12:30–1:10 PM

Aggressive NHL

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

Controversies in Relapsed & Refractory DLBCL

HCA Healthcare®
Sarah Cannon
Cancer Network

SARAH CANNON
Transplant & Cellular Therapy Program
at Methodist Hospital | San Antonio

Methodist
HEALTHCARE

Presenter

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Methodist Hospital

Disclosures

In the past 24 months:

- I have served as a consultant for: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, Beigene, Ipsen, Kite (Gilead), Lilly/Loxo and Ono Therapeutics

- I have served as a speaker for: AstraZeneca, Beigene, Kite (Gilead), Pfizer

- I may discuss:
  - On-label indications for Yescarta, Breyanzi, Kymriah, glofitamab, epcoritamab, brentuximab vedotin, loncastuximab tesirine, polatuzumab, tafasitimab, selinexor
  - Off-label indications for lenalidomide, ibrutinib, and mosunetuzumab

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Outline

- Auto-HCT versus CAR-T for R/R DLBCL?
- Bispecific TCEs vs CAR-T for R/R DLBCL? How to sequence
- Best option for pts who are not auto-HCT or CAR-T candidates

Auto-HCT versus CAR-T for R/R DLBCL in 2nd line

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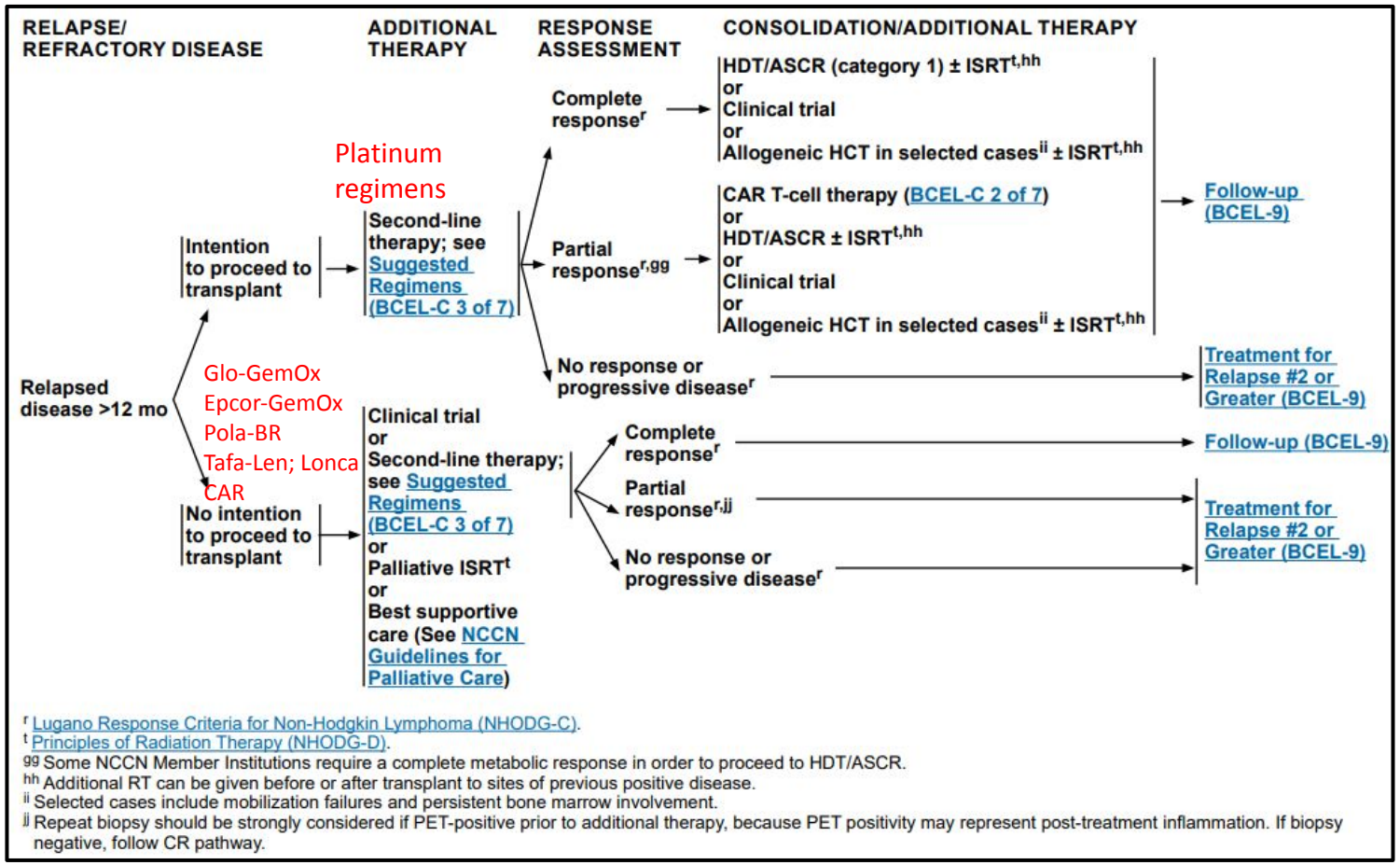
NCCN Guidelines



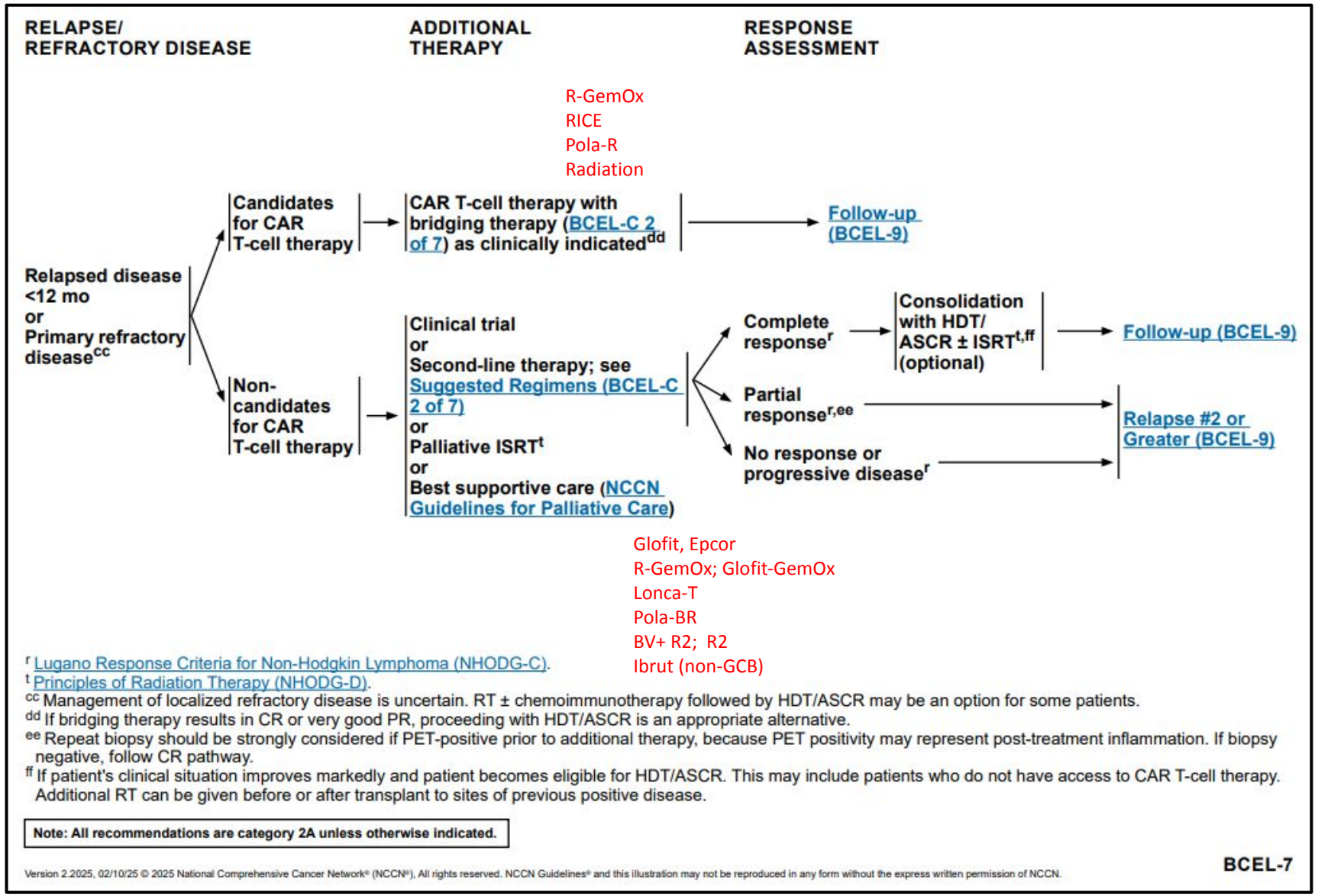
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[t] Principles of Radiation Therapy (NHODG-D).
[gg] Some NCCN Member Institutions require a complete metabolic response in order to proceed to HDT/ASCR.
[hh] Additional RT can be given before or after transplant to sites of previous positive disease.
[ii] Selected cases include mobilization failures and persistent bone marrow involvement.
[jj] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.

TREATMENT FOR RELAPSE #2 OR GREATER

Glofit, Epcor
CAR-T
Bv + R2
Lonca-T
Selinexor

Third-line therapy (BCEL-C 4 of 7) or Alternative systemic therapy for relapsed/refractory disease (not previously given)[ll] (BCEL-C 2 of 7 and BCEL-C 3 of 7) → If CR/PR, consider allogeneic HCT in selected cases[ii,nn] ± ISRT[t,hh]
or Clinical trial[mm]
or Palliative ISRT[t,mm]
or Best supportive care[mm] (See NCCN Guidelines for Palliative Care)

NCCN Guidelines



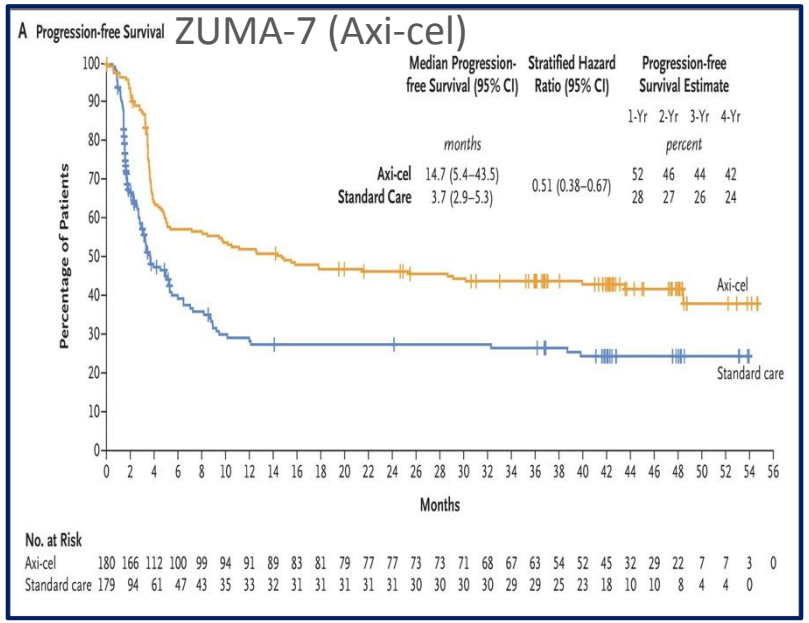
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[t] Principles of Radiation Therapy (NHODG-D).
[cc] Management of localized refractory disease is uncertain. RT ± chemoimmunotherapy followed by HDT/ASCR may be an option for some patients.
[dd] If bridging therapy results in CR or very good PR, proceeding with HDT/ASCR is an appropriate alternative.
[ee] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[ff] If patient's clinical situation improves markedly and patient becomes eligible for HDT/ASCR. This may include patients who do not have access to CAR T-cell therapy. Additional RT can be given before or after transplant to sites of previous positive disease.

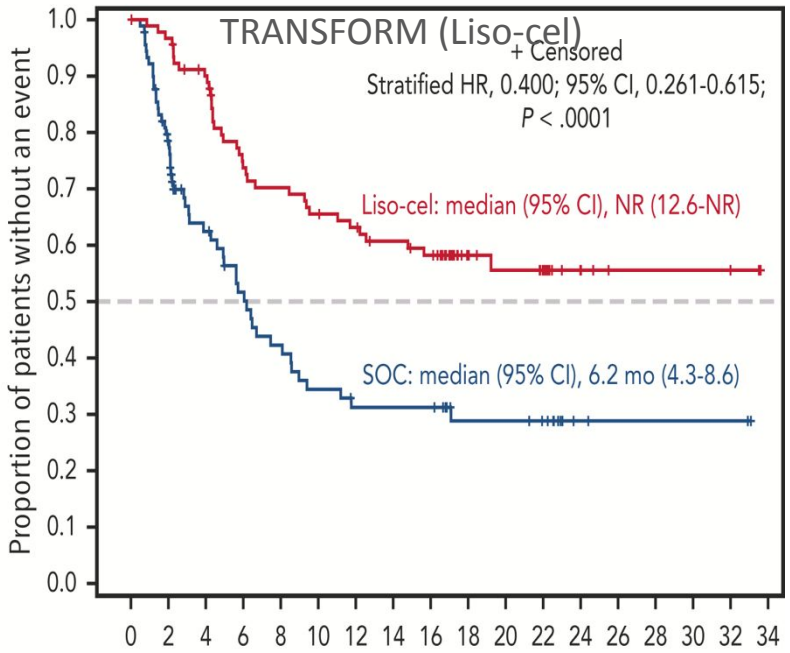
Note: All recommendations are category 2A unless otherwise indicated.

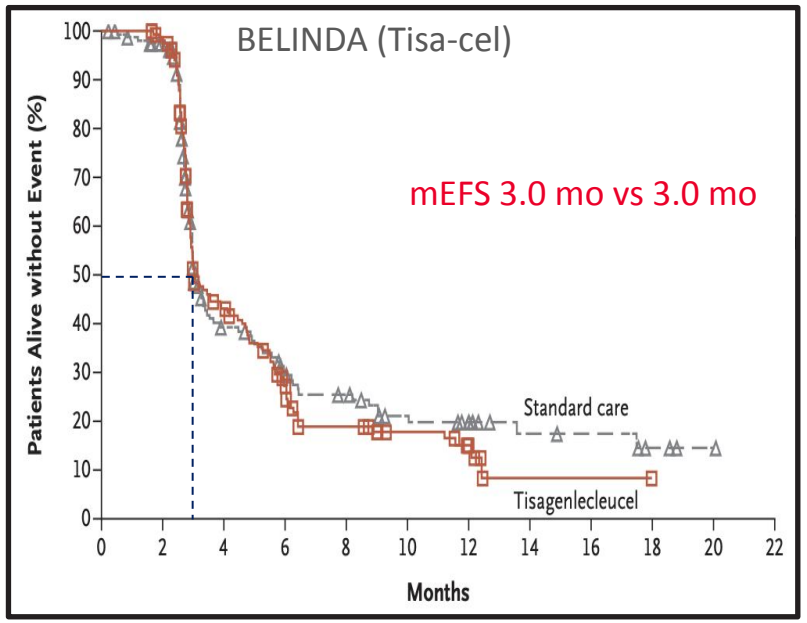
BCEL-7

Randomized Trials of CD19 CAR-T vs auto-HCT in 2L

- All 3 studies had similar design – enroll pts at time of 1L treatment failure
- For pts randomized to std therapy (salvage Rx □ auto if chemosensitive), if not chemosensitive, this was counted as an event
  - We know at least 50% will not be chemosensitive!!
- ZUMA-7 did not allow crossover to SOC CAR; TRANSFORM and BELINDA did
- EFS benefit in favor of CAR in ZUMA-7 and TRANSFORM; not seen in BELINDA



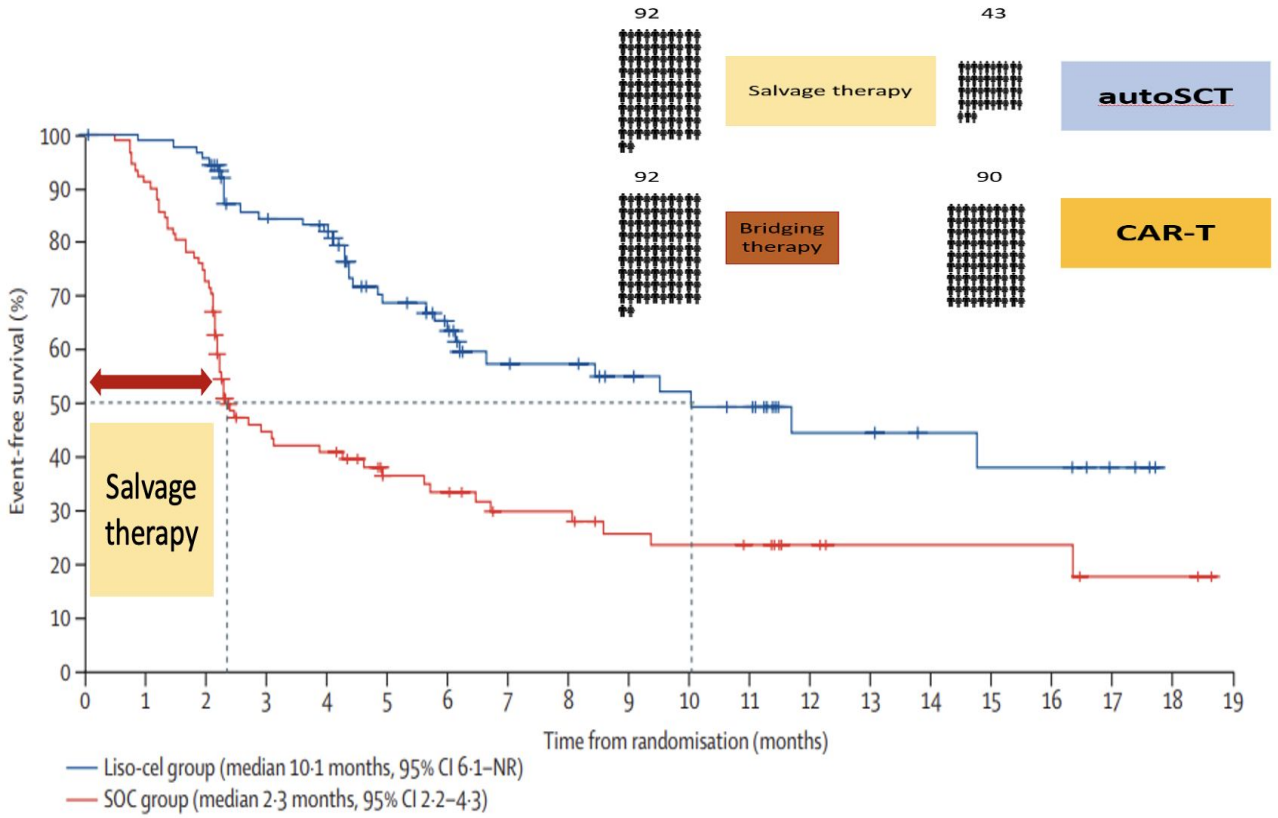




Westin. *N Engl J Med*. 2023; Abramson. *Blood*. 2023; Bishop. *N Engl J Med*. 2022.

ZUMA-7 and TRANSFORM Were Designed To Get 2L Approval

- There was really no way the SOC arm could win in terms of EFS. EFS immediately drops to 50% after salvage Rx.

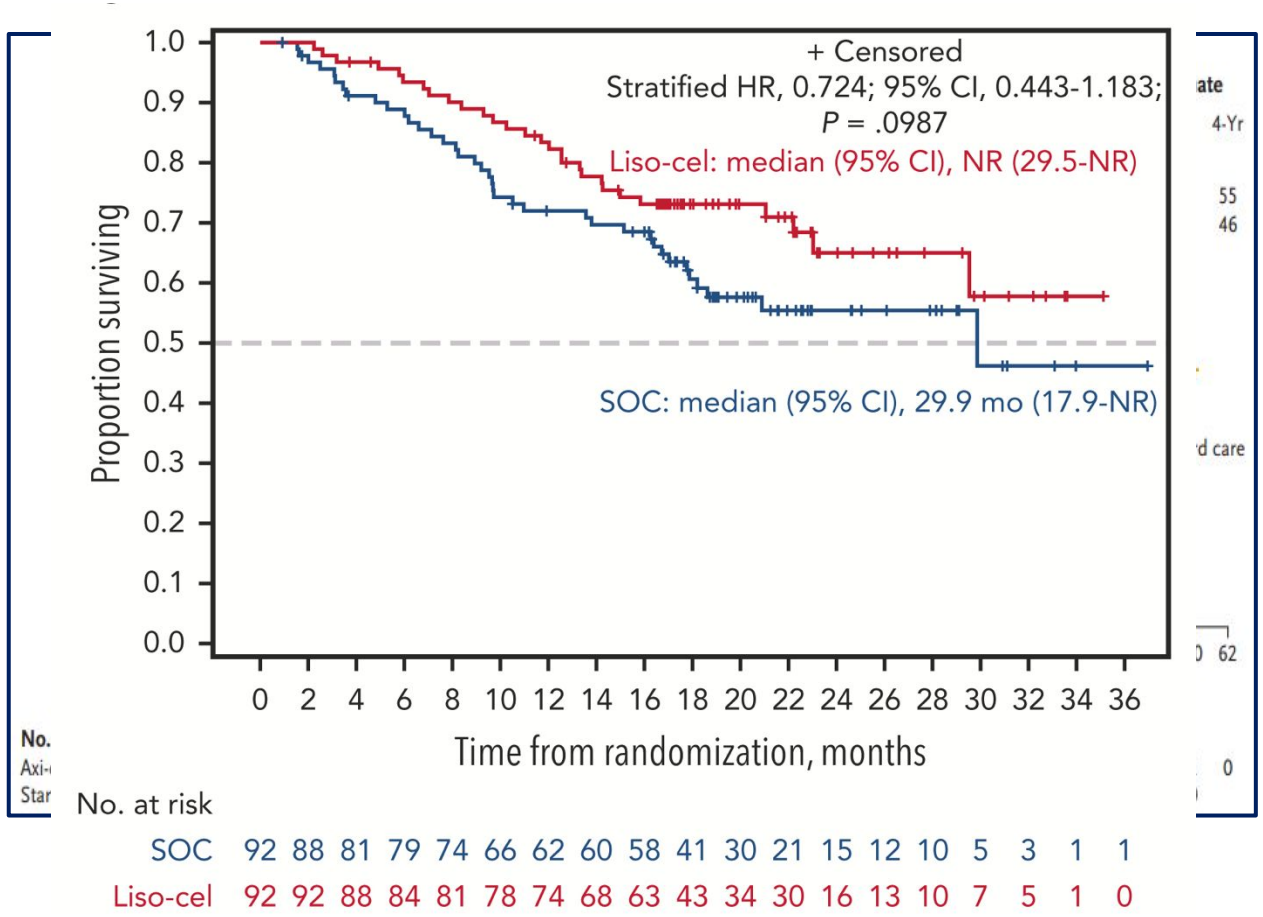


Graphic courtesy of M. Shadman

ZUMA-7 and TRANSFORM: OS Outcomes

- At median follow-up of 47 mo, an OS benefit emerged
- 3-yr OS 56% vs 48%
- For TRANSFORM, at median f/u of 34 mo, OS benefit not seen but trending

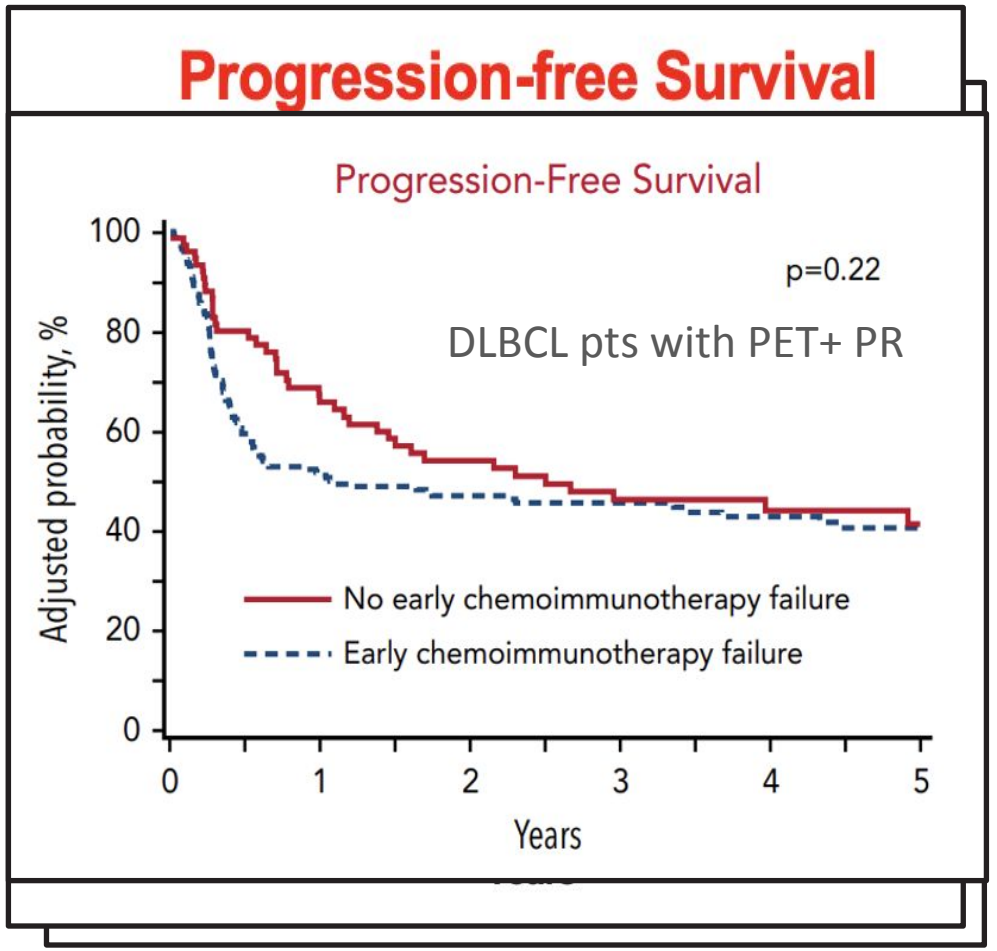
- So is there a population who relapse < 12 mo to whom we might offer transplant? Which patients?



Westin et al. *N Engl J Med*. 2023; Kamdar. ASCO 2024.

Why Consider Auto for Pts With Early-Relapse DLBCL still?

- We have known for years that we can cure about 40% of chemosensitive patients with EARLY (<1 year) FAILURE with auto-HCT
- Multiple studies have shown this
- Yet with the advent of CAR-T, many are not even considering auto-HCT for these patients (even NCCN)
- Also, we know that we can successfully offer CAR-T to patients who relapse after auto-HCT



Gisselbrecht et al. *J Clin Oncol*. 2010; Hamadani et al. *Biol Blood Marrow Transplant*. 2014; Shah et al. *Blood*. 2021.

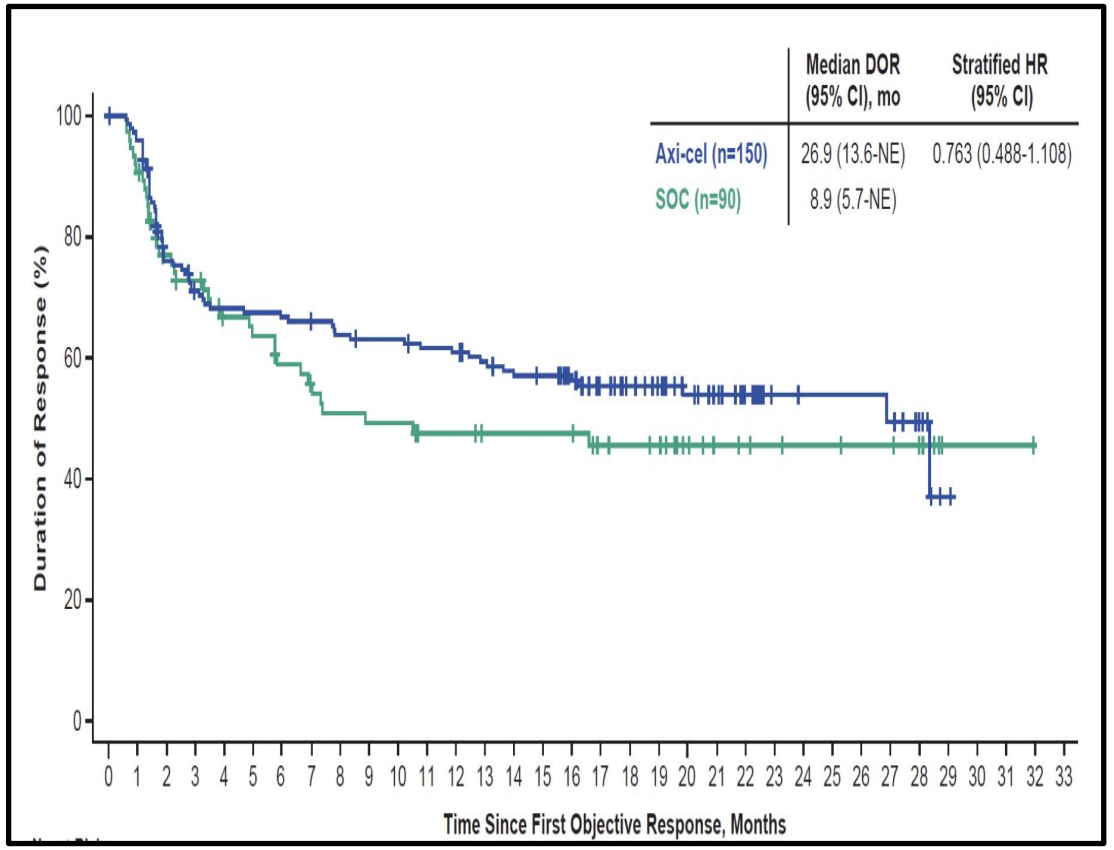
How Can We Offer Auto to Pts With Early-Relapse DLBCL With the ZUMA-7 OS Benefit That Was Seen for CAR-T?

- 74% were primary refractory and 26% were “relapse <12 mo”
- Of the pts in the SOC arm who received 3L therapy, only 48% received CD19 CAR-T therapy. Additional 6% received other experimental or unspecified CAR-T therapies
- In practice today
  - We would not pursue auto-HCT for a patient with primary refractory disease
  - For a patient with a relapse <12 mo, we may attempt salvage chemotherapy but be ready to quickly change gears to CAR-T
- The main argument is that we want to tease out the subgroup of patients with early relapse whom we can offer TWO ATTEMPTS at cure. If they are chemosensitive:
  - 40% chance of cure with auto-HCT
  - Another 30%-40% chance for cure with subsequent CAR-T, if needed

Why would we just “give away” a chance at cure?

What About Those Who Made It to Transplant in ZUMA-7?

- "In patients who received and had a response to salvage chemoimmunotherapy and thus were able to proceed to high-dose chemotherapy with autologous stem-cell transplantation, **outcomes were not as poor**. Although the duration of response was numerically favorable for axi-cel, the 95% confidence interval was broad and **consistent with the possibility of no effect** (Fig S4)."



Locke. *N Engl J Med*. 2022.

Two Shots On Goal Are Better Than One

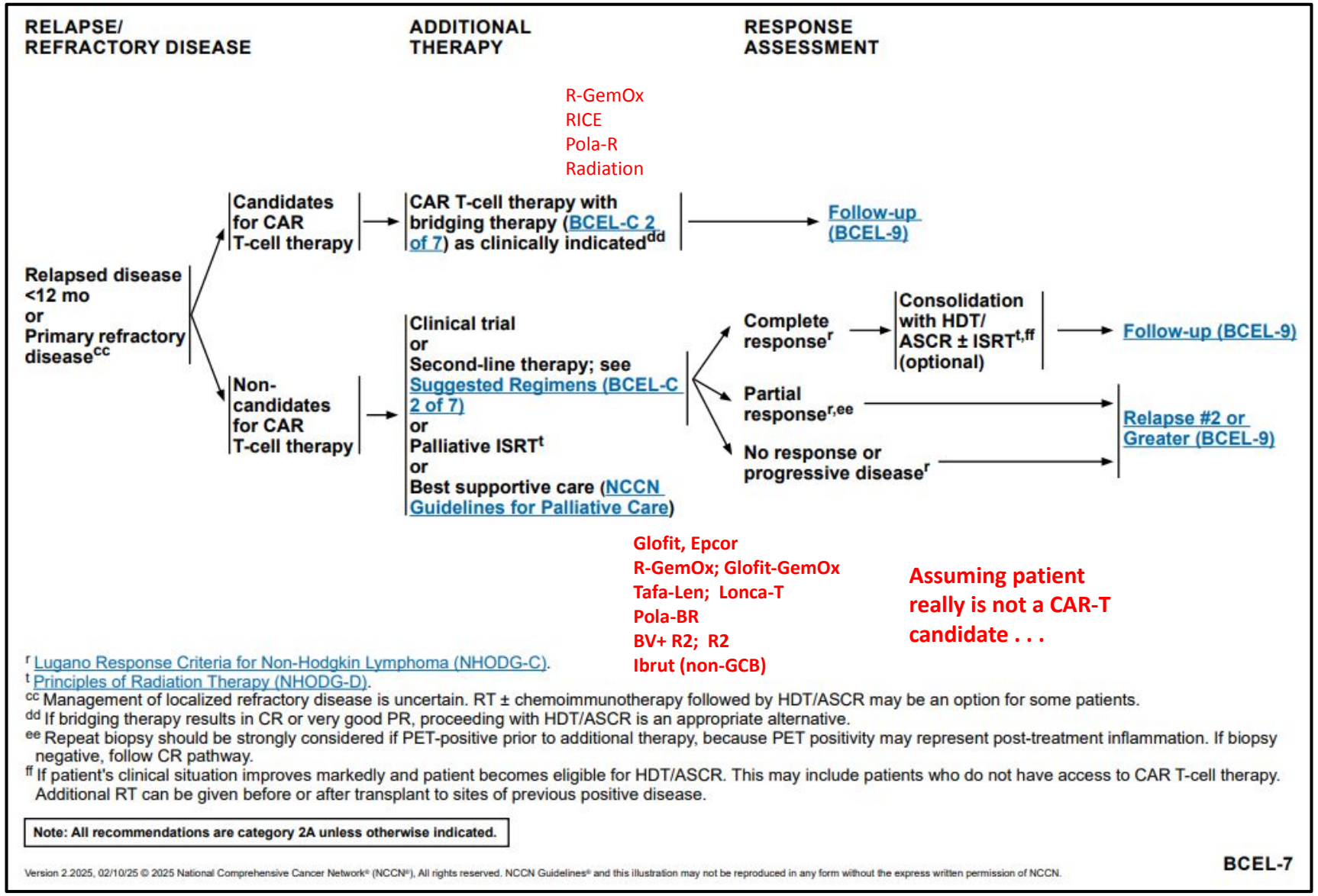
Bispecifics vs CAR? How to sequence?

Personally, I don't think there is a debate here…

In 2L, try for CAR vs auto as we just discussed

In 3L+, try for CAR, if at all possible

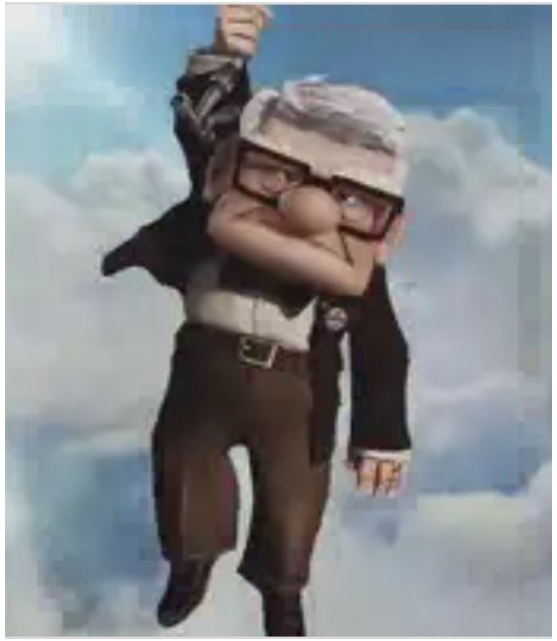
NCCN Guidelines

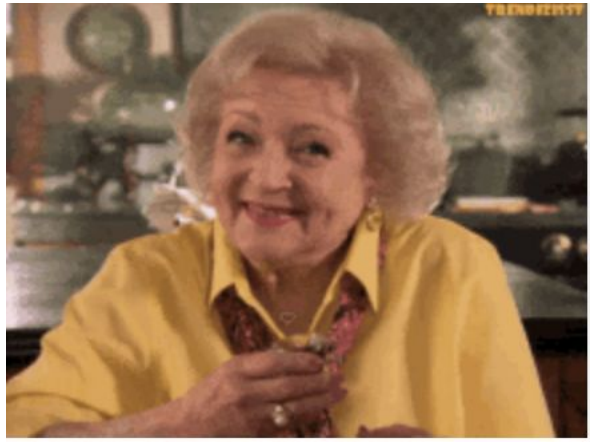


Best Option for Pts With R/R DLBCL Who Are Not Auto-HCT or CAR-T Candidates?

Example: 80+ years old, ECOG PS=2, lives far from CAR-T center

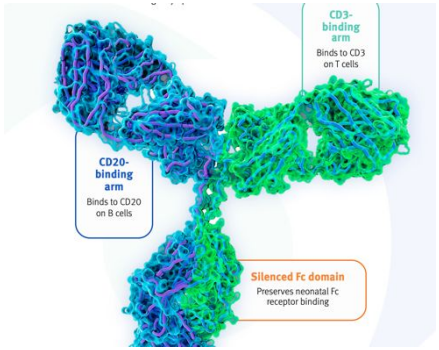
But Is Anyone Really Not a CAR-T Candidate…?





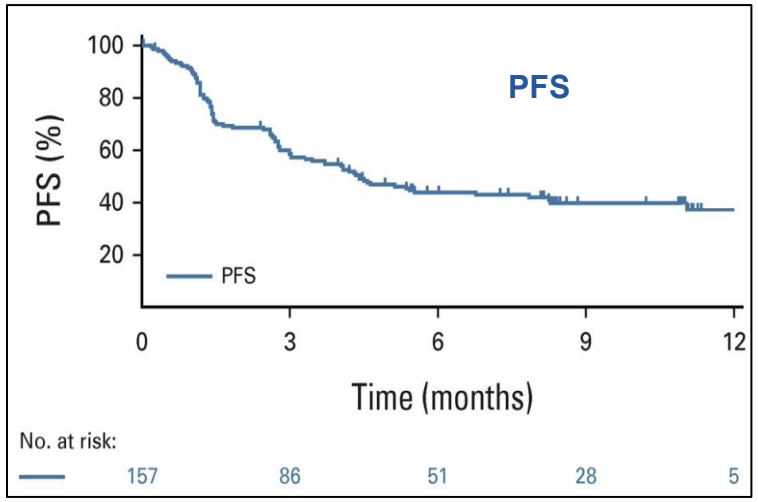
But Is Anyone Really Not a CAR-T Candidate…?

Epcoritamab



C1D1, D8 0.16 mg/0.8 mg SC step up
C1D15 to C3 48 mg weekly SC
C4-9 48 mg SC q2w
C10+ 48 mg SC q4w

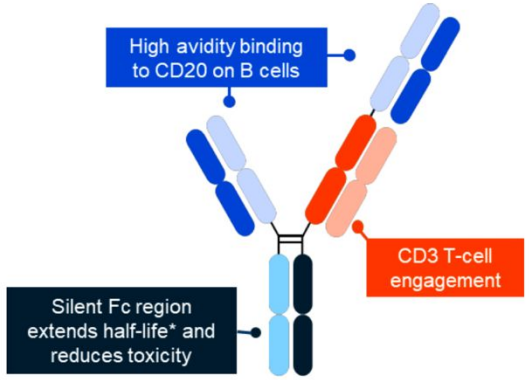
ORR 63%, CR 40%



Median PFS 4.4 mo
6 mo PFS 44%

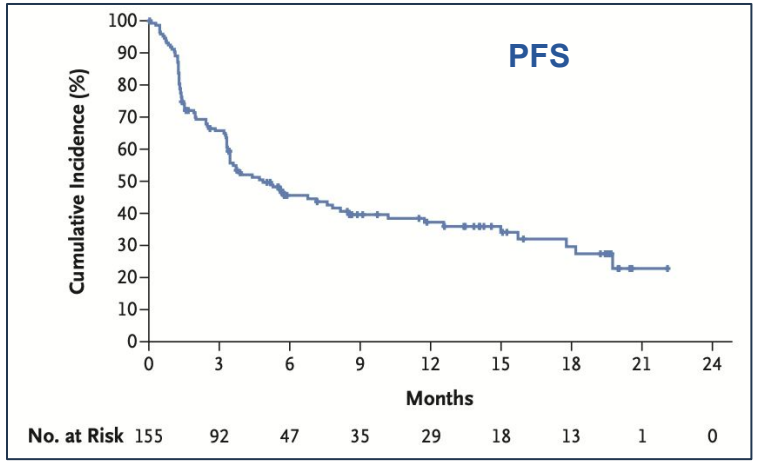
Landmark PFS (C3 CR)
24 mo 62% PFS

Glofitamab



C1D1 Obinutuzumab
C1D8, D15 2.5 mg/10 mg IV Step up
C2-12 30 mg IV once every 21 days

ORR 62%, CR 40%



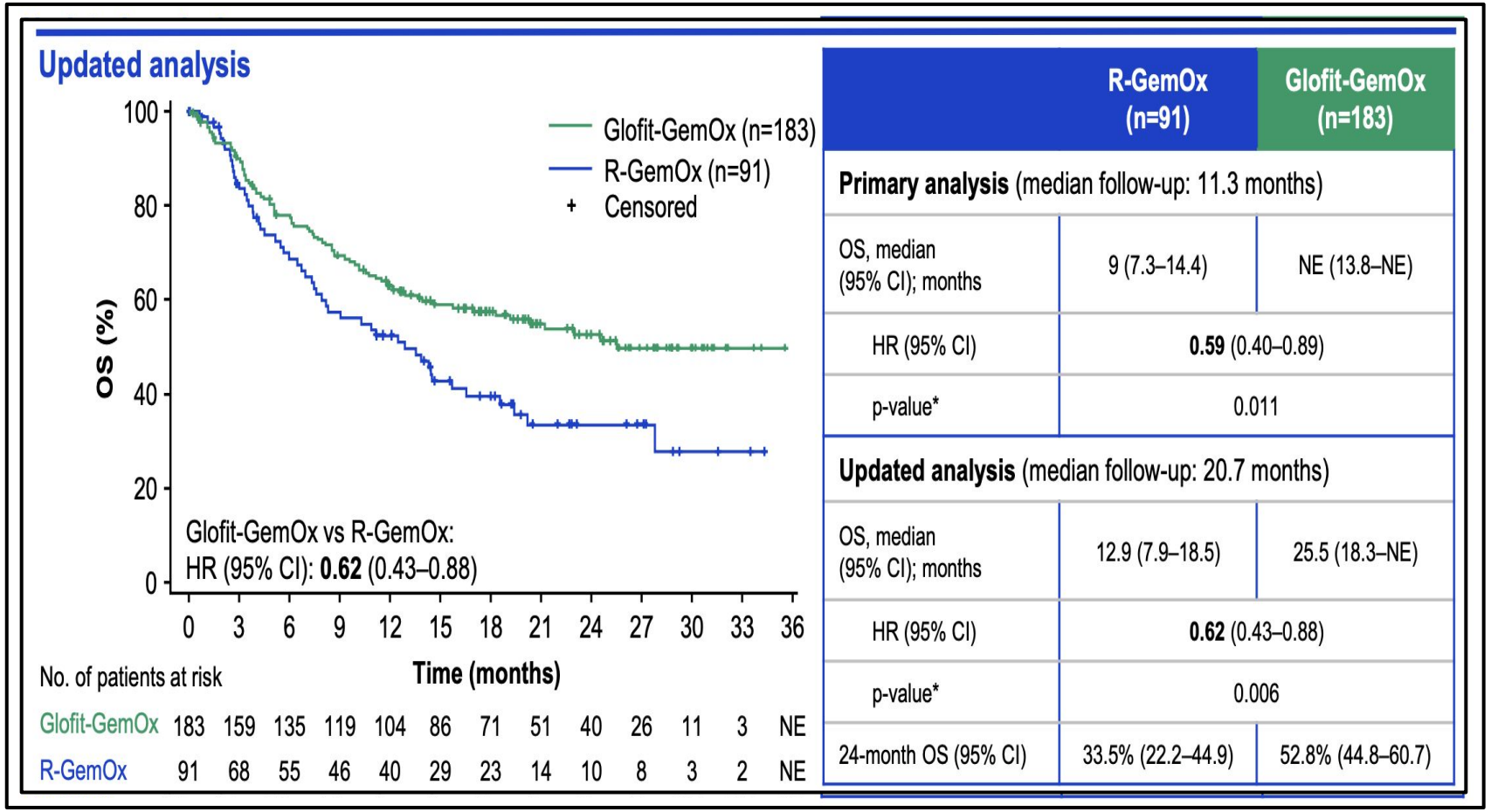
Median PFS 4.9 mo
12 mo PFS 37%

Landmark PFS (C3 CR)
24 mo 63.5% PFS

Karimi Y et al., ASCO 2024; Thieblemont C et al. *J Clin Oncol*. 2022.
Dickinson M et al. *N Engl J Med*. 2022; Hutchings M et al. ASH 2023.

STARGLO Study

- R-Gem-Oxali vs Glofit-Gem-Oxali
- N=274
- Randomized 2:1
- Median 1 pLOT but also included pts with 2 or more pLOT (102 pts - 37%)
- ORR 68% fs 41%
- CR 58% vs 25%
- Med PFS 13.8 vs 3.6 mo
- Among pts with 2 or more pLOT, median PFS 9.2 vs 2.0 mo

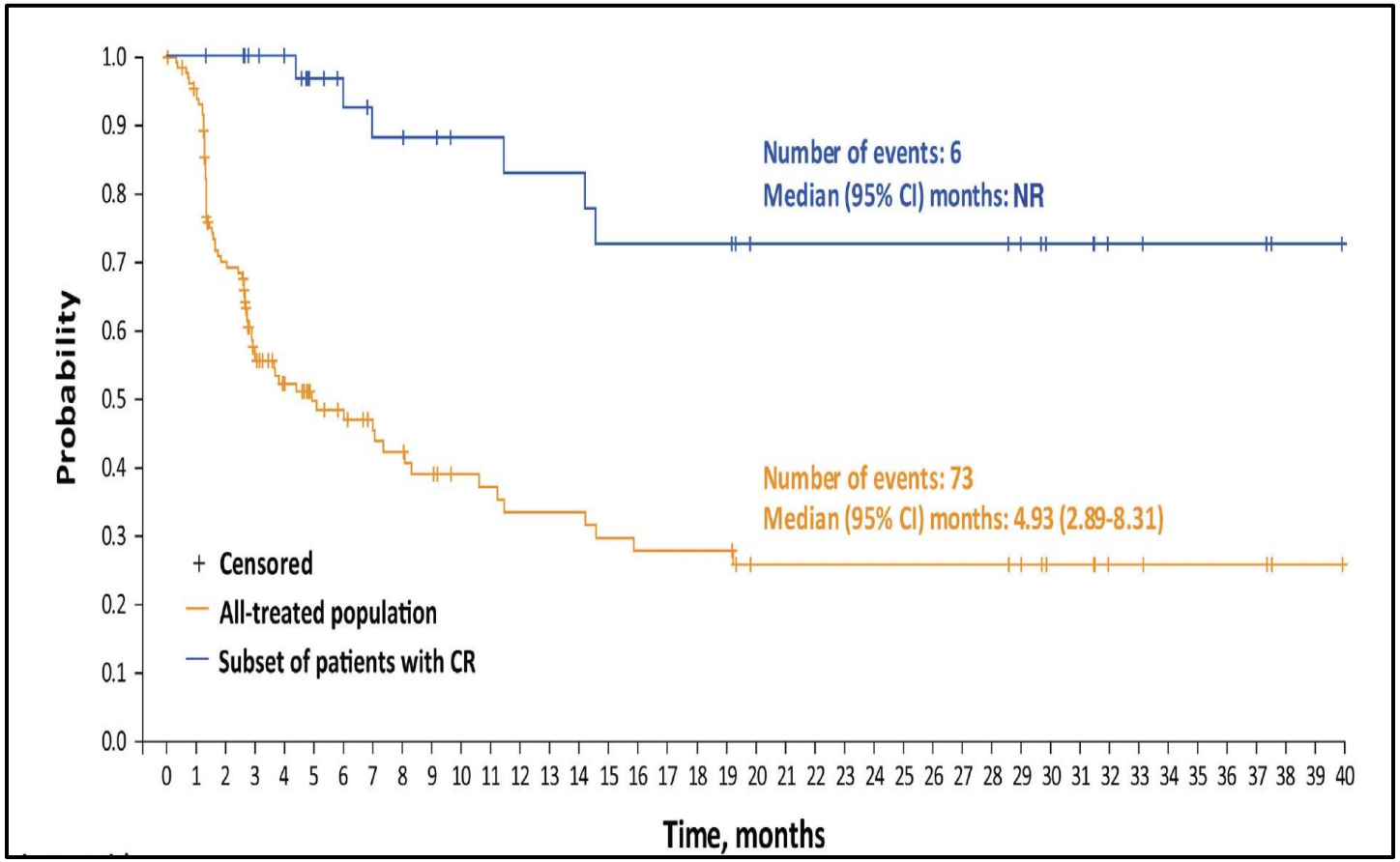


	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
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)

Abramson et al. *Lancet*. 2024.

LOTIS-2 – LoncaT in R/R DLBCL

- 145 patients
- 3 median pLOT
- ORR 48%; CR 25%
- Median PFS 4.9 mo
- Among pts with CR, few relapses after 12-18 mo
- Q21d outpt 30-min infusion



Caimi et al. *Haematologica*. 2024.

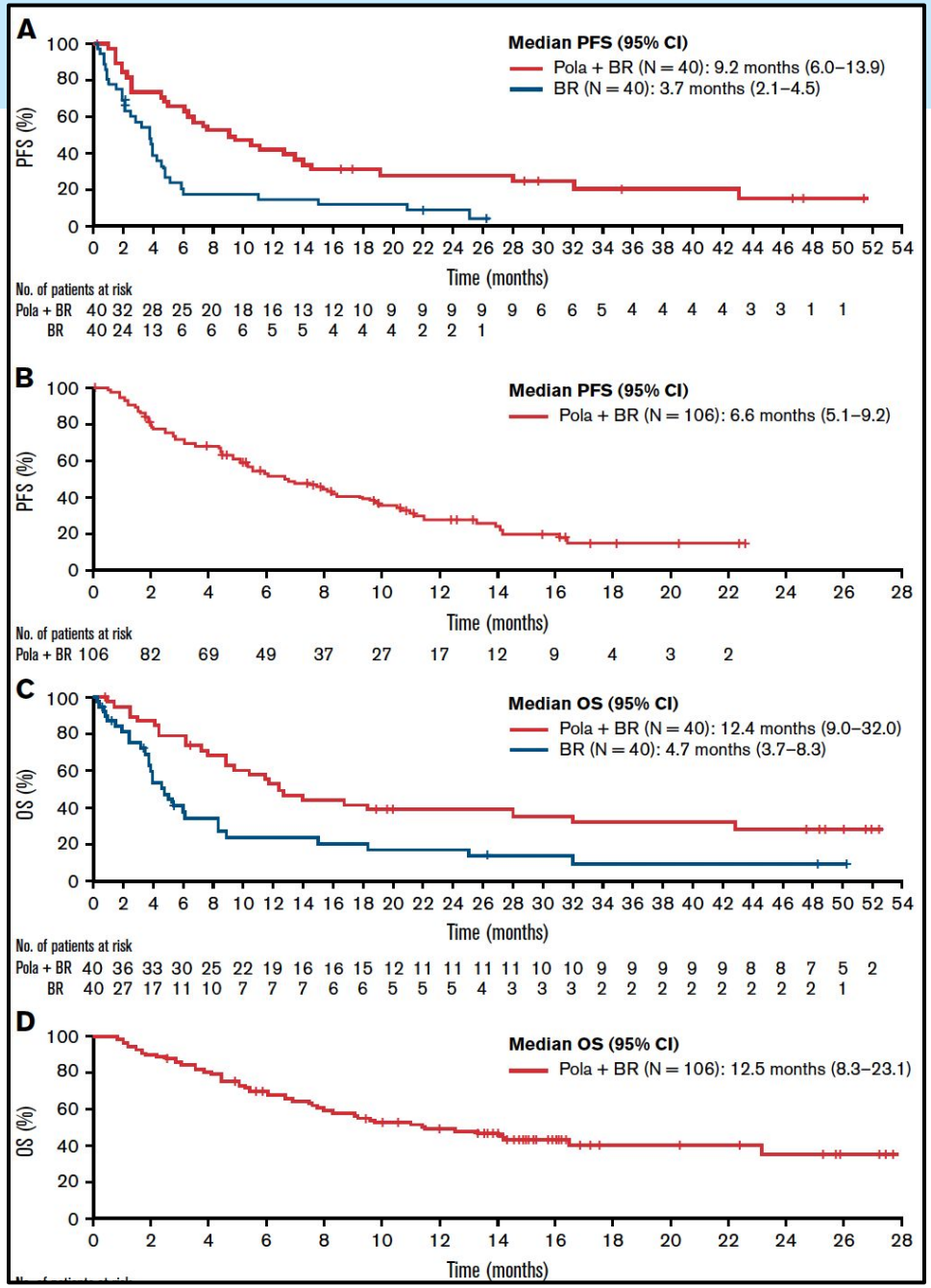
Pola-BR Trial

- 80 pts randomized (40 BR, 40 PolaBR)
- 106 more pts on expansion cohort (PolaBR)
- 57% ORR
- 53% CR
- Median PFS 6.6 mo
- Median OS 9.5 mo

- PFS and OS benefit in favor of Pola-BR in randomized cohort

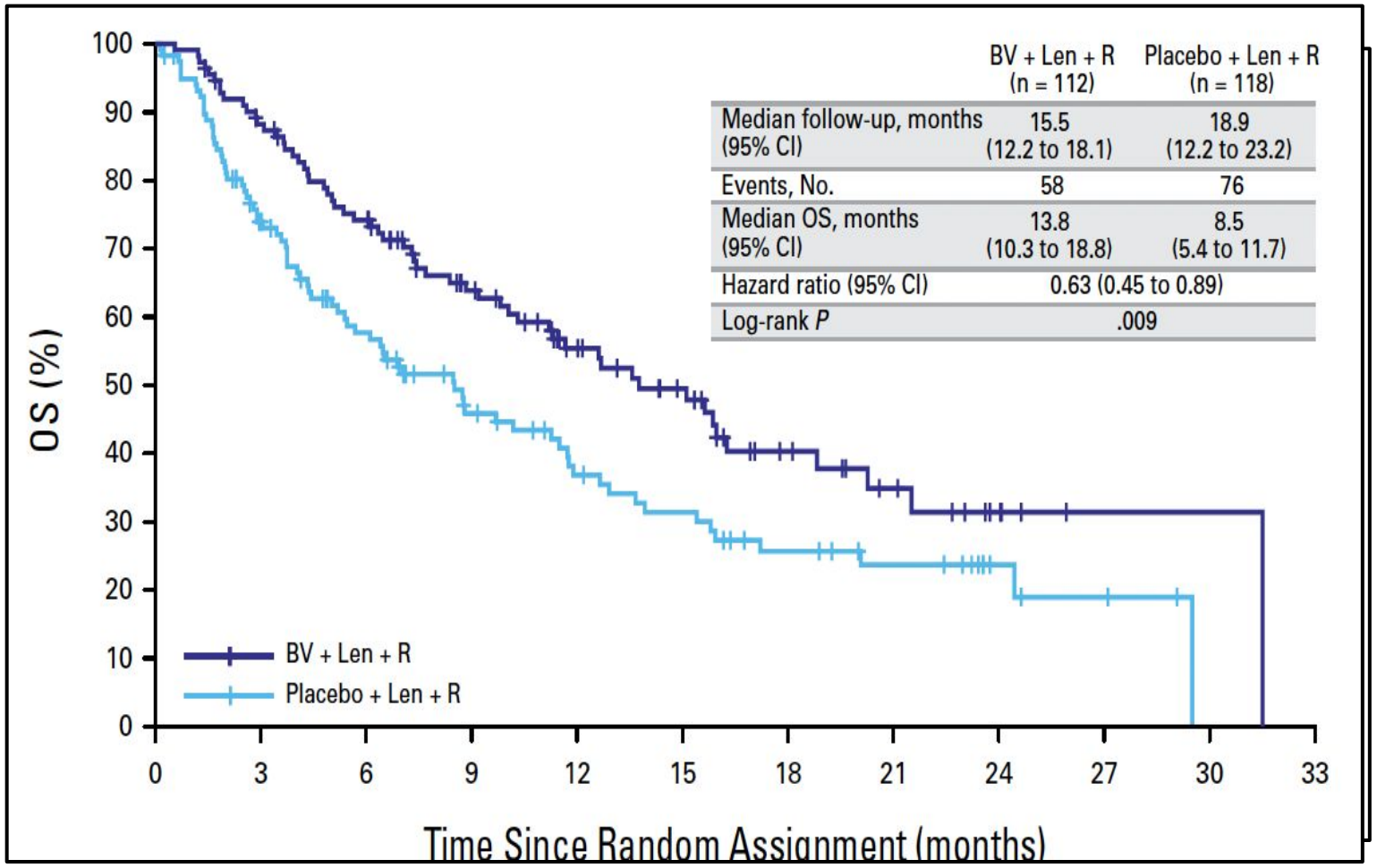
- In practice, cytopenias can be a challenge
- 49% Gr3-4 neutropenia, 31% Gr3-4 thrombocytopenia
- 33% Gr3-4 infection
- Also, if patient even *might* be a CAR candidate, **avoid bendamustine**

Sehn et al. *Blood Adv*. 2022.



ECHELON-3 (R2 +/- Bv)

- 230 pts, randomized 1:1
- R2 vs Bv+R2
- CD30 expression not required
- ORR 64% vs 42%
- CR rate 40% vs 19%
- Med PFS 4.2 mo vs 2.6 mo
- Med OS 13.8 mo vs 8.5 mo
- PFS and OS not affected by CD30+ or CD30-



	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 et al. *J Clin Oncol*. 2025.

Options for R/R DLBCL If Not CAR-T Eligible

Regimen	# pts	med pLOT	ORR	CR	PFS	Comments
Glofitamab	154	3 (2-7)	62%	40%	med 4.9 mo	Prior auto 18%; prior CAR 33%
Epcoritamab	157	3 (2-11)	63%	40%	med 4.4 mo	48% Gr1-2 CRS; 3% Gr3 CRS Prior auto 20%; prior CAR 39%
Glofit-GemOx R-GemOx	183 91	1 (1-4) 1 (1-4)	68% 41%	58% 25%	med 13.8 mo med 3.6 mo	Prior CAR 8%, prior auto 4% For pts 1 pLOT, mPFS 20.4 vs 5.6 mo For pts ≥ 2 pLOT, mPFS 9.2 vs 2.0 mo
Pola-BR	106	2 (1-7)	57%	53%	med 6.6 mo	Prior auto 16%; prior CAR 1%
Lonca-T	145	3 (2-7)	48%	25%	med 4.9 mo	Prior auto 17%; prior CAR 10%
Bv + R^2 R^2	112 118	3 (2-7) 3 (2-8)	64% 42%	40% 19%	med 4.2 mo med 2.6 mo	68% of pts CD30-neg Prior auto 30%, CAR 15%, BiTE 17%
Tafa-Len	80	1 (1-4)	58%	41%	med 11.6 mo	No PIF or relapse within 3-6 mo
Selinexor	127	2 (1-5)	28%	12%	med 2.6 mo	Freq dose mods / GI tox. Pts had to respond to last LOT or last LOT >14 wk
Ibrutinib + R^2	89	2 (2-3)	49%	28%	med 5.4 mo	Prior auto 22%
Mosun + Pola R+Pola	40 40	2 (1-5) 3 (1-9)	78% 50%	58% 35%	med NR med 6.4 mo	8 cycles fixed duration Prior CAR 36%

Ongoing ph3 trials versus R-GemOx: Lonca-T (LOTIS-5); Epcor+Len (EPCOR DLBCL-4); and Mosun+Pola (SUNMO)

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PANEL DISCUSSION

THE 2nd ANNUAL
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Q & A

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