Novel Therapies for Aggressive Non-Hodgkin Lymphomas

Kami Maddocks, MD
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PRIMO 2025

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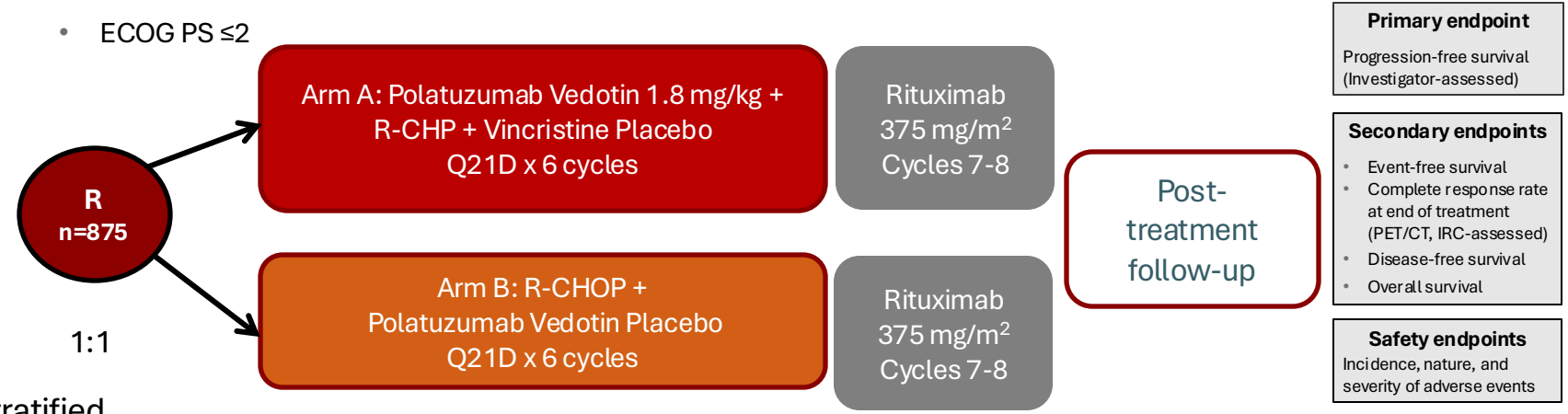
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

POLARIX: *R-CHOP vs R-CHP + Polatuzumab*

Key eligibility criteria

- Previously untreated DLBCL
- Stage II to IV disease
- IPI ≥2
- ECOG PS ≤2



Stratified

- IPI Score (2 vs 3-5)
- Bulky Disease (present vs absent)
- Region

Tilly H et al. *N Engl J Med.* 2022

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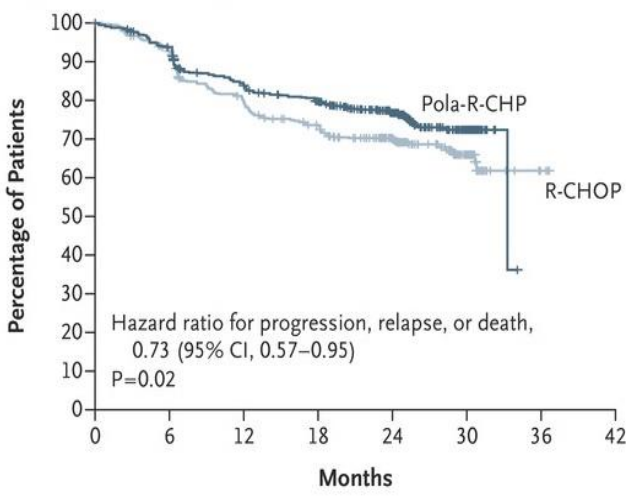
POLARIX: *Efficacy*

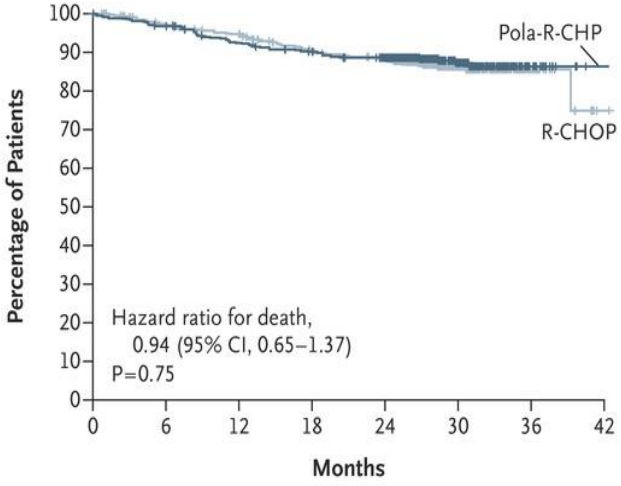
Progression-free survival



No. at Risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

2-year PFS 76.7 vs 70.2

Overall survival



No. at Risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

2-year OS 88.7 vs 88.6

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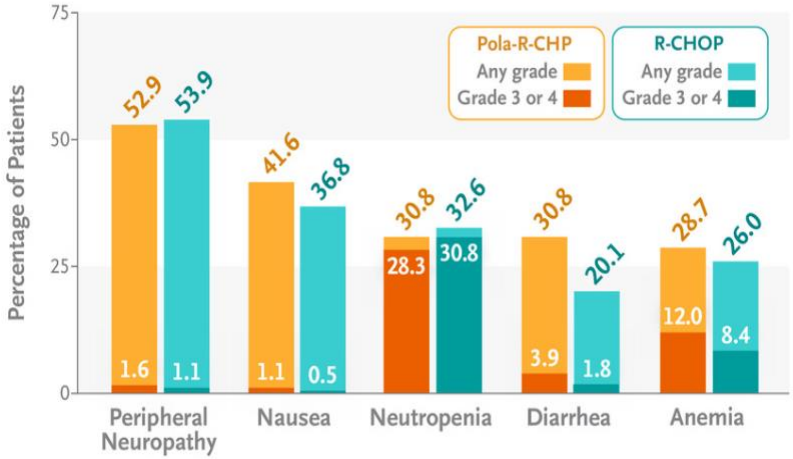
Tilly H et al. *N Engl J Med.* 2022

POLARIX: *Safety*

Adverse Events



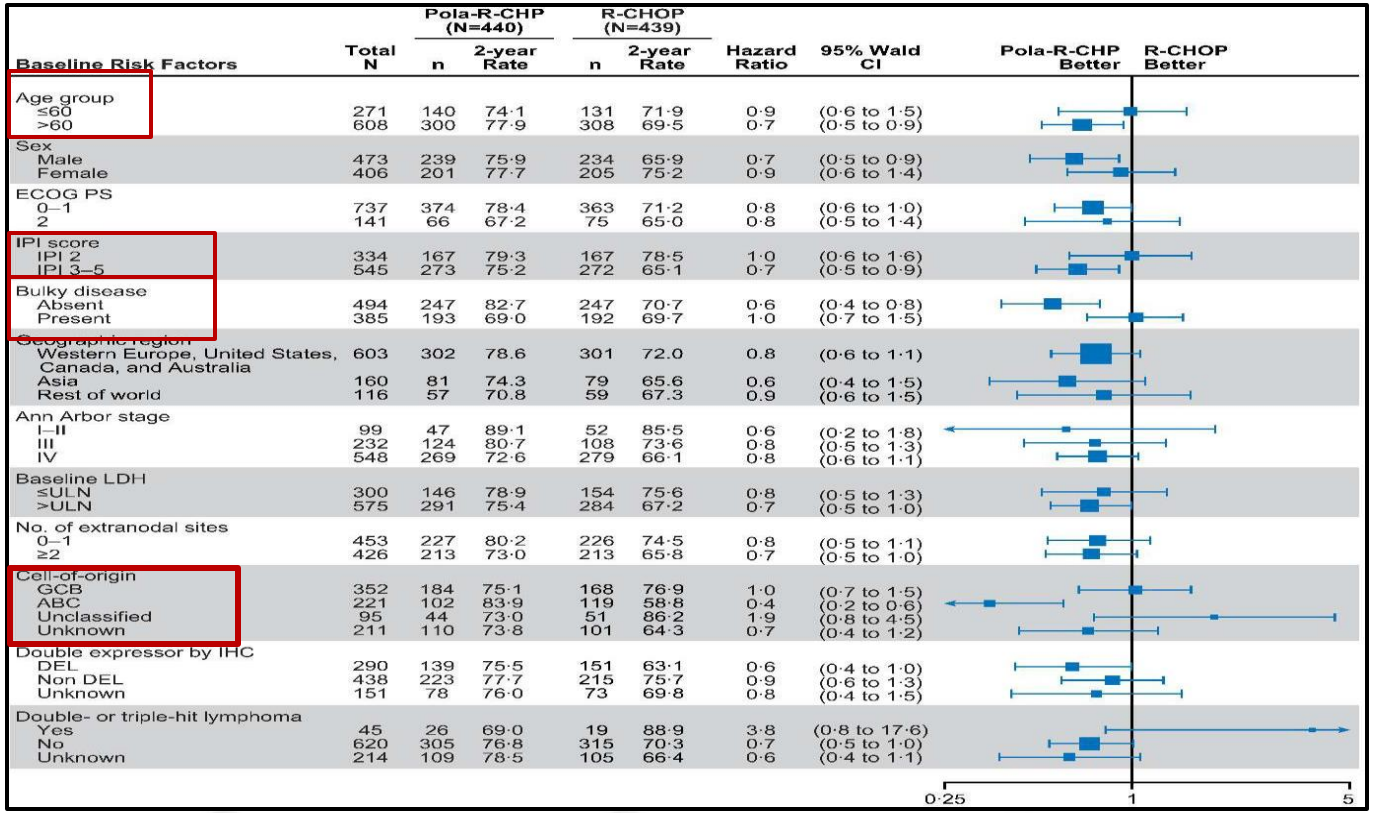
Adverse Event, n (%)	Pola–R-CHP (n = 435)	R-CHOP (n = 438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin/ vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

ITT population. Data cutoff: June 28, 2021; median 28.2 months' follow-up.

	Any Grade	Grade 3-4	Any Grade	Grade 3-4
PN	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
FN	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)

Tilly H et al. *N Engl J Med.* 2022

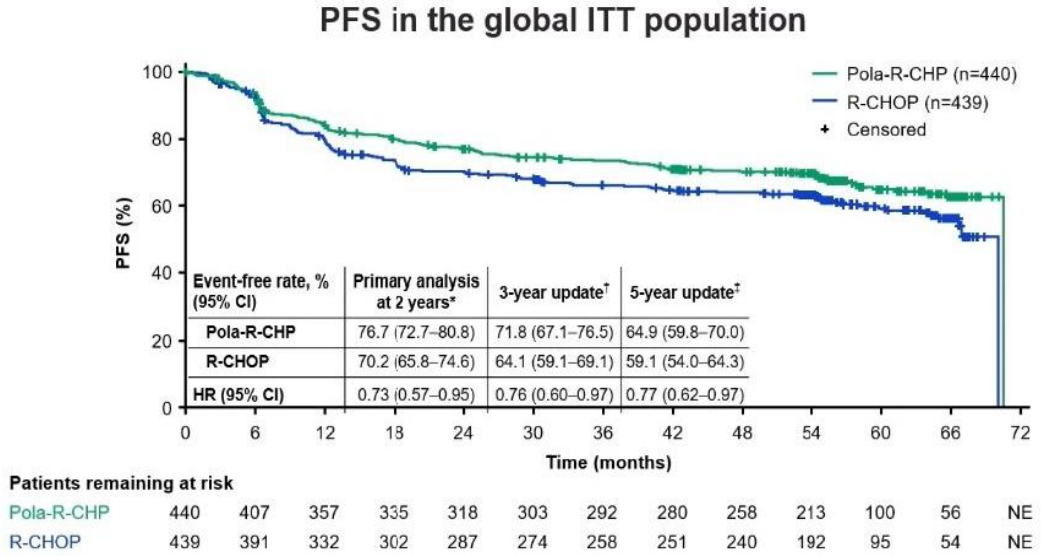
POLARIX: *Subgroup Analysis*



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

Tilly H et al. *N Engl J Med.* 2022

POLARIX: *5-Year Update in Global ITT Patients*



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update†
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).[1]

Tilly H et al. *N Engl J Med.* 2022; Salles et al ASH 2024.

ZUMA-7: Axi-cel vs. SoC as Second-Line Therapy

Median Follow-up, 47.2 mo

CRS

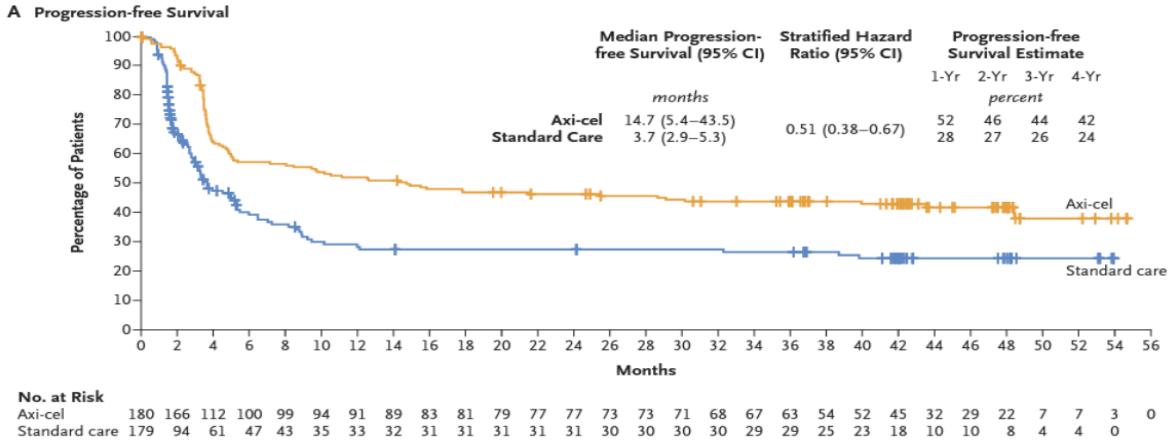
Any grade: 92%; grade ≥3: 6%

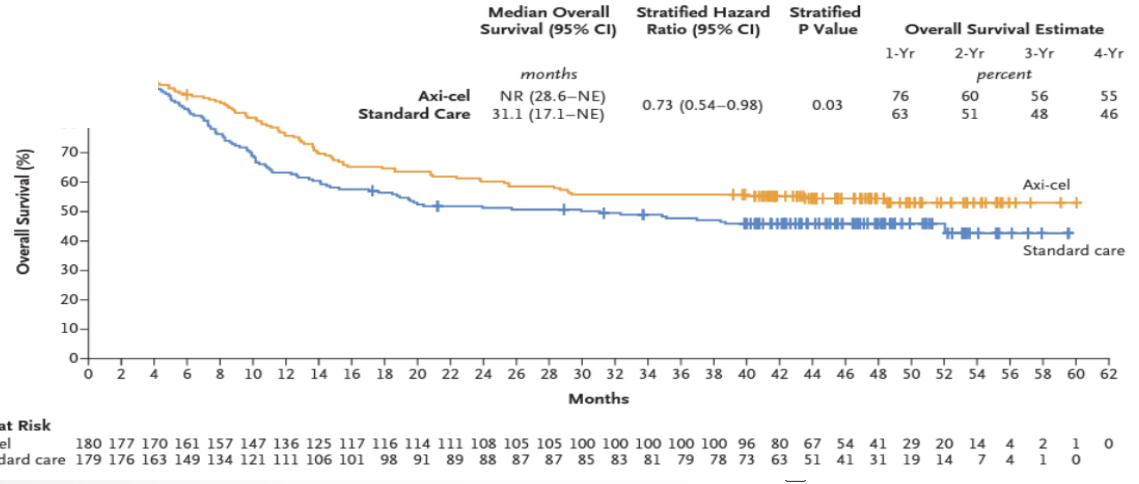
Median onset 3 days, median duration 7 days

Neurotoxicity

Most common: tremor, confusional state, aphasia

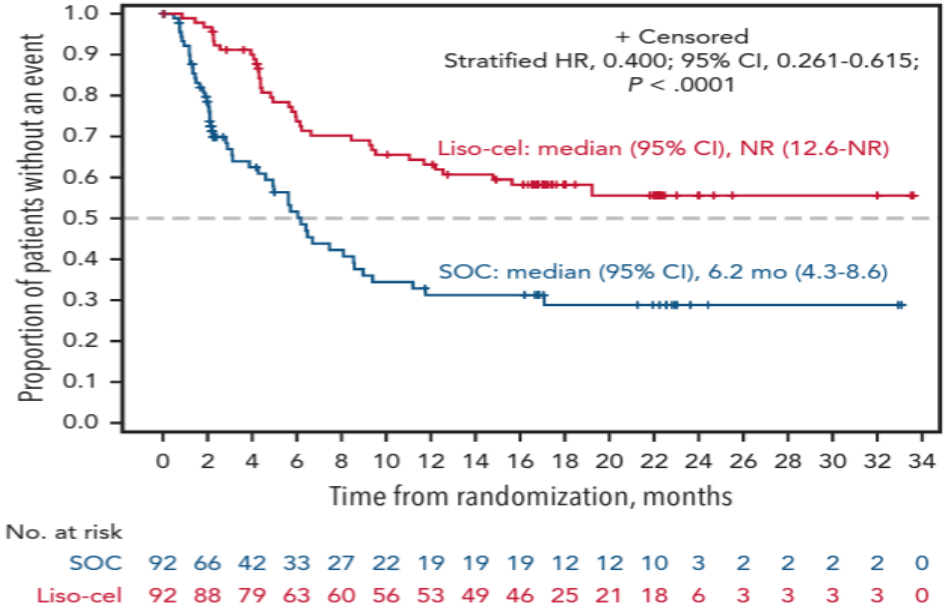
Any grade: 60%; grade ≥3: 21%

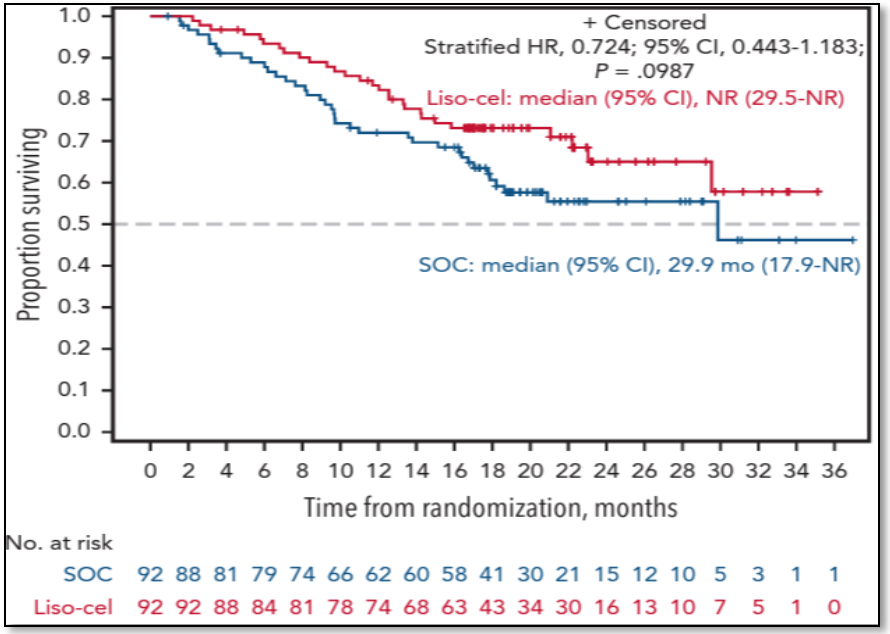




Westin JR, et al. N Engl *J Med.* 2023

TRANSFORM: Liso-cel vs. SoC as Second-Line Therapy





CRS

Any grade: 49%; grade ≥3: 1%

Median onset 5 days, median duration 4 days

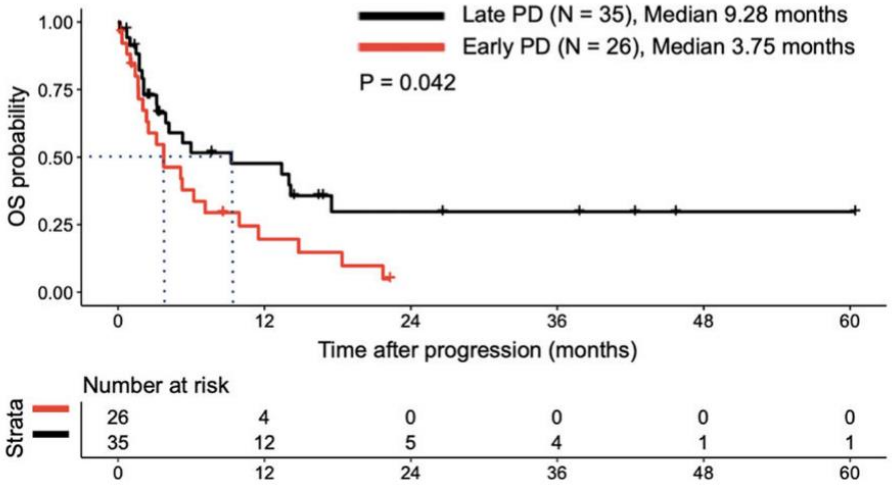
Neurologic events

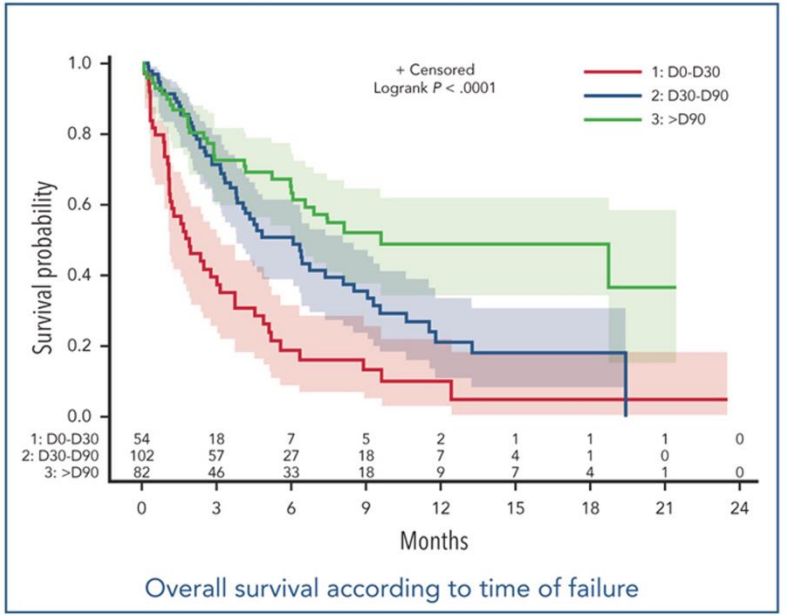
Grade 3 events include encephalopathy, mental status change, aphasia, tremor, muscular weakness

Any grade: 12%; grade ≥3: 4%

Abramson JS, et al. *Blood.* 2023

Outcomes of Patients With Post CART Progression





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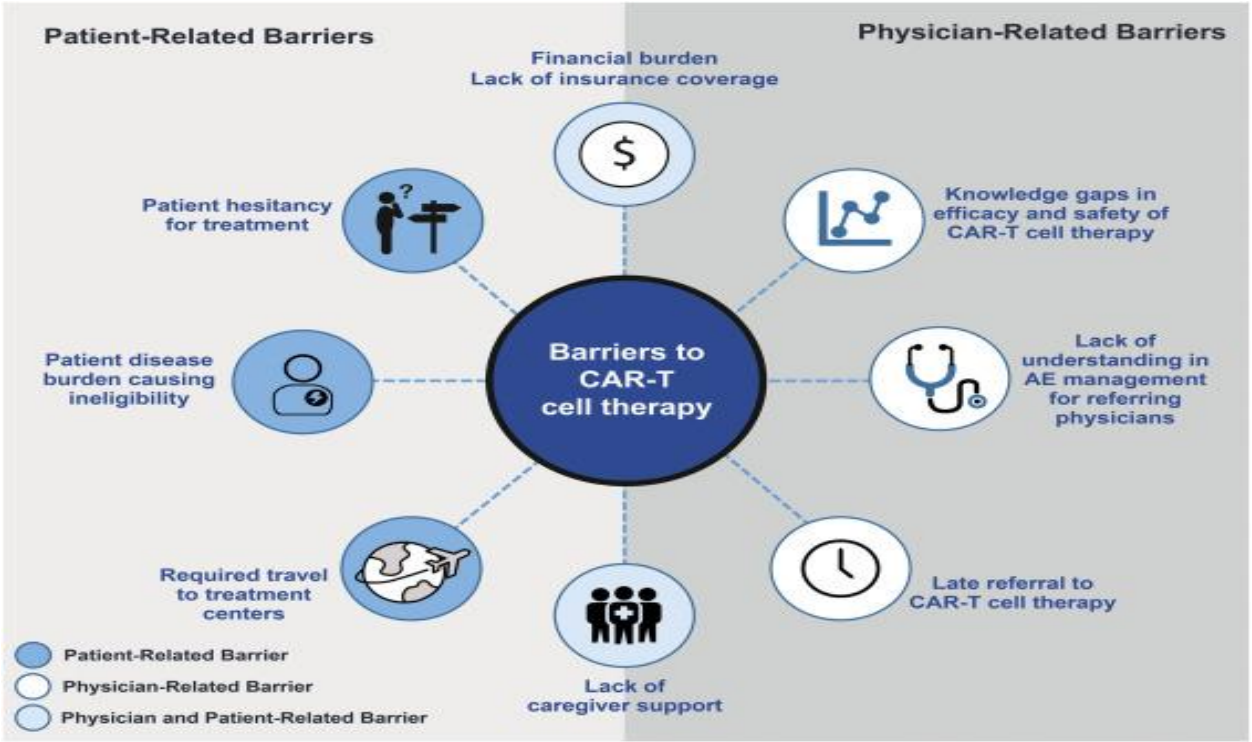
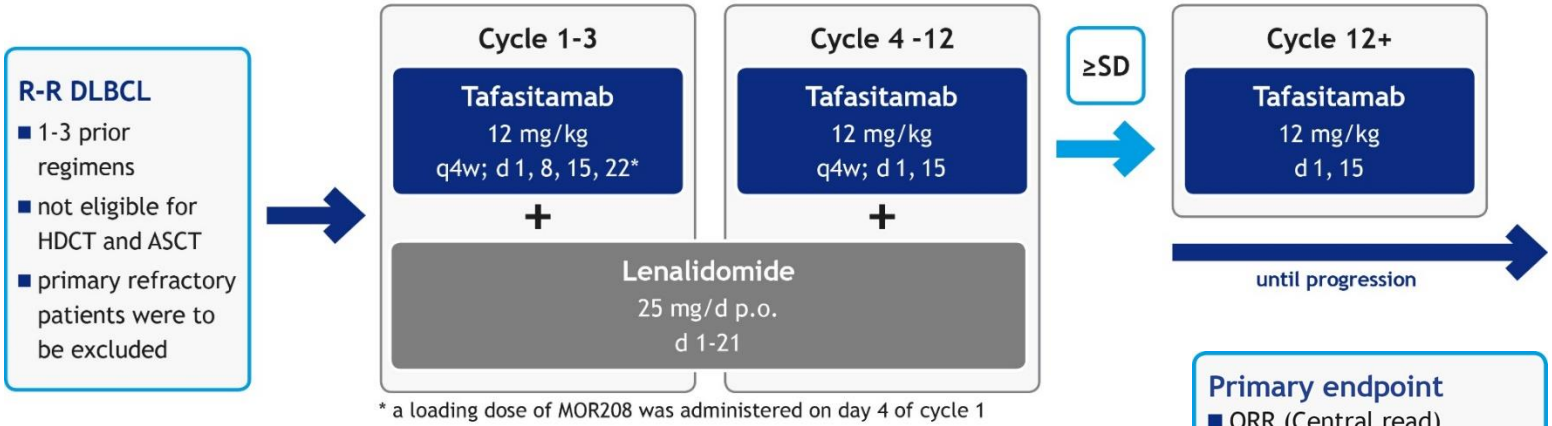
Chow VA et al. *Am J Hematol.* 2019; Di Blasi R et al. *Blood.* 2022

Addressing Access



Hoffmann MS, et al. *Transplant Cell Ther*. 2023.

L-MIND Study Design



Primary endpoint
- ORR (Central read)

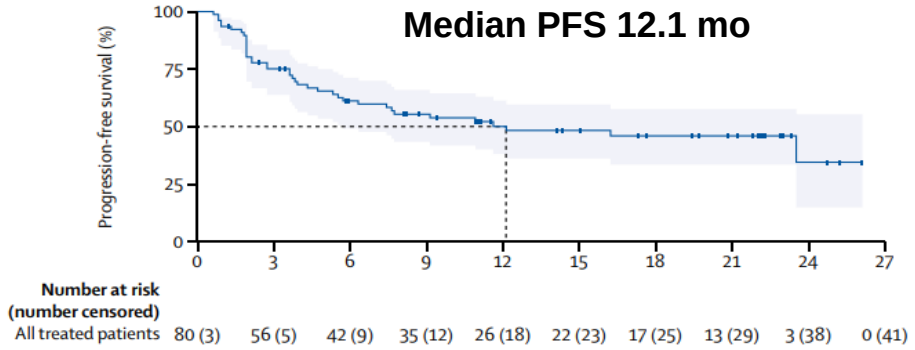
Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

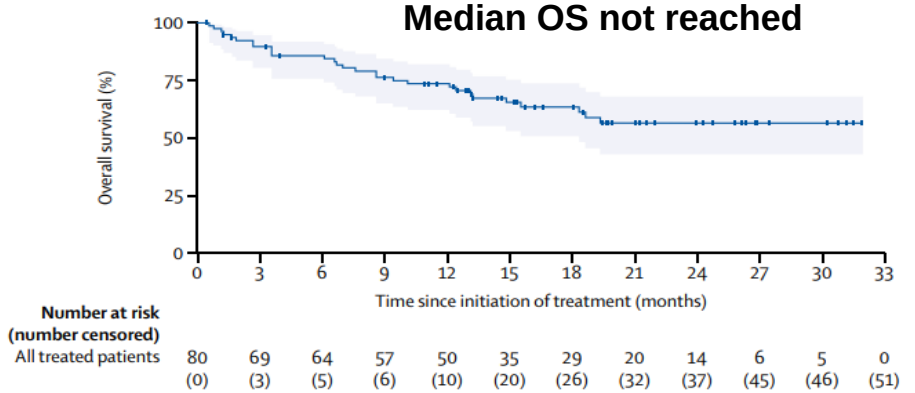
- Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab-LEN combination vs LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature data: Primary endpoint analysis with data cutoff Nov 30, 2018; minimum follow-up 12 mo, median follow-up 17.3 mo

Salles G, et al. ICML 2019. Abstract 124.

L-MIND

	N = 80
Overall response rate	60 (48)
Complete response	43 (34)
Partial response	17 (14)
PET-confirmed CR	88 (30/34)
Median duration of response	21.7 mo
Complete response	Not reached
Partial response	4.4 mo

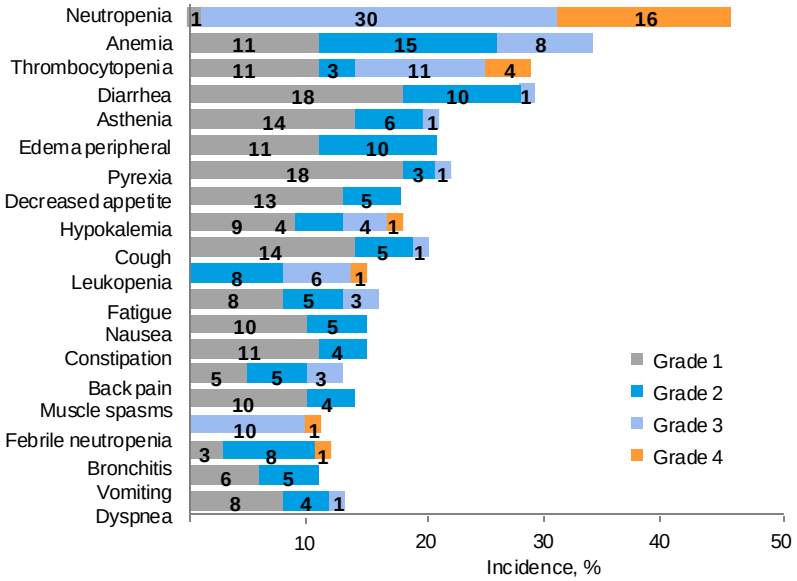




Salles G, et al. *Lancet Oncol.* 2020.

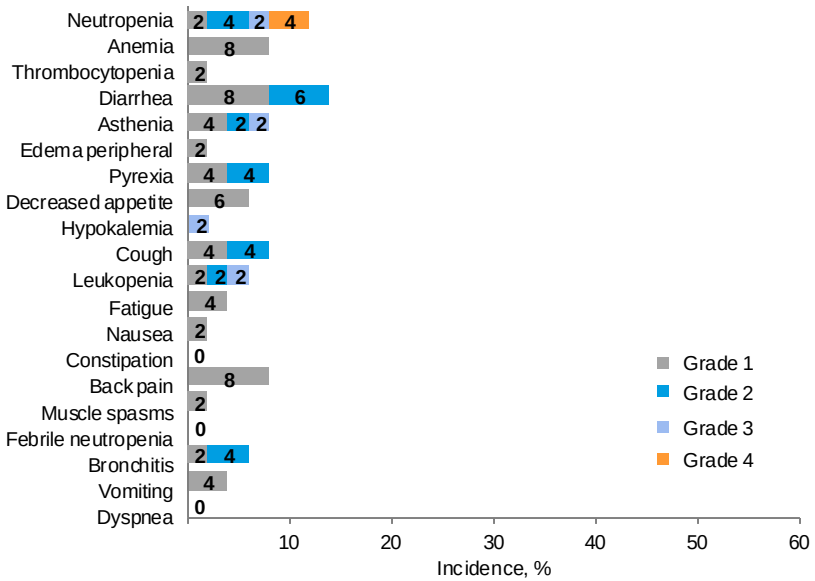
Safety by Treatment Phase

Tafasitamab + LEN combination (up to 12 cycles) n = 80, median exposure 6.2 mo*



- 37 patients (43%) required lenalidomide dose reduction
- 62/80 patients (78%) were able to stay at dose ≥20 mg/d

Tafasitamab monotherapy (cycle 13 onward or after LEN discontinuation) n = 51, median exposure 4.1 mo*



- Incidence and severity of TEAEs are lower during the tafasitamab monotherapy phase
- 10 patients (12%) discontinued tafasitamab + LEN because of AEs

*AE (adverse event) collection period included 30 days after end of treatment. Salles G, et al. *Lancet Oncol.* 2020

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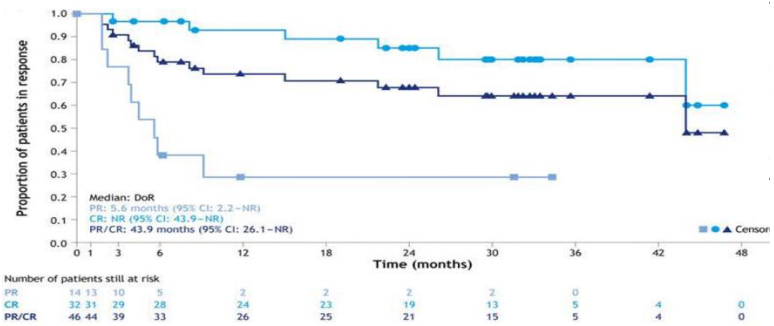
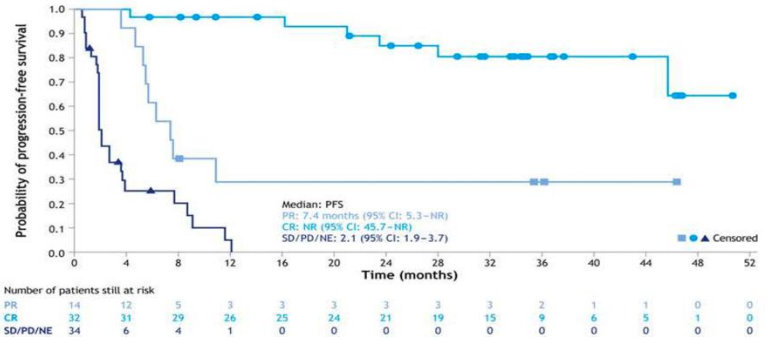
L-MIND: Long-Term Follow-Up

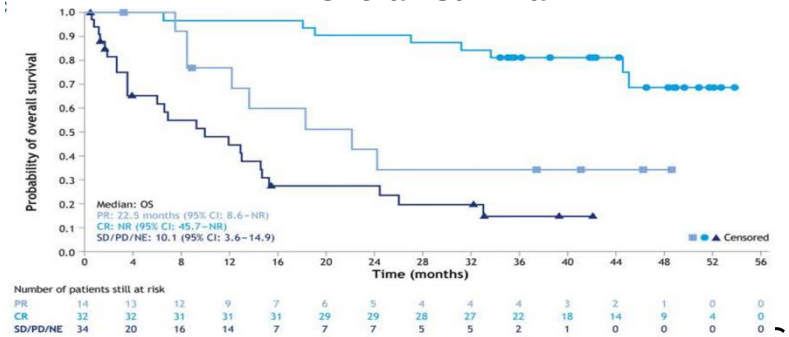
Duration of response



Progression-free survival



Overall survival



Median DOR, PFS, and OS were 43.9 mo, 11.6 mo, and 33.5 mo, respectively, at median f/u 42.7 mo

Duell J, et al. *Haematologica.* 2021;106(9):2417-2426; Duell J, et al. AACR 2023. Abstract 9810.

L-MIND: Long-Term Follow-Up

Tafasitamab + LEN	1 Prior Treatment (n = 40)	≥2 Prior Treatments (n = 40)	Overall (N = 80)
Best objective response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DOR, mo (95% CI)	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)
Median PFS, mo (95% CI)	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3-45.7)
Median OS, mo (95% CI)	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

Duell J, et al. ASCO 2021. Abstract 7513.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Study Design

Dose escalation

Dose expansion data cutoff: November 18, 2022
Median follow-up: 20.0 mo

Key Inclusion Criteria

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0-2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed

Step-up dosing[a]

Epcoritamab SUBQ RP2D 48 mg	Treatment until PD[b,c] or unacceptable toxicity	LBCL Cohort N=157
qw C1-3, q2w C4-9, q4w C10+		DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by IRC
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, safety/tolerability

[a] Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b] Radiographic disease evaluation was performed every 6 weeks for the first 24 weeks (6, 12, 18, and 24 weeks), then every 12 weeks (36 and 48 weeks), and every 6 months thereafter. [c] Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG PET scan that demonstrates positive lesion(s) compatible with CT-defined (or MRI-defined) anatomical tumor sites for FDG-avid lymphomas.

Karimi Y, et al. ASCO 2023. Abstract 7525. 2. Jurczak W, et al. EHA 2023. Abstract P1118. 3. Thieblemont C, et al. EHA 2022. Abstract LB2364.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Efficacy

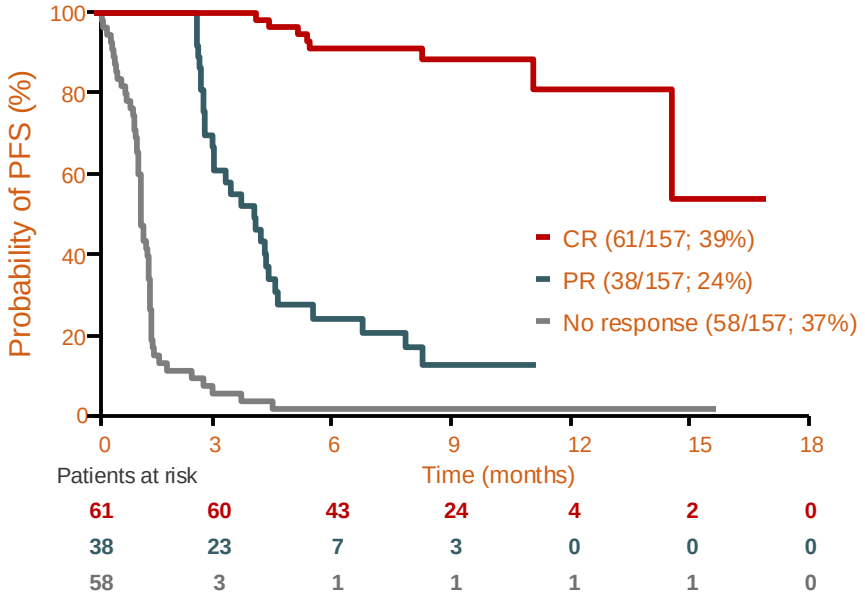
Best response rates[2]
- CR: 39.0%
- ORR: 63.0%

Subgroup CR rate[2]
- After CAR T cell: 34%
- Refractory: 30%

Survival
- Median PFS: 4.4 mo[2]
- OS: 57% at 12 mo[1]
- Median DOR: 12 mo[2]
- Median DOR of CR: NR[2]

Kaplan-Meier Estimate	DLBCL (n=55)
Median DOR for patients who achieved a CR, mo (95% CI)	20.8 (17.3-NR)
Median PFS for patients who achieved a CR, mo (95% CI)	NR (18.5-NR)
Median OS for patients who achieved a CR, mo (95% CI)	NR (NR-NR)
Median OS for all patients with DLBCL, mo (95% CI)[c]	19.4 (11.7-NR)

PFS in Patients with LBCL[2]



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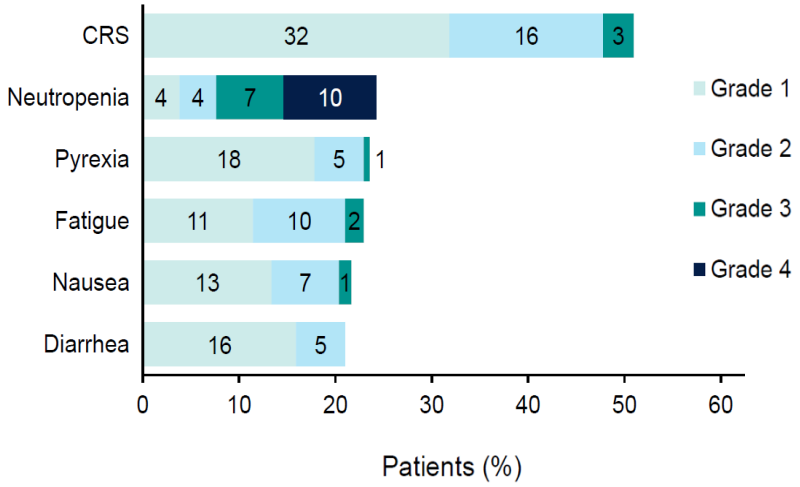
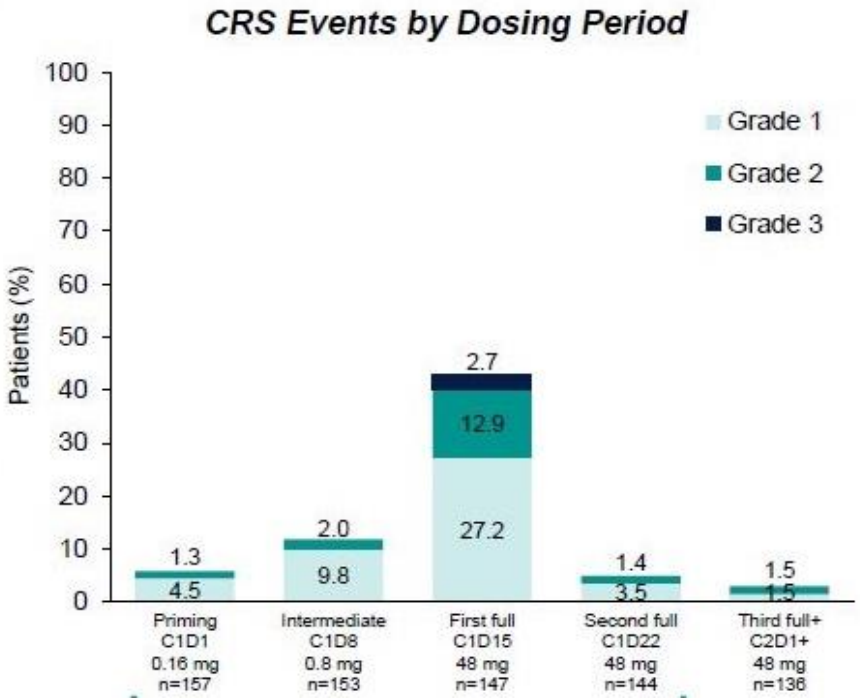
Thieblemont C, et al. EHA 2022. Abstract LB2364; 2. Thieblemont C, et al. *J Clin Oncol*. 2023.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Safety

Treatment-Emergent Adverse Events (≥20%) of Patients with LBCL (N=157)





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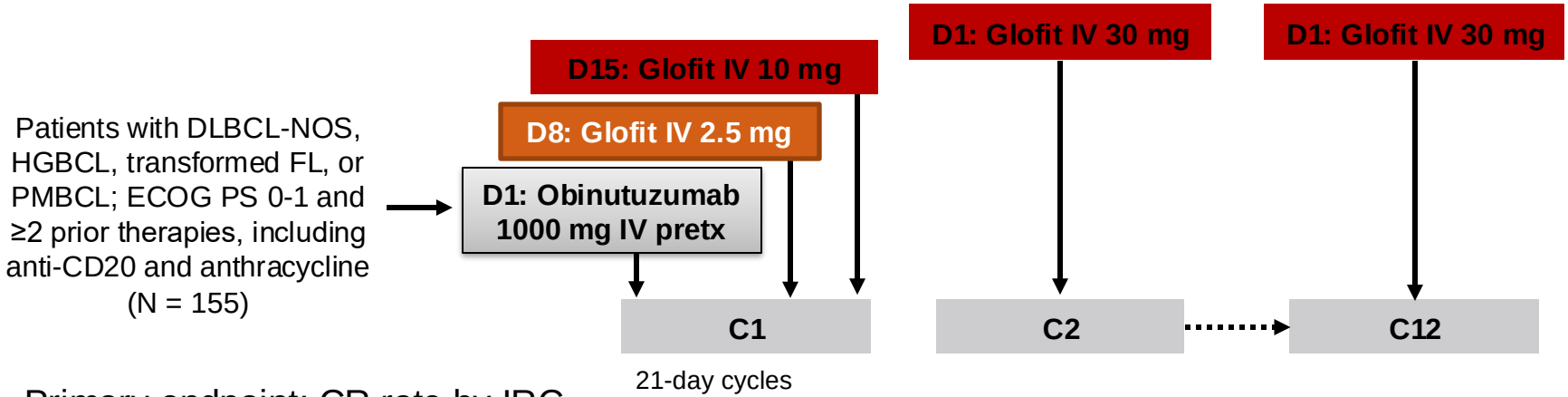
Karimi Y, et al. ASCO 2023. Abstract 7525. 2. Jurczak W, et al. EHA 2023. Abstract P1118. 3. Thieblemont C, et al. EHA 2022. Abstract LB2364.

Phase II Expansion Study: Glofitamab in R/R DLBCL

Single-arm phase II expansion trial



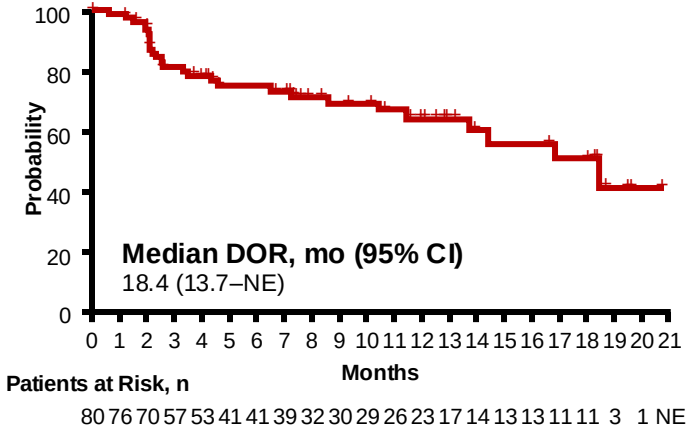
- Primary endpoint: CR rate by IRC
- Key secondary endpoints: ORR rate, DoR, DoCR, PFS, and OS

Dickinson MJ et al. *N Engl J Med.* 2022.

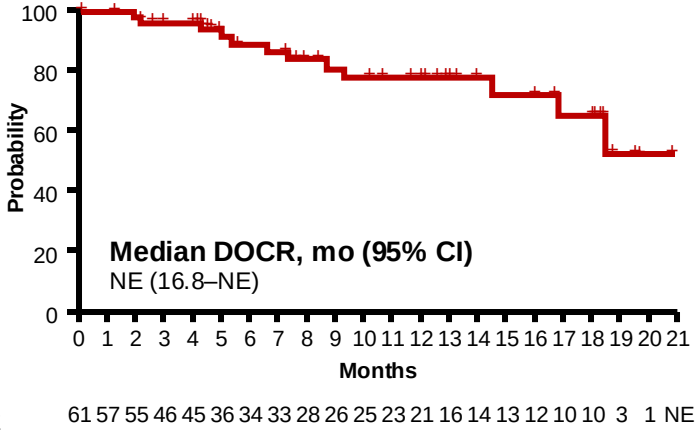
Phase II Expansion Study of Glofitamab: Efficacy

Median follow-up: 12.6 mo

Duration of overall response by IRC



Duration of complete response by IRC



Response, %	N = 155
Best response	
▪ ORR	51.6
▪ CR	39.4
Subgroup CR rate	
▪ After CAR T-cell	35
▪ Relapsed	70
▪ Refractory	34

Survival, Mo	N = 155
Median PFS	4.9
Median OS	11.5

	N = 80
Median DOR follow-up, mo (range)	10.6 (0–21)
12-mo DOR, % (95% CI)	63.6 (51.1–76.2)
Ongoing response at CCOD, n (%)	53 (66.3)

	n = 61
Median DOCR follow-up, mo (range)	10.6 (0–21)
12-mo DOCR, % (95% CI)	77.6 (64.3–90.8)
CRs ongoing at CCOD, n (%)	49 (80.3)

Median F/U 32 mos
Median DOCR 26.9 mo
Median PFS 24 mo
Median OS NE

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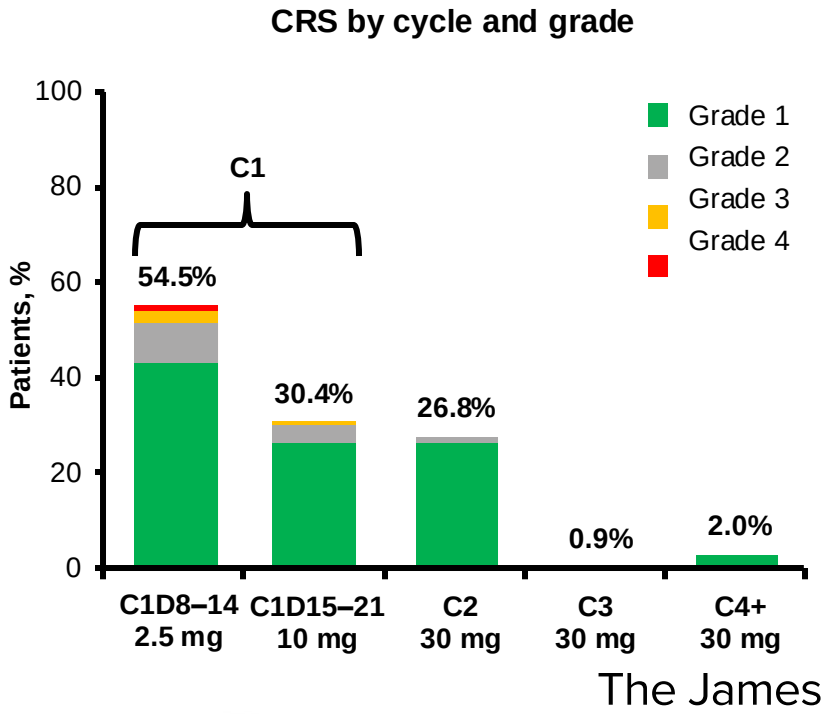
Dickinson MJ, et al. EHA 2022. Abstract S220; Dickinson MJ, et al. *N Engl J Med.* 2022.

Phase II Expansion Study of Glofitamab: Safety

CRS Parameter	Glofitamab (N = 154)
Any-grade CRS, n (%) ▪ Grade 1 ▪ Grade 2 ▪ Grade 3 ▪ Grade 4	97 (63.0) 73 (47.4) 18 (11.7) 4 (2.6) 2 (1.3)
Median time to CRS onset from C1D8 dose, hr (range)	13.6 (6.2–51.8)
Corticosteroids given, n/N (%)	27/97 (27.8)
Tocilizumab given, n/N (%)	31/97 (32.0)
Any ICANS, n (%) ▪ Grade ≥3	12 (7.8) 4 (2.6)

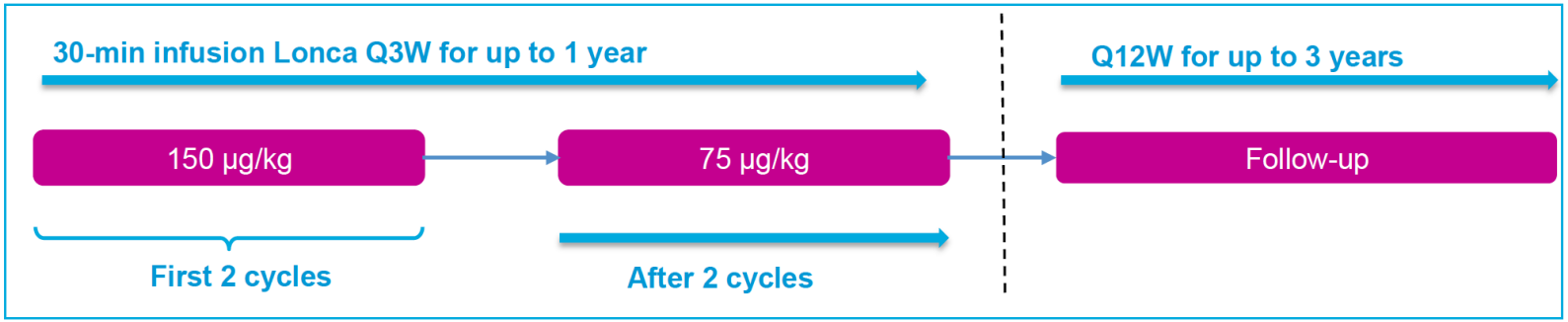


Dickinson MJ, et al. *N Engl J Med.* 2022.

Loncastuximab Tesirine: LOTIS-2 Trial
Single-Arm Open-Label Phase II Study in DLBCL

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

Primary objective:
Evaluate efficacy, **using ORR** (central review), and **safety** of the full Phase 2 study population



Key inclusion criteria: transplant-eligible and -ineligible patients; DLBCL NOS; DLBCL arising from low-grade lymphoma; HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements; ECOG PS 0–2; patients with prior CD19-directed therapy if CD19 positive.

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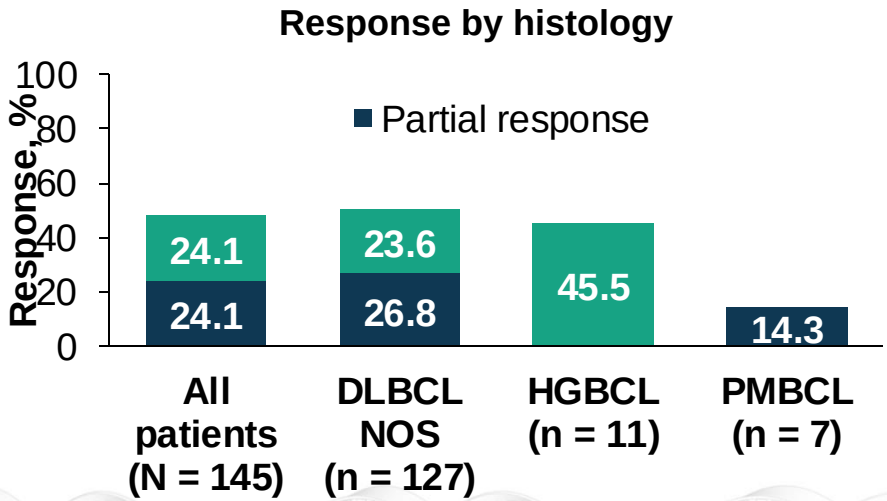
Caimi P, et al. *Lancet Oncol.* 2021.

Loncastuximab Tesirine: CD19 ADC

- Median 3 prior therapies (range, 2–7)
- Primary refractory, n = 29 (20%)
- Double/triple hit, n = 15 (10.3%)
- Prior ASCT, n = 21 (14.5%)



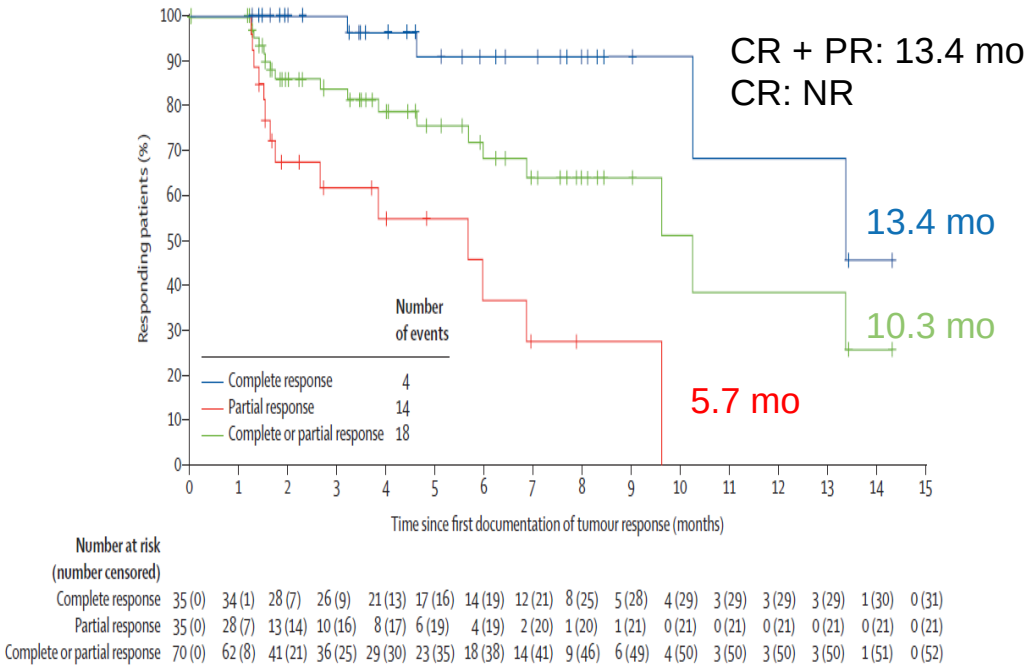
	N = 145 (%)
Overall response rate	70 (48.3)
Complete response	35 (24.1)
Partial response	35 (24.1)
Stable disease	22 (15)
Progressive disease	53 (37)
Median PFS	4.9 mo
Median overall survival	9.9 mo
Median DOR	10.3 mo

Activity across high-risk subgroups

Refractory Disease
High Grade B Cell
Prior ASCT
Prior CAR-T

Caimi P, et al. *Lancet Oncol.* 2021

LOTIS-2: Duration of Response and Safety



Adverse Event	Patients, n (%)
Any TEAE	143 (98.6)
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral edema	29 (20.0)

16 (44%) patients had CRs >1 yr, which were ongoing at the 1-yr follow-up, and 11 (31%) had CRs >2 yr

TEAE (related) leading to treatment discontinuation: 27 (18.6%)
Treatment delays: 62 (42.8%)

Caimi P, et al. *Lancet Oncol.* 2021; Kahl BS, et al. SOHO 2021. Abstract ABCL-022.

STARGLO Phase 3 Study of Glofit + GemOx vs R-GemOx in 2L DLBCL

Key Eligibility Criteria
- R/R DLBCL NOS after ≥1 prior therapy
- ASCT-ineligible patients with 1 prior LOT
- ECOG PS 0-2

R 2:1
N=274

Glofit + GemOx
Glofitamab SUD cycle 1, 30 mg day 1 cycle 2+
Gemcitabine 1000 mg/m² IV
Oxaliplatin 100 mg/m² IV
- Cycle 1: Obin pre-tx day 1; GemOx day 2; Glofit 2.5 mg day 8; Glofit 10 mg day 15
- Cycles 2-8: Glofit 30 mg and GemOx day 1

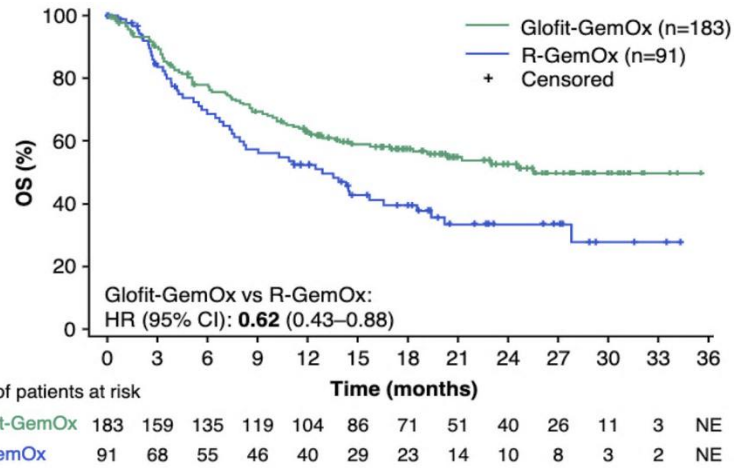
→ **Glofit** 30 mg, day 1 cycles 9-12

Cycles 1-8 (21-day cycles)

R-GemOx
Rituximab 375 mg/m²
Gemcitabine 1000 mg/m² IV
Oxaliplatin 100 mg/m² IV
- Cycles 1-8: day 1

Primary endpoint: OS
Key secondary endpoints: PFS, CR, DoCR (all by IRC), AEs

OS: Updated Analysis (Primary Endpoint)



OS Analyses		Glofit-GemOx (n=183)	R-GemOx (n=91)
Updated	Median (95% CI), months	25.5 (18.3-NE)	12.9 (7.9-18.5)
	HR (95% CI)	0.62 (0.43-0.88)	
	P value	0.006	
	24-month (95% CI), %	52.8 (44.8-60.7)	33.5 (22.2-44.9)
	Median follow-up	20.7 months	

Abramson JS, et al. *Lancet* 2024.

EPCORE NHL-2: Epcoritamab + GemOX in Patients With R/R LBCL

Key Eligibility Criteria

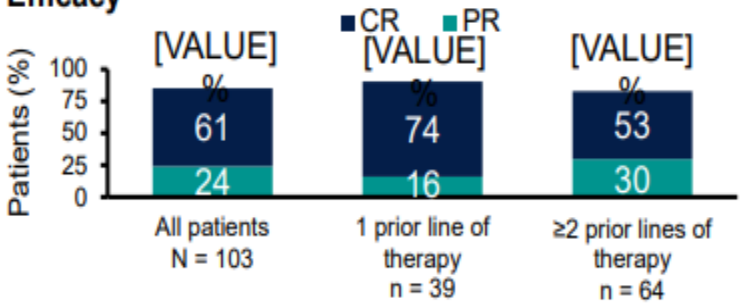
- R/R CD20+ DLBCL (NOS, de novo, tFL/tMZL, DH or THL, TCRBL)
- ASCT-ineligible patients with 1 prior LOT
- ECOG PS 0-2

Treatment regimen: Epcoritamab SC 48 mg + GemOx IV

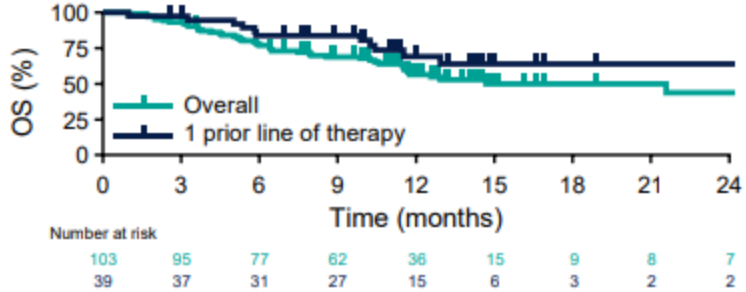
Agent	C1	C2	C3	C4	C5–9	C10+
Epcoritamab	QW	QW	QW	Q2W	Q2W	Q4W
Gemcitabine	Q2W					
Oxaliplatin						

Primary endpoint: ORR
Key secondary endpoints: PFS, CR, DoCR (all by IRC), AEs

Efficacy



- Median DOCR was 23.6 months



- Median OS was 21.6 months overall and not reached in patients with CR
  - 12-month OS estimate in patients with 1 prior line of therapy was 69%

Brody J, et al. *Blood* 2024.

ECHELON-3: R-Len-BV vs R-Len-Placebo (≥2 Prior Tx)

R
1:1

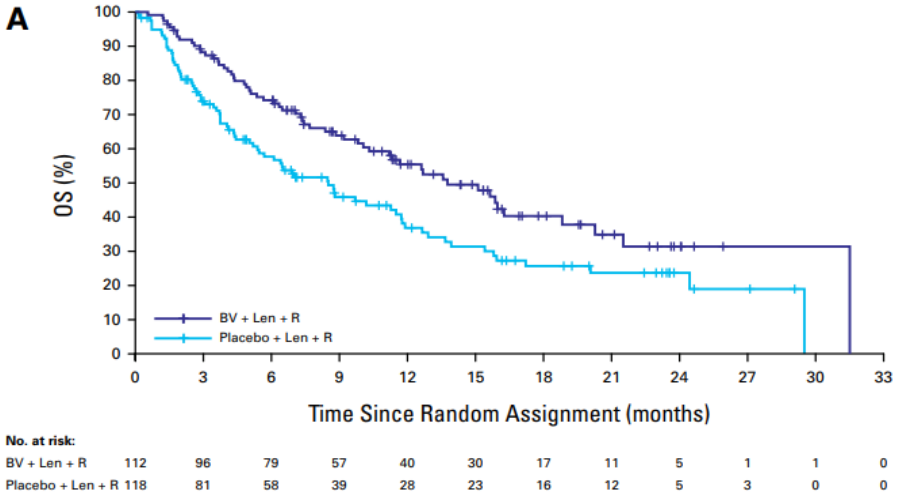
N=230

R-Len-BV
Rituximab 375 mg/m^2
Lenalidomide 20 mg po D1-21
Brentuximab Vedotin 1.2 mg/kg
IV q3 weeks

R-Len-Placebo
Rituximab 375 mg/m^2
Lenalidomide 20 mg po D1-21
Placebo IV q3 weeks

Primary endpoint: OS
Key secondary endpoints: PFS, ORR, CR, DOR

OS: Primary Endpoint



Median OS (95% CI) 13.8 vs 8.5 months

Bartlett, et al. *JCO* 2024.

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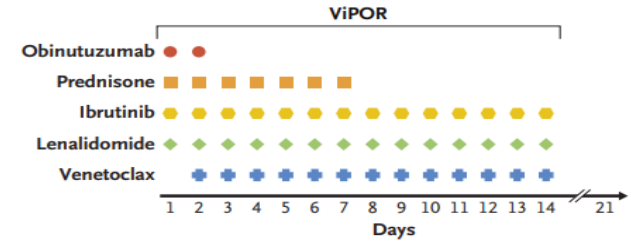

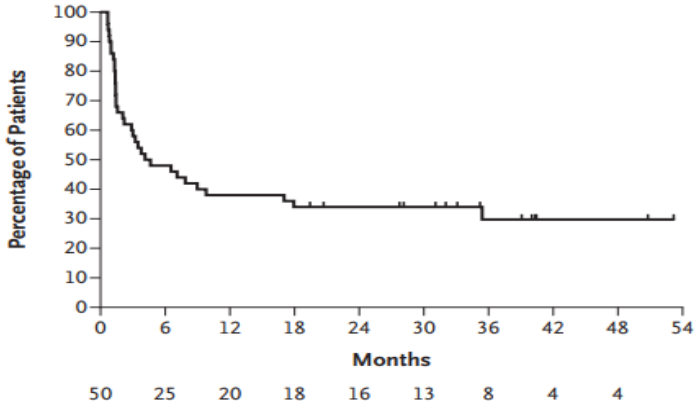

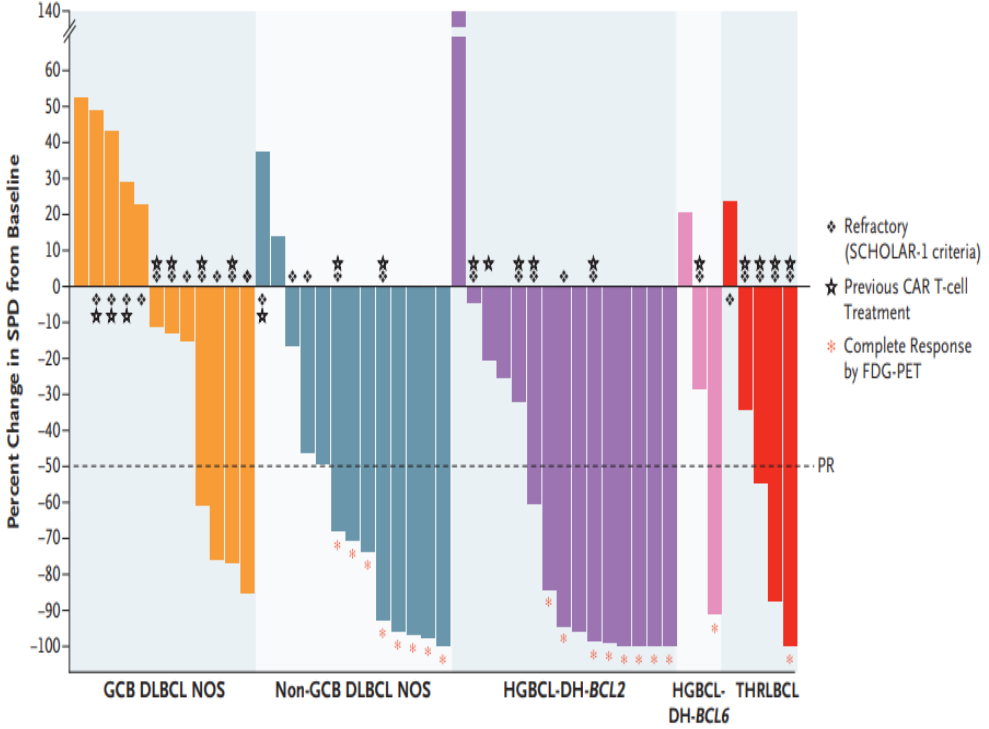

Melani, et al. *NEJM* 2024.

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Conclusions

- Novel therapies changed treatment landscape for aggressive BCL
- Improved outcomes seen with incorporation of novel therapies into all lines of treatment
- Numerous ongoing trials evaluating combinations of agents approved in 2nd or later lines in the frontline setting