Bispecific Antibodies: Combination Strategies in LBCL: Relapsed/Refractory Disease and Beyond

Professor Mark Hertzberg AM
Department of Haematology
Prince of Wales Hospital and University NSW
Sydney, AUSTRALIA

Disclosures

Advisory:	Takeda, Roche, Specialised Therapeutics
Honoraria:	Roche, Janssen, Takeda
Stock:	nil

Relapsed/refractory Large B-cell Lymphoma

Defining the problem

Most R/R DLBCL manifest early and are often ineligible for and/or can't complete intensive regimens → dismal survival (n=769)

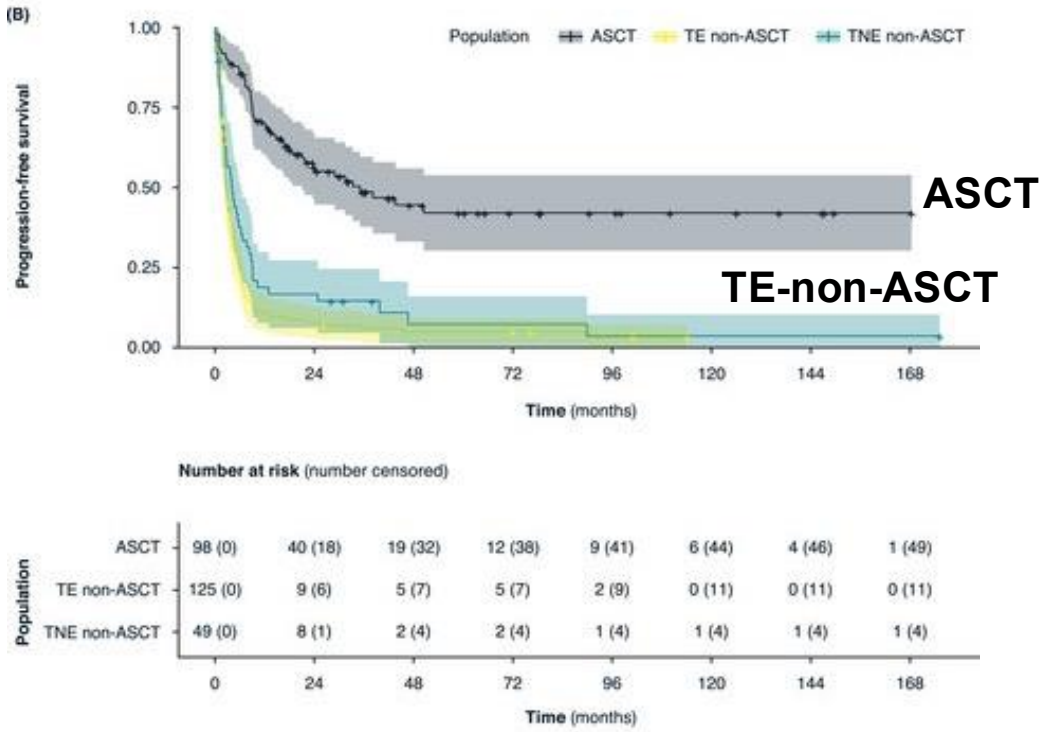
N = 769 R/R LBCL patients	All	< 70 yrs	≥ 70 yrs
Intensive chemoRx (IC) for ASCT	35%	63%	9%
Proceeded to ASCT		34%	
Remission-inducing chemoRx	28%	18%	36%
Palliative therapies	20%	8%	31%
Unfit for any active therapies	18%	11%	24%

- Early relapse ≤ 12 m was strongly associated with selection of less intensive treatment and poor survival

A minority of pats ≤ 76 yrs (35%, n=178/506) actually fitted CAR T-cell trial criteria and also did poorly, thereby providing a benchmark for efficacy of novel therapies in future trials

Harrysson S et al Brit J Haem 2022;198:267–277

Real-world outcomes of patients with RelRefr- LBCL receiving 2nd-line therapy in England (n=299)



N=299	ASCT	ASCT-eligible, but no ASCT	ASCT-ineligible
No. (27 excluded)	98 (32.8%)	125 (41.8%)	49 (16.4%)
Med PFS	35.2 m	2.7 m	4.3 m

Considering the large proportion of patients (42%) who were eligible for ASCT yet unable to receive it, this represents a significant unmet need.

Fox C et al eJHaem; 2024;5:992–997

Why Many Patients Do Not Reach ASCT or CAR-T in 2L

ASCT:

- Prognosis is particularly poor for ASCT-ineligible patients, those who fail salvage therapy, and/or progress/relapse following 2L therapy
- Requires good ECOG PS, favourable organ function, and chemo-sensitivity (seen in only ~40-50%)

CAR-T:

- Approved in 2L PrRefr / Early relapse ≤ 12 m: but access, leukapheresis, logistical, and manufacturing barriers remain
- Patient-related CAR-T barriers: age >75, ECOG ≥2, organ dysfunction, 4–6 week wait, tumour burden and disease kinetics; and only Axi-cel at present in 2L in Australia

→ Large 'gap' population needs off-the-shelf, rapidly deliverable therapy

Ref: 1. Harrysson S et al. Br J Haematol 2022; 2. Abramson et al. ASH 2025; 3. Van Imhoff GW et al. J Clin Oncol 2016; 35:544-551; 4. Fox C et al eJHaem; 2024;5:992–997

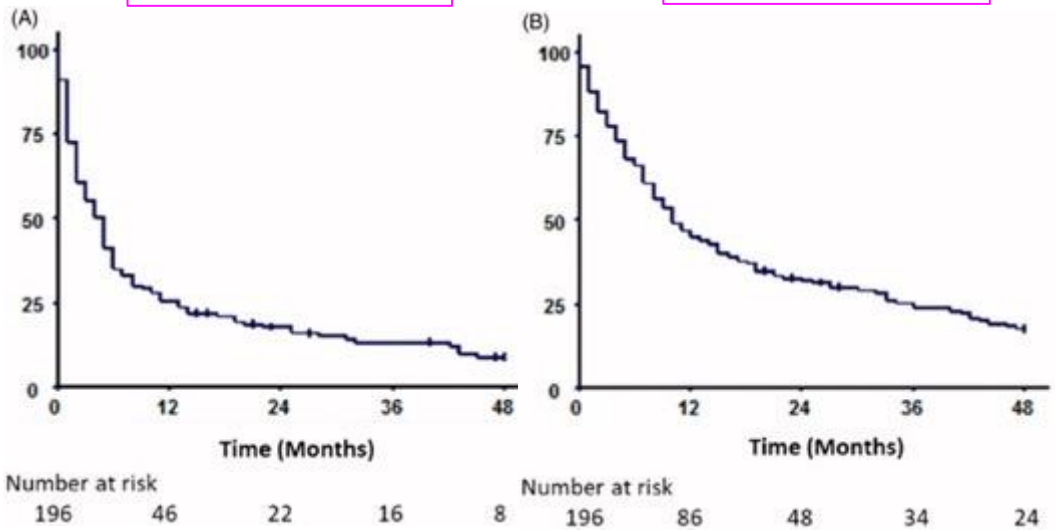
In Transplant-Ineligible and CAR-T-Unsuitable Patients Standard Options Deliver Limited Outcomes

- R-GemOx: until recently the most widely used 2L regimen in transplant-ineligible R/R-LBCL pats
- ORR ~45–55%; CR ~20–30%
- Median PFS ~3–5 mo; median OS ~6–10 mo
- Poor outcomes especially in:
  - Primary refractory and early relapsed (≤ 12 m) disease
  - 2° IPI > 2
  - DH / HGBL

→ No established standard of care with curative intent

PFS: med 5 m

OS: med 10 m



- N = 196; median age = 72 yrs (24-89), 57% refractory to the last treatment
- Gde 3-4 hematological toxicities in 31%

Ref: Cazelles C et al. Leuk Lymphoma 2021;62(9):2161–2168; Caserta S et al. Eur J Haematol 2026

Large B-cell Lymphoma

Bi-specific Antibodies: Combination strategies

Combination Strategies Using Bispecific Antibodies with either chemotherapy and/or ADCs in 2L LBCL

Trial Regimens	Phase	Status
Glofitamab-GemOx *vs* R-GemOx (STARGLO)	**Ph 3**	**Data available**
Glofitamab and R-ICE	Ph 2	Data available
Glofitamab + Polatuzumab	Ph 1b / Ph 2	Data available
Mosunetuzumab + Polatuzumab	Ph 1b / 2	Data available
Mosunetuzumab + Polatuzumab *vs* R-Pola	Ph 2 rand.	Data available
Mosunetuzumab + Polatuzumab *vs* R-GemOx (SUNMO)	**Ph 3**	**Data available**
Polatuzumab + R-GemOx *vs* R-GemOx (POLARGO)	**Ph 3**	**Data available**

Ref: Abramson, et al. Proc ASH 2025; Kim WS et al. ASH 2024 (NHL-2); Budde E et al J Clin Oncol 2025;20;43(36):3799-3811; Sancho J-M et al ICML 2025; Matasar M et al J Clin Oncol 2026

Epcoritamab Combination Therapy in 2L LBCL

Study / Arm	Regimen	Phase	Status
DLBCL-1	**Epcoritamab vs R-GemOx** or BR	Ph 3	Active
DLBCL-4	Epcoritamab + lenalidomide vs R-GemOx	Ph 3	Active
NHL-2 Arm 4	**[2]Epcoritamab + R-DHAX (pre-ASCT)**	Ph 1b/2	Data available
NHL-2 Arm 5	**[1]Epcoritamab + GemOx (transplant-ineligible)**	Ph 1b/2	Data available
NHL-2 Arm 10	**Epcoritamab + R-ICE (transplant-eligible)**	Ph 1b/2	Ltd data available

1. Brody JD et al Blood 2025; 145(15);1622-1630; 2. Abrisqueta P et al Haemasphere 2026 ahead of print;

STARGLO: Randomised Phase III trial in patients with R/R DLBCL

Phase 3, open-label, randomised trial

Patients with R/R DLBCL (N=274)

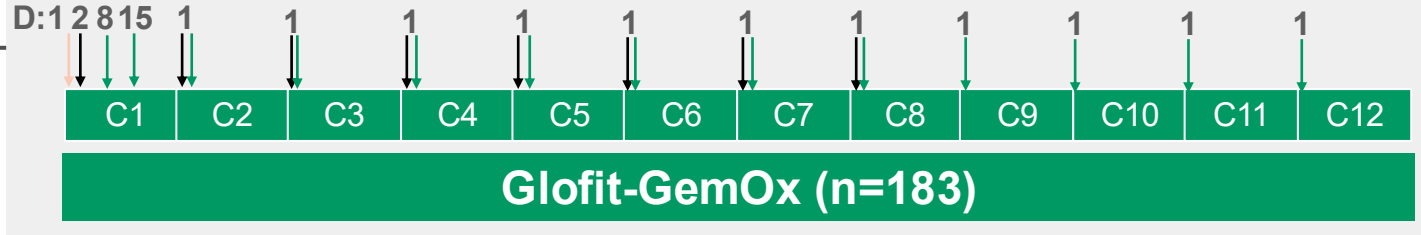
- R/R DLBCL NOS after ≥1 prior systemic therapy
- Patients with one prior line must be transplant ineligible
- ECOG PS 0–2

Stratification factors

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

R 2:1

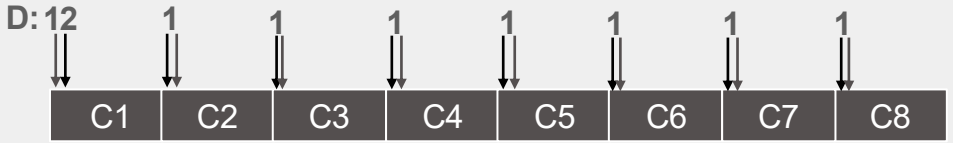
Glofitamab (C1 SUD;* 30 mg C2–12)
Gem (1000 mg/m²) + Ox (100 mg/m²)
Gpt (1000mg)



Glofit-GemOx (n=183)

21-day cycles

Rituximab (375 mg/m²)
Gem (1000 mg/m²) + Ox (100 mg/m²)



R-GemOx (n=91)

	STARGLO Ph 3
After 1L Rx, n (%)	115 (62.8%)
Prior CAR-T	7%
Median age	68 (58-74) yrs
Prim refr, n (%)	106 (58%)
Late relapse >12 m	31 (26.9%)

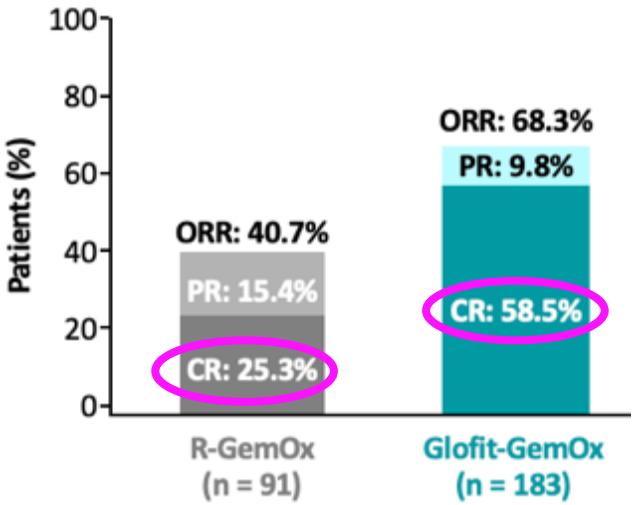
Baseline Characteristics:

- ~30% ECOG PS 2; ~20% transformed FL
- Arms well-balanced at baseline

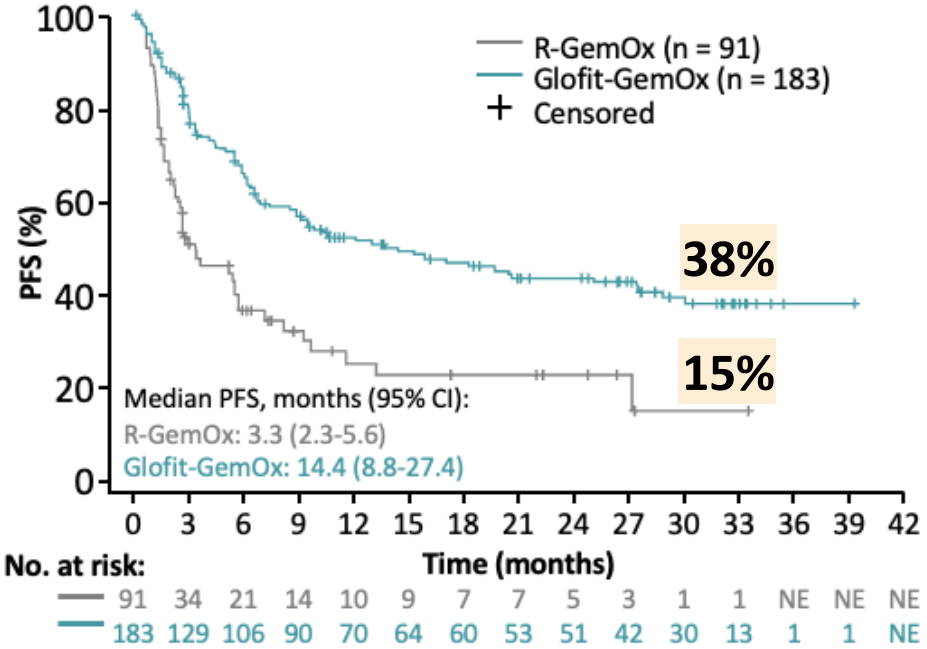
Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438);
Abramson JS, et al. Lancet 2024;404(10466, Suppl).

Glofit-GemOx improves response, PFS & OS at 3-yr follow-up

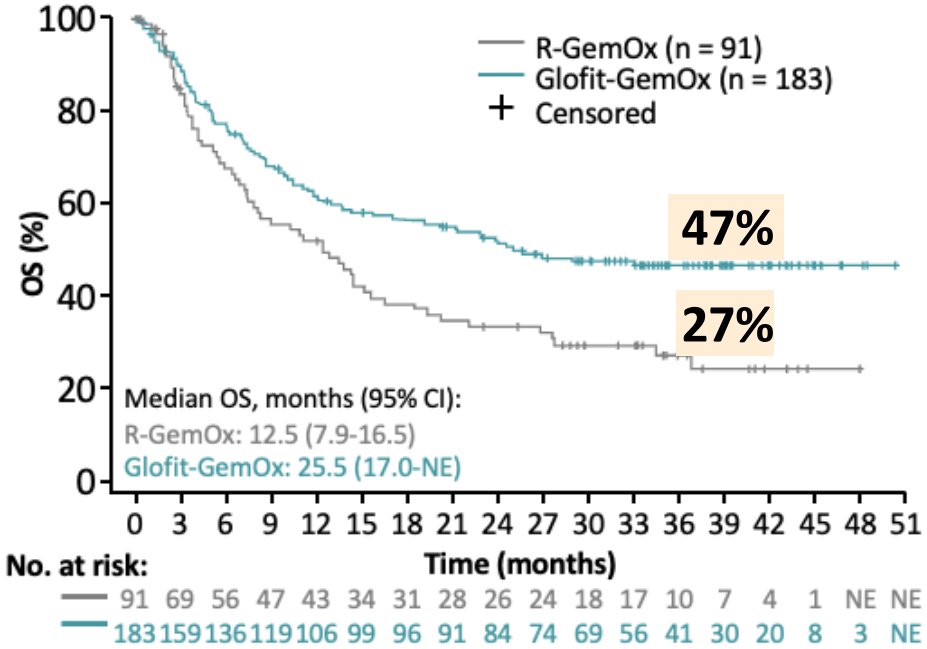
Response



3-yr PFS



3-yr OS



CRS, n (%)	Glofit-GemOx n=172
Any grade	77 (44.8)
Grade 1	55 (32)
Grade 2	18 (10.5)
Grade 3	4 (2.3)

n (%)	R-GemOx (n=88)	Glofit-GemOx (n=180)
ICANS	NA	4 (2.3)
Grade ≥3	NA	1 (0.6)
Infections, any	26 (29.5)	95 (55.2)
Grade ≥3	8 (9.1)	26 (16.9)
Grade 5	3 (3.4)	6 (3.5) †

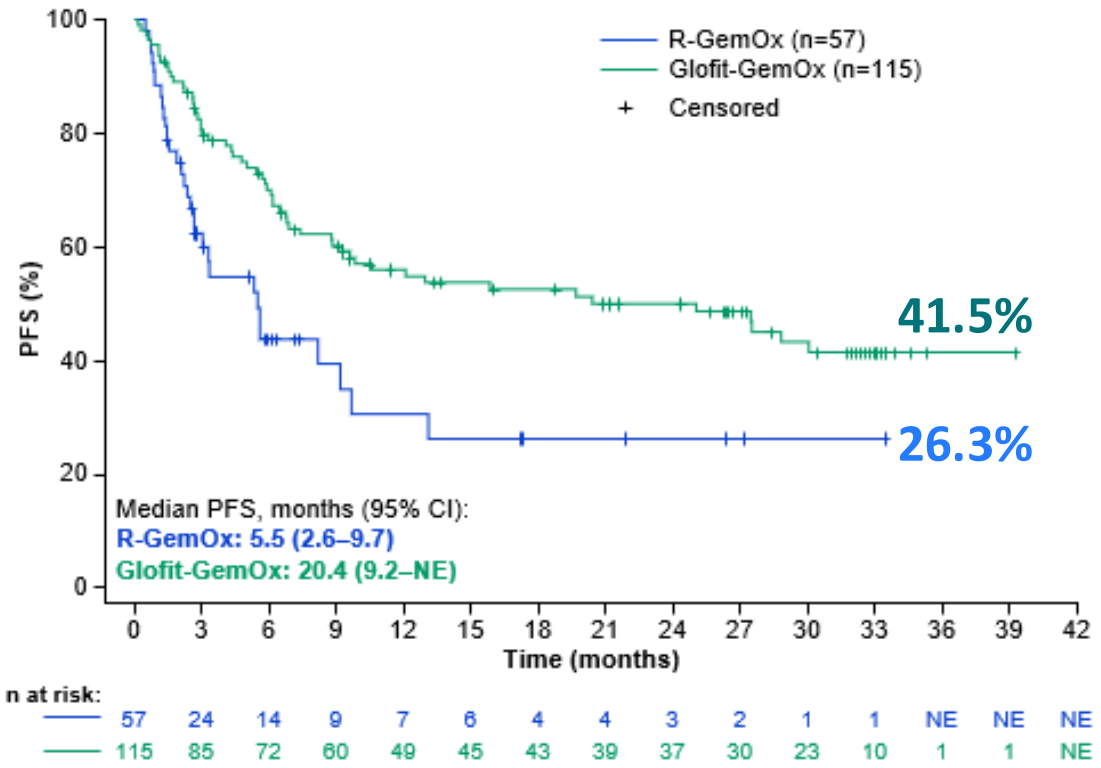
†3 patients had COVID-19, 1 patient had a respiratory tract infection (COVID-19 associated), 1 patient had pneumonia, and 1 patient had septic shock.

Lancet 2024;404(10466, Suppl ; Abramson J et al. Proc ASH 2025.

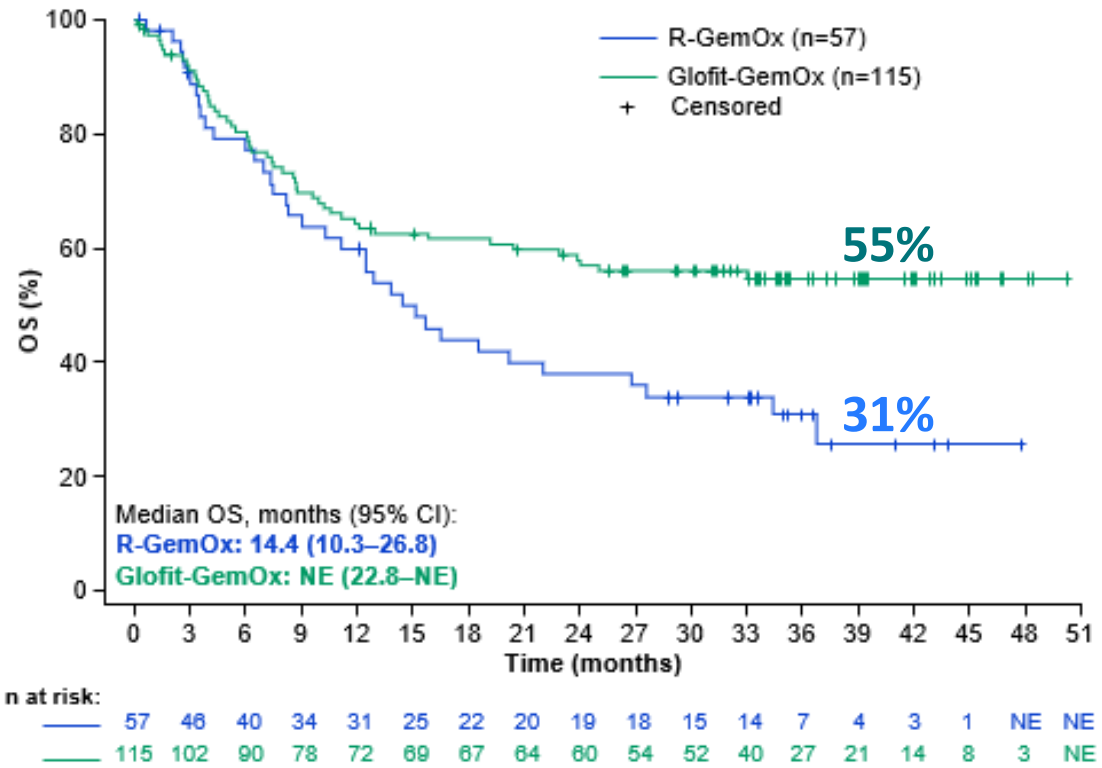
Glofit-GemOx is particularly effective in 2nd line patients

Complete Response Rate	
Glofit-GemOx (63% pats)	63.5%
R-GemOx (63% pats)	28.1%

3-yr PFS



3-yr OS



Lancet 2024;404(10466, Suppl ; Abramson J et al. Proc ASH 2025.

Ph 2 trial: Epcoritamab + GemOx in R/R-LBCL ASCT-ineligible: EPCORE NHL-2 Arm 5 (n=103)

Study Design

Phase 1b/2 EPCORE® NHL-2 Arm 5

Key Inclusion Criteria

- R/R CD20$^+$ DLBCL[a]
  - DLBCL, NOS
  - Double-hit or triple-hit DLBCL
  - FL grade 3B
  - T-cell/histiocyte-rich DLBCL
- Ineligible for ASCT (due to age, performance status, or failure of prior ASCT)

[a]De novo or histologically transformed from FL or nodal marginal zone lymphoma based on World Health Organization 2016 classification.

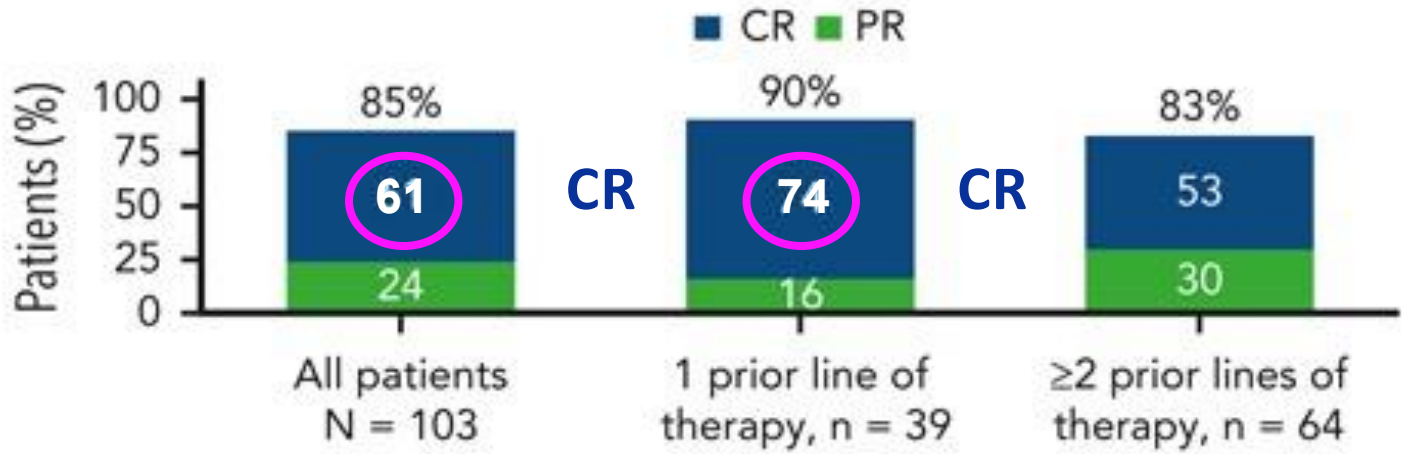
Treatment regimen: Epcoritamab SC 48 mg + GemOx IV

Agent	C1	C2	C3	C4	C5–9	C10+
Epcoritamab	QW	QW	QW	Q2W	Q2W	Q4W
Gemcitabine	Q2W					
Oxaliplatin						

	Ph 2 Trial
After 1L Rx, n (%)	39 (38%)
Prior CAR-T	28%
Prim refr, n (%)	54 (52.4%)

Key Results

Efficacy



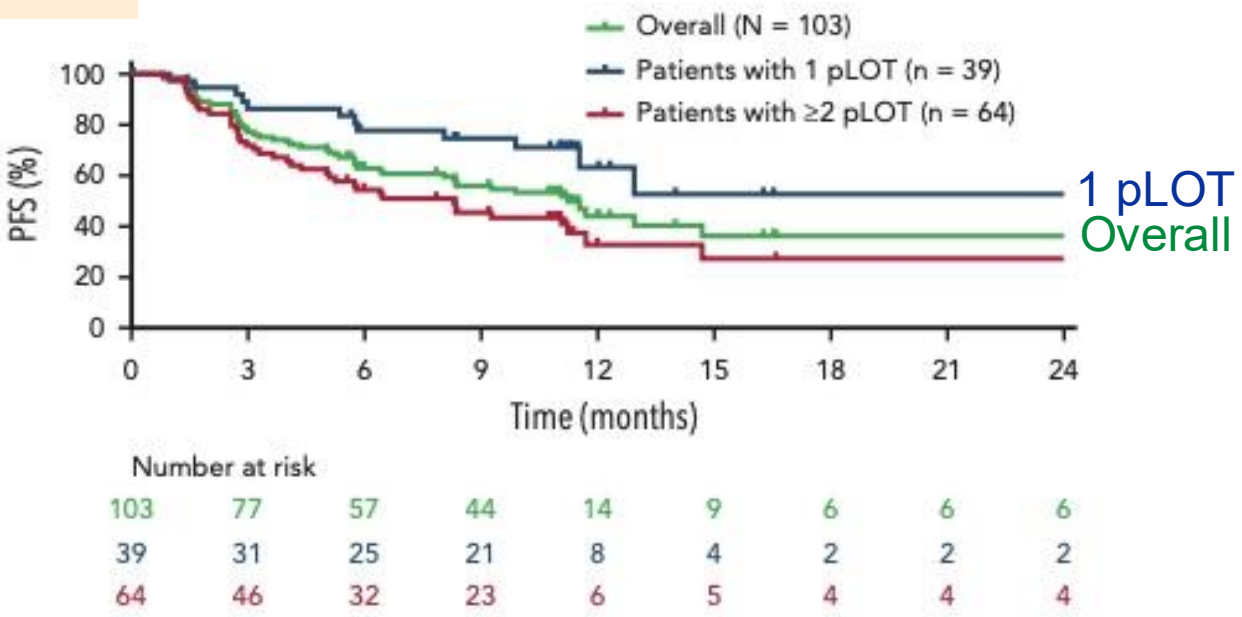
- Median DOCR was 23.6 months

Brody JD et al Blood 2025; 145(15);1622-1630

Epcoritamab + GemOx in R/R-LBCL ASCT-ineligible: EPCORE NHL-2 Arm 5 (n=103)

- Median duration of Rx = 8.3 m; median f/up = 25.1 m
- 32/59 who ceased Rx did so due to PD of whom 30 were on epcoritamab

PFS



Outcome	
Overall median PFS	11.2 m
1 prior LOT 12 m PFS	63.2%
Overall median OS	21.6 m
1 Prior LOT 12 m OS	69.1%

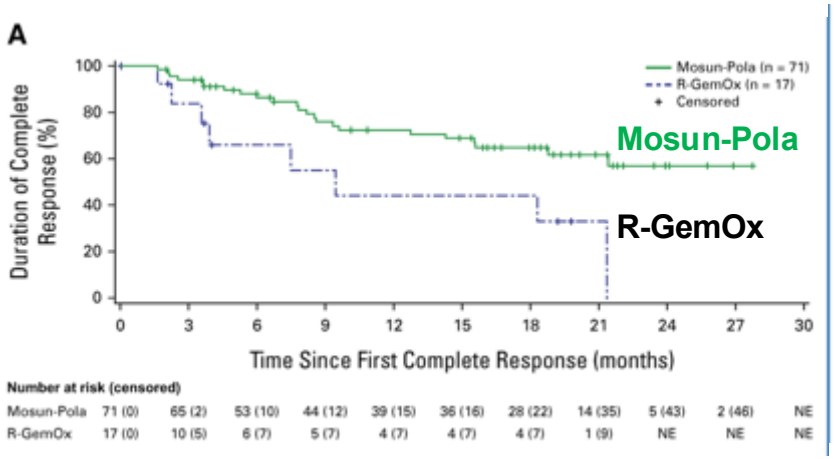
Adverse Events	Frequency
Gde ≥ 3 neutropenia	57%
Gde ≥ 3 thrombocytopenia	59%
Gde ≥ 3 anaemia	43%
Gde ≥ 3 infection	29%
Gde 5 events*	13%

*Mostly COVID-19 / other infectn

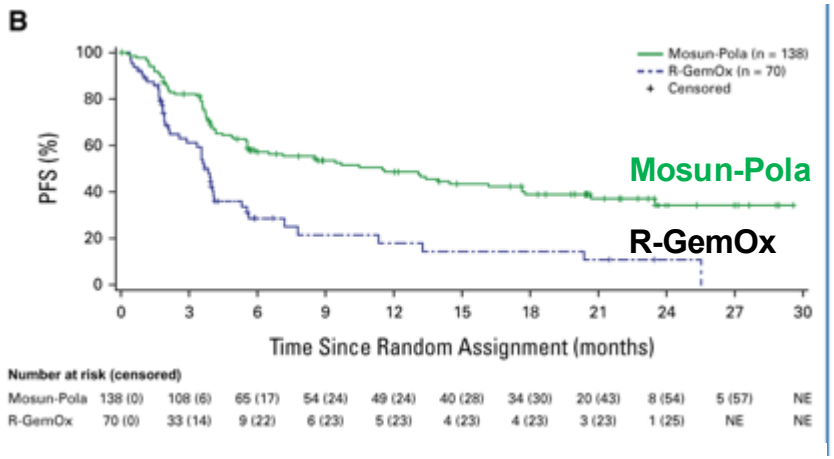
Brody JD et al Blood 2025; 145(15);1622-1630

Phase III SUNMO trial of BiSp Ab Mosunetuzumab + Polatuzumab: Interim analysis showed prolonged PFS and OS *vs* R-GemOx (n=208)

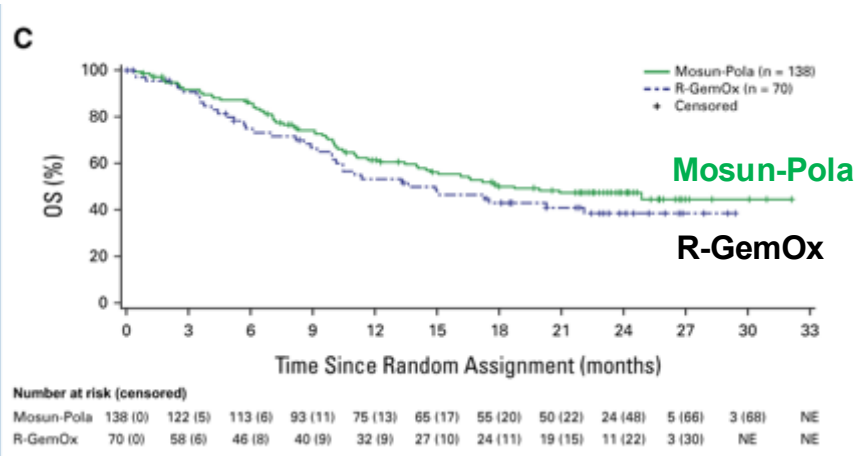
DoCR



PFS



OS



med f/up 23.2 m	Mosun-Pola	R-GemOx	HR
n	138	70	
Prior LOT 1 / 2	44% / 41%	43% / 36%	
PrRef / Early Rel	72%	76%	
ORR	70%	40%	P < 0.0001
CR	51%	24%	
Median PFS	11.5 m (5.6-18)	3.8 m (2.9-4.1)	0.41 (0.3-0.6) P<0.0001
CRS ≥ gde 2	< 5%	n/a	
Median OS	18.7 m	13.6 m	

Budde E et al J Clin Oncol 2025;20;43(36):3799-3811

Relapsed/Refractory Large B-cell Lymphoma

ASCT-ineligible: Bispecific combinations and CAR-T

Trials of CAR-T and BiSp Ab Combinations in ASCT-ineligible patients

- The 2L treatment landscape for ASCT-ineligible patients with Primary Refractory or Early Relapse LBCL has not been addressed in ph 3 trials
- Structural impossibility of head-to-head RCT
- Only indirect comparisons are available:

➢ CAR-T: **ALYCANTE** and **PILOT** phase 2 studies of CAR-T

➢ BiSp antibody combinations: **STARGLO** phase 3 and **EPCORE NHL-2** phase 2 trials

Dimou M and Vassilakopoulos TP Brit J Haem 2026; ahead of print

Trials of CAR-T and BiSp Ab Combinations in ASCT-ineligible patients

	ALYCANTE Ph 2	PILOT Ph 2	STARGLO Ph 3	EPCORE NHL-2 Ph 2
Intervention	Axi-cel	Liso-cel	Glofit-GemOx	Epcor-GemOx
Population	R/R LBCL ≤ 12 m 1LoT	R/R LBCL after 1LoT	R/R LBCL	R/R LBCL
Patients, n	69 (leuk 62)	74 (leuk 61)	183	105
After 1L Rx, n (%)	62 (100%)	61 (100%)	115 (62.8%)	39 (37.9%)
Prior CAR-T	NA	NA	7%	28%
Median age	70 (49-81)	74 (53-84)	68 (58-74)	73 (40-86)
Prim refr, n (%)	38 (55%)	33 (54%)	106 (58%)	54 (52.4%)
Late relapse >12 m	1 (1%)	15 (25%)	31 (26.9%)	NA
Median f/up (m)	24 m	18.2 m	35.1 m	13.2 m
Median OS; rate	NR; 2-yr 70.8%	NR; 1.5-yr 59%	19.2 m; 2-yr 56%; 3-yr 50%	NR; 1-yr ~69%
Median PFS; rate	11.8 m; 2-yr 46.8%, 3-yr 34%; 3 late events	9.0 m; 1-yr 47%, 1.5-yr 43%	9.2 m; 1-yr 50%, 2-yr 45% ? plateau	NR; 1-yr 63.2%
ORR/CR	90.3%/79%	80%/54%	NA/56.0%	87%/74%
CRS (any/Gr ≥3)	94% / 8%	38% / 2%	44.8% / 2.3%	52% / 1%
ICANS (any/Gr ≥3)	52% / 15%	31% / 5%	2.1% / 0.5%	2.9% / 1%
NRM, n (%)	6 (9.7%)	6 (9.3%)	15 (8%)	13 (13%)

Dimou M and Vassilakopoulos TP Brit J Haem 2026; ahead of print

Summary of Trials of CAR-T and BiSp Ab combinations in ASCT-ineligible patients

- Biologically aligned albeit indirect cross-trial comparisons focused on the same setting
- All included a substantial % of 2L ASCT-ineligible patients
- These have a similar % of Primary Refractory / Early Relapsed (PrR / ER) disease = 52-55%
- Comparable responses; broadly similar PFS and OS in these ASCT-ineligible R/R LBCL pats
- BUT: comparisons are complicated by NRM interpretations esp in the COVID-19 era

Note:

- CAR-T trials may inherently include a biologically more favourable group
- Even with bridging Rx those getting to infusion are more likely fit with outcomes more favourable than more frail pats with biologically similar disease

Dimou M and Vassilakopoulos TP Brit J Haem 2026; ahead of print

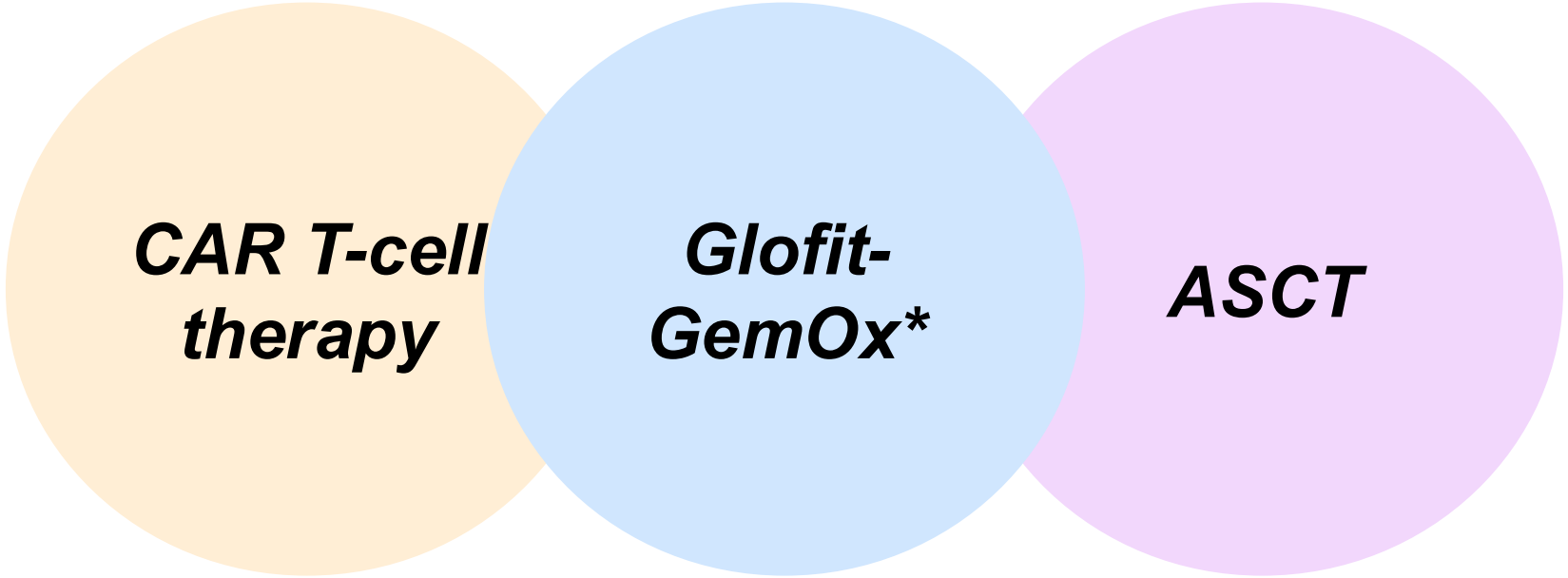
Factors to Consider When Selecting treatment in 2L DLBCL

	CAR T-cell therapy	Glofit-GemOx (or *Epco-GemOx)
Patient eligibility	Often aligned w transplant-eligible populations[1]	**Includes ASCT-ineligible populations[2]**
Disease kinetics impact	Rapid progression may prevent infusion[3]	**Less relevant due to accessibility[4]**
Manufacturing, coordination, logistics	Complex (leukapheresis, manufacture, transport, infusion)[3]	**Off-the-shelf[4]**
Treatment Centres	Specialised centres[3]	**Broad access[4]**
Patient preference	One-time infusion albeit with possible delays[3]	**Fixed-duration-up to 12 cycles; immediately available[4]**
Social/geographic factors	Need to live close to treatment centre with a caregiver for up to a month[3]	**Less relevant given accessibility[4]**
Toxicity	CRS and ICANS; need specialized monitoring[5]	**CRS (often low grade); minimal ICANS[4,5]**
Cost effectiveness	May not be cost-effective vs autoSCT[7]	**Predicted cost lower than other therapies[8]**
Reimbursement	Variable; transplant-eligible in 2L[9,10]	**Variable[1, 11]**

*Not reimbursed in Australia

1. Shadman M et al Transplant Cell Ther 2026;32: 277*87; 2. Thieblemont C et al Hemasphere 2025;9e70207; 3. Nze C and Flowers CR; ASH educ 2023; 382-85; 4. Abramson JS et al Lancet 2024;404;1940-54; 5. Ferreri CJ and Bhutani M Front Oncol 2024;14:13965490; 6. Abramson JS et al ASH 20255519a; 7. Loftus TJ et al J Med Econ 2025;28:2216-35; 8. Fox D et al ASH 2024;3646a; 9. Tan YZ et al J Med Econ 2026;29:481-97; 10. NICE Technology appraisal guidance www.nice.org; 11. NICE Tachnology appraisal guidance www.org.uk/guidance

Selecting the right treatment for the right patient in 2L+ LBCL



Among patients who are not intended for CAR T-cell therapy *or* ASCT
→ *Glofit-GemOx may address unmet needs

*Potentially Epco-GemOx

Randomised Phase III Frontline DLBCL/LBCL Trials

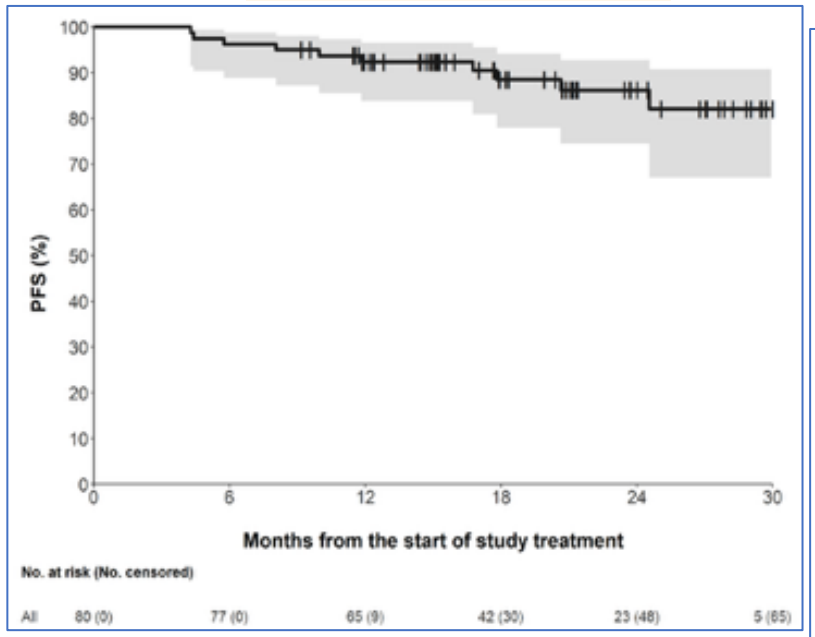
Qualls et al. Blood 2025 + recent additions

Trial	Agent / strategy	Experimental arm	Control	IPI / selection	N	NCT
1. General frontline trials						
POLARIX	ADC	Pola-R-CHP	R-CHOP	IPI 2–5	879	NCT03274492
frontMIND	anti-CD19 mAb + IMiD	Tafasitamab + lenalidomide + R-CHOP	R-CHOP	IPI 3–5; aaIPI 2–3 if ≤60	899	NCT04824092
SKYGLO	CD20×CD3 bispecific	Glofitamab + Pola-R-CHP	Pola-R-CHP	IPI 2–5	1,130	NCT06047080
EPCORE DLBCL-2	CD20×CD3 bispecific	Epcoritamab + R-CHOP → epcoritamab	R-CHOP → rituximab	IPI ≥2	900	NCT05578976
OLYMPIA-3	CD20×CD3 bispecific	Odronextamab + CHOP	R-CHOP	IPI ≥2 (part 2)	904	NCT06091865
ZUMA-23	CAR-T	Axi-cel	R-CHOP or DA-EPOCH-R	IPI 3–5	300	NCT05605899
2. Molecular / biomarker-directed trials						
Tucidinostat / DEB	HDAC inhibitor	Tucidinostat + R-CHOP	R-CHOP	MYC/BCL2 double-expressor	423	NCT04231448
ESCALADE	BTK inhibitor	Acalabrutinib + R-CHOP	R-CHOP	non-GCB DLBCL	611	NCT04529772
GUIDANCE-02	genomically selected	Genomically selected R-CHOP-X	R-CHOP	IPI 2–5 or IPI 1 + bulky	1,100	NCT05351346
BELIEVE-01	BTK inhibitor	Orelabrutinib + R-CHOP	R-CHOP	MCD subtype	150	NCT05234684
ENGINE-1	PKCβ inhibitor	Enzastaurin + R-CHOP	R-CHOP	IPI 3–5; primary DGM1+	256	NCT03263026
3. Older / frail patient trials						
POLAR BEAR	ADC	Pola-R-miniCHP	R-miniCHOP	≥80 y or frail ≥75 y	300	NCT04332822
SWOG S1918	hypomethylating agent	R-miniCHOP + oral azacitidine	R-miniCHOP	Age ≥75 y	422	NCT04799275
PEARL (ZR2)	BTK inhibitor / lenalid	Zanubrutinib + rituximab + lenalidomide	R-miniCHOP	Unfit / frail older patients	280	NCT05179733
ARCHED	BTK inhibitor	R-miniCHOP + acalabrutinib	R-miniCHOP	>80 y or 60–80 y unfit	330	NCT05820841
4. Recent additions beyond Qualls 2025						
GOLSEEK-1	CELMoD	Golcadomide + R-CHOP	Placebo + R-CHOP	IPI 2–5	850	NCT06356129
waveLINE-010	ROR1 ADC	Zilovertamab vedotin + R-CHP	R-CHOP	Untreated DLBCL	1,046	NCT06717347

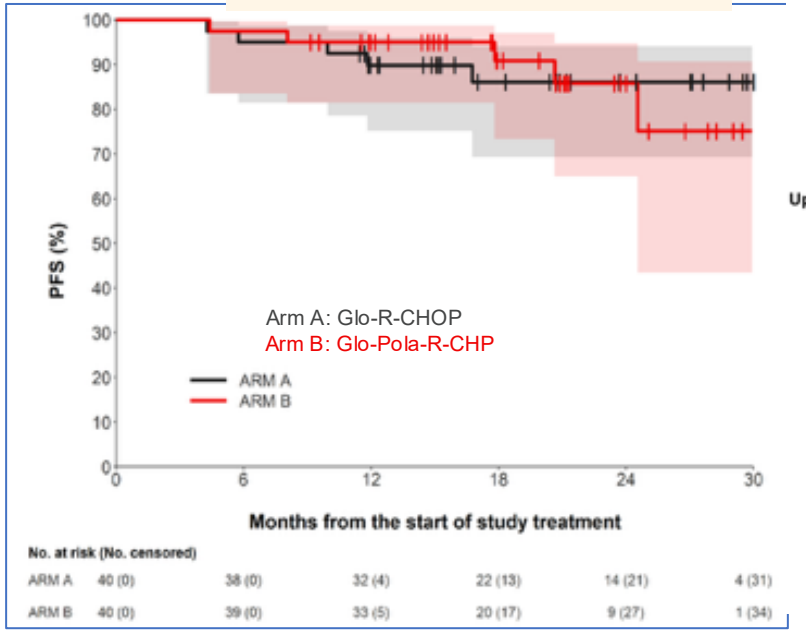
COALITION: High Risk DLBCL: Ph 2 randomised trial
R-CHOP + Glofitamab *vs* R-CHP + Glofitamab + Polatuzumab

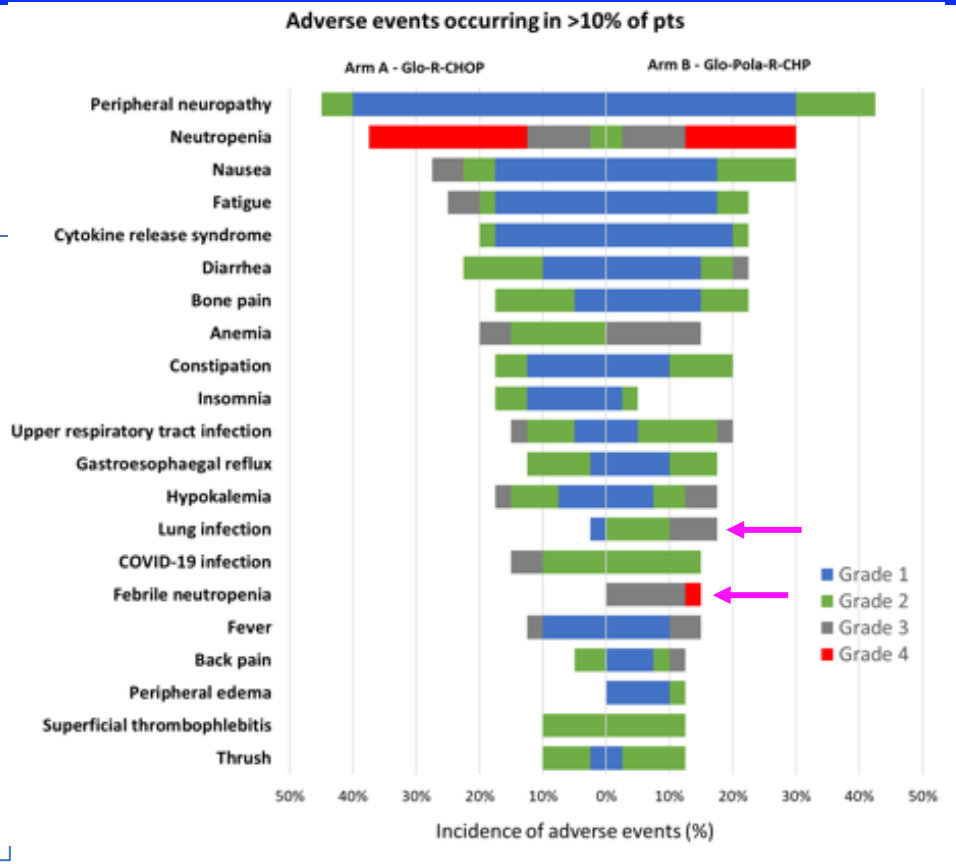
≤ 65 yrs with IPI 3-5 or NCCN IPI ≥ 4 or HGBL
Stage IV = 88%; IPI 3-5 = 83%

PFS all patients



PFS by study arm





PFS estimate	Arm A Glo-R-CHOP (n=40)	Arm B Glo-Pola-R-CHP (n=40)	All patients (n=80)
24-month PFS, %	**86%** (69%-94%)	**86%** (65%-95%)	**86%** (75%-93%)

PFS is very promising in this high-risk patient population

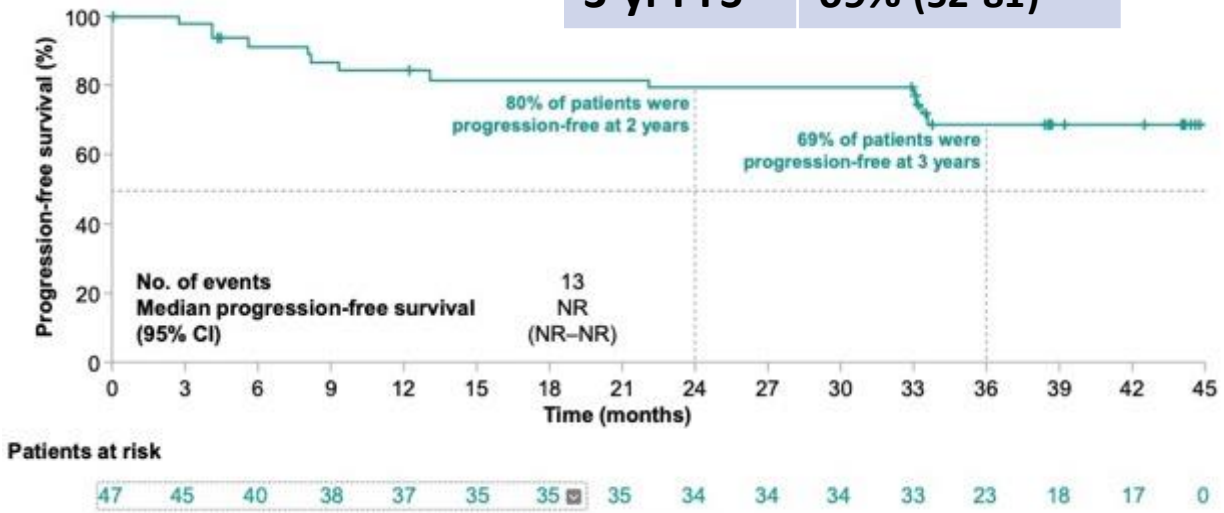
Median follow up 20.7 months

Minson A et al J Clin Oncol 2025; 43(23):2595-2605

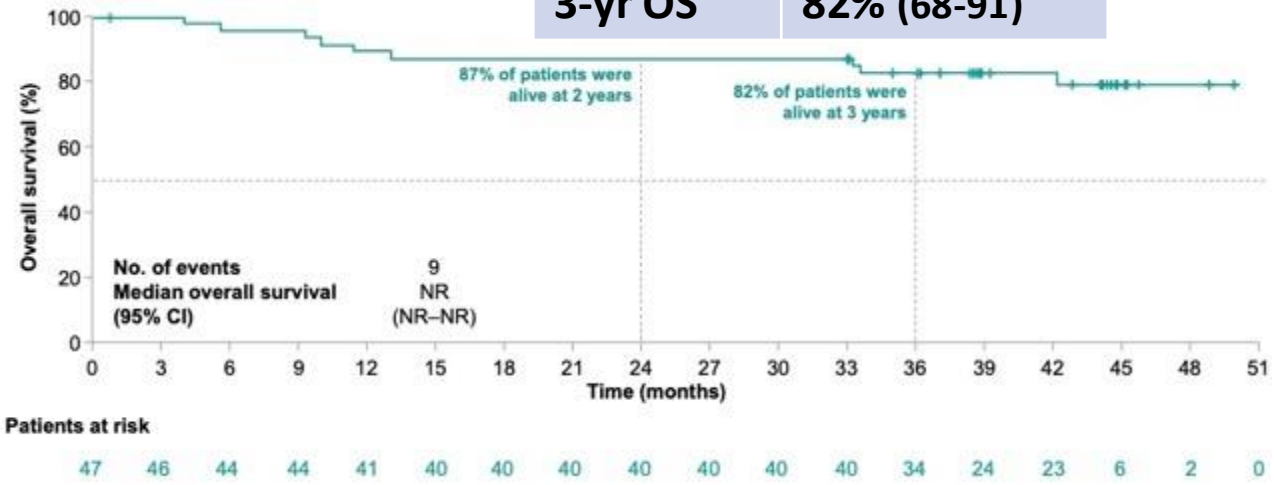
Epcoritamab + R-CHOP in LBCL: Ph 2 trial IPI 3-5 (med f/u 44.2m)

No.	N = 47
Median age	64 yrs
Stage IV; bulk ≥ 7 cm	**89%; 53%**
IPI 3-5	**100%**
ORR / CR	98% / 85%
MRD-ve	100%
Neutrop / anaemia	74% / 72%
CRS all / gde 1 / gd 2	60% / 47% / 11%

2-yr PFS	**80% (65-89)**
3-yr PFS	**69% (52-81)**

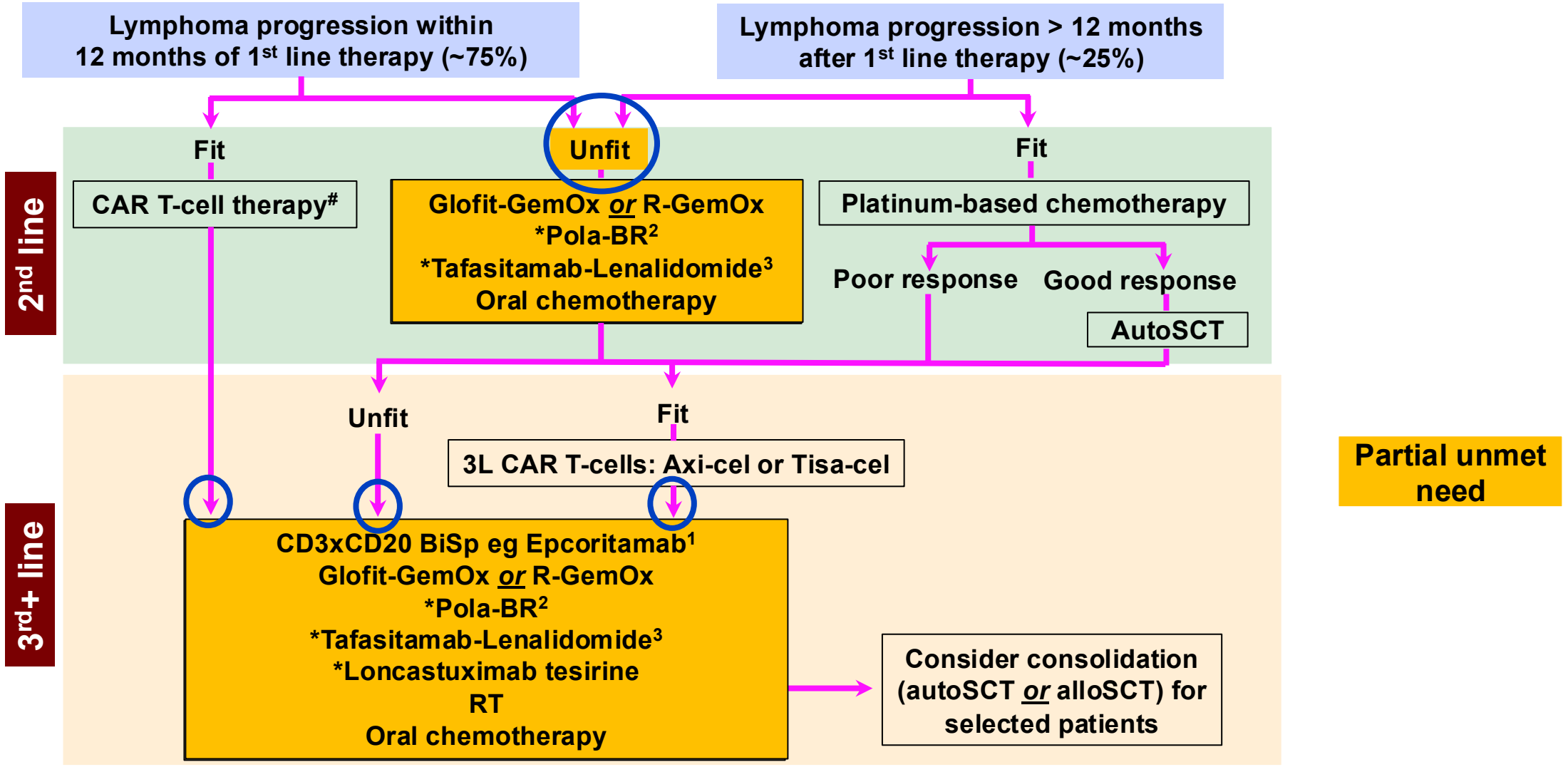


2-yr OS	**87% (73-94)**
3-yr OS	**82% (68-91)**



Falchi L et al Blood 2026; ahead of print

Large B-cell Lymphoma: 35-40% of patients are relapsed/refractory



* Not available/reimbursed in Australia

[1] Epcoritamab available in 3L in those who have had prior CAR T-cells or who are not suitable/fit for CAR T-cells; cannot have had a prior BiSpecific antibody
[2] Pola-BR: offers higher initial response rates but shorter durability
[3] Tafa-Len: chemo-free with durable responses in select ASCT-ineligible pats who are not refractory since limited efficacy in primary refractory disease
CAR T-cells may not be appropriate in those with ECOG ≥ 2, or large tumour burden, or rapidly progressive disease;
Axi-cel is available in 2nd line fit patients with R/R-LBCL within 12 m of 1st line therapy; Tisa-cel is available in 3rd line fit patients

Adapted Chaganti S et al Brit J Haemat 2025

Summary: Considerations in assessing CAR-T and BiSp Ab combinations in ASCT-ineligible R/R-LBCL patients

- BiSp antibody combinations (Glofit-GemOx) can be given in older, more frail R/R-LBCL pats with more aggressive, rapidly progressive disease for whom CAR-T may not be feasible
- Nevertheless, the comparable efficacy is achieved simultaneously with lower rates of high grade CRS, neurotoxicity, infection, and NRM suggesting a more favourable safety profile
- Biological impact of prior BiSp Ab exposure on CAR-T fitness and persistence remains ill-defined

→ In ASCT-ineligible patients with PrR/ER BiSp Ab-based combination treatment such as *Glofit-GemOx is a biologically sound clinically effective and realistic alternative

*potentially Epco-GemOx

Dimou M and Vassilakopoulos TP Brit J Haem 2026; ahead of print