R DLBCL

- Phase I study of surovatamig for R/R CD19+ B-NHL that was R/R to ≥2 prior lines of therapy (N = 106)

Baseline Characteristics	N = 106
Median age, yr (range)	68 (22-94)
Median prior tx (range)	3 (2-13)
Prior CAR T-cell tx, %	42
Refractory to last line of therapy, %	75

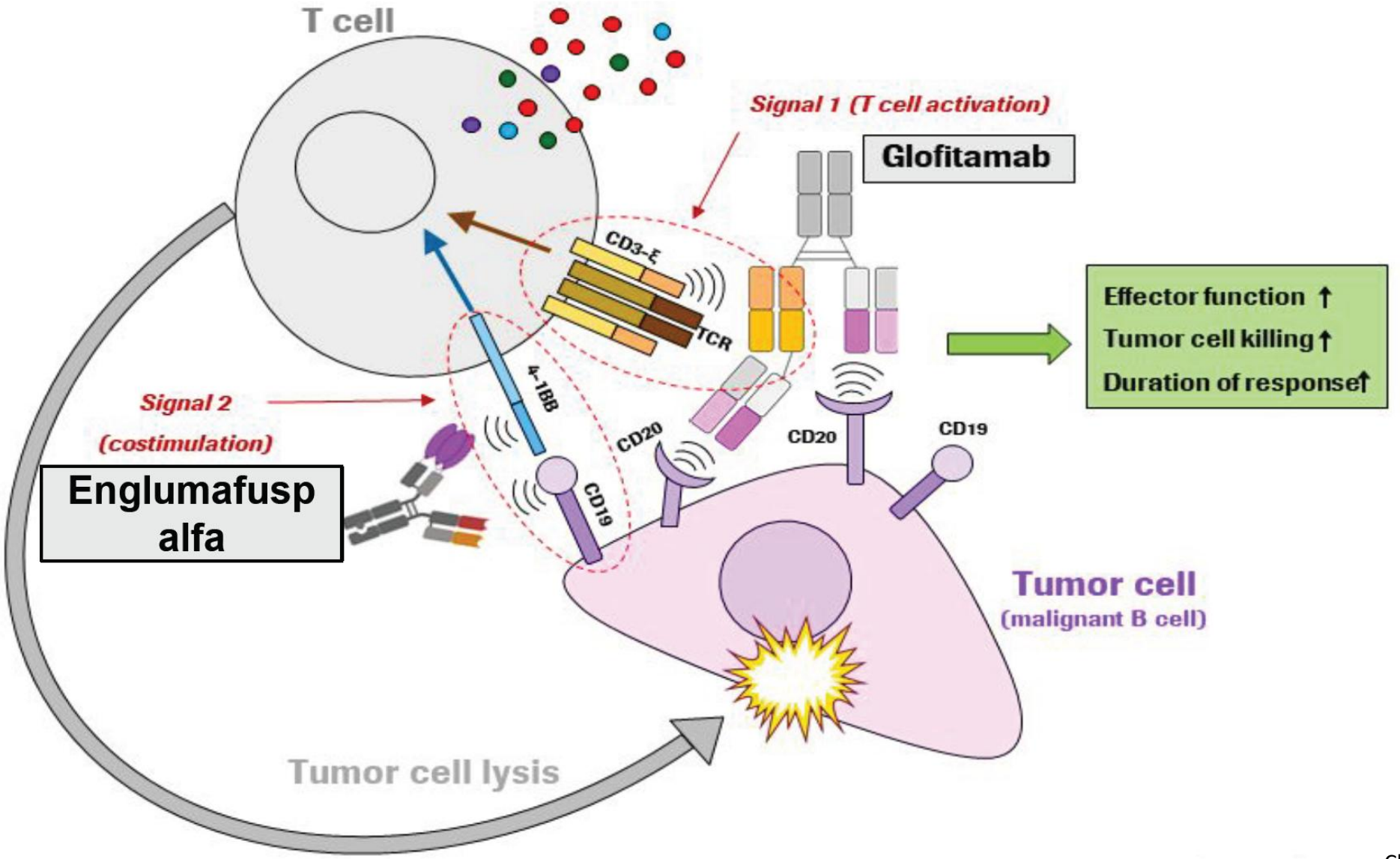






Kim. ASH 2025. Abstr 5514.

Englumafusp alfa mechanism of action



Claus et al, Sci Transl Med 2019.

Englumafusp alfa

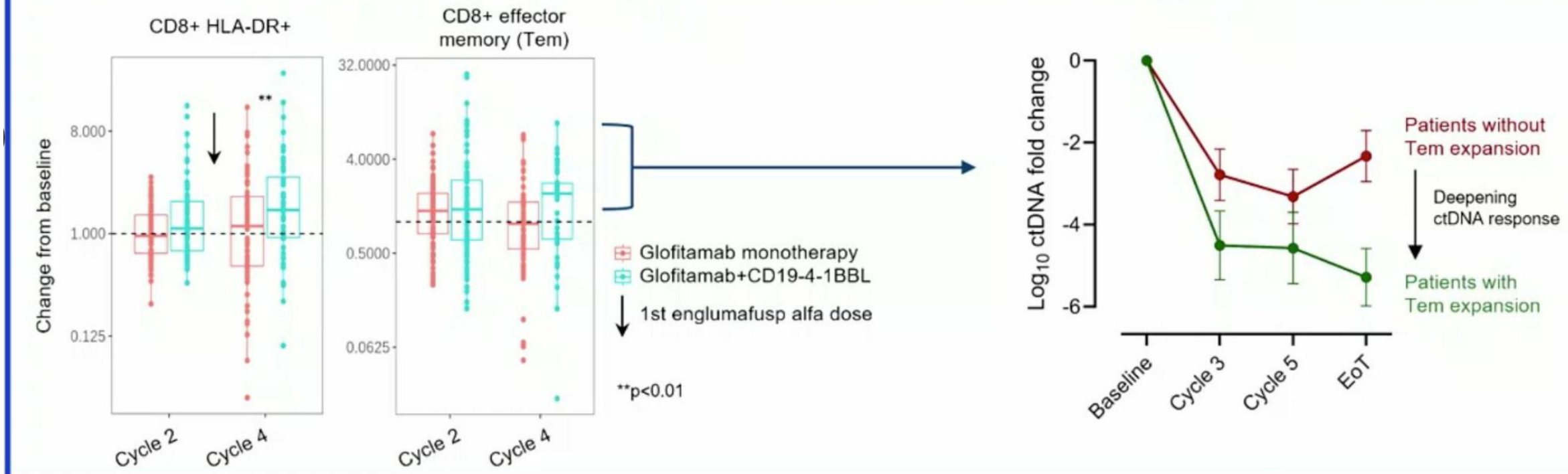
Response rates across all dosing levels in evaluable patients with 2L+ R/R aNHL

n (%)	n	BOR	CR
R/R aNHL			
2L+	83	56 (67.0)	47 (57.0)
3L+	70	46 (65.7)	37 (52.8)
R/R aNHL with prior CAR-T	42	26 (61.9)	20 (47.6)
R/R aNHL without prior CAR-T			
2L+	41	30 (73.2)	27 (66.0)
3L+	28	20 (71.4)	17 (60.7)
2L	13	10 (77.0)	10 (77.0)
R/R aNHL with *TP53* mutation	22	17 (77.0)	15 (68.0)

Morschhauser F et al, EHA 2024 (S237).

Englumafusp alfa boosts memory formation that leads to deeper molecular response

Englumafusp alfa boosts effector memory expansion and deepening of ctDNA response



Significantly greater expansion of activated and effector memory T cells in combination setting vs monotherapy
Effector memory boost is more pronounced in CMR patients and associated with deep ctDNA response at EoT

Morschhauser F et al, EHA 2024 (S237).

Outline

- Current suquencing
- CAR T-cell
- ADC
- Bispecific antibodies
- Combinations
- Other options and challenges

STARGLO: Study design (GO41944; NCT04408638)

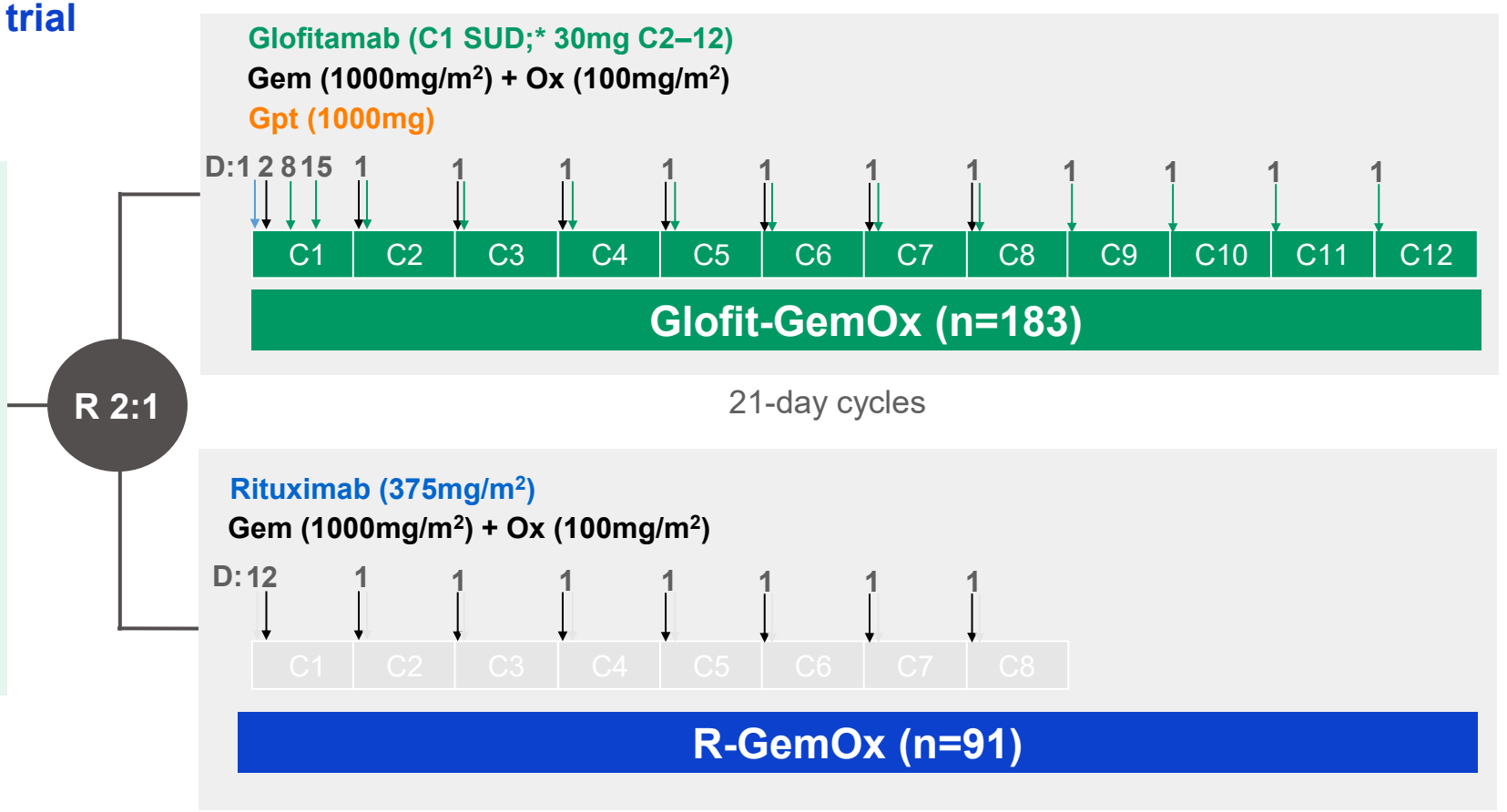
Phase 3, open-label, randomised trial

Patients with R/R DLBCL (N=274)

- R/R DLBCL NOS after ≥1 prior systemic therapy
- Patients with one prior line must be transplant ineligible
- ECOG PS 0–2

Stratification factors

- Relapsed vs refractory disease†
- 1 vs ≥2 prior lines of therapy

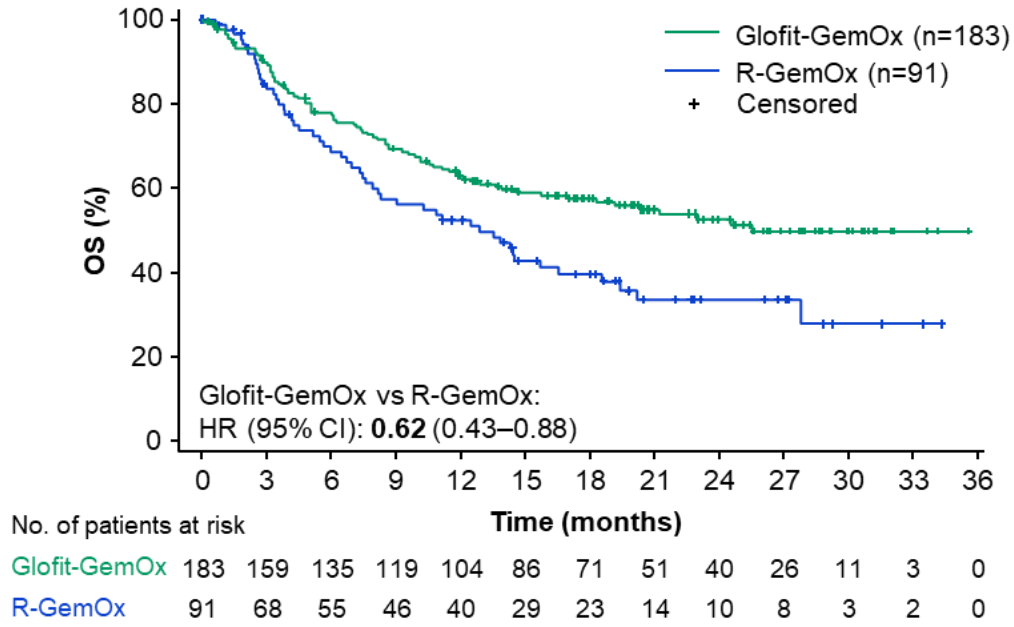


*Glofit 2.5mg on D8 and 10mg on D15. †Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; DLBCL, diffuse large B-cell lymphoma; Gem-Ox, gemcitabine and oxaliplatin; Glofit, glofitamab; Gpt, obinutuzumab pretreatment; NOS, not otherwise specified; R 2:1, patients randomised in a 2:1 ratio; R, rituximab.

Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438);
Abramson JS, et al. Lancet 2024;404(10466, Suppl).

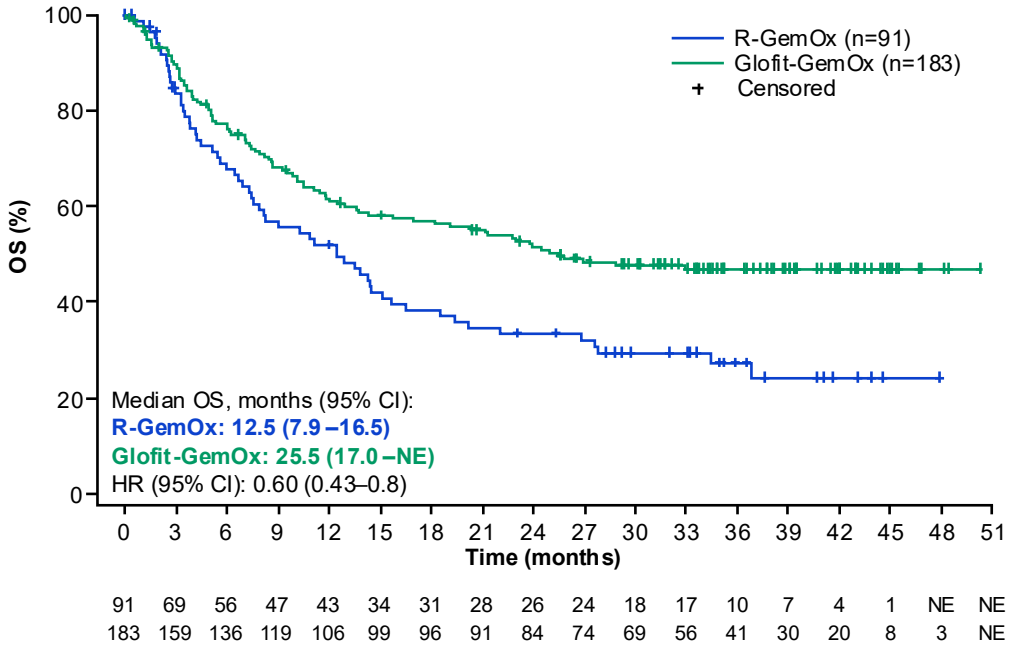
STARGLO: Primary endpoint: Overall survival

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
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)

Extended follow-up analysis

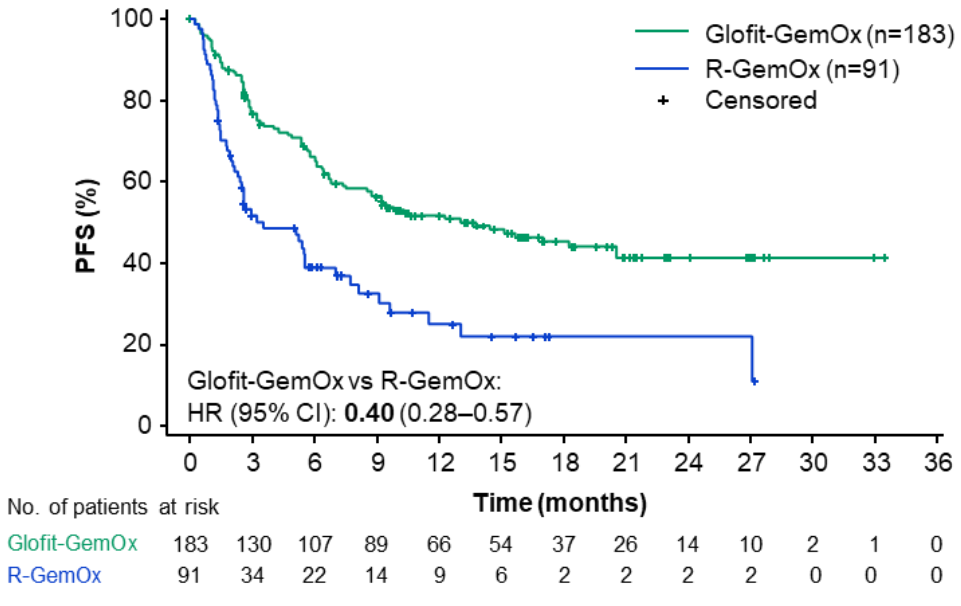


Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
3-year follow-up analysis (median follow-up: 35.1 months [95% CI: 33.6–37.6])		
OS, median (95% CI); months	**12.5** (7.9–16.5)	**25.5** (17.0–NE)
36-month OS, % (95% CI)	**27.4** (17.3–37.5)	**47.1** (39.5–54.6)

Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438), Abramson JS, et al. Lancet 2024;404(10466):1940–54 Abramson JS, et al. ASH 2025; Poster presentation (P-5519).

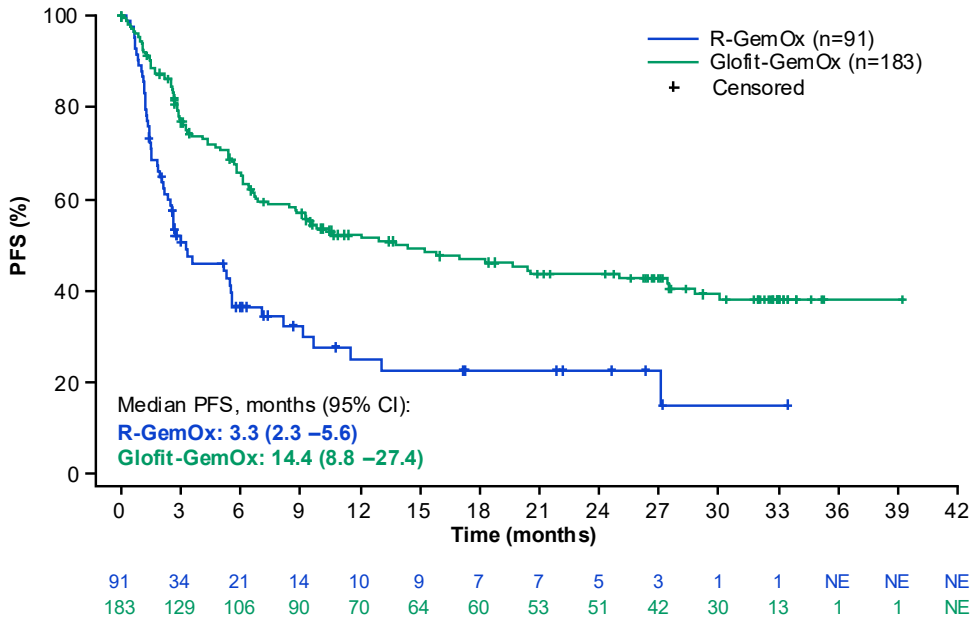
Progression-free survival by IRC assessment

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.40** (0.28–0.57)	
p-value*†	<0.0001	
12-month PFS, % (95% CI)	25.2 (13.6–36.9)	51.7 (44.0–59.4)

Extended follow-up analysis

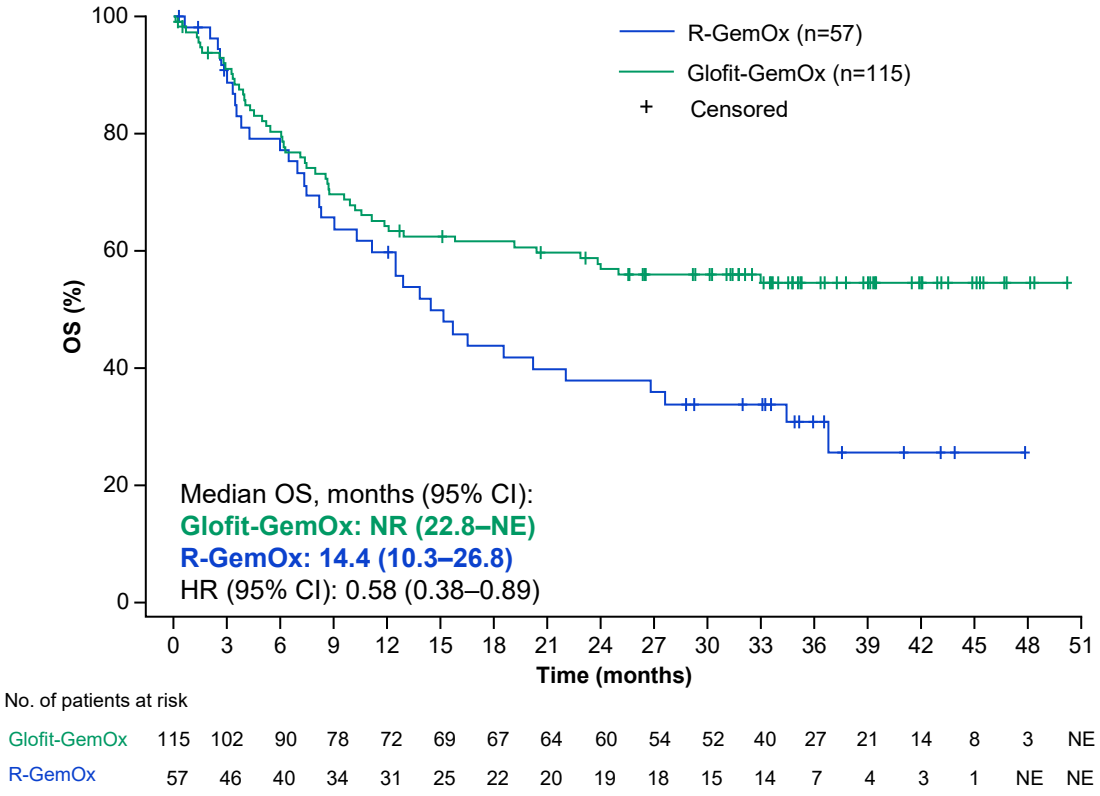


Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
PFS, median (95% CI); months	**3.3** (2.3–5.6)	**14.4** (8.8–27.4)
30-month PFS, % (95% CI)	**15.2** (0.9–29.5)	**38.1** (29.8–46.3

Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438), Abramson JS, et al. Lancet 2024;404(10466):1940–54 Abramson JS, et al. ASH 2025; Poster presentation (P-5519).

STARGLO: OS by line of therapy – 2L sub-group analysis

Overall survival in 2L patients[1]



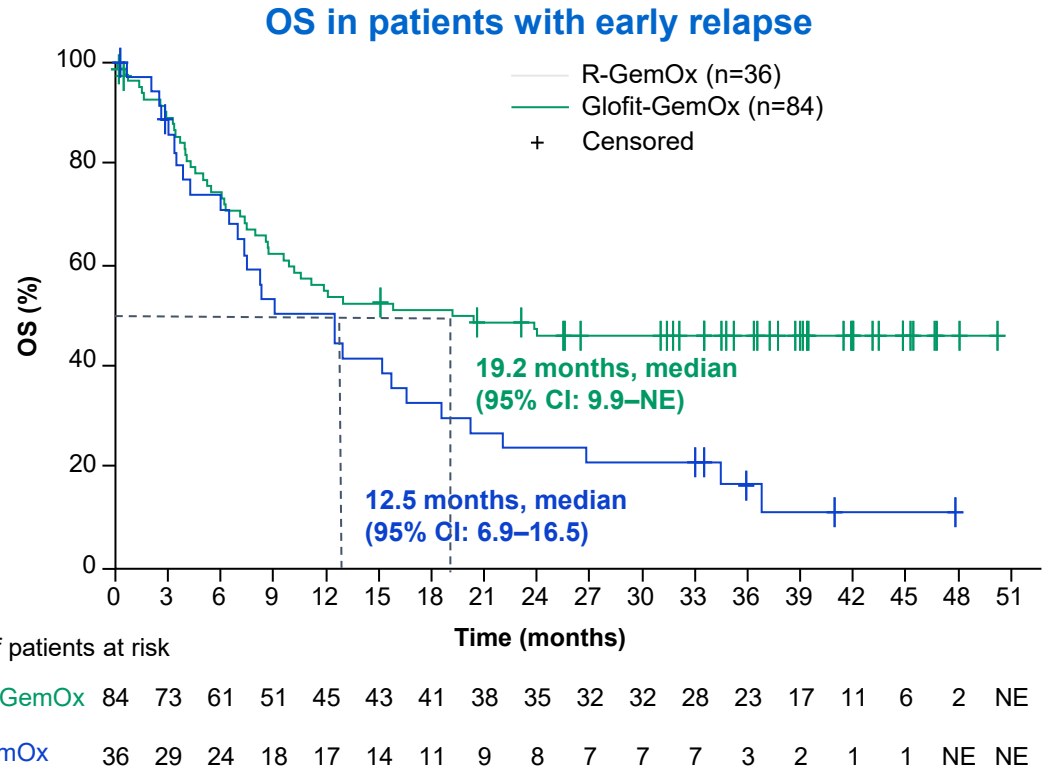
Outcome[2]	R-GemOx 2L (n=57)	Glofit-GemOx 2L (n=115)	R-GemOx 3L+ (n=34)	Glofit-GemOx 3L+ (n=68)
Median follow-up: 35.1 months (95% CI: 33.6–37.6)				
OS, median (95% CI); months	**14.4** (10.3–26.8)	**NR** (22.8–NE)	**6.7** (4.2–14.3)	**17.0** (10.7–25.8)
36-month OS, % (95% CI)	**30.8** (17.7-44.0)	**54.6** (45.2–64.0)	**21.8** (6.7–36.9	**33.2** (21.2–45.3)

A clinically meaningful OS benefit was observed for Glofit-GemOx versus R-GemOx in 2L and 3L+ patients[1–3]

CCOD: May 1, 2025. 2L, second-line; 3L, third line; CI, confidence interval; GemOx, gemcitabine plus oxaliplatin; Glofit, glofitamab; HR, hazard ratio; NE, not evaluable; NR, not reached; OS, overall survival; R, rituximab.

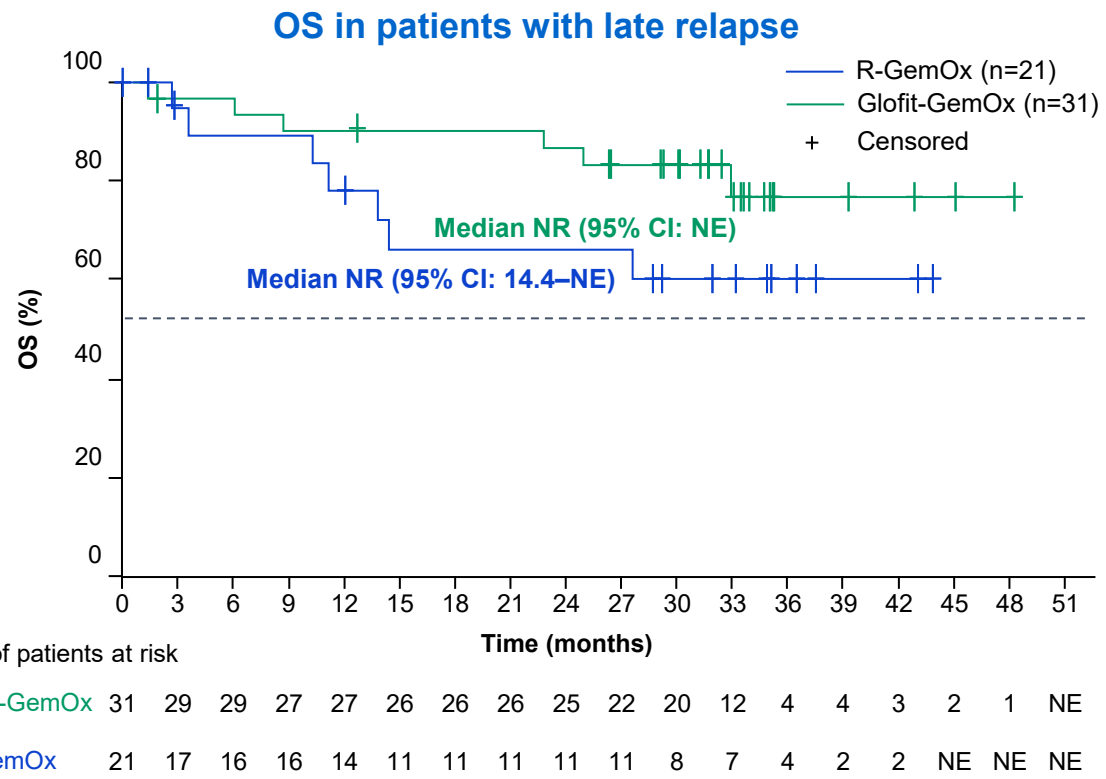
1. Abramson JS, et al. ASH 2025; Poster presentation (P-5519;
2. Abdulhaq H, et al. ASH 2025; Poster presentation (P-3743);
3. Herbaux C, et al. ESH 2025; Poster presentation (P-6986893).

STARGLO: OS in 2L : *early and late relapse subgroups*



No. of patients at risk

Glofit-GemOx	84	73	61	51	45	43	41	38	35	32	32	28	23	17	11	6	2	NE
R-GemOx	36	29	24	18	17	14	11	9	8	7	7	7	3	2	1	1	NE	NE



No. of patients at risk

Glofit-GemOx	31	29	29	27	27	26	26	26	25	22	20	12	4	4	3	2	1	NE
R-GemOx	21	17	16	16	14	11	11	11	11	11	8	7	4	2	2	NE	NE	NE

- 36-month OS rates (95% CI) with Glofit-GemOx versus R-GemOx, respectively, were 46.1% (35.2–56.9) versus 16.5% (3.4–29.6) in patients with early relapse and 76.8% (59.5–94.1) versus 60.0% (36.9–83.1) in patients with late relapse in the 2L setting

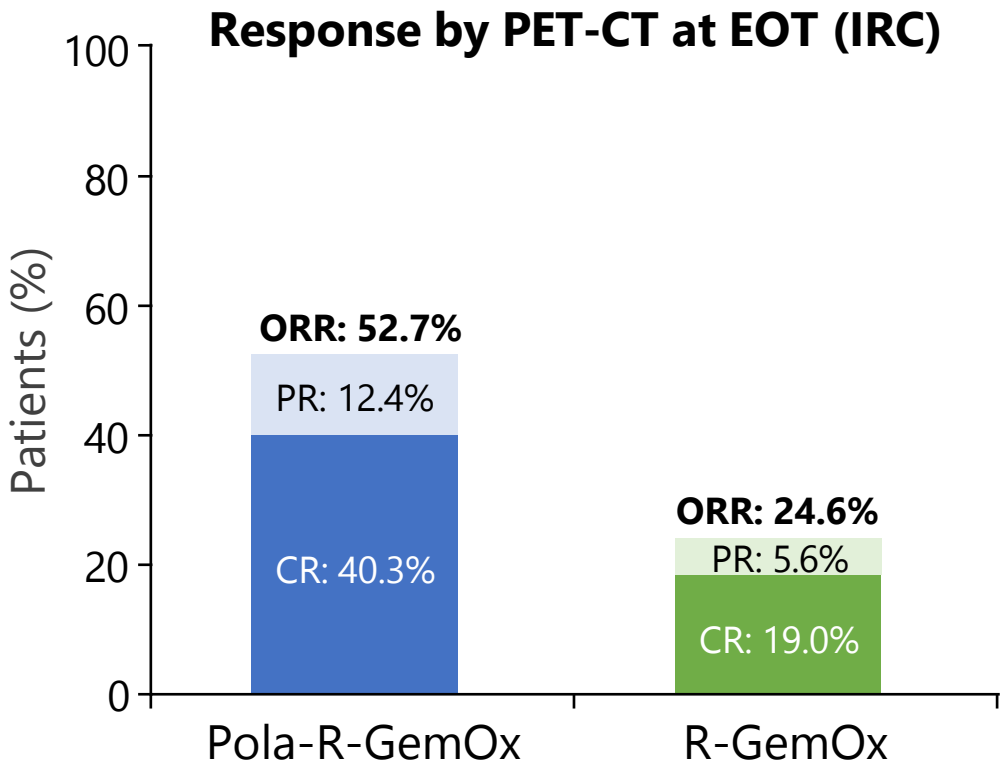
Longer OS was observed with Glofit-GemOx versus R-GemOx in 2L patients, regardless of time of relapse

CCOD: May 1, 2025. 2L, second-line; CI, confidence interval; GemOx, gemcitabine plus oxaliplatin; Glofit, glofitamab; NE, not evaluable; NR, not reached; OS, overall survival; R, rituximab.

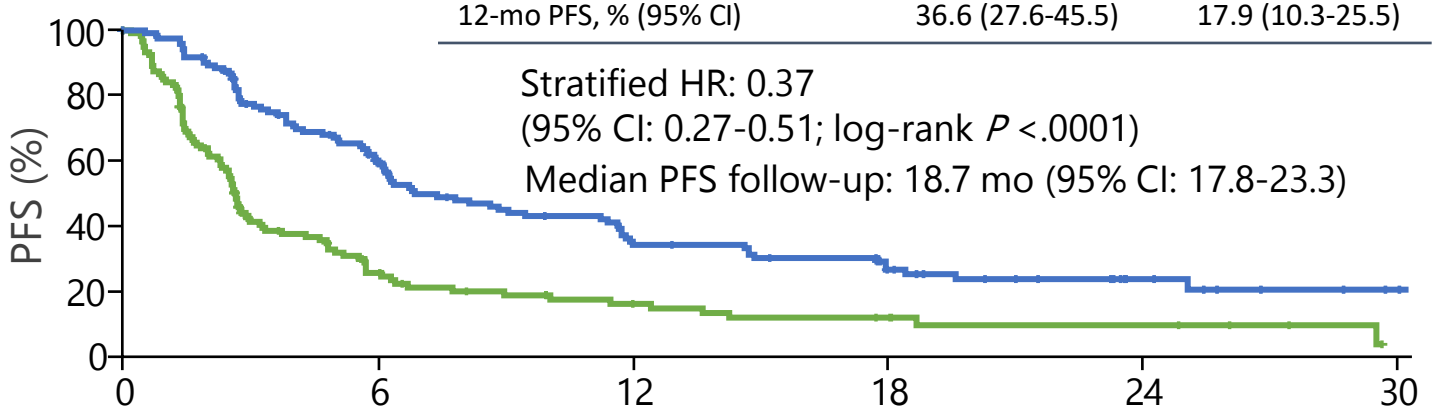
Abdulhaq H, et al. ASH 2025; Poster presentation (P-3743).

POLARGO: Pola-R-GemOx vs R-GemOx in R/R Transplant Ineligible DLBCL

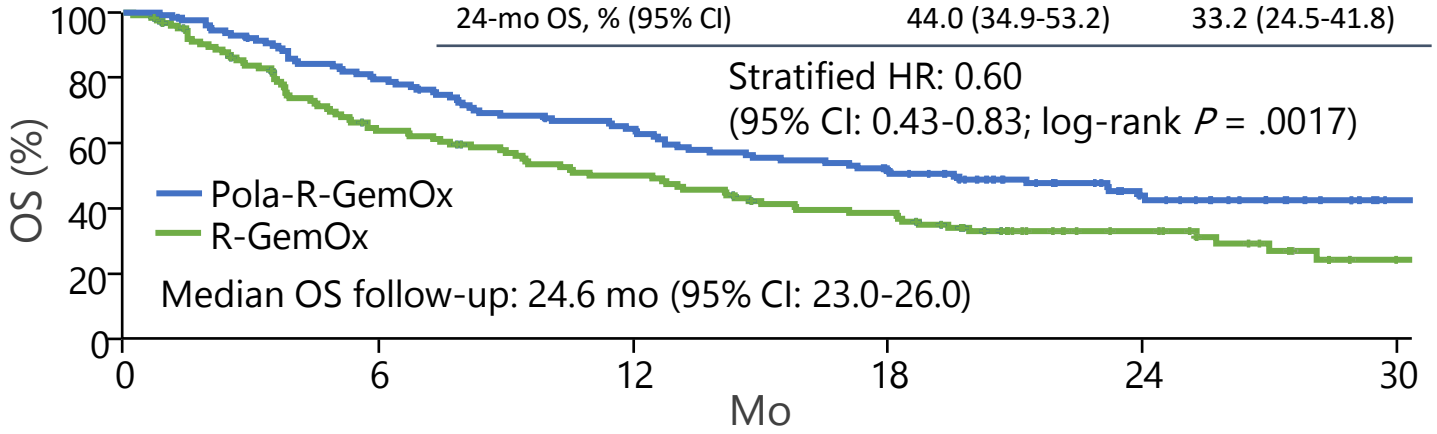
- Randomized phase III study of Pola-R-GemOx vs R-GemOx for patients with R/R DLBCL NOS after ≥1 prior line of treatment; ineligible for transplant (N = 255)



	Pola-R-GemOx (n = 129)	R-GemOx (n = 126)
Median PFS, mo (95% CI)	7.4 (6.2-11.7)	2.7 (2.4-3.3)
12-mo PFS, % (95% CI)	36.6 (27.6-45.5)	17.9 (10.3-25.5)



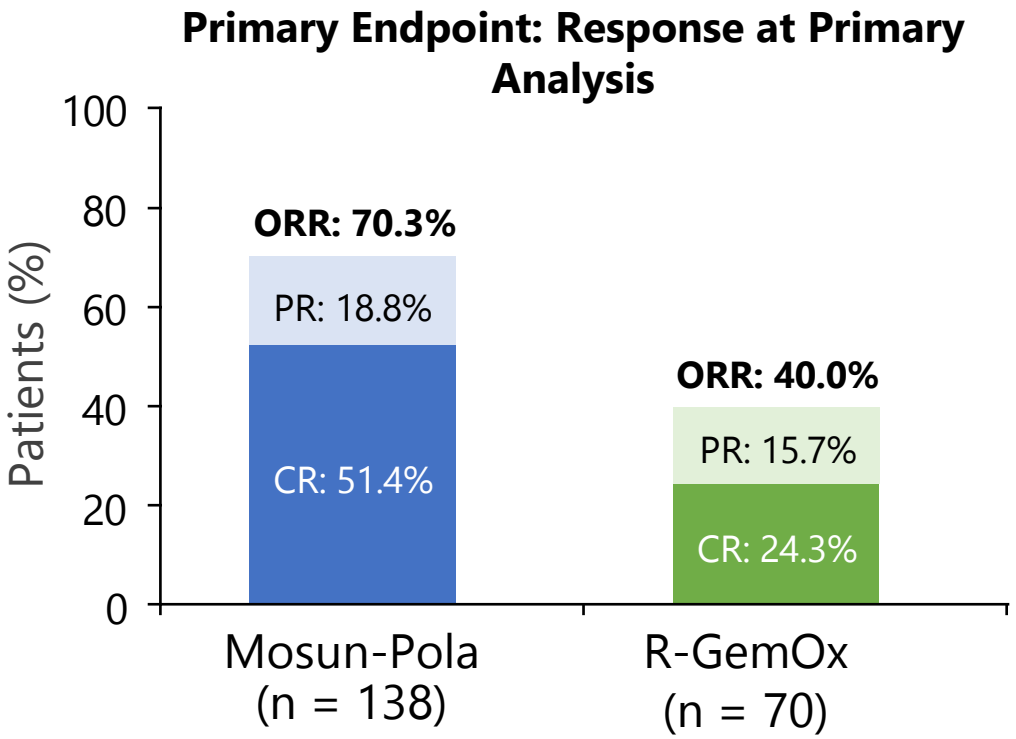
	Pola-R-GemOx (n = 129)	R-GemOx (n = 126)
Median OS, mo (95% CI)	19.5 (13.3-NE)	12.5 (8.9-15.8)
24-mo OS, % (95% CI)	44.0 (34.9-53.2)	33.2 (24.5-41.8)

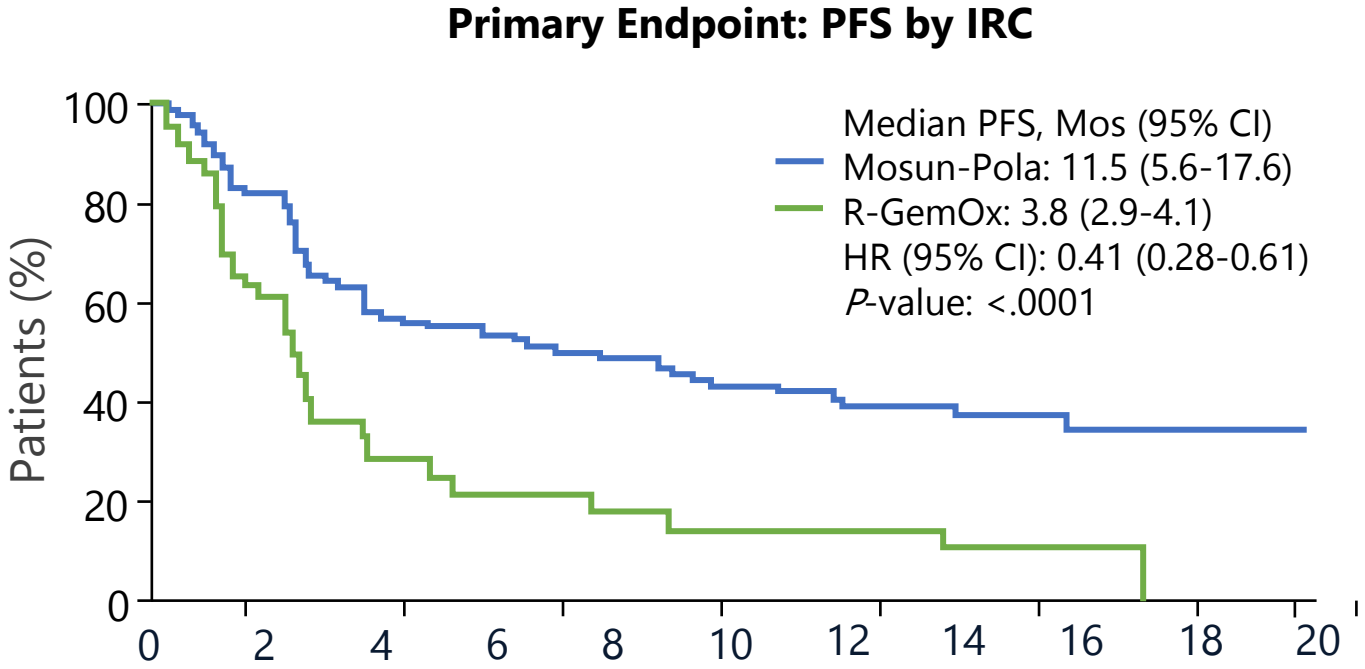


Matasar. EHA 2025. Abstr S101.

SUNMO: Mosunetuzumab + Polatuzumab Vedotin vs R-GemOx for R/R Transplant-Ineligible DLBCL

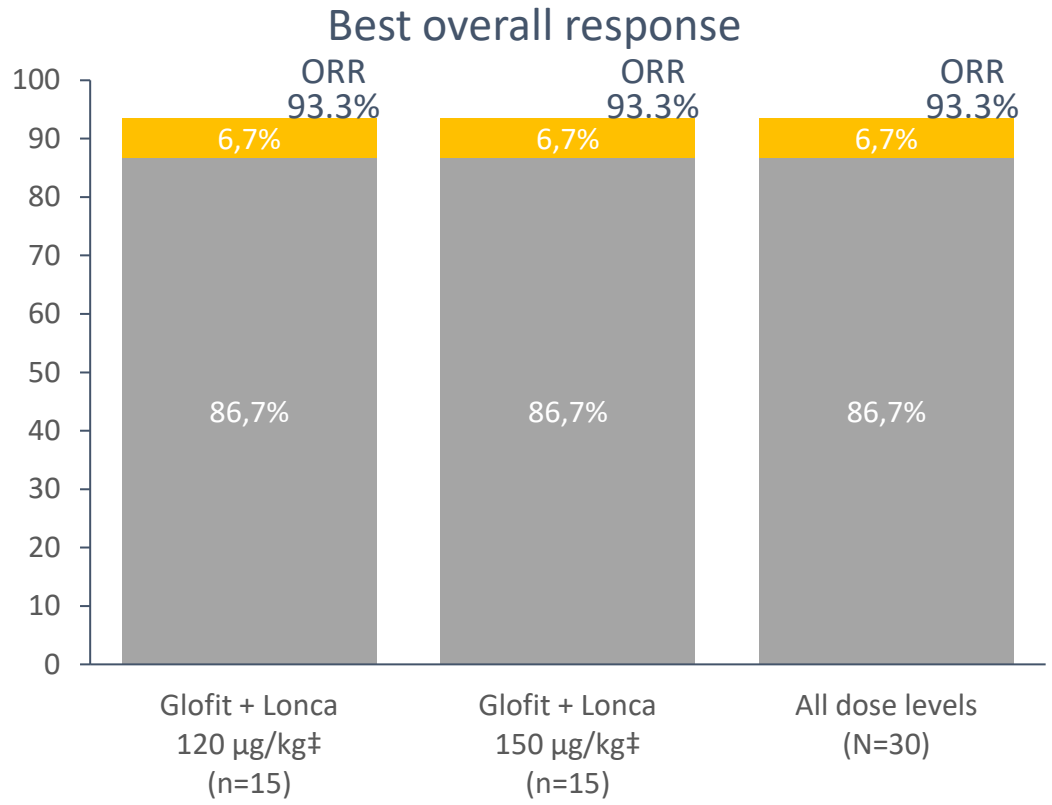
- Randomized phase III study of SC mosunetuzumab + polatuzumab vedotin vs rituximab + gemcitabine + oxaliplatin for CD20+ aggressive NHL (DLBCL or NOS, HGBCL DH/TH or NOS, tFL, FL grade 3b); ≥1 prior systemic therapy; ineligible for ASCT



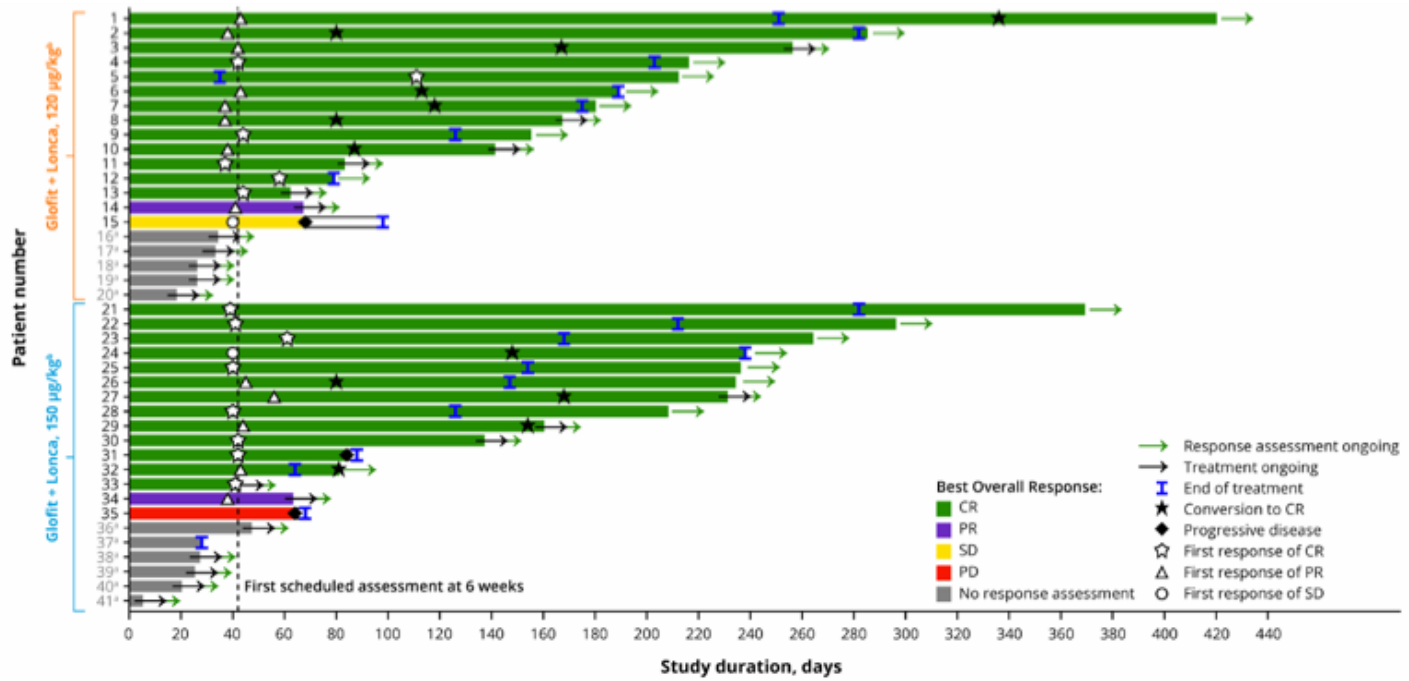


Budde E et al, J Clin Oncol2025 Dec 20;43(36):3799-3811.

Loncastuximab + glofitamab



Characteristic, n (%)	Glofit + Lonca 120 µg/kg‡ (n=15)	Glofit + Lonca 150 µg/kg‡ (n=15)	All dose levels (N=30)
Median DOR§	(n=14) NE	(n=14) NE	(n=28) NE
Median time to first response (CR or PR), days	(n=14) 42.0	(n=14) 42.0	(n=28) 42.0
Median time to first CR, days	(n=13) 80.0	(n=13) 42.0	(n=26) 70.5

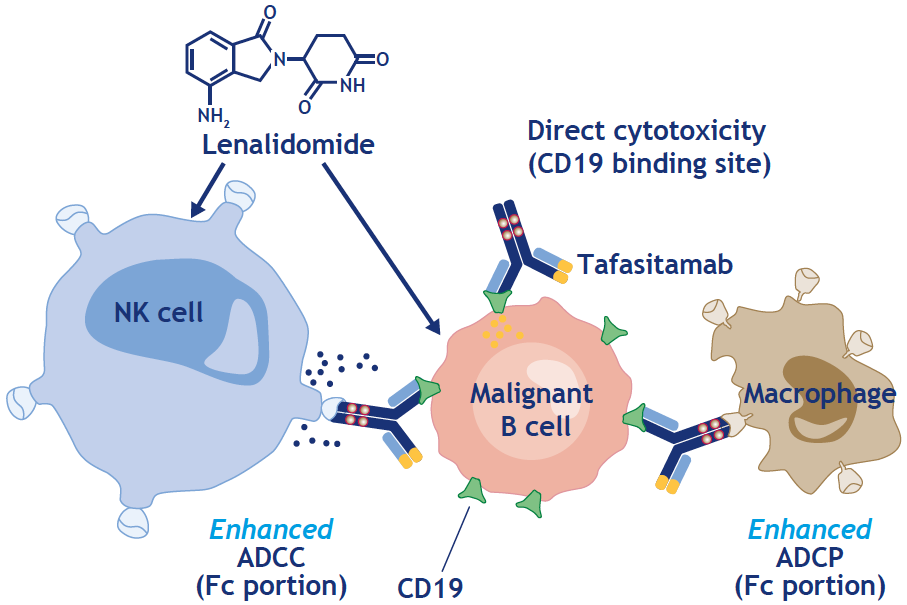


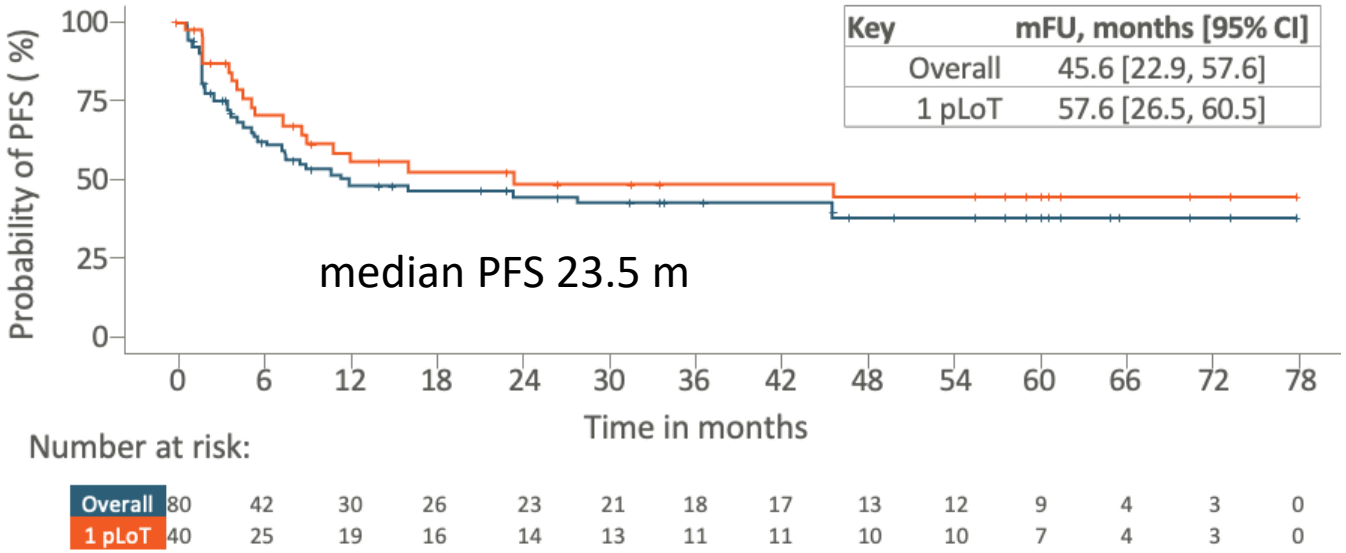
Alderuccio et al. ICML 2025; Oral presentation #078.

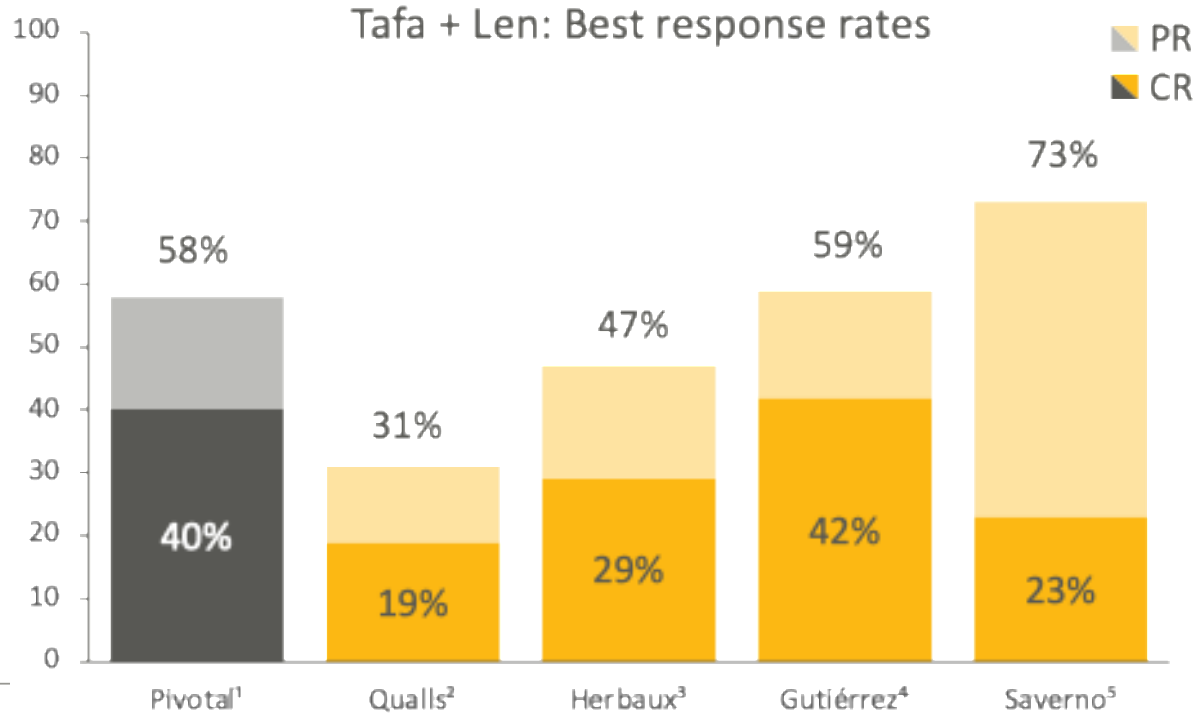
Outline

- Current suquencing
- CAR T-cell
- ADC
- Bispecific antibodies
- Combinations
- Other options and challenges

L-Mind study: Tafasitamab + lenalidomide







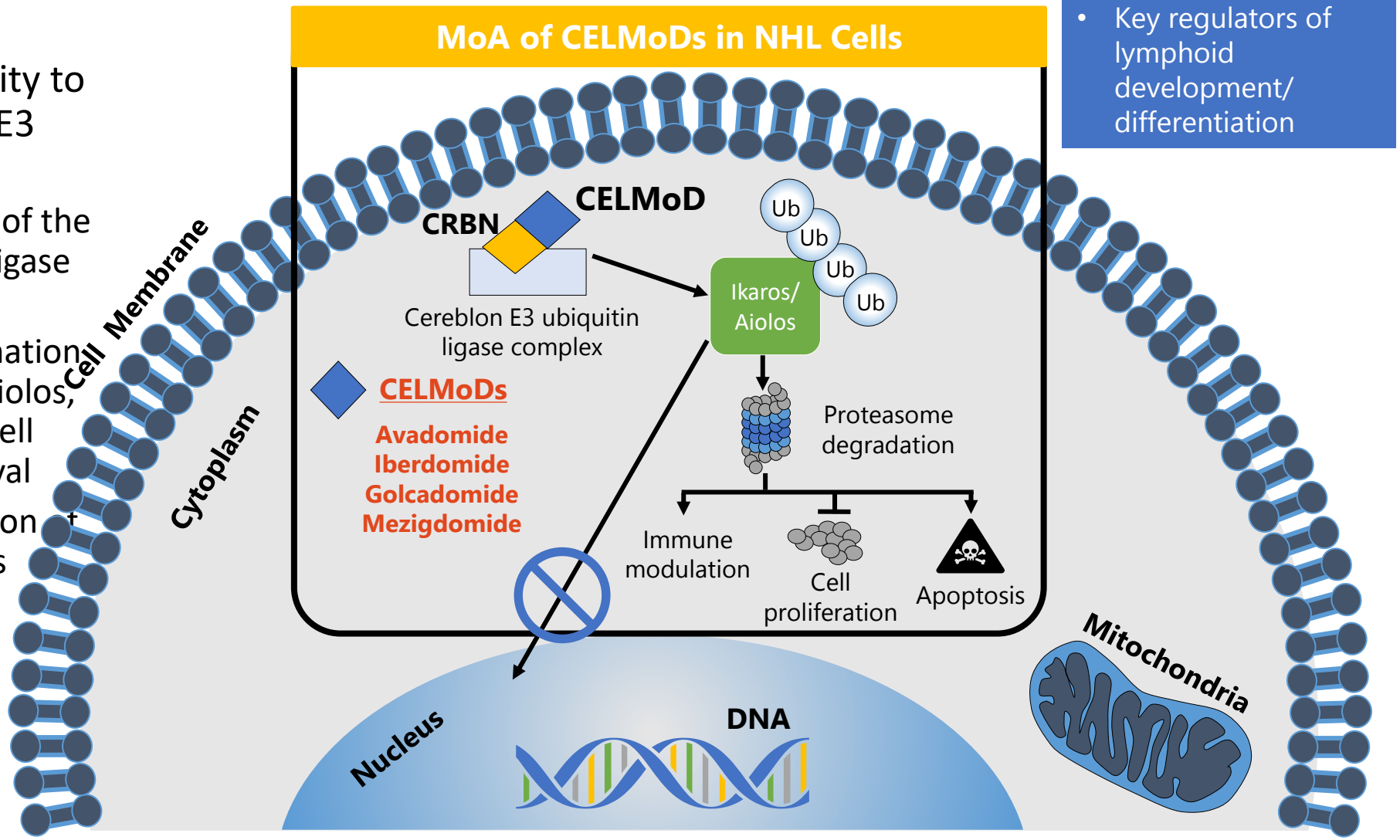
1. Salles G et al, Lancet Oncol 2020; Duell et al, Haematologica 2024 2. Qualls et al. *Blood* 2023 3. Herbaux et al. EHA 2024; Abstract #P1214 4. Gutiérrez et al. EHA 2024; Abstract #P1203 5. Saverno et al. *Blood* 2024.

CELMoD Agents: Mechanism of Action

Ikaros and Aiolos:

- Lymphomagenic proteins
- Key regulators of lymphoid development/ differentiation

- CELMoDs bind with high affinity to CRBN, a part of the cereblon E3 ubiquitin ligase complex
  - Modulates the activity of the cereblon E3 ubiquitin ligase complex
  - Increases polyubiquitination of the TFs Ikaros and Aiolos, which are involved in cell proliferation and survival
  - Results in the recognition of different neosubstrates for ubiquitination and protein degradation



Chavez. ASH 2023. Abstr 4496. Ioannou. Int J Mol Sci. 2021;9;22:8572. Szewczyk. J Med Chem. 2024;67:1327. Costacurta. J Pers Med. 2021;11:1185. Barankiewicz. Cancers. 2022;14:4492.

CC-99282-NHL-001: Efficacy of Golcadomide for Patients With R/R DLBCL

- Phase I/II trial

Response by dose level	Golcadomide + R		
	0.2 mg Golca (n = 34)	0.4 mg Golca (n = 35)	Overall (n = 69)
ORR, %	35	60	48
• CR	18	43	30
• PR	18	17	17
Median DoR, mo (range)	8.34 (1.5-26.7)		
Median DoT, mo (range)	8 (3-24.2)		
Median follow-up, mo (range)	5.85 (1.0-28.5)		

Response by Prior CAR T-cell Therapy	0.4 mg Golcadomide + R	
	Prior CAR T-cell (n = 21)	No Prior CAR T-cell (n = 17)
ORR, %	50	71
• CR	33	53
• PR	17	18

Neutropenia is most common any grade and severe toxicity

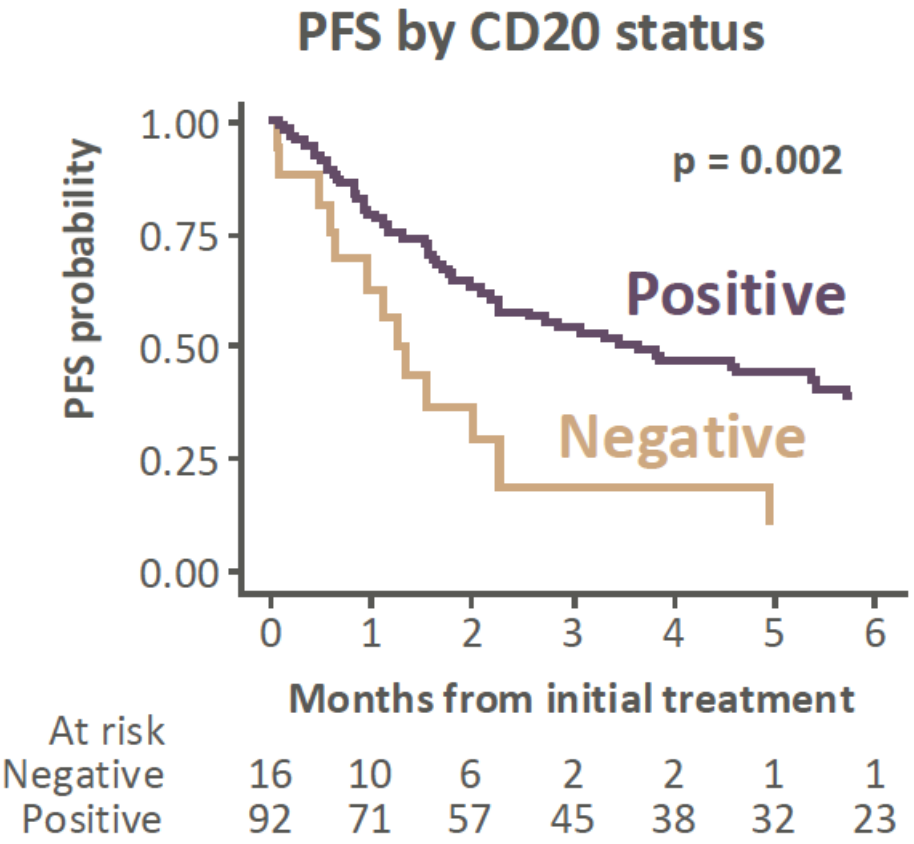
Additional trials ongoing and planned in upfront (phase III GOLSEEK, NCT06356129) and relapsed/refractory DLBCL

Michot. ASH 2024. Abstr 869.

Real-world data: Impact of CD20 loss post-bispecifics

Patient and disease characteristics	Overall N=208
DLBCL NOS	158 (76%)
Primary refractory	55 (30%)
Prior CD19 CAR-T	124 (60%)
Undetectable CD20 prior to bispecific (n=122)	16 (13%)
By flow cytometry (n=73)	16 (22%)
By IHC (n=122)	9 (7%)

89% of patients* (17/19) lost detectable CD20 on post-bispecific biopsies



Median time to progression in those who lost CD20: 3.7 months

Brooks et al. ASH 2024; Oral presentation #111

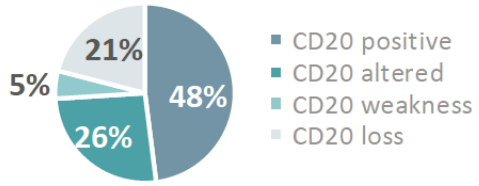
LNH-EPI study: Frequency of CD20/CD19 loss and impact on outcomes in R/R DLBCL [1]

Patient and disease characteristics

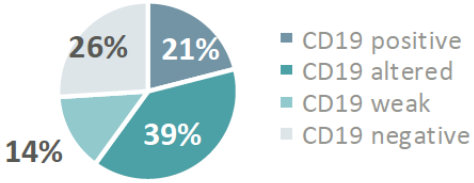
	N=200
Median age, years (range)	66 (26–87)
Primary refractory, %	74
Median no. of prior LoT	2 (1–9)
Prior CAR-T, %	22
GCB disease, %	49
Non-GCB disease, %	45

mOS was 11 months in the overall population

CD20 status
(192 patients were evaluable)



CD19 status
(51 patients were evaluable)



	Median OS, months (95% CI)	p value
CD20 positive	12 (9–15)	0.0012
CD20 altered	6 (4–12)	
CD19 positive	10 (8–22)	0.8312
CD19 altered	4 (3–NA)	
GCB disease	12 (9–15)	0.6220
Non-GCB disease	9 (7–14)	
Primary refractory	9 (8–12)	0.0002
Non-primary refractory	46 (23–NA)	

In retrospective study which evaluated CD20 expression in 25 pediatric/young adult with R/R mature B-NHL or B-ALL[2]:

- 40% showed loss of CD20 expression
- CD20-loss was characterised by a more aggressive disease and worse outcome

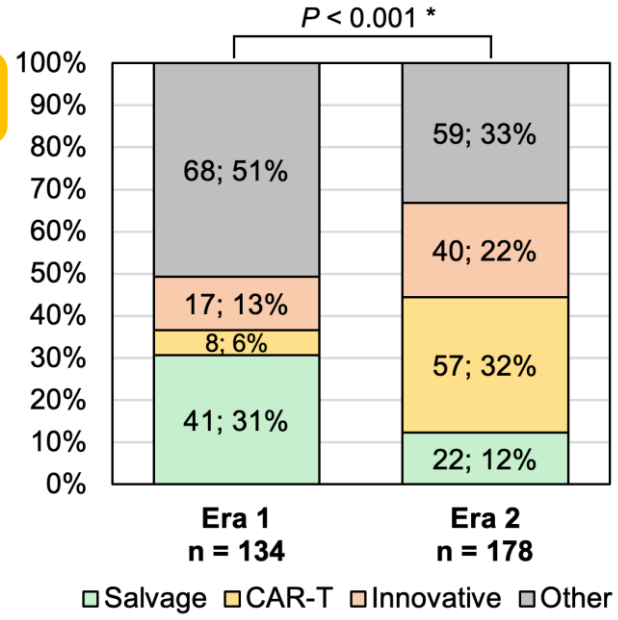
Post-therapeutic CD20 and CD19 tumour loss were 21% and 26%, respectively, in this population.
CD20 loss was associated with a poor prognosis. More data are required to determine the impact of CD19 loss on outcomes

1. Hueso et al. ASH 2024; Oral presentation #474
2. 2. Vinti et al. ASH 2024; Abstract #3086.

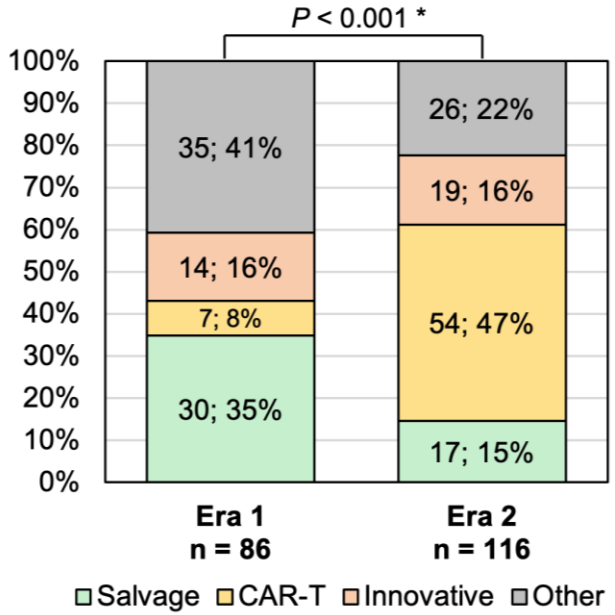
Summary

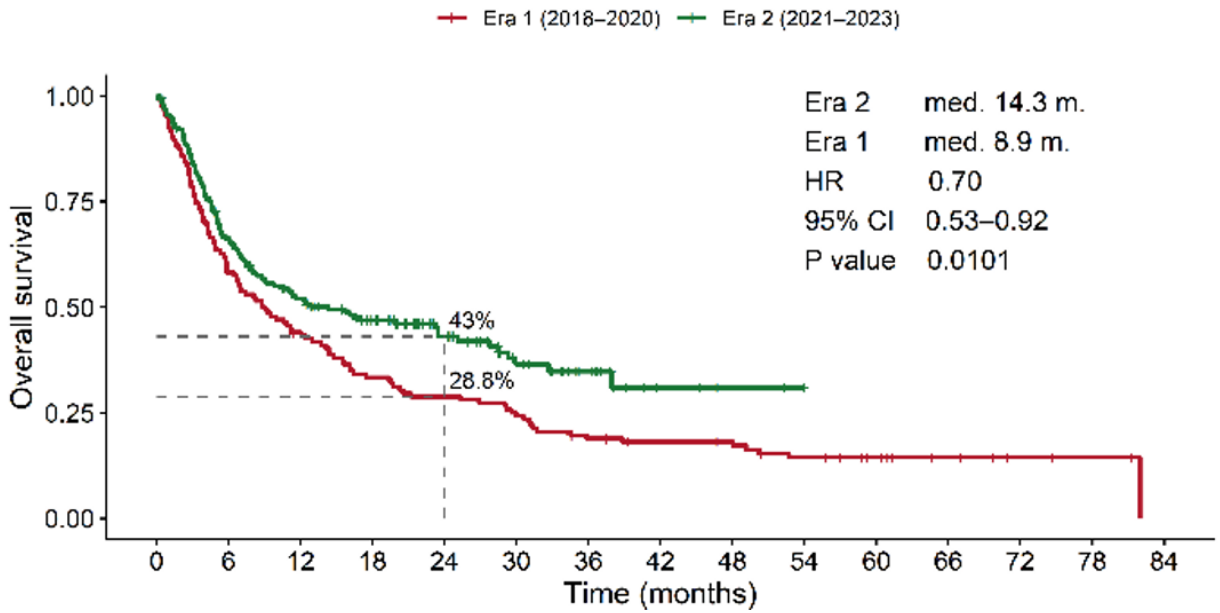
Evolution of R/R DLBCL management and population overall survival improvement (Era 2018-2020 vs 2021 vs 2023)

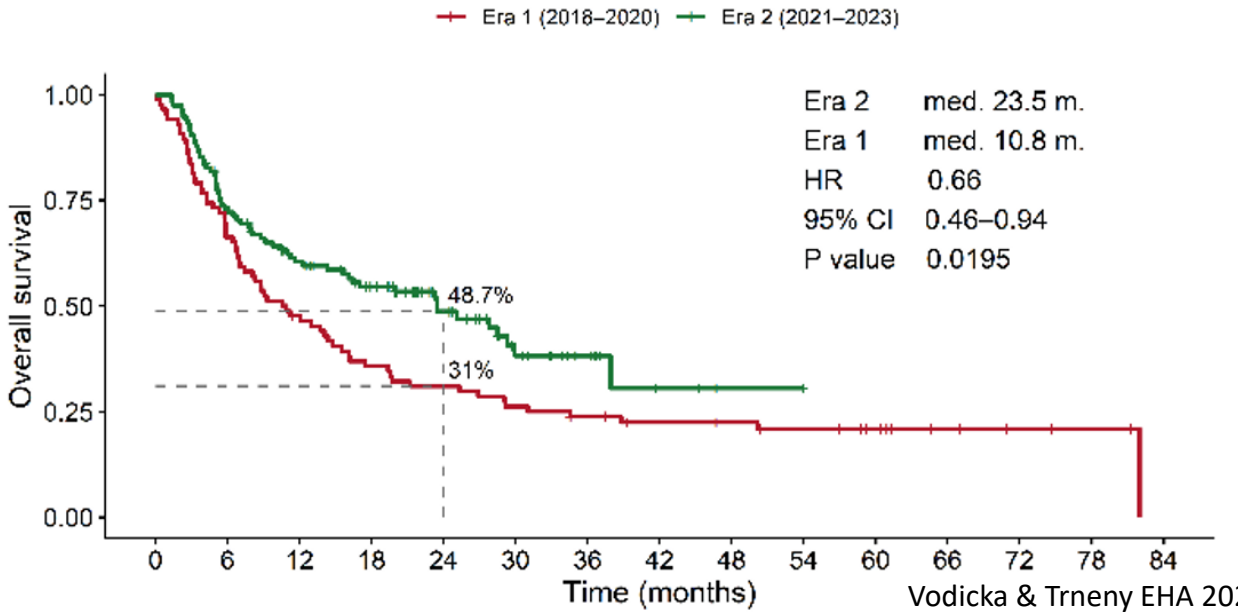
All R/R DLBCL pts



CAR T-cell eligible R/R DLBCL pts

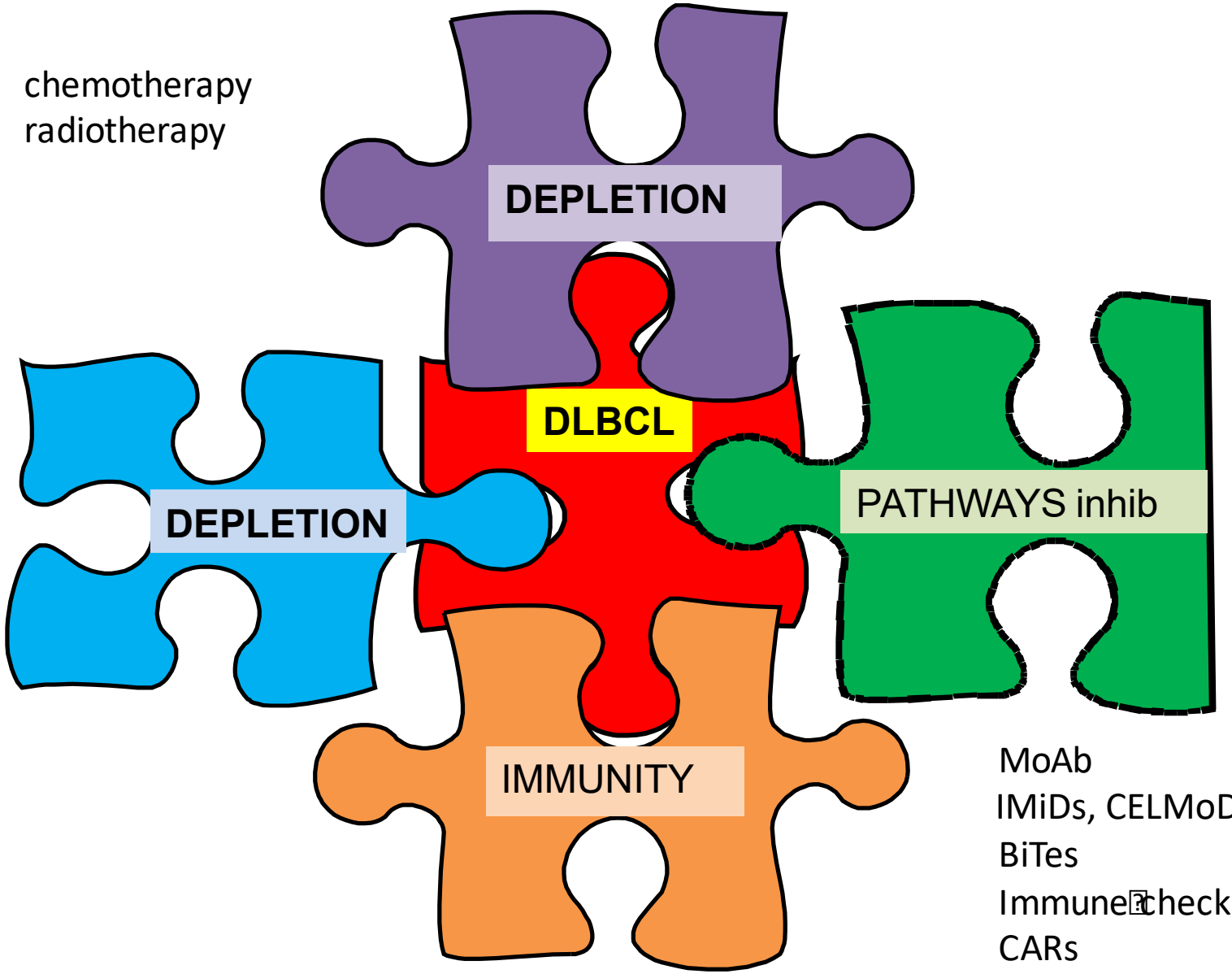






Vodicka & Trneny EHA 2025

How to proceed? Sequence and Combine



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Thank you

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