Relapsed Aggressive B-cell NHL: CAR-T vs Bispecific Antibodies

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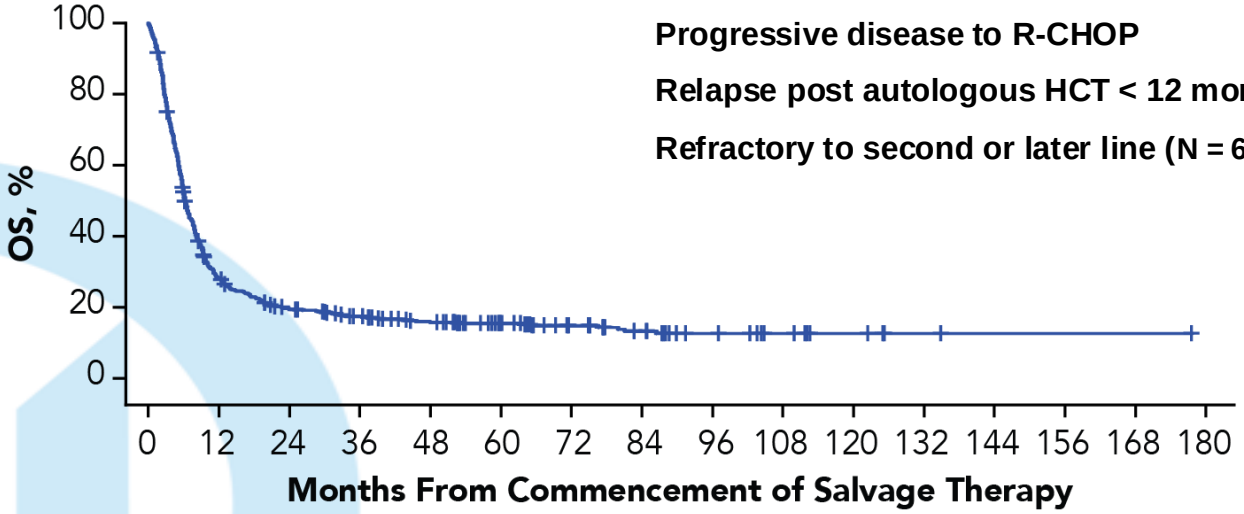
Refractory Diffuse Large B cell Lymphoma carries a poor prognosis

- SCHOLAR-1 patient level meta-analysis of refractory Aggressive NHL
  - ORR of 26% (CR of 7%, PR of 19%)
  - **Median OS of 6.6 months**



Progressive disease to R-CHOP

Relapse post autologous HCT < 12 months-

Refractory to second or later line (N = 636)

Crump M, et al. *Blood.* 2017; blood-2017-03-769620.

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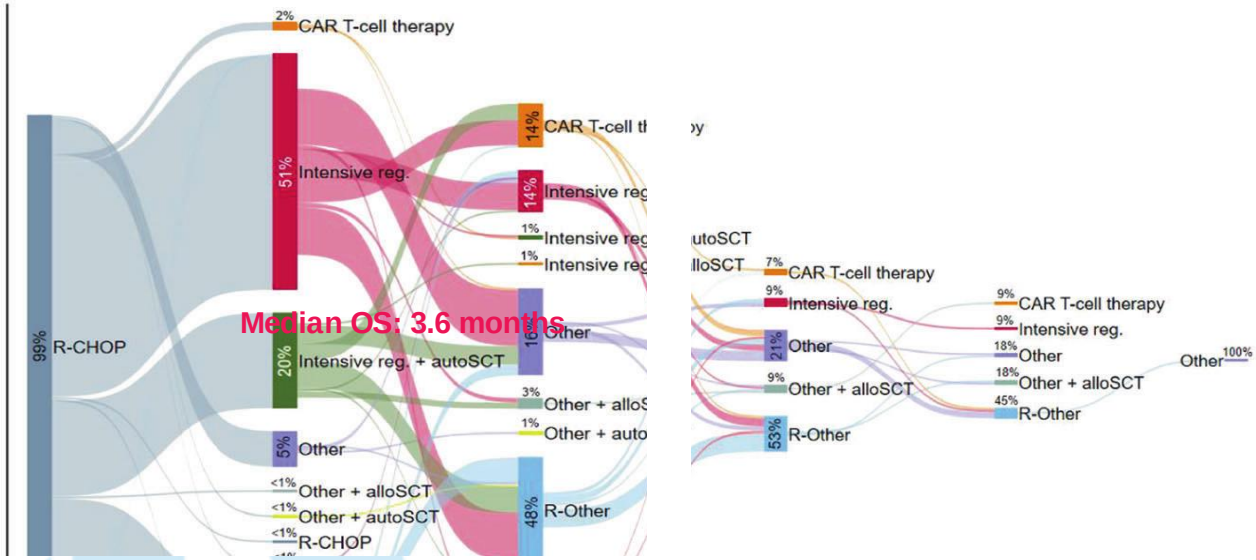
Real-Life R/R DLBCL: Population Based Analysis-Netherlands



Pennings E et Al. B Can Journ 2023

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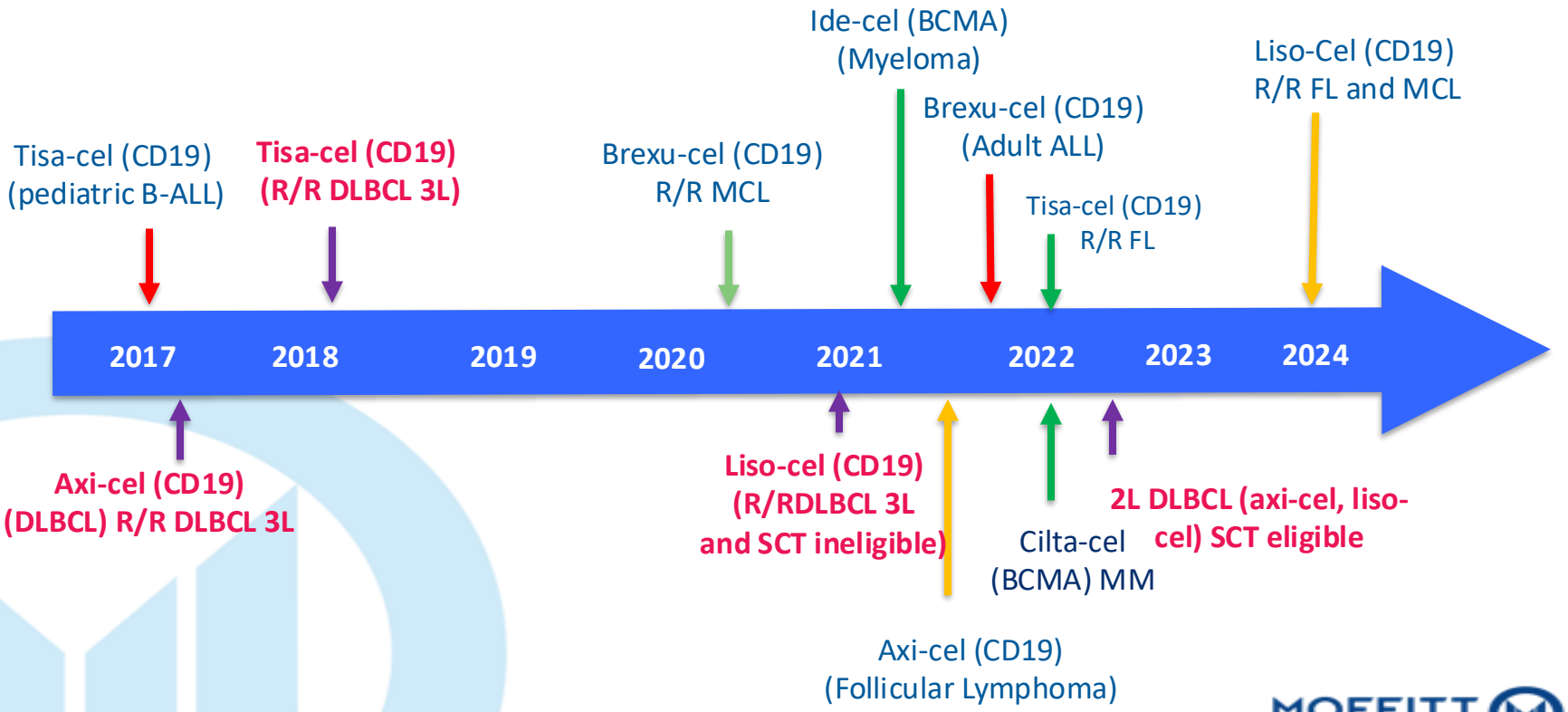
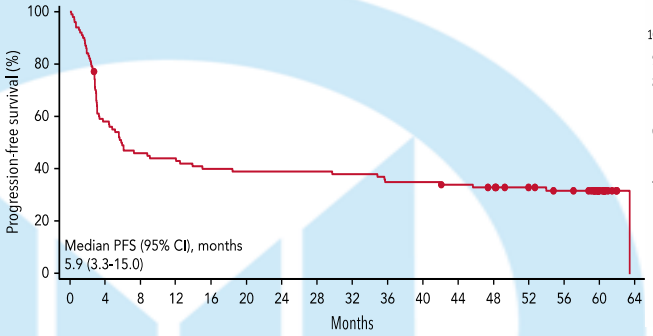
CAR-T advances in DLBCL: US FDA approvals



Pivotal Anti-CD19 CAR T-Cell Therapy Trials: Long term follow-up

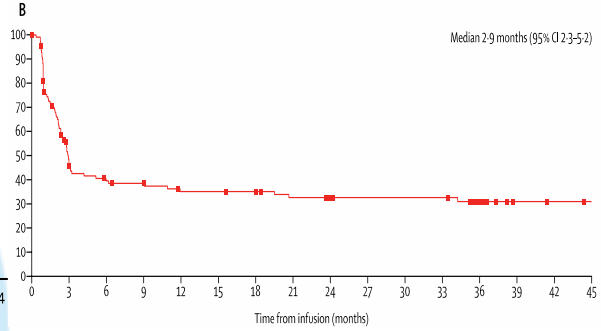
ZUMA-1
Axicabtagene Ciloleucel

Median F/U 5 years
Median age: 58 (23 – 76)
Enrolled (treated): 111 (101)
Best ORR: 83%
Best CR: 54%
PFS: 5.9 months
Ongoing CR: 39%



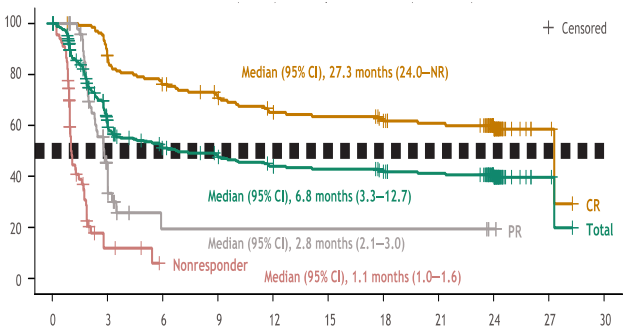
JULIET
Tisagenlecleucel

Median F/U 40.3 months
Median age: 56 (22 – 76)
Enrolled (treated): 165 (111)
Best ORR: 52%
Best CR: 40 %
PFS: 2.9 months
Ongoing CR: 37%



TRANSCEND NHL 001
Lisocabtagene Maraleucel

Median F/U 24 months
Median age: 63 (18 – 86)
Enrolled (treated): 244 (269)
Best ORR: 73%
Best CR: 53 %
PFS: 6.8 months
Ongoing CR: 45%



Neelapu et Al. Blood 2023. Schuster et Al. Lancet Oncol 2021. Abramson et Al. Blood 2023

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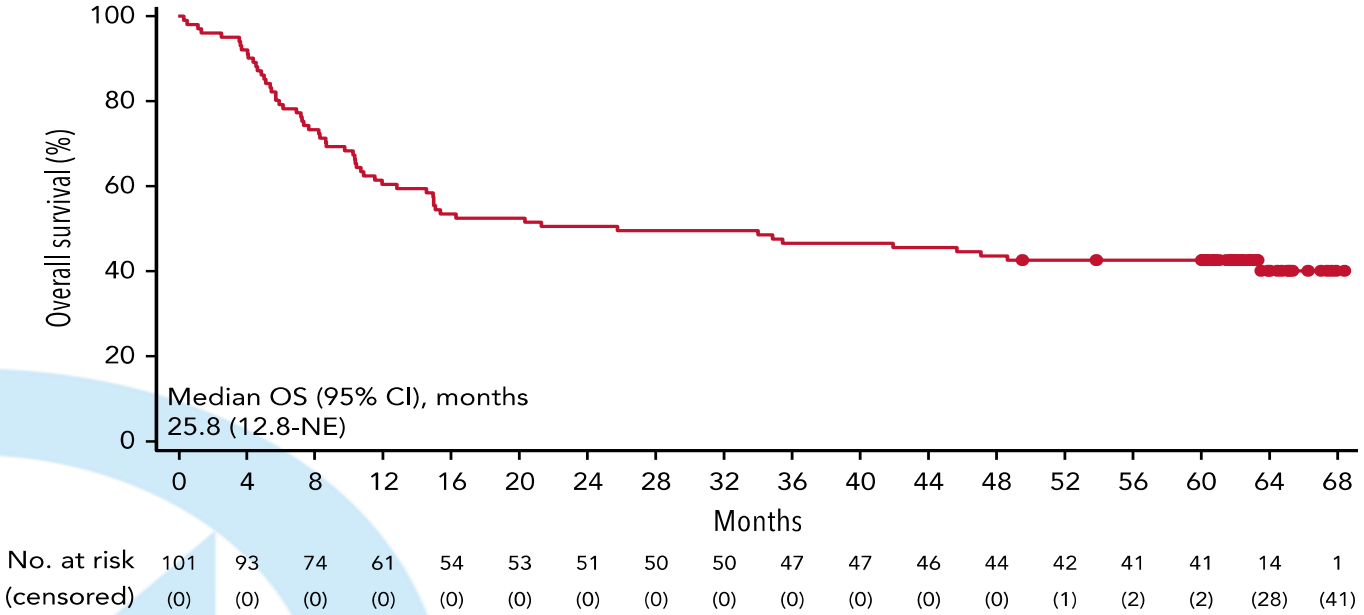
ZUMA-1: Long term efficacy of Axi-Cel in R/R DLBCL-Overall Survival Update At 5 Years (mITT, n = 101): Curative potential



- With ≥ 5 years of follow-up, median OS was 25.8 months, and the KM estimate of the 5-year OS rate was 42.6%
- Since the 4-y cut-off there was 1 dead (month 63) and 1 PD (month 54)

Jacobson et al. ASH Meeting 2021: 1760, Neelapu et al. Blood 2023

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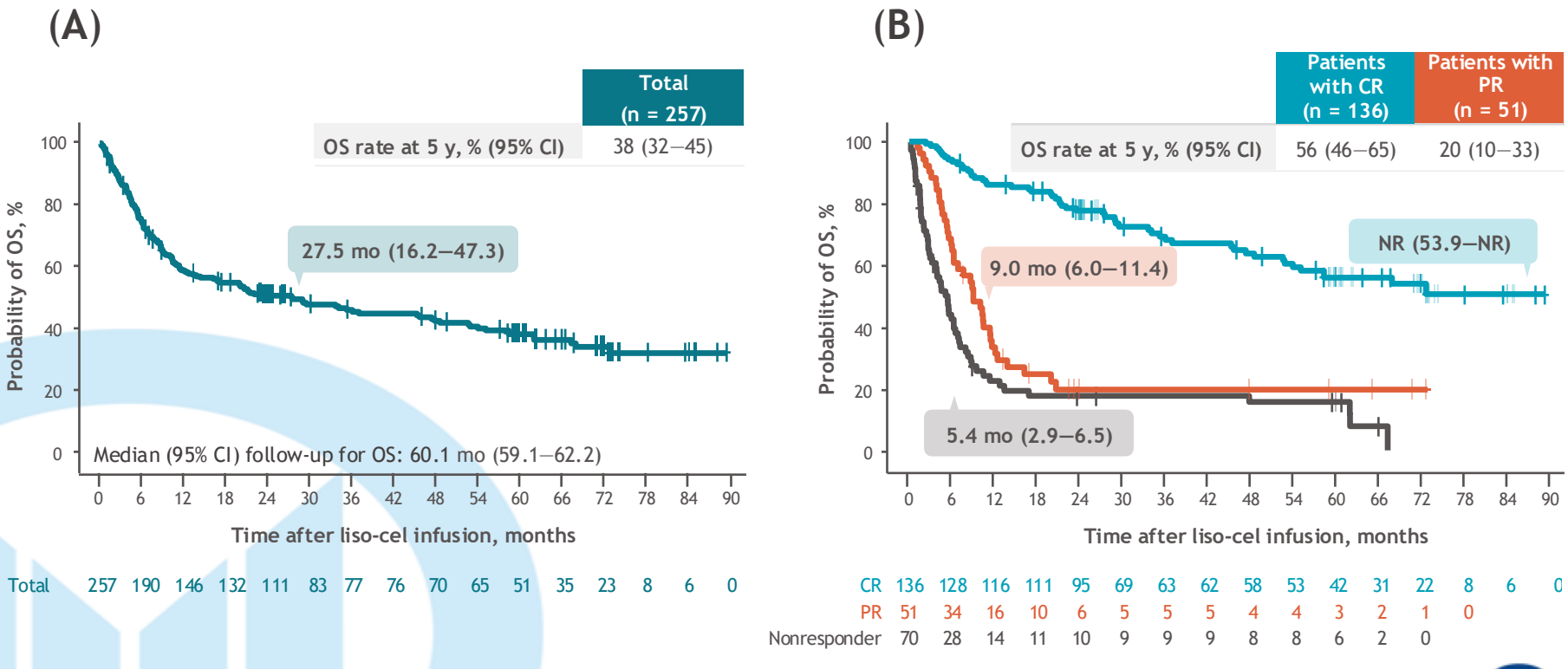
ASH 2024: TRANSCEND NHL 001 Overall survival (liso-cel in 3L R/R DLBCL): 5 year follow up



Data on KM curves are expressed as median (95% CI). The nonresponder group included patients with a best response of stable disease or PD.
KM, Kaplan-Meier; PR, partial response.

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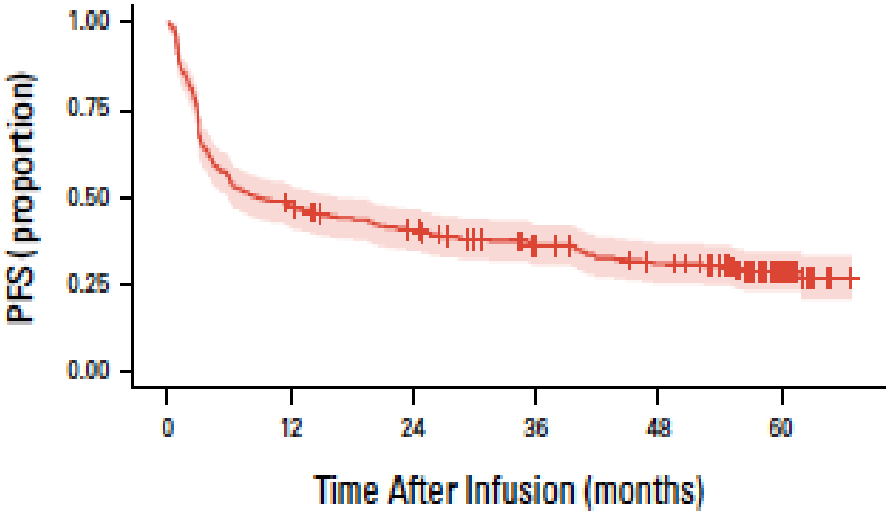
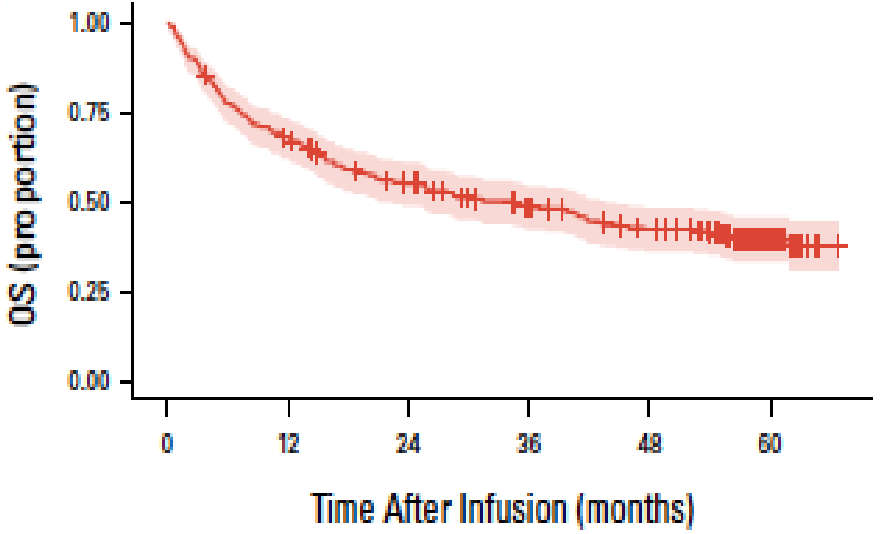
US CAR-T Consortium: 5-year follow up of axi-cel as SOC for R/R DLBCL 3L



Median PFS: 8.7 months
5-y PFS 47.3%



Median OS: 34.9 months
5-y OS: 40.3 %

Jain MD et Al. *J Clin Oncol* 2024

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CAR-T in DLBCL real life: US experience Comparison to Pivotal Trials

Study	ZUMA-1[1,2]	JULIET[3]	TRANS-CEND[4]	Jacobson et al[5]	Nastoupil et al[6]	CIBMTR [7] (Axi-cel)	CIBMTR [8](Tisa-Cel)
Product	Axi-cel	Tisa-cel	Liso-cel	Axi-cel	Axi-cel	Axi-cel	Tisa-cel
Treated, n	101	111	269	122	275	533	80
ORR, %	82	52	73	70	82	74	58
CR, %	54	40	53	50	64	54	40
6-mo ORR, %	41	29	NR	41	NR	NR	NR
Gr 3+ CRS	**13**	**22**	**2**	**16**	**7**	**9**	**3**
Gr 3+ ICANS	**28**	**12**	**10**	**35**	**31**	**17**	**5**

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839. 5. Jacobson. JCO. 2020;38:3095. 6. Nastoupil. JCO. 2020;38:3119. 7. Pasquini. ASH 2019. Abstr 764. 8. Pasquini. Blood Adv. 2020;4:5414.

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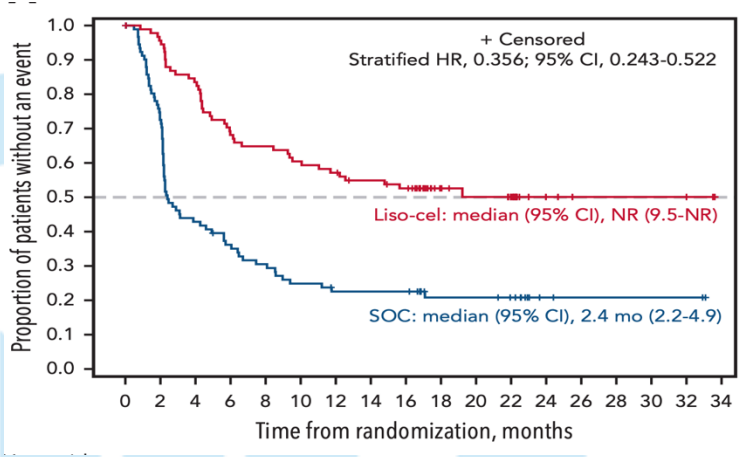
Phase III randomized trials in transplant eligible: EFS and PFS results

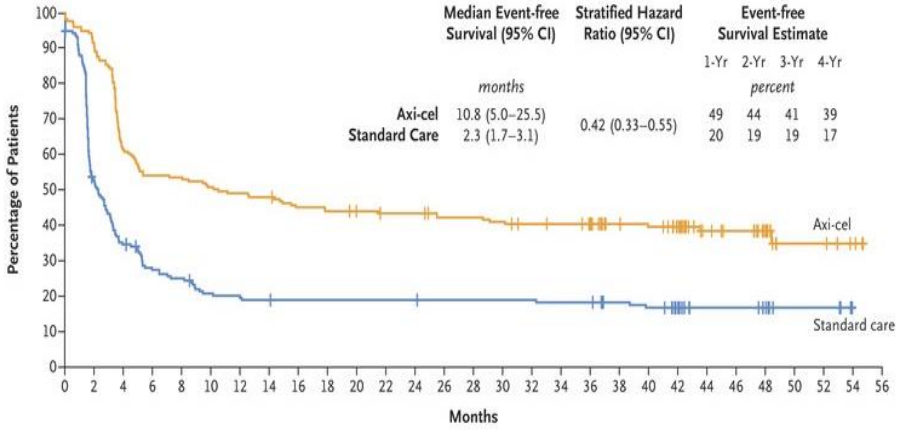
TRANSFORM
Lisocabtagene maraleucel vs SOC

Median F/U: 24.9 months
Median age: 60 (20 – 74)
Enrolled (CAR-T) 92
Best ORR: 87%
Best CR: 74%
PFS: NR



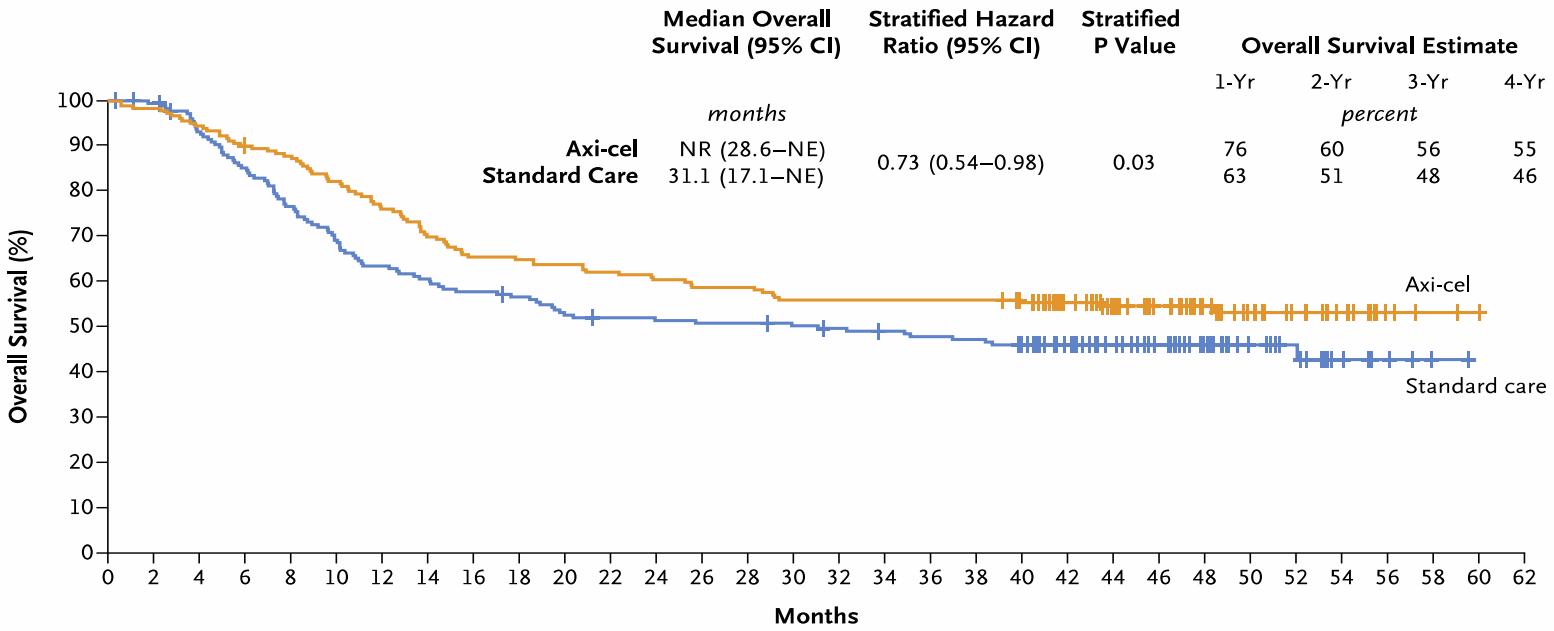
ZUMA-7
Axicabtagene Ciloleucel vs SOC

Median F/U 47.2 months
Median age: 58 (21 – 80)
Enrolled (CAR-T): 180
Best ORR: 83%
Best CR: 65%
PFS: 14.7 months



Abramson et al. Blood 2023; Locke et al. NEJM 2021

ZUMA-7 Improved OS with CAR-T as second line therapy



Westin J et Al. N Eng J Med 2023

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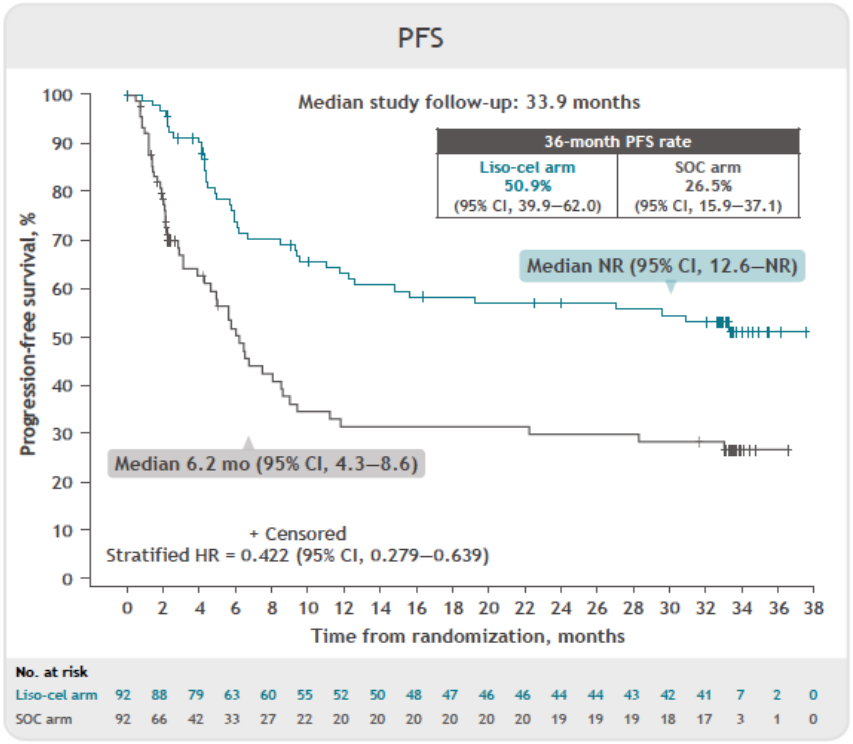
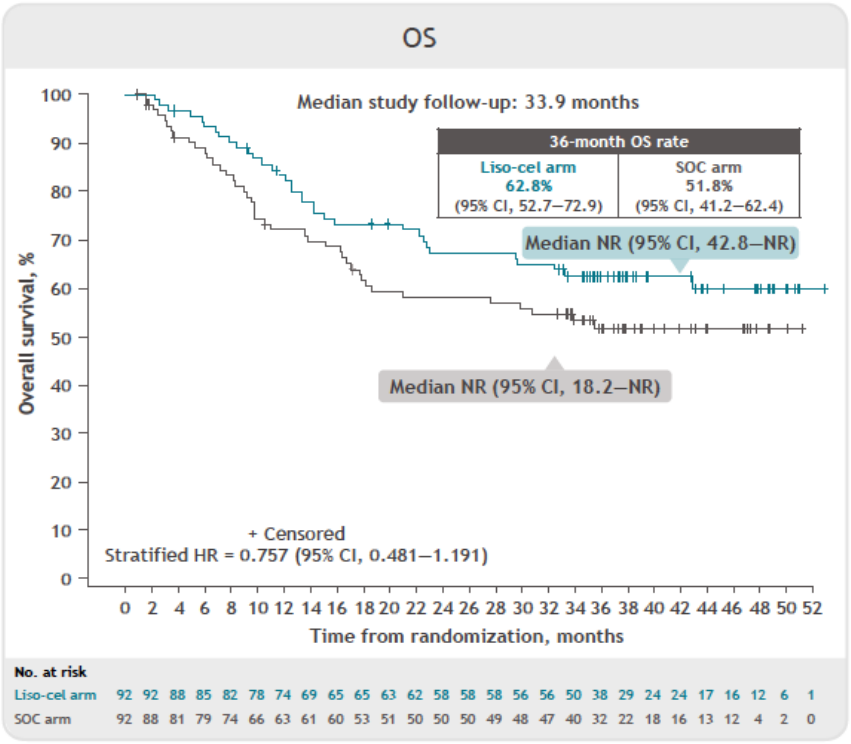
TRANSFORM (liso-cel vs SOC): 3-year follow up, PFS and OS





Kamdar M et Al. *ASCO Meeting Abstracts* 2024

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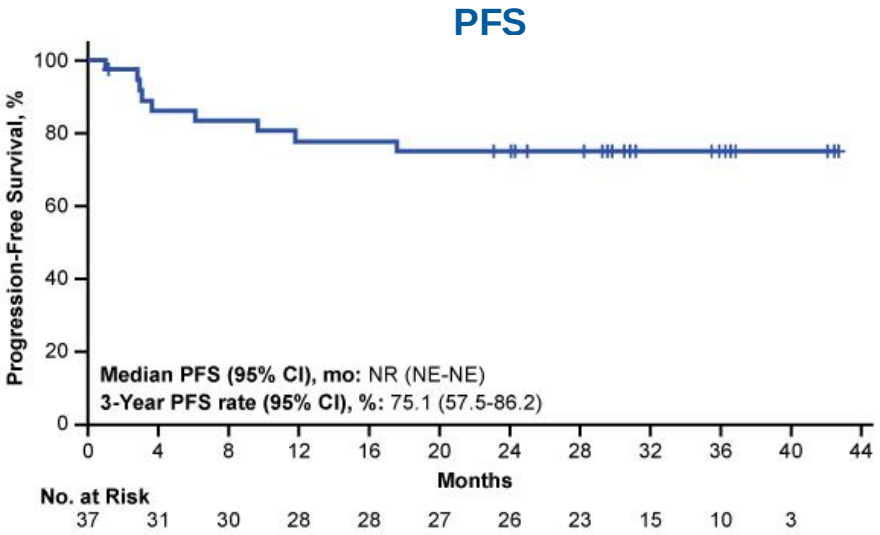
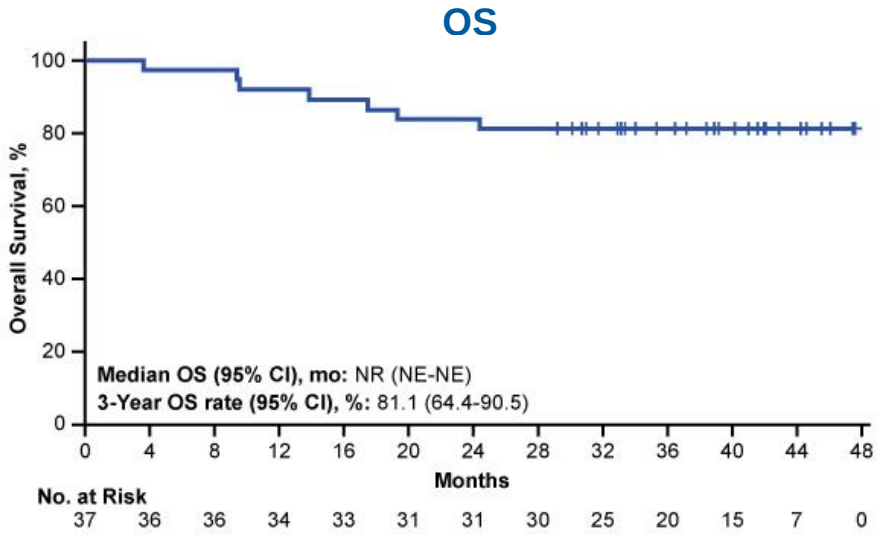
ZUMA-12 Axi-Cel as Frontline Therapy for High Risk DLBCL: 3-year follow up





- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates **were 84.4%** (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

Chavez JC et Al. *ASH Meeting Abstracts* 2023

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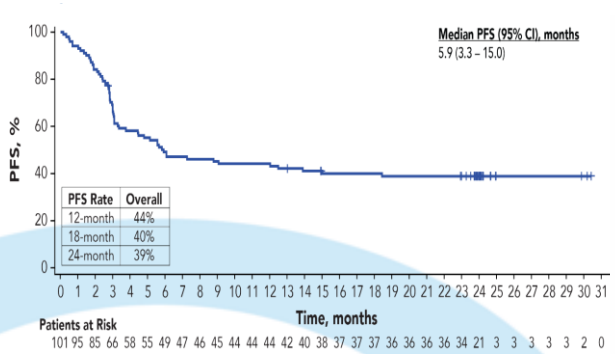
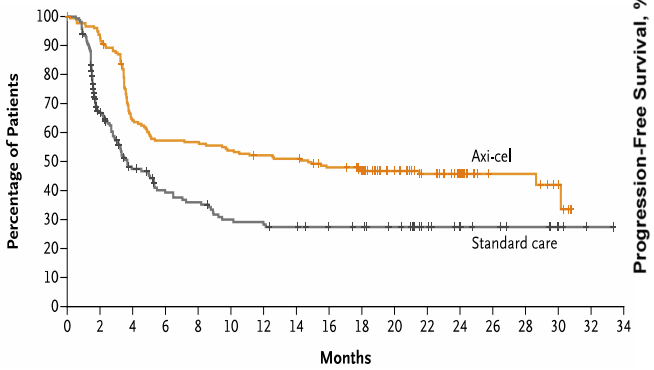
Earlier use of CART may improve outcome

ZUMA-1



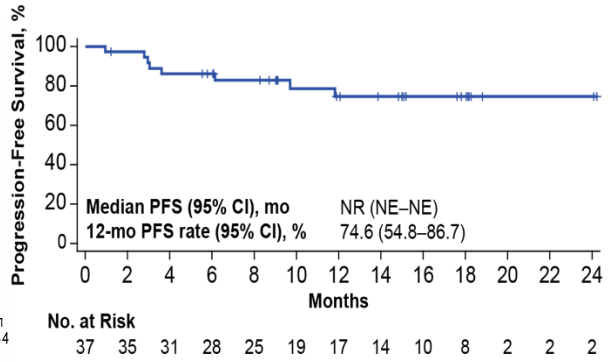
Median PFS 5.9 months

ZUMA-7



Median PFS (axi-cel arm): 14.6 months

ZUMA-12



Median PFS: Not reached

Locke et al. *Lancet Oncol* 2018, Locke et al. *N Eng J Med* 2021, Neelapu ASH Meeting Abstracts 2021

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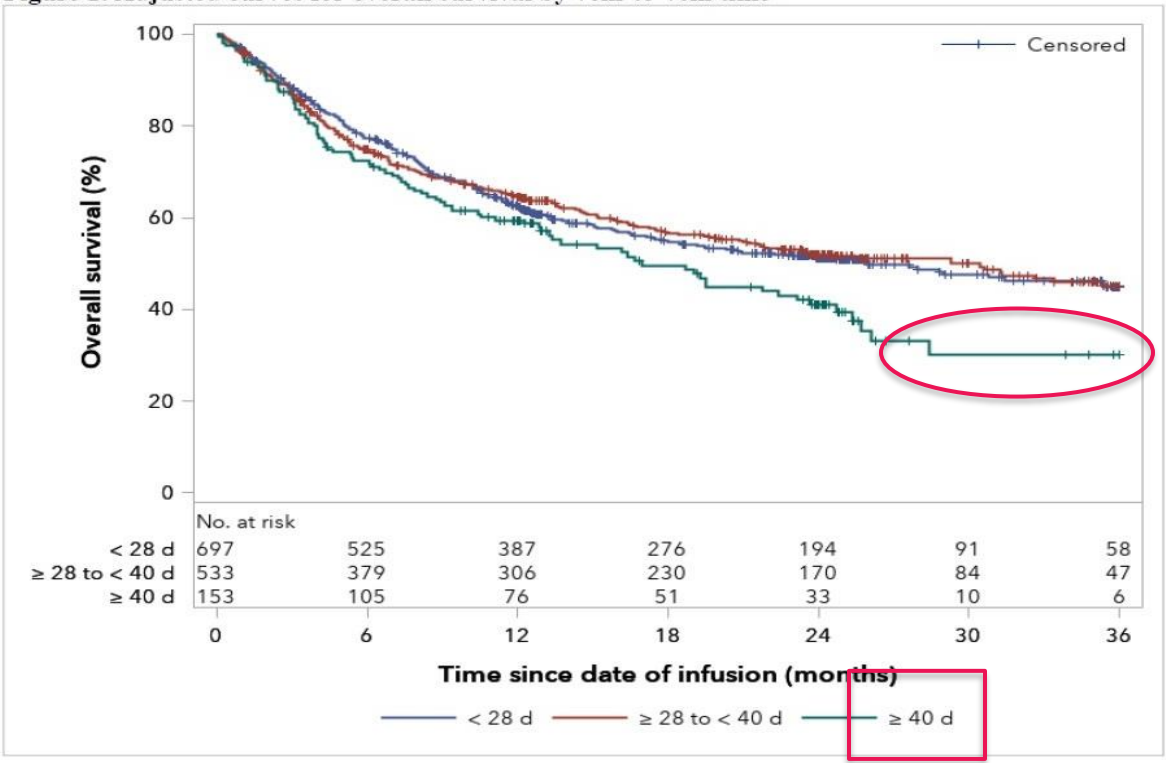
Impact of CAR-T infusion waiting times in DLBCL: CIBMTR analysis (> 1300 pts)

Figure 1: Adjusted curves for overall survival by vein-to-vein time

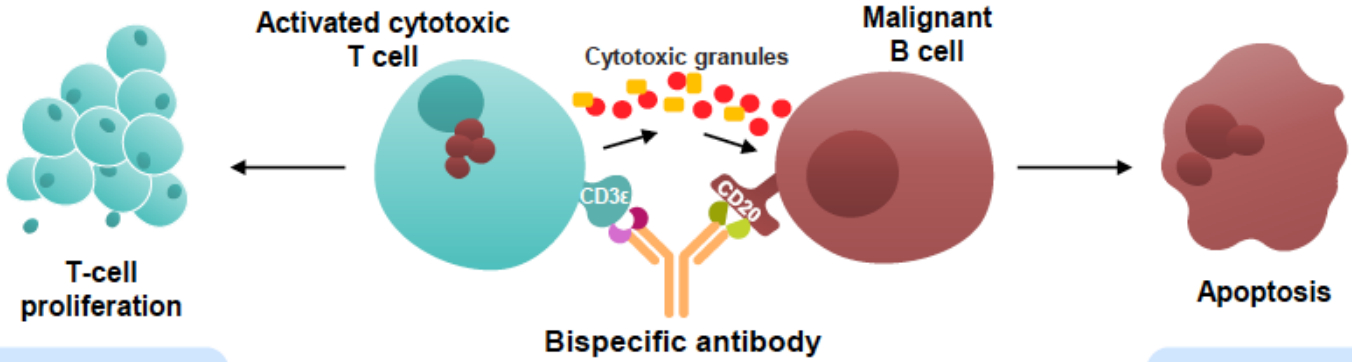


Locke et al ASH Meeting Abstract 2022: 3345

Bispecific antibodies for LBCL

Bispecific Antibody Mechanism of Action

T-cell activation via TCR binding leads to the secretion of granzymes and perforin and subsequent T-cell-dependent target cell death



T-cell proliferation and expansion at tumour site

T-cell-mediated tumour killing

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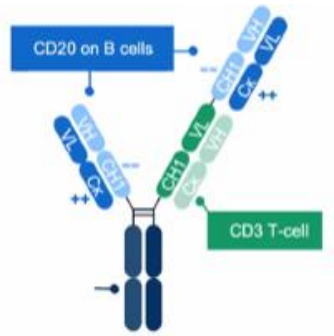
Bispecific Abs: FDA approvals R/R LBCL

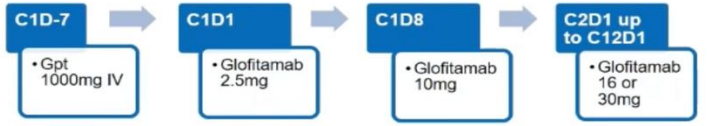
Glofitamab

FDA approved June 2023
ORR: 52% CR: 39%
PFS 4.9 months



Treatment schedule

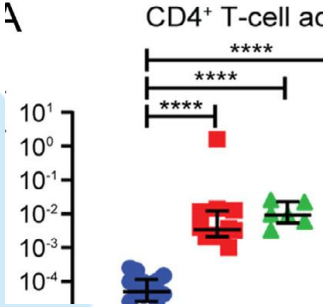
- 1000mg Gpt 7 days prior to glofitamab administration
- Glofitamab IV step-up doses on C1D1 and D8 and at target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg)
- Cycle 1 was 14-days long; glofitamab was given Q3W thereafter for up to 12 cycles



Fixed duration therapy

Epcoritamab

FDA approved May 2023
ORR: 63% CR: 39%
PFS 4.4 months



Continuous therapy

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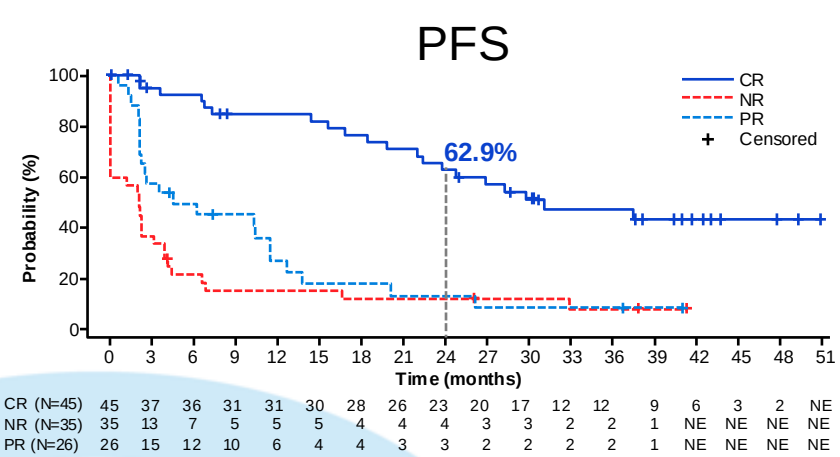
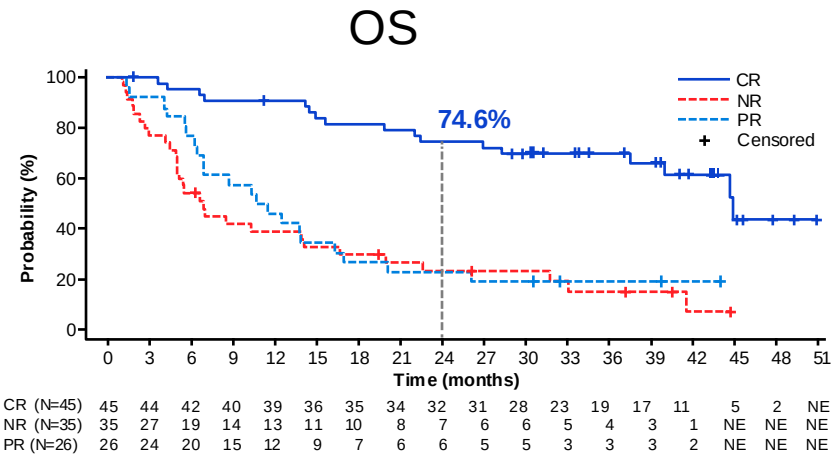
ASH 2024: 3-year follow up Glofitamab in 3L R/R DLBCL





Landmark PFS from C3 in patients with CR at C3*	N=45
Median PFS, months (95% CI)	31.1 (23.8–NE)
24-month PFS rate, % (95% CI)	62.9 (47.5–78.4)

Landmark OS from C3 in patients with CR at C3*	N=45
Median OS, months (95% CI)	**44.8** (40.0–NE)
24-month OS rate, % (95% CI)	74.6 (61.6–87.6)

Most patients with a CR at C3 remained progression-free and alive after 24 months

Dickinson M al. *ASH Meeting Abstracts* 2024.

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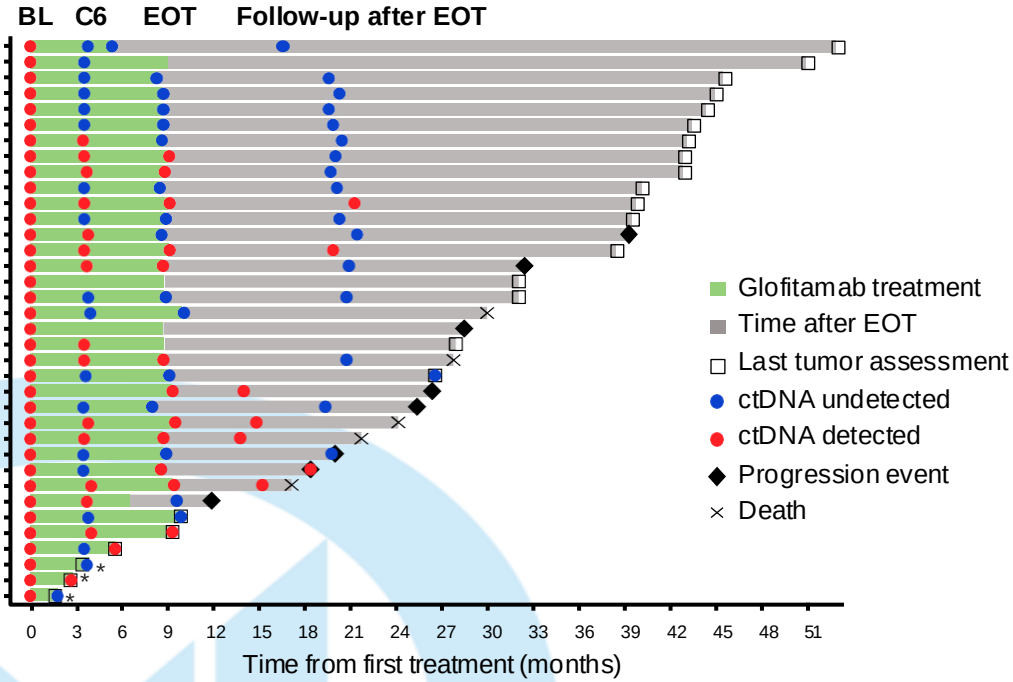
ASH 2024: Glofitamab and ctDNA kinetics in R/R DLBCL patients in CR at end of treatment



- **ctDNA kinetics are consistent with a rapid and durable response to fixed-duration glofitamab treatment**
- **In patients in CR at EOT†:**
  - 53% (16/30) had undetectable ctDNA at C6
  - 55% (17/31) had undetectable ctDNA at EOT
  - **72% (18/25) had undetectable ctDNA during follow-up after EOT**

The majority of patients with a CR at EOT had undetectable ctDNA during follow-up after EOT

Exploratory nalysis using AVENIO NHL CAPP-Seq assay. Undetectable ctDNA status was defined using a detection cutoff of p=0.005[1].
*Data for these 3 patients were collected at EOT. †Analysis included patients with available ctDNA status at baseline (36/45, 80%); percentages are based

Dickinson M al. *ASH Meeting Abstracts* 2024.

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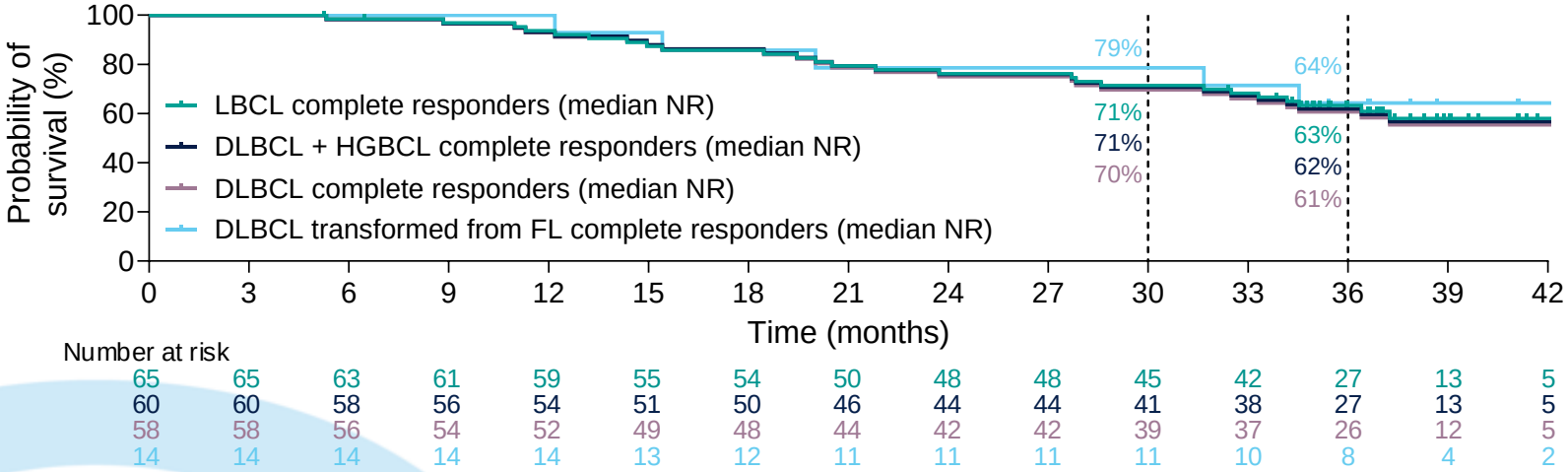
ASH 2024: 3-year follow up Epcoritamab R/R LBCL: PFS and OS Benefits With Complete Response



- Median **PFS for the overall population (N=157) was 4.2 mo** (95% CI, 2.8–5.5)
- Among complete responders (n=65), median PFS was 37.3 mo (95% CI, 26.0–NR)
  - 36-mo PFS estimate was 53%
- **Median OS for the overall population (N=157) was 18.5 mo** (95% CI, 11.7–27.7); among **complete responders, it was NR**
- At 36 mo, an estimated 75% of complete responders had not initiated a new antilymphoma therapy

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

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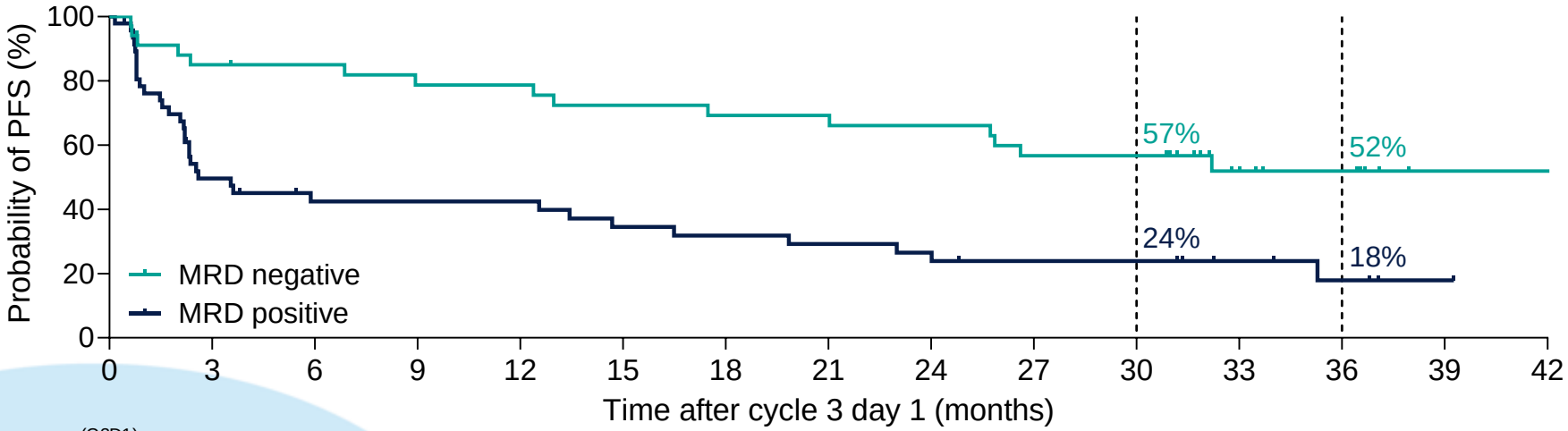
ASH 2024: MRD Analysis and correlation with PFS



(C3D1)

Number at risk

34	28	27	25	25	23	22	22	21	18	18	10	7	1	1
47	22	16	16	16	13	12	11	10	8	8	5	3	1	0

- Of 119 MRD-evaluable patients, 54 (45%) were MRD negative at any time
- In an exploratory landmark analysis, 98% (40/41) of MRD-evaluable patients were MRD negative at C13D1

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

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Efficacy of FDA approved CAR-T and BiAbs in R/R LBCL

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
Median F/U	60 months	60 months	40.3 months	36 months	36 months
ORR	83%	75%	52%	63.1%	52%
CR	54%	53%	40%	38.9%	39%
PFS	5.9 months	6.8 months	2.9 months	4.4 months	4.9 months
OS	25.8 months	27.3 months	11.1 months	18.5 months	NR

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *ASH meeting abstract* 2022, Vose J at Al. ASH meeting abstracts 2024

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Key Immune-Related Toxicities: CAR-T and BiAbs in LBCL

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
CRS (all grades)	93%	39%	58%	47.9%	63%
CRS $\geq$ 3	13%	1%	22%	2.5%	4%
ICANS (all grades)	64%	23%	21%	6.4%	8%
ICANS $\geq$ 3	28%	10%	12%	0.6%	3%

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *N Eng J Med* 2022.

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Bispecific Abs Combinations

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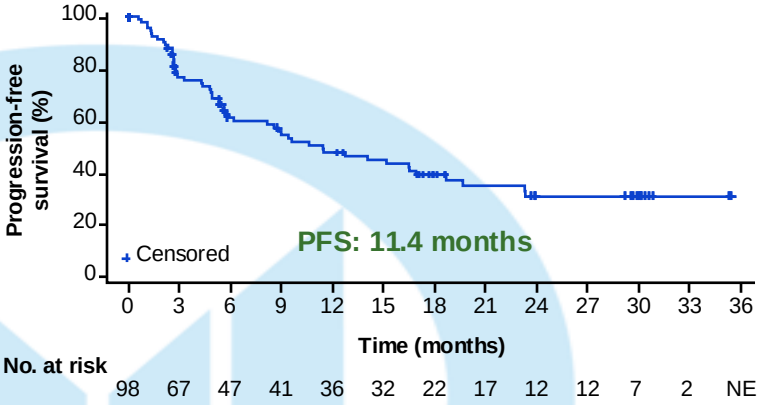
Combination of BiAbs seems to increase efficacy without increasing toxicity

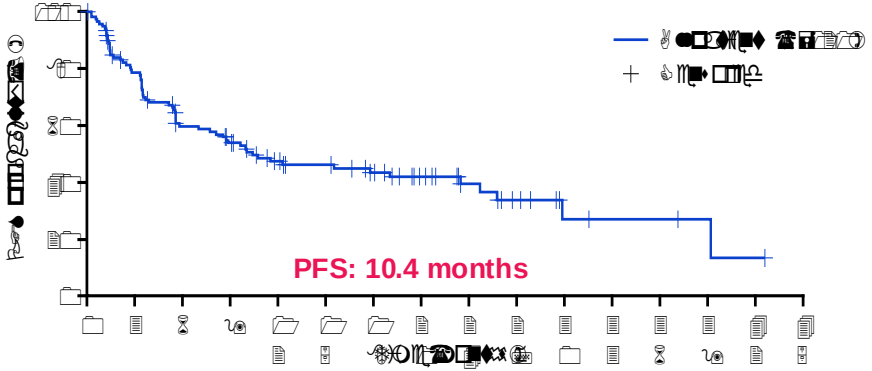
Mosunetuzumab - Polatuzumab

N= 98. Median F/U: 23.9 months
Median lines: 2 (1-8)
Post CAR-T: 35.7%
ORR= 63.5% CR= 51%
CRS all (G≥3)= 18.4% (3.1%)



Glofitamab - Polatuzumab

N= 121. Median F/U: 20.4 months
Median lines: 2 (1-7)
Post CAR-T: 22.4%
ORR= 80.2% CR= 59.2%
CRS all (G≥3)= 50% (0.8%)



Budde E, Chavez JC et Al. *Nat Medicine* 2023, Hutchings M et Al. ASH Meeting 2023

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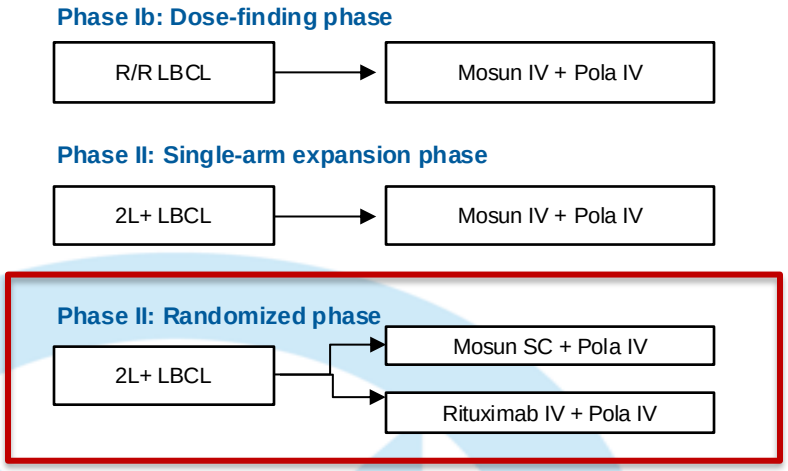
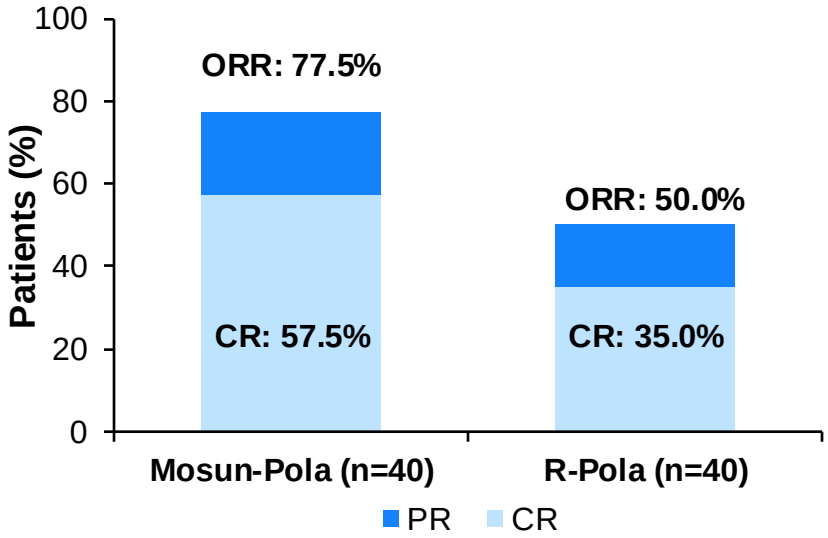
ASH 2024: Mosun (SC)-Polatuzumab vs Pola-R for R/R LBCL

Study schema





1. Budde LE, et al. Nat Med 2024;30:229–39;. 2. Chavez JC, et al. ASH 2024; Oral presentation .

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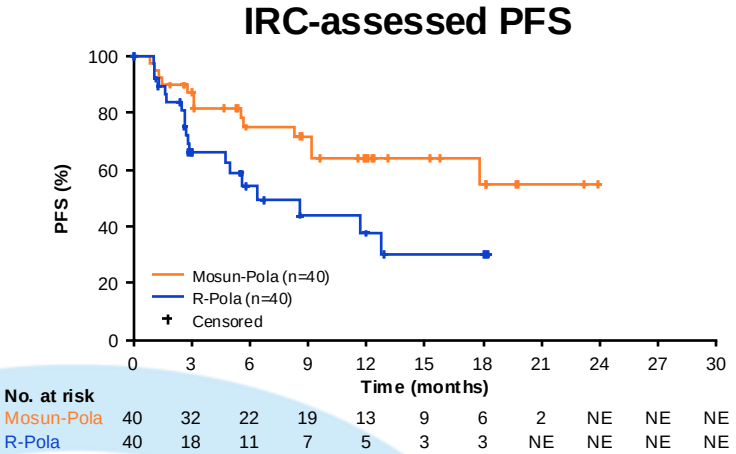
PFS and CRS: Mosun (SC)-Pola vs Pola-R



	Mosun-Pola (n=40)	R-Pola (n=40)
Median PFS*, months (95% CI)	NE (9.2–NE)	6.4 (4.7–NE)
Hazard ratio (95% CI), p-value*	0.45 (0.22–0.92), p=0.0250	
9-month event-free rate, % (95% CI)	71.7 (56.6–86.8)	43.8 (24.4–63.3)
12-month event-free rate, % (95% CI)	64.2 (47.4–80.9)	37.6 (17.4–57.7)

CRS by ASTCT criteria[1]	Mosun-Pola (n=40)
Any grade, n (%)*	4 (10.0)
Grade 1	3 (7.5)
Grade 2	1 (2.5)
Grade ≥3	0
Median CRS duration, days (range)	3 (2–5)
Median time to onset, days (range)	2 (2–3)
CRS management, n (%)	
Corticosteroids	4 (10.0)
Tocilizumab	1 (2.5)
Low-oxygen	1 (2.5)
Events resolved, %	100

Chavez JC, et al. ASH 2024; Oral presentation .

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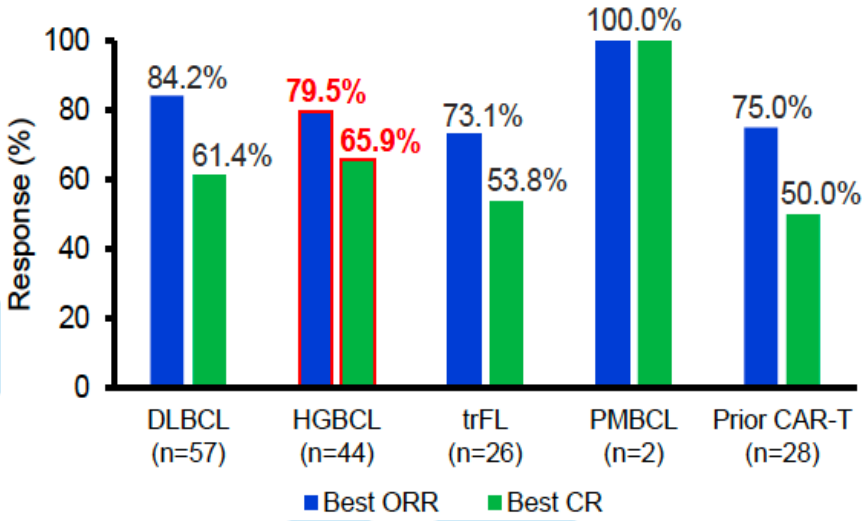
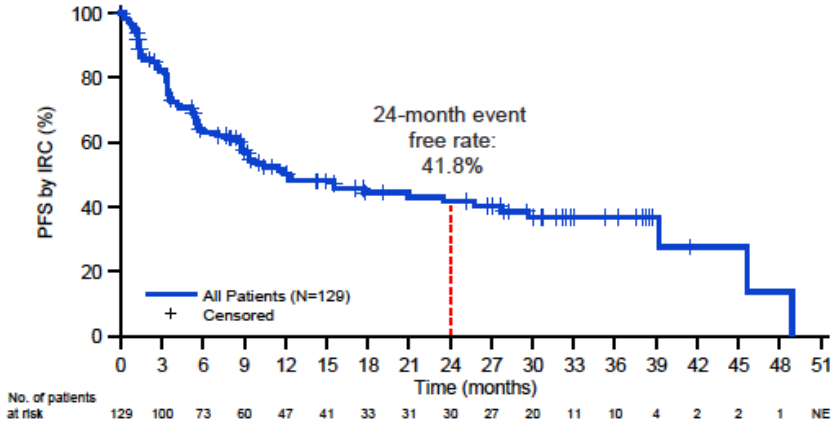
ASH 2024: Glofi-Pola in R/R LBCL, extended follow up





Median PFS: 12.3 months

Hutchings M, et al. ASH 2024; Oral presentation .

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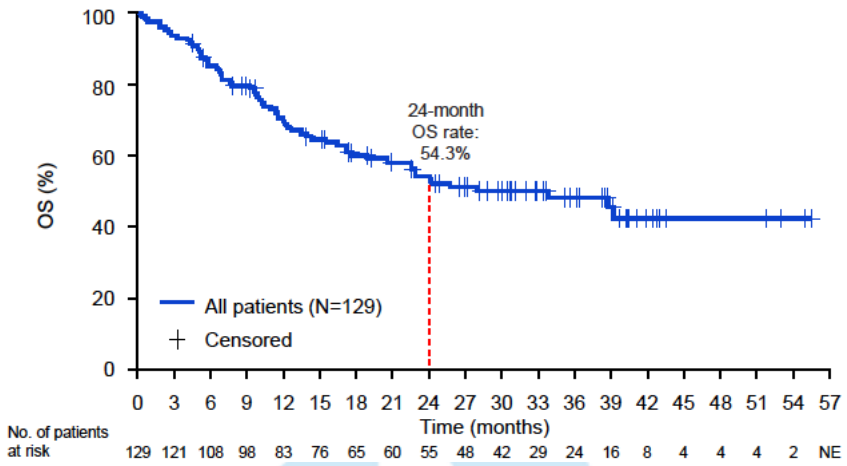
ASH 2024: Glofi-Pola in R/R LBCL, extended follow up: OS and CRS

Overall Survival: 2-y 50%



Median OS: 33.8 months

N (%)	N=126*
CRS by grade†	**56 (44.4)**
Grade 1	35 (27.8)
Grade 2	19 (15.1)
Grade 3	1 (0.8)
Grade 4	0
Grade 5	1 (0.8)‡
Median time to CRS after glofitamab dose, hours (range)	
2.5 mg	16.3 (5.4–42.1)
10 mg	34.6 (8.9–86.0)
30 mg	36.2 (18.5–55.9)
CRS management	
Tocilizumab	19 (33.9)
Corticosteroids	8 (14.3)
Fluids	13 (23.2)
Single pressor	2 (3.6)
Low flow oxygen	11 (19.6)
High flow oxygen	1 (1.8)
Intensive care unit	3 (5.4)

Hutchings M, et al. ASH 2024; Oral presentation .

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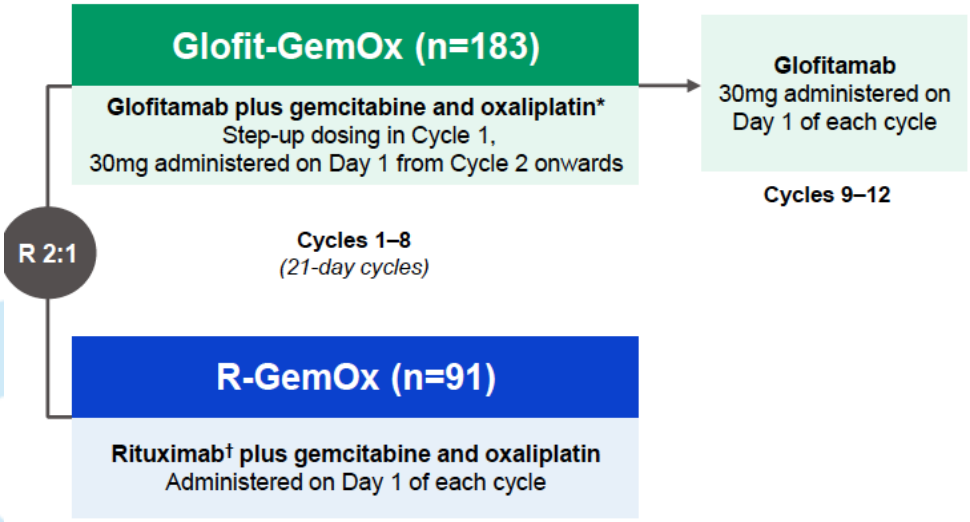
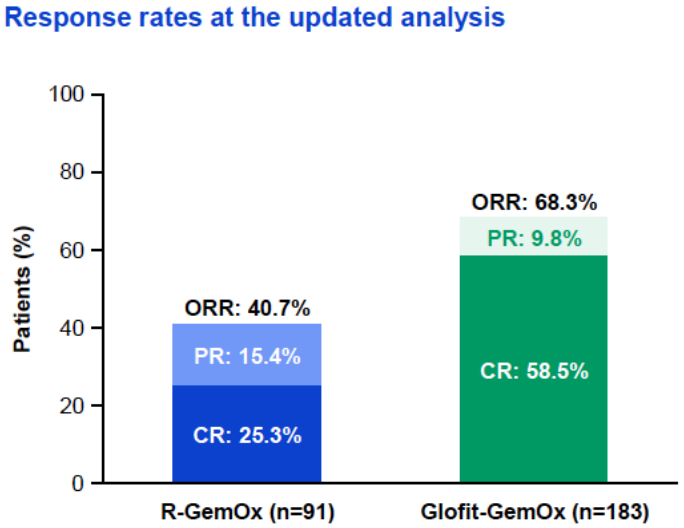
BiAbs in 2nd Line setting R/R LBCL: STARGLO

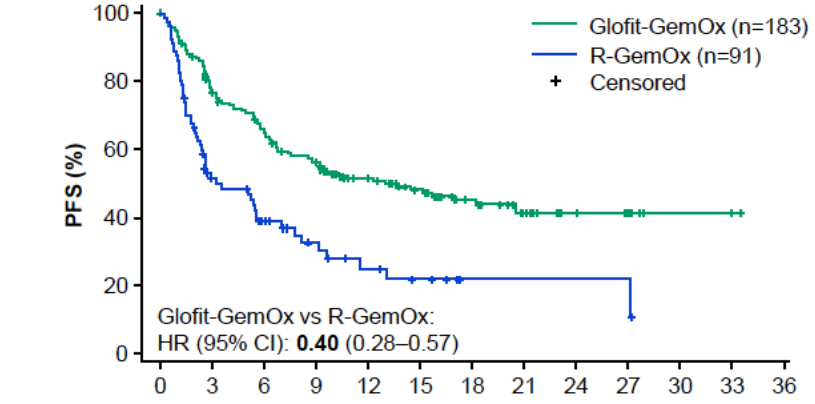




Abramson J et al. EHA 2024; Oral presentation, Abramson J et Al. Lancet 2024.

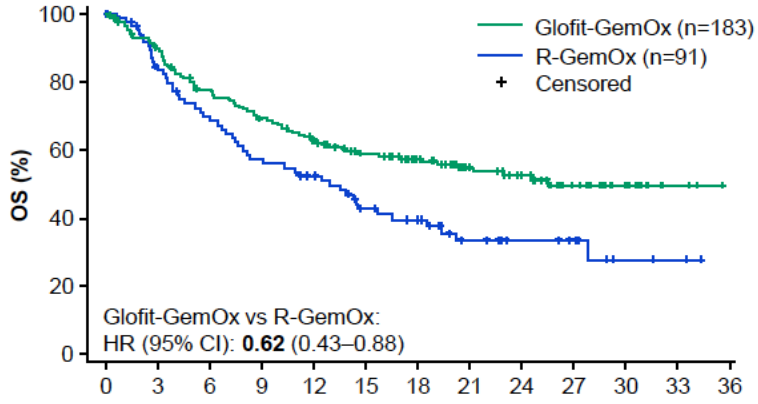
STARGLO: Glofi-GemOx vs GemOx for ASCT ineligible R/R DLBCL

Updated analysis



No. of patients at risk													
Glofit-GemOx	183	130	107	89	66	54	37	26	14	10	2	1	NE
R-GemOx	91	34	22	14	9	6	2	2	2	2	NE	NE	NE

Updated analysis



No. of patients at risk													
Glofit-GemOx	183	159	135	119	104	86	71	51	40	26	11	3	NE
R-GemOx	91	68	55	46	40	29	23	14	10	8	3	2	NE

Abramson J et al. EHA 2024; Oral presentation, Abramson J et Al. Lancet 2024.

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Is there a better combination?

	Mosun (SC)-Pola	Glofi-Pola	Glofi-GemOx
Median follow up	18 months	28.2 months	20.7 months
Stage III/IV	77.5%	76.7%	76.9%
HGBCL/DHL	25%	34.1%	NR
Median lines Rx	2 (1 – 5)	2 (1 – 7)	2 (1– 2)
Prior CART	35%	21.7%	7.1%
ORR% (CR%)	77.5 (57.5)	80.6 (62)	68.3 (58.8)
Median PFS	NE	12.3 months	12.1 months
CRS all % (G $\geq$ 3 %)	10 (0)	44.4 (1.6)	44.2 (2.3)

Chavez JC at Al. ASH 2024, Hutchings M et Al. ASH 2024, Abramson J et AL. Lancet 2024

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BiAbs in the frontline setting: DLBCL

- Glofi-R-CHOP
- Glofi-Pola-R-CHP
- Epco-R-CHOP
- Epco-Pola-R-CHP
- Mosunetuzumab in elderly
- Mosun-Pola in elderly
- Epcoritamab in elderly

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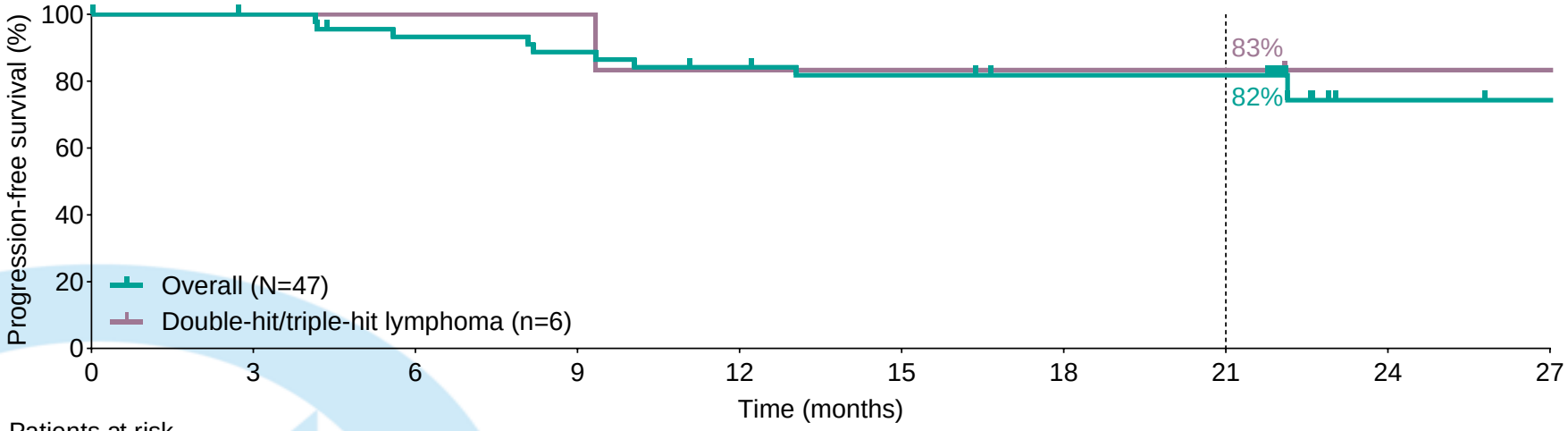
Epcoritamab + R-CHOP in high risk DLBCL (IPI 3-5/DHL): Progression-Free Survival (median F/U 22.9 months)



Patients at risk

47	45	41	39	36	34	32	32	16	15
6	6	6	6	5	5	5	5	3	3

Falchi L et Al. ASH 2024; Oral presentation .

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BiAbs are very effective post CAR-T relapse

Glofitamab

N Pts: 51 (33%)
ORR: NR
CR: 32%

Epcoritamab

N pts: 61(38.9%)
ORR: 54.1%
CR: 34.4%

Odronextamab

N pts: 41 (~33%)
ORR: 48%
CR: 30%

Dickinson M et Al. *N Eng J Med* 2022. Thieblemont C at Al. *J Clin Oncol* 2022, Crombie J at Al. ASH Meeting 2023

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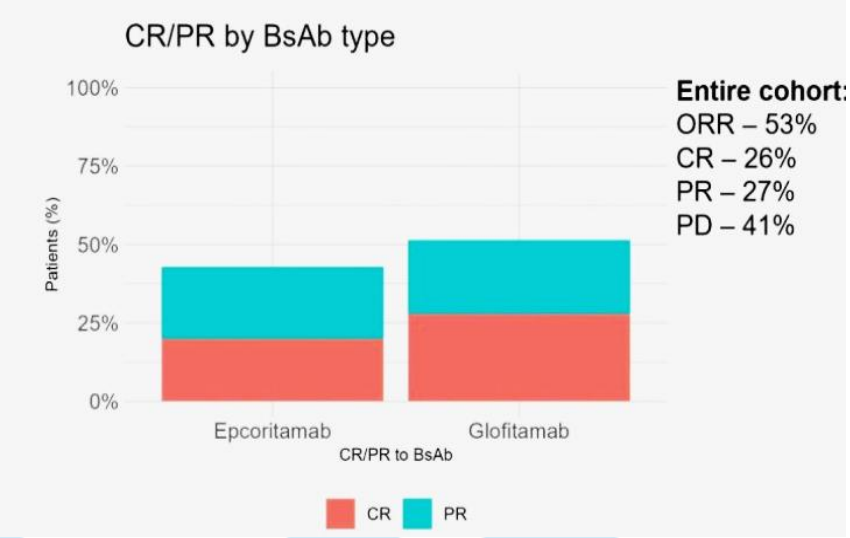
Real-Life Experience: Epcoritamab and Glofitamab (N= 208)



Glofitamab: 68
Epcoritamab: 140

CRS all grades: 39.2%
CRS $\geq$ 3: 4.5%
ICANS all grades: 11.5%
ICNAS $\geq$ 3: 2.9%

Brooks T et Al. ASH 2024; Oral presentation .

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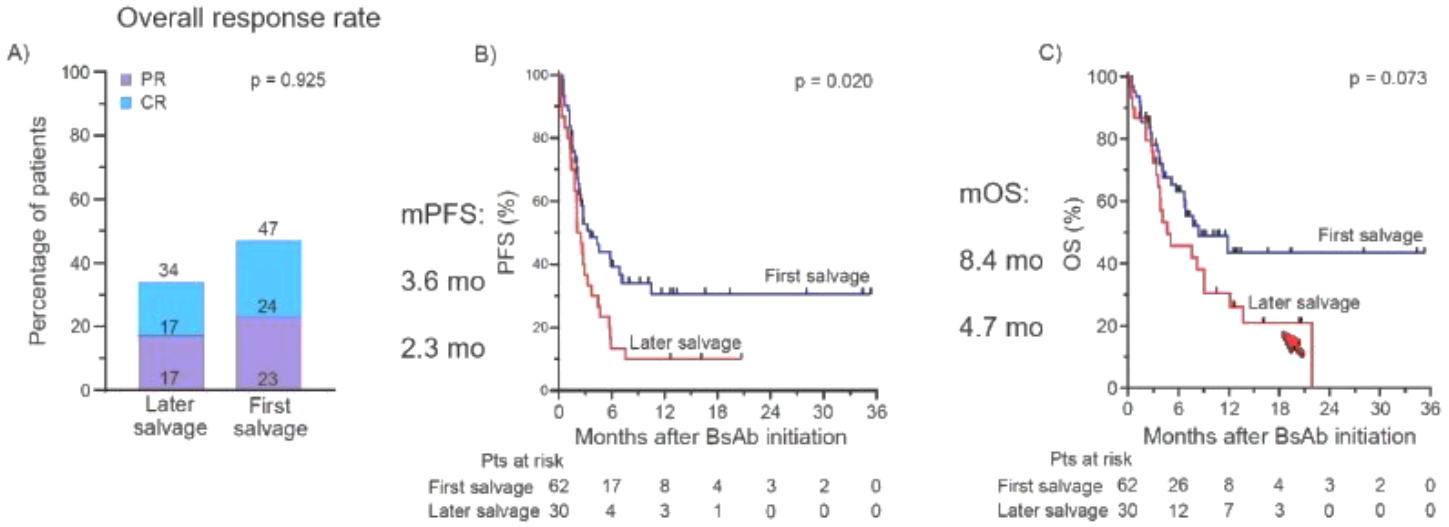
Efficacy of BiAbs according to timing and pattern of CAR-T relapse



Shumilov E et Al. ASH 2024; Oral presentation .

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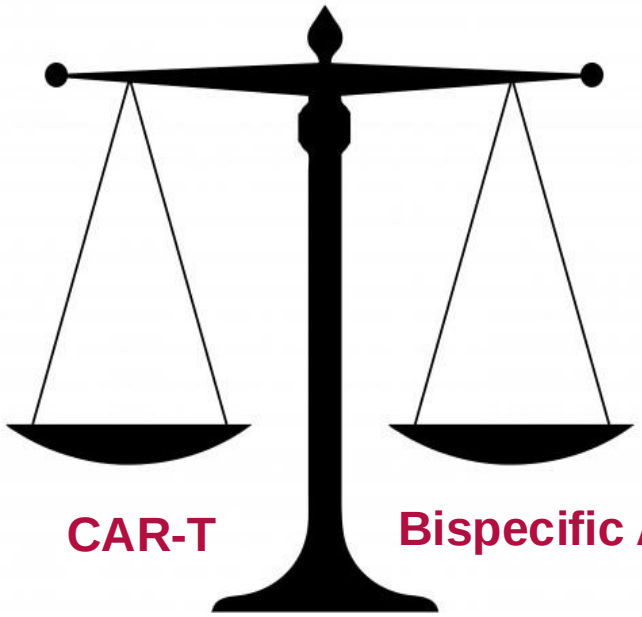
Choosing CAR-T vs BiAbs

- Curative: Long-term efficacy data (ZUMA-1: 5-years)
- OS benefit over SOC (ZUMA-7, TRANSFORM)
- One time treatment
- RWE confirms efficacy
- Higher frequency/severity CRS/ICANS
- Logistics (distance, caregiver)
- Manufacturing time/failure
- Other toxicities (cytopenias, infections)



- "Off the shelf"
- Similar efficacy
- Lower risk/severity CRS/ICANS
- Combination is more feasible and effective (mosun-pola, glofi-pola)
- Curative? Possible
- RWE confirms efficacy
- Repetitive dosing and indefinite (Epcoritamab)
- Specialized training still required

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