Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

# ¿Cómo ha cambiado el algoritmo terapéutico en el linfoma de células grandes?


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# Conflictos de interés

## Advisory Boards:

Abbvie, Amgen, Celgene, Gilead, Incyte, Johnson & Johnson, Kern, LIlly, Roche, Sobi, Servier

## Ponencias en simposios:

Abbvie, Amgen, Astra-Zeneca, Celgene, Johnson & Johnson, Roche, Takeda

## Asistencia a congresos:

Abbvie, Amgen, Johnson & Johnson, Kern, Pfizer, Roche, Sandoz, Takeda

## Ayudas a investigación:

Roche

# Large B-cell lymphoma
# Diagnosis and Risk Stratification

**High-grade B-cell lymphoma with MYC and BCL2 rearrangements**
*(High-grade B-cell lymphoma, NOS)*

*Consider intensive therapy*
*e.g., **DA-EPOCH-R**, BURKIMAB*

**Diffuse large B-cell lymphoma, NOS**

**Other large B-cell lymphoma**

*Consider alternative treatments*

**Limited-Stage**

***R-CHOP +/- XRT:***

*4 cycles of R-CHOP (bulk < 7,5 cm, aaIPI=0*
*4-6 cycles of R-CHOP + PET guided XRT*

**Advanced-Stage**

**IPI 0-1**

***R-CHOP x 6***

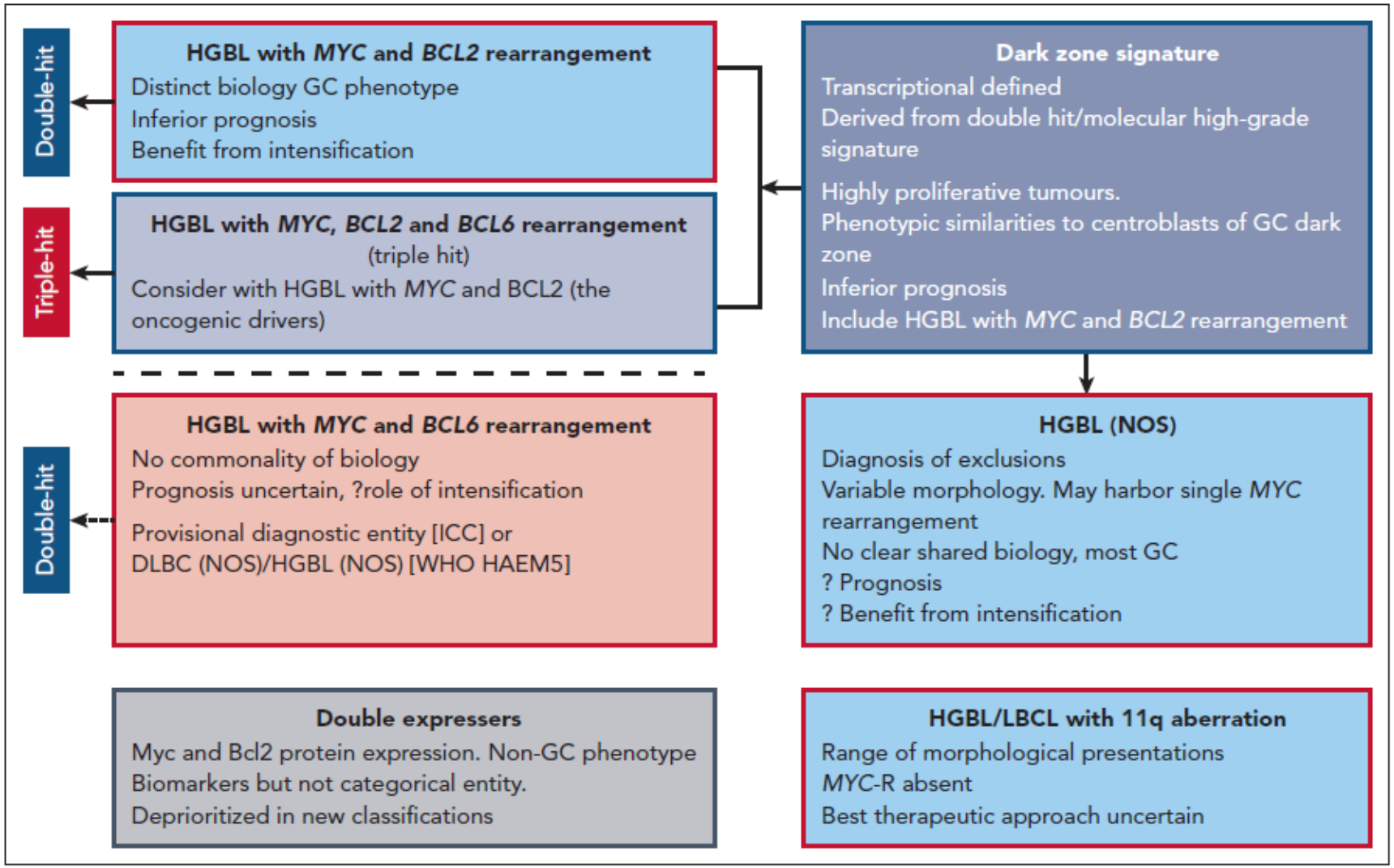
**IPI 2-5**

***Pola-R-CHP x 6***

*High CNS risk: 2-3 HDMTX at the end*

*Adapted from: Laurie H. Sehn and Gilles Salles. N Engl J Med. 2021; Tavakkoli M and Barta S. Am J Hematol. 2023*

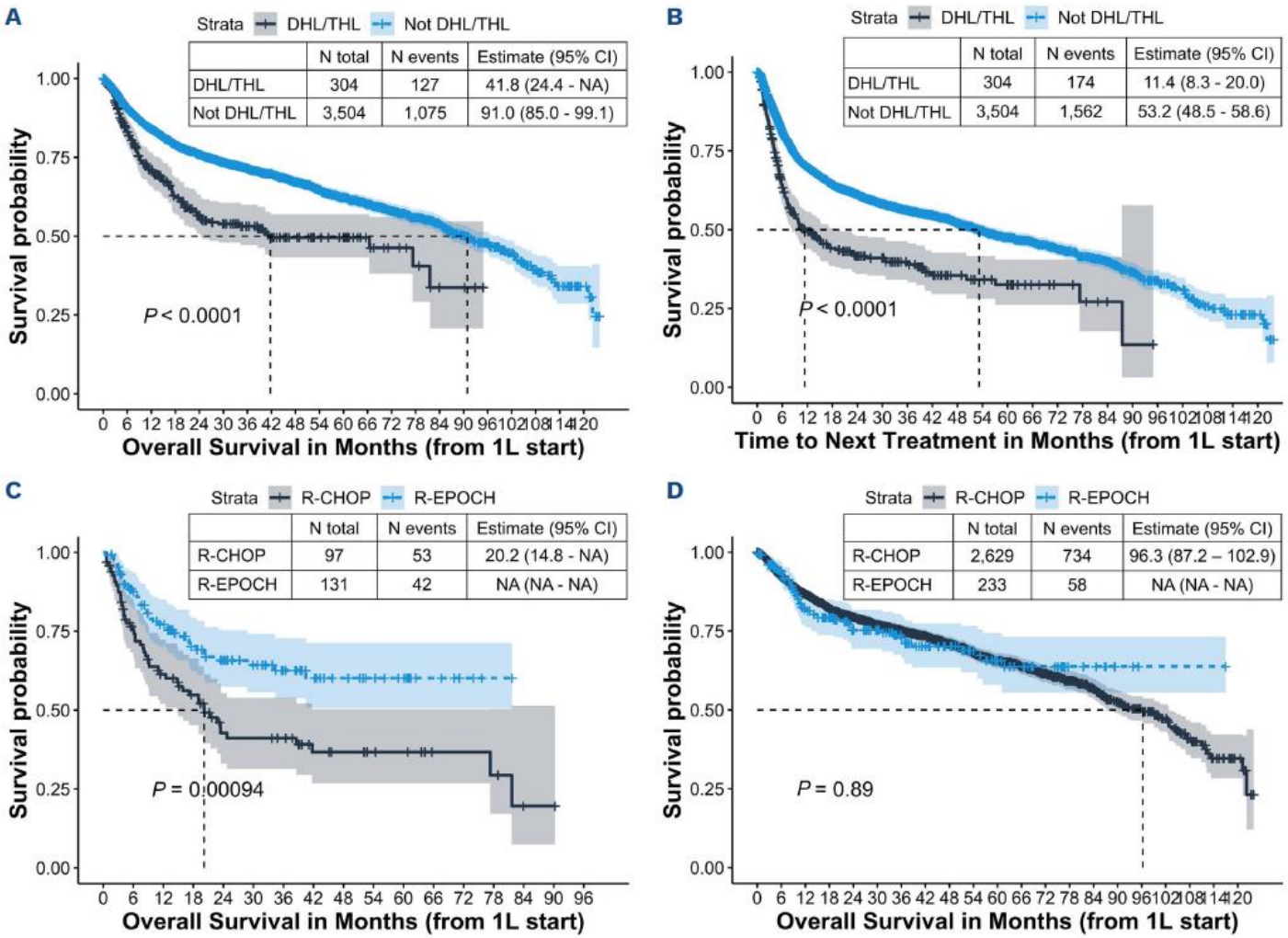
# High grade B cell lymphoma classification




*Andrew J. Davies. Blood (2024) 144 (25): 2583-2592.*

# Clinical outcomes in DLBCL with or without double/triple-hit

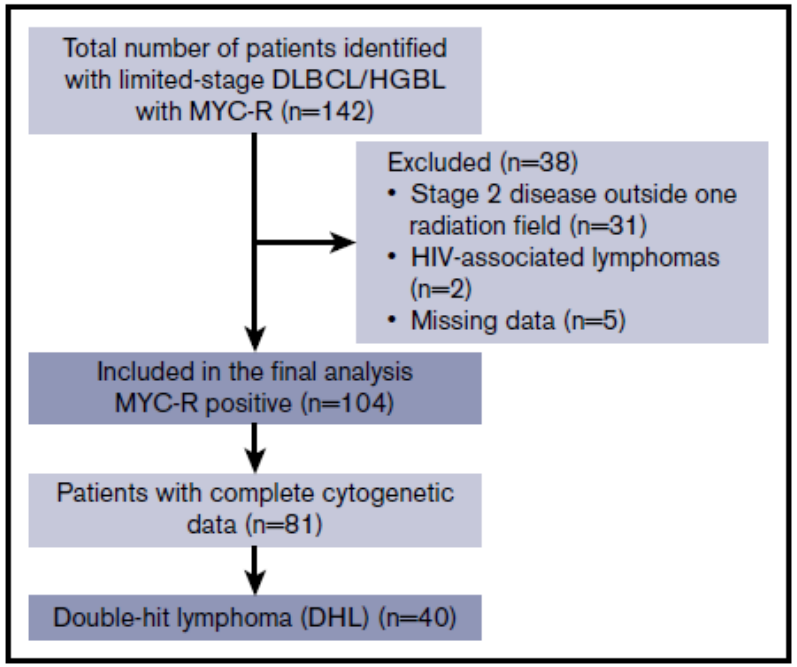
## Analysis *from the Flatiron Health registry*

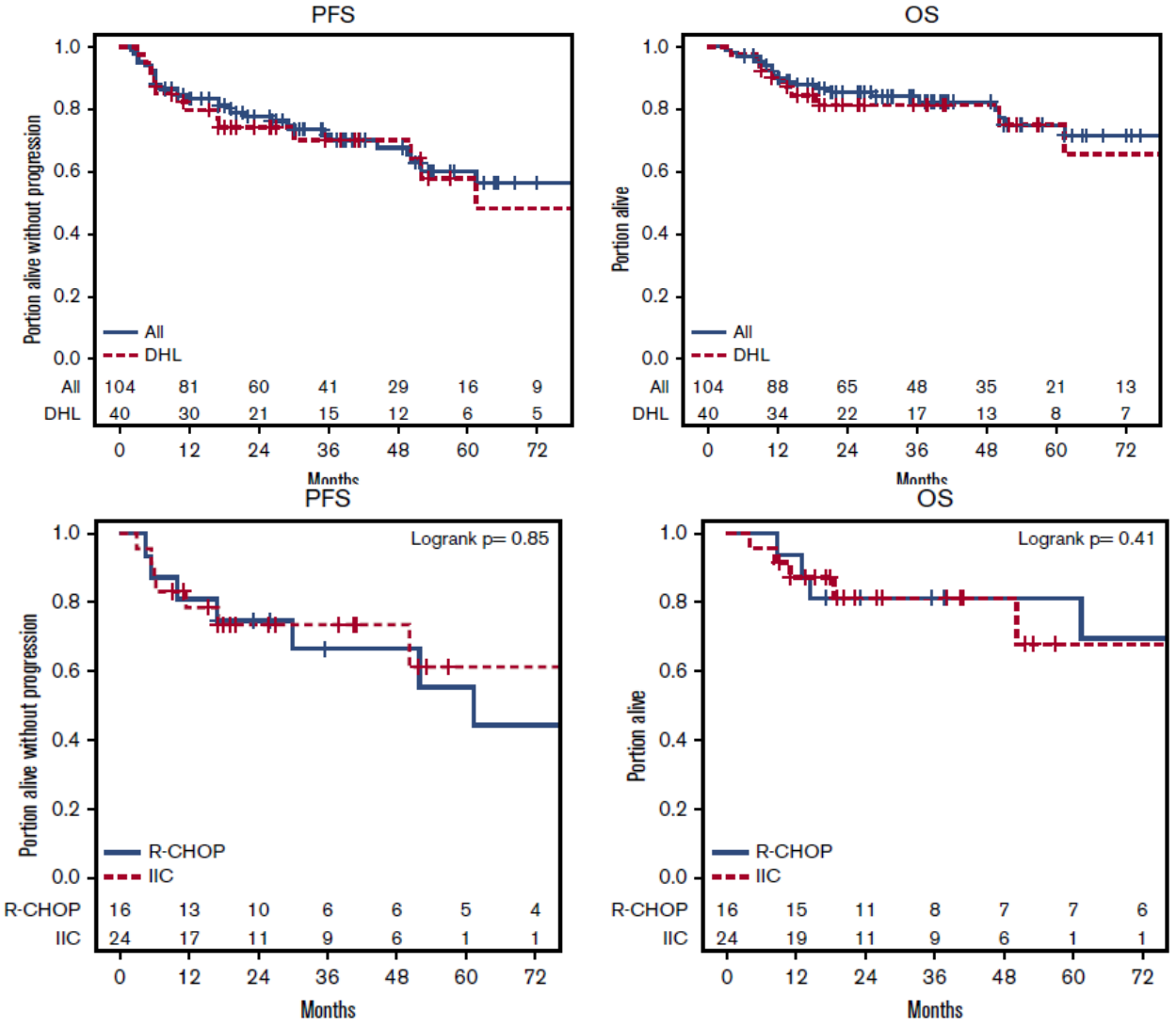



*Goyal G, et al. Haematologica 2023.*

# Limited-stage aggressive large B-cell lymphoma with high-risk cytogenetics

*No benefit of using intensive immunochemotherapy*



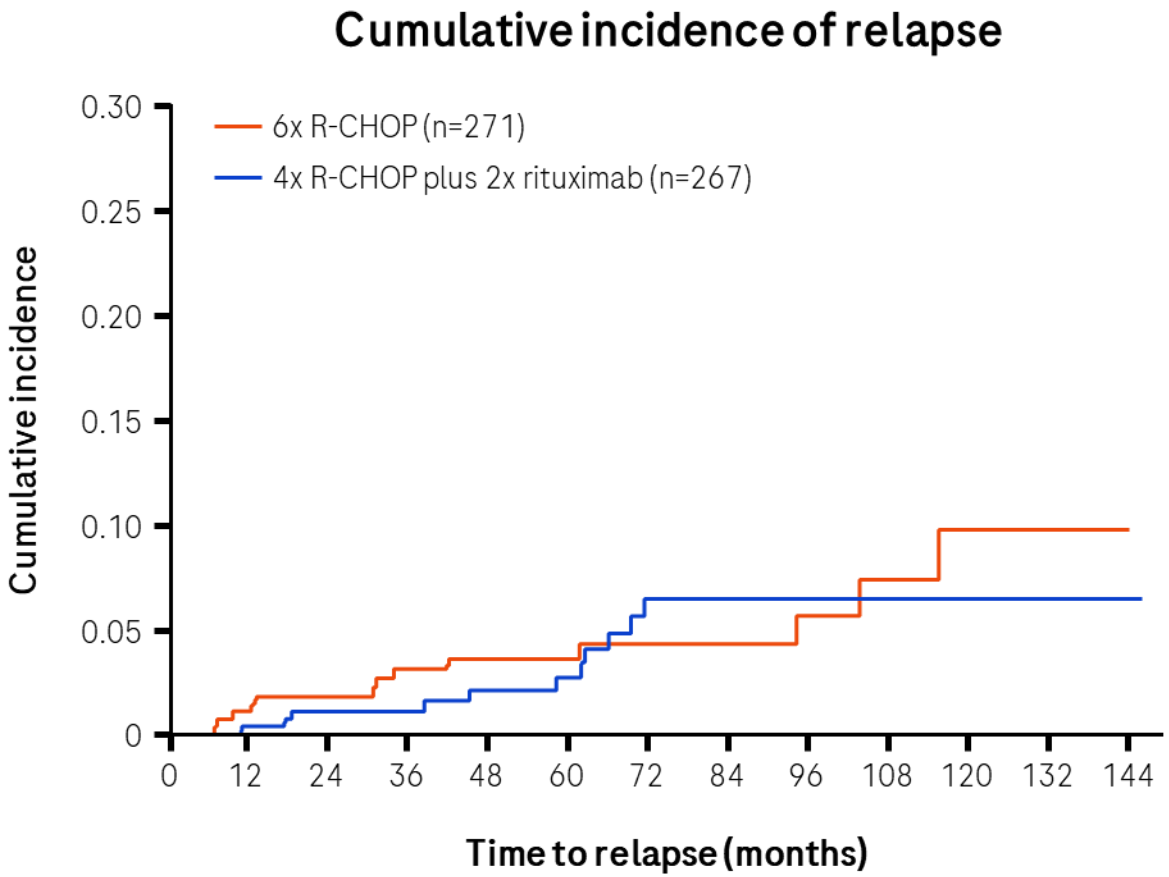

*Torka P. et al.Blood Advances 2020*

# R-CHOP can be safely de-escalated in favourable limited stage DLBCL

**FLYER study:** four cycles of R-CHOP followed by two cycles of rituximab versus six cycles of R-CHOP

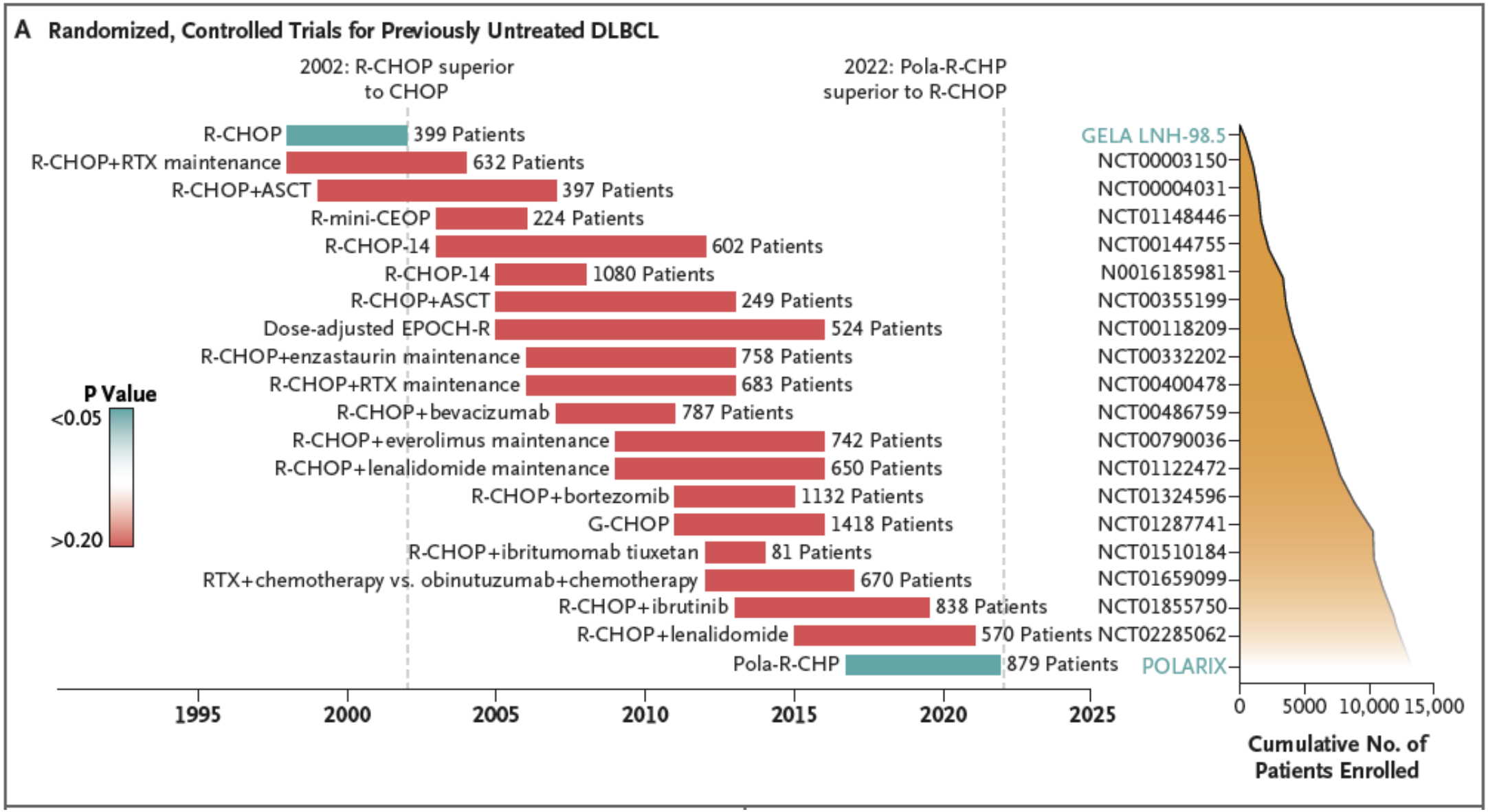
Patients were aged 18–60 years

Patients had no risk factors according to age-adjusted IPI (0 points) and did not have bulky disease




*Poeschel V, et al. Lancet 2019*

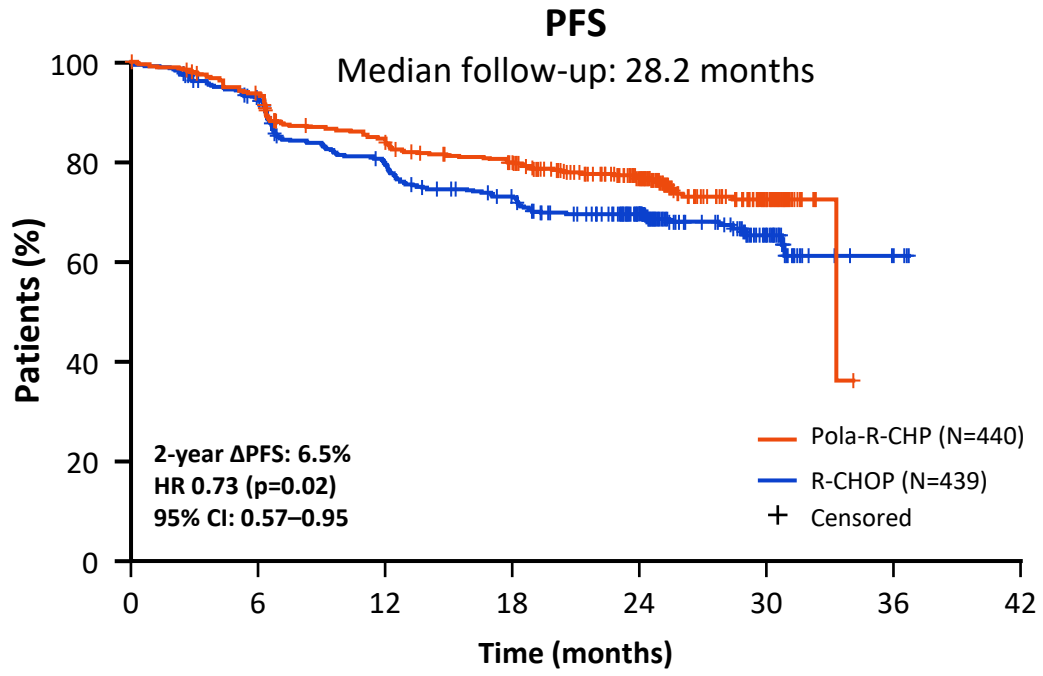
# There have been many attempts to improve on R-CHOP for 1L DLBCL



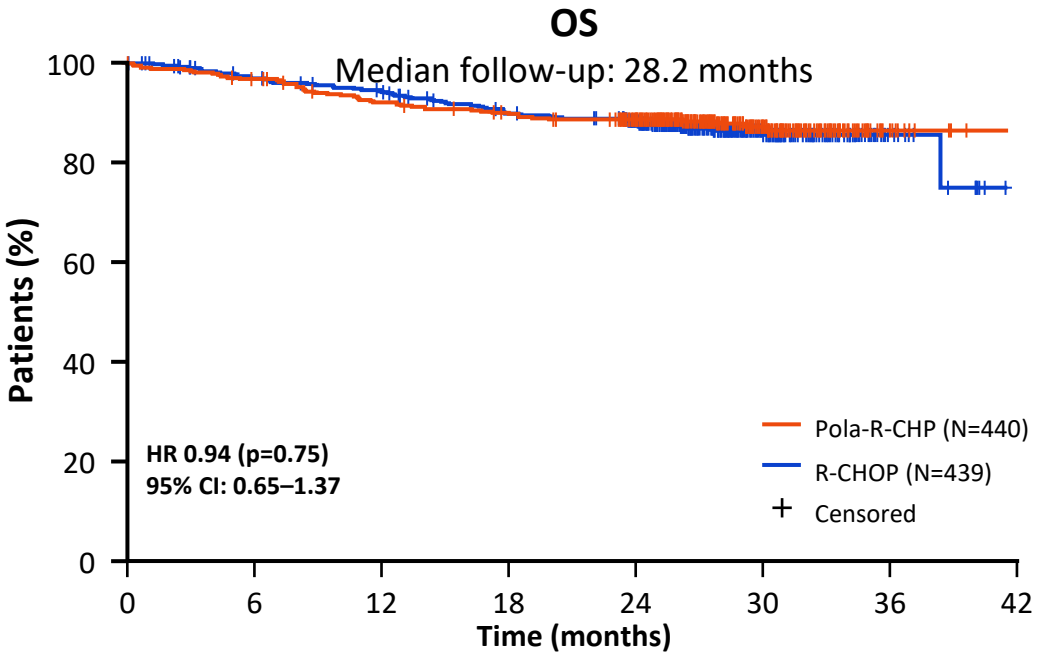

*1. Palmer AC, Kurtz DM, Alizadeh AA. N Engl J Med. 2023; 389(8):764-766.*

# Improved outcomes in 1L DLBCL with Pola-R-CHP

*POLARIX trial*




Pola-R-CHP

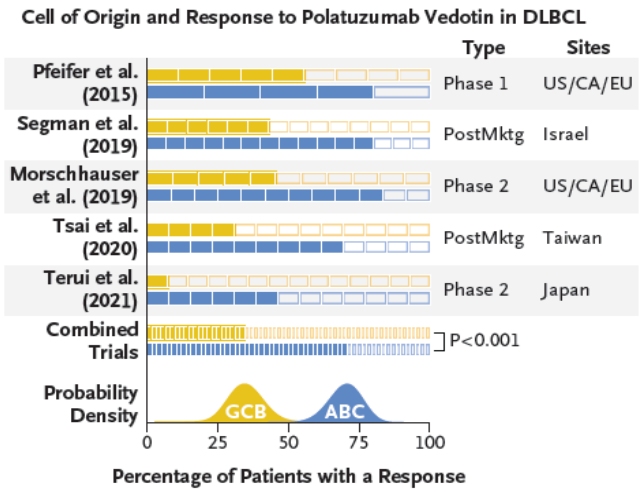


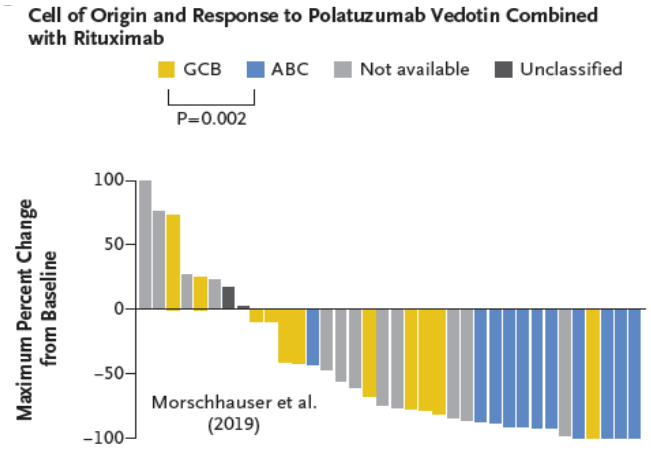

Pola-R-CHP

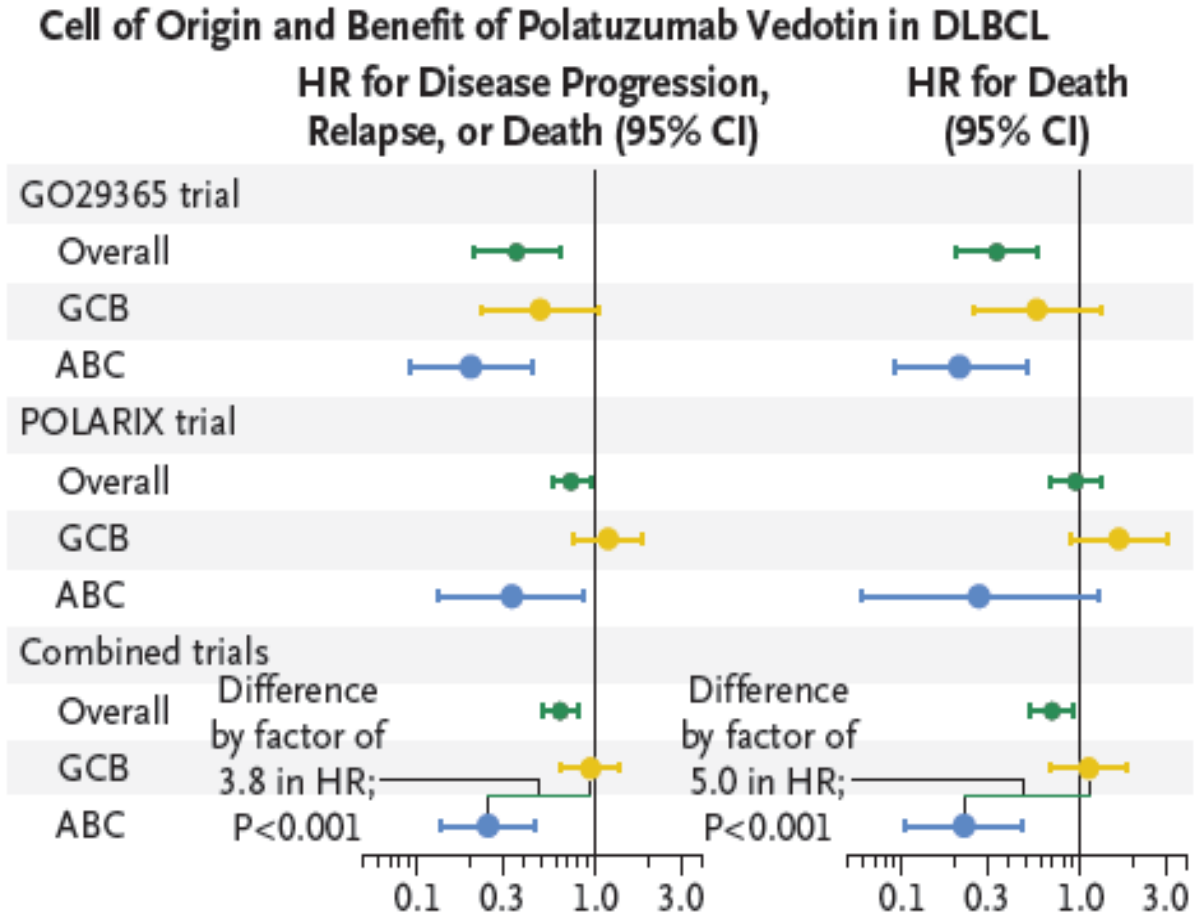
In the primary analysis, Pola-R-CHP significantly improved PFS and demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death versus R-CHOP

*1. H. Tilly, F. Morschhauser, L.H. Sehn, et al. N Engl J Med 2022;386:351-63*

# Cell-of-Origin Subtypes and Therapeutic benefit from Polatuzumab Vedotin




*1. Palmer AC, Kurtz DM, Alizadeh AA. N Engl J Med. 2023; 389(8):764-766.*

# Prior Paradigm for R/R LBCL: Chemotherapy Followed by HDT-ASCT

For nearly 30 years, treatment for patients with refractory or relapsed Diffuse Large B-cell Lymphoma in the second-line curative setting was chemotherapy followed by HDT-ASCT.

Most patients could not receive HDT-ASCT, and their prognosis was poor.

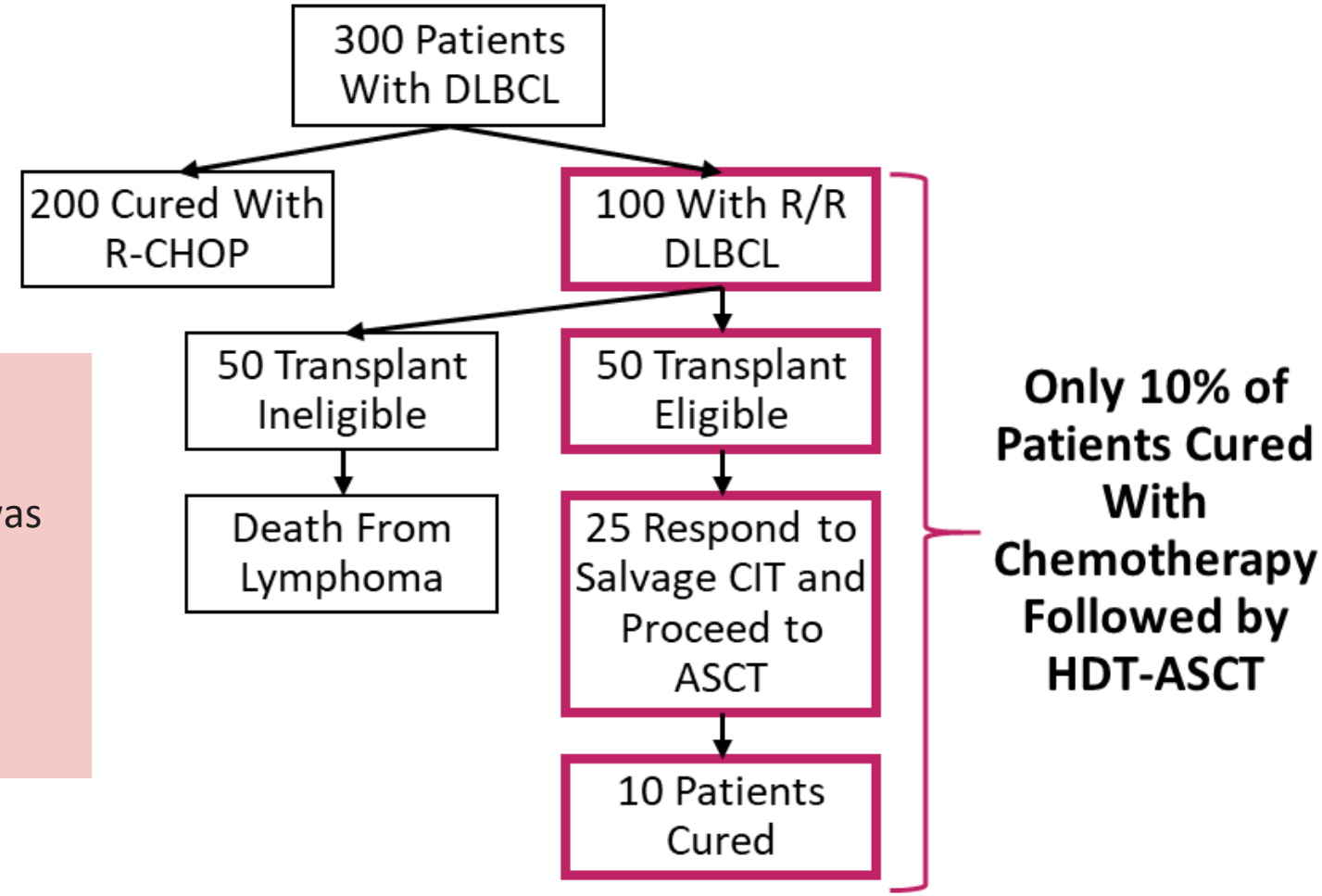



*Figure adapted from Friedberg JW. Hematology Am Soc Hematol Educ Program. 2011.*

# Axi-cel: ZUMA-1 Phase II study

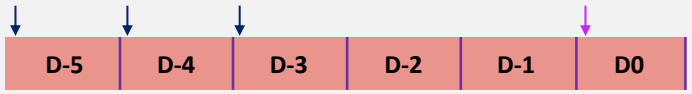
**Eligibility criteria**

- Histologically confirmed LBCL (including DLBCL, PMBCL and trFL)
- Refractory disease or relapse after ASCT
- ECOG PS 0 or 1

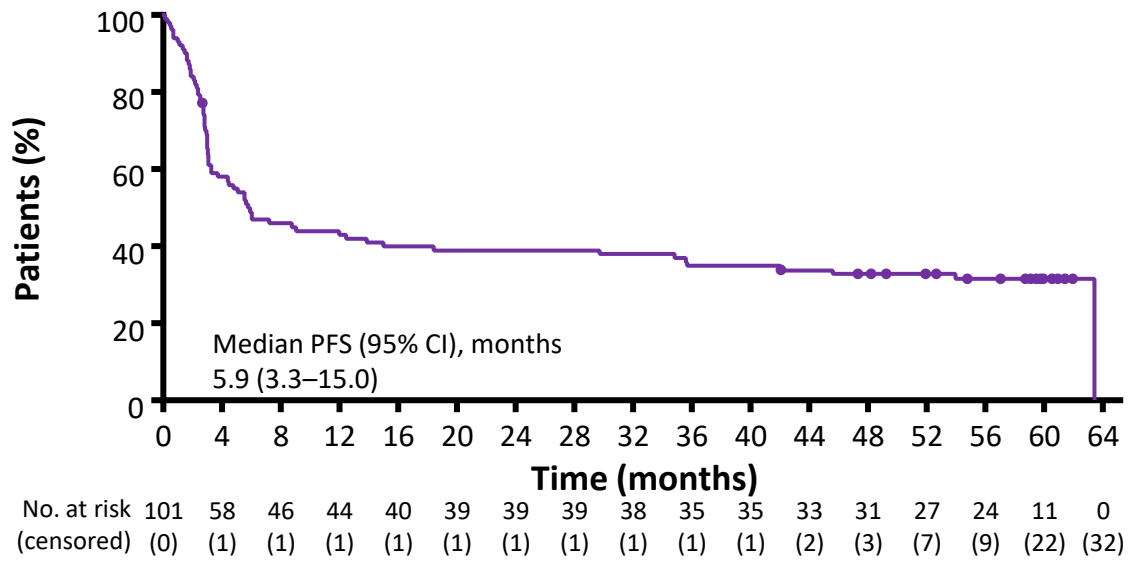
**(N=111)[1,2]**

**Fludarabine** 30mg/m$^2$ plus **cyclophosphamide** 500mg/m$^2$

**Axi-cel** 2 x 10$^6$ CAR T-cells/ kg body weight




**PFS[2]**




**Key AEs, any Gr (≥Gr3)[1]**

| | |
|---|---|
| CRS | 93% (11%) |
| Neurologic AEs | 67% (32%) |
| Cytopenias | 93% (86%) |
| Infections | (28%) |

**ORR:[2] 83%**

**CR:[2] 58%**

**Median PFS:[2] 5.9 mo**
**Median OS:[2] 25.8 mo**

**Most common Gr 3/4 AEs:[2]**

- Anemia (45%)
- Neutropenia (39%)

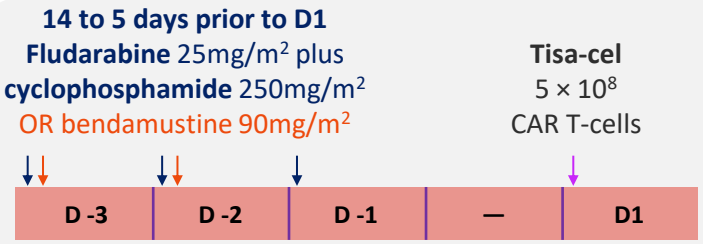
*1. Locke FL, et al. Lancet Oncol 2019;20:31-4; 2. Neelapu S, et al. Blood 2023;141:2307-15*

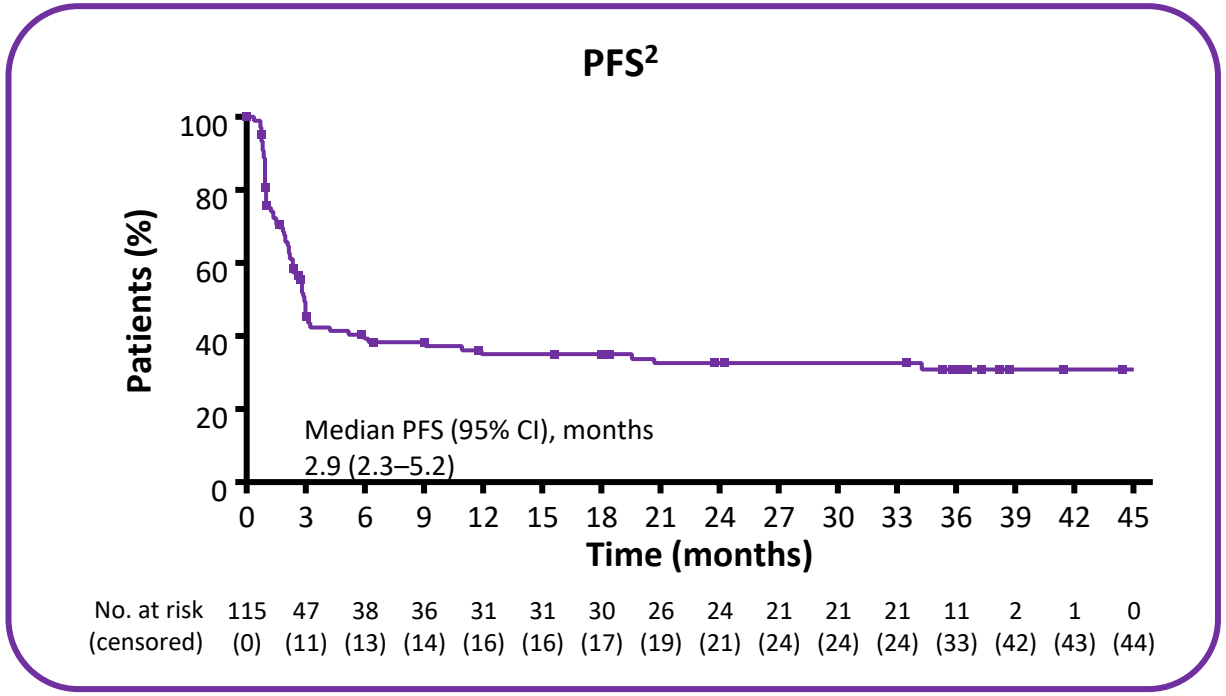
# Tisa-cel: JULIET Phase II study

**Eligibility criteria**

- Histologically confirmed LBCL
- trFL, HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements also eligible
- Refractory disease or relapse after ASCT
- ECOG PS 0 or 1

**(N=115)**




| Key AEs, any Gr (≥Gr3) | |
|---|---|
| CRS* | 57% (23%) |
| Neurologic AEs | 20% (11%) |
| Cytopenias | 45% (34%) |
| Infections | 37% (19%) |

**ORR: 53%**

**CR: 39%**

**Median PFS: 2.9 mo**
**Median OS: 11.1 mo**

**Most common Gr 3/4 AEs:**

- Anemia (39%)
- Decreased neutrophil (34%)

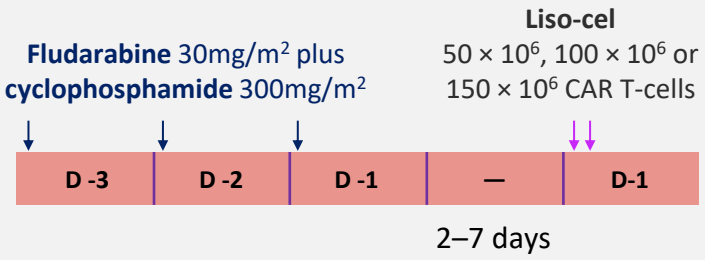
*1. Schuster SJ, et al. Lancet Oncol 2021;22:1403-15.*

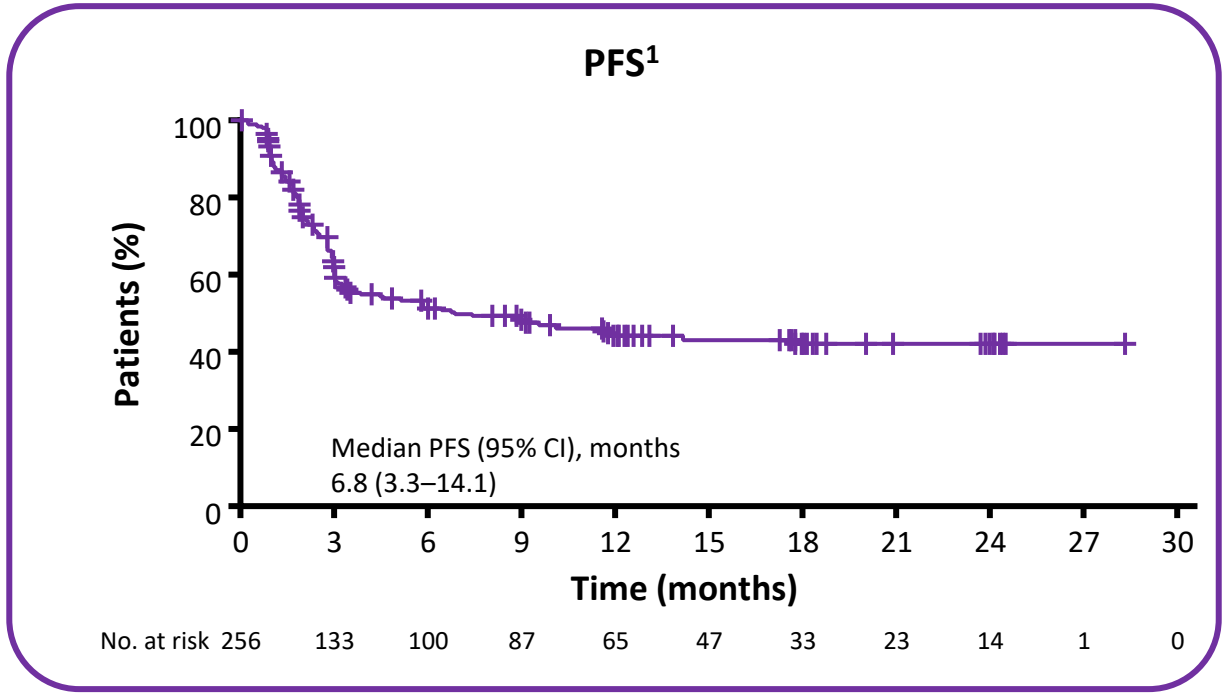
# Liso-cel: TRANSCEND Phase I study

**Eligibility criteria**

- PET-positive DLBCL (*de novo* or transformed), HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements), PMBCL or FL Gr 3b
- Refractory disease or relapse after ASCT (≥2 prior lines of therapy)

**(N=270)**




**Key AEs, any Gr (≥Gr3)[1]**

| | |
|---|---|
| CRS† | 42% (2%) |
| Neurologic AEs | 30% (10%) |
| Cytopenias | (37%) |
| Infections | 41%[2] (12%) |

**ORR:[2*] 73 %**

**CR: [2*] 53 %**

**Median PFS:[2*] 6.8 mo**
**Median OS:[2*] 27.3 mo**

**Most common Gr 3/4 AEs:[2]**

- Neutropenia (60%)
- Anemia (37%)

*1. Abramson JS, et al. Lancet 2020;396:839-52; 2. Abramson JS, et al. Blood 2024;143:404-16*

# Phase III studies of anti-CD19 CAR T-cells in 2L LBCL

## ZUMA-7[1]

**Patients N=359**

- ✓ R/R LBCL after ≤12 months of adequate 1L chemotherapy
- ✓ ECOG PS 0 or 1
- ✗ Prior SCT, prior CD19-targeted therapy[2]

1:1

- Axi-cel
- SoC* (2–3 cycles) → HDCT-ASCT

**Primary endpoint:**[2] EFS†
**Secondary endpoints:**[2] response, OS

## TRANSFORM[3]

**Patients N=184**

- ✓ R/R LBCL after ≤12 months of adequate 1L chemotherapy
- ✓ ECOG PS ≤1
- ✗ Prior SCT, prior CD19-targeted therapy[4]

1:1

- Liso-cel
- SoC‡ (3 cycles) → HDCT-ASCT

**Primary endpoint:**[4] EFS§
**Secondary endpoints:**[4] CR, PFS, OS

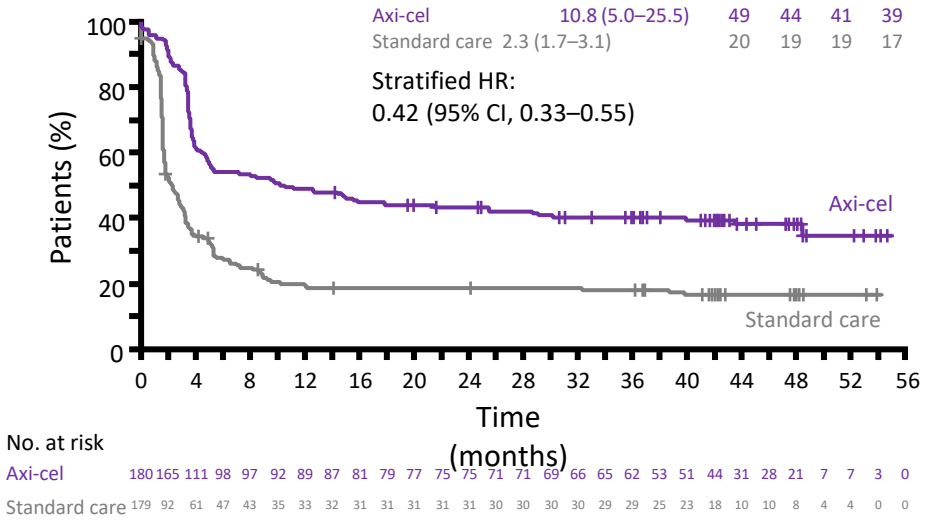
**Axi-cel and liso-cell are superior to SoC as 2L therapy for early R/R LBCL**

*1. Locke F, et al. N Engl J Med 2022;386:640-45; 2. NCT03391466. Available at: https://clinicaltrials.gov;*
*3. NCT 03575351. Available at: https://clinicaltrials.gov; 4. Abramson J, et al. Blood 2023;141;1675-845;*
*5.Cheson BD, et al. J Clin Oncol 2014;32;3059–68*

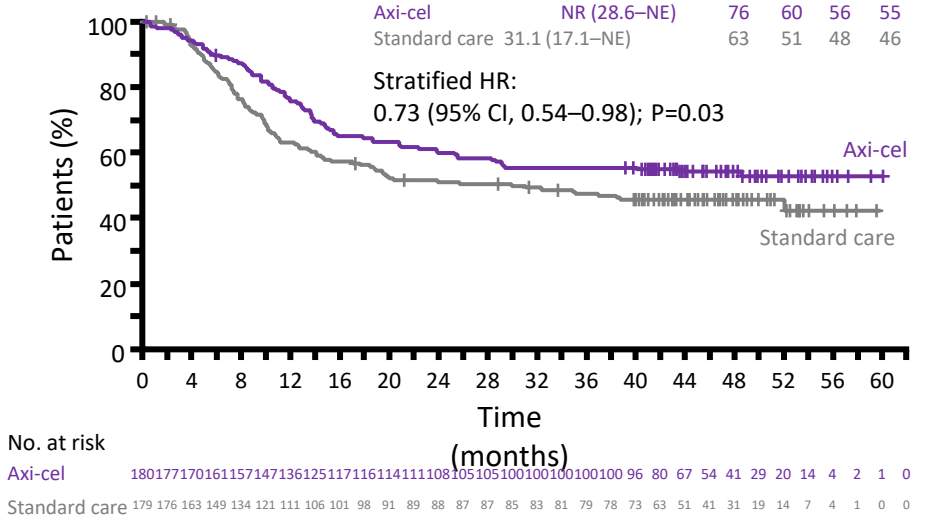
# ZUMA-7

## *Phase III study of axi-cel versus SoC in 2L R/R LBCL*

### EFS[2]




### OS[2]




### Safety (N=170)*[3]

**CRS: 92%**

**Gr ≥3: 6%**

**Gr ≥3 AEs: 91%**

**21% neurotoxicity**

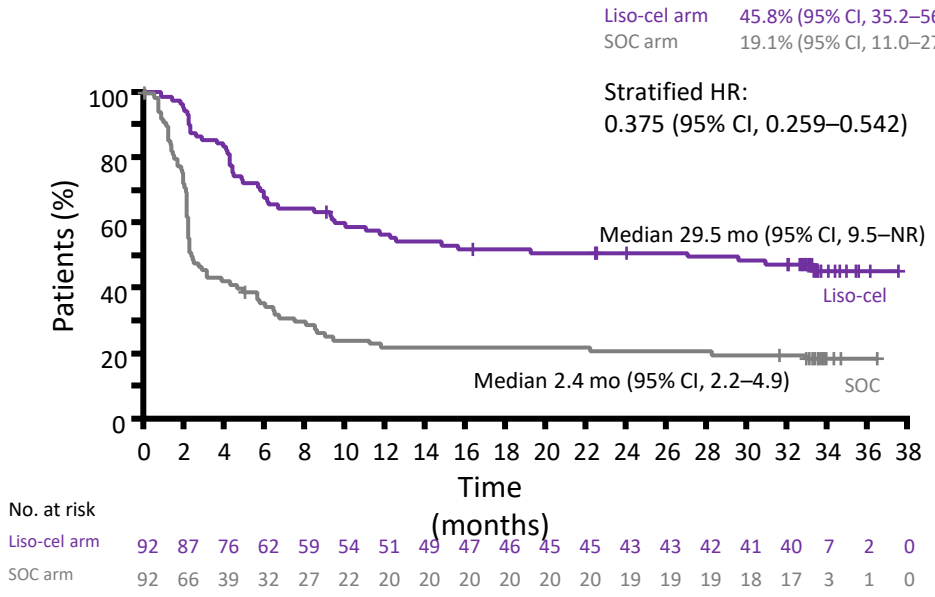
Median EFS was superior with **axi-cel** (**10.8 months**; 95% CI: 5.0–25.5) vs **SoC** (**2.3 months**; 95% CI: 1.7–3.1)
HR 0.42 (95% CI: 0.33–0.55) and no new safety signals were observed[2]

*1. NCT03391466. Available at: https://clinicaltrials.gov; 2. Westin J, et al. New Engl J Med 2023;389:148-57; 3. Locke F, et al. N Engl J Med 2022;386:640-45.*

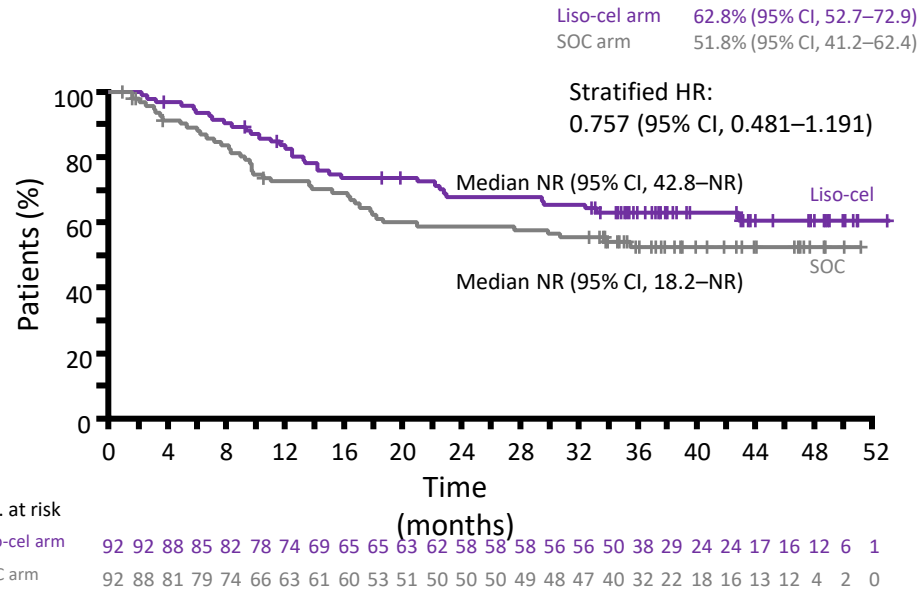
# TRANSFORM

*Phase III study of liso-cel versus SoC in 2L R/R LBCL*

## EFS[2]




## OS[2]




Median study follow-up: 33.9 months

## Safety (n=92)†[3]

**CRS: 49%**

**Gr ≥3: 1%**

**Gr ≥3 TEAEs: 92%**

**4% neurotoxicity**

In a 3-year follow-up analysis, median EFS was superior with **liso-cel** (**29.5 months**; 95% CI: 9.5–NR) versus **SoC** (**2.4 months**; 95% CI: 2.2–4.9); HR 0.375 (95% CI: 0.259–0.542). No new safety signals were observed[2]


*1. NCT 03575351. Available at: https://clinicaltrials.gov; 2. Kamdar M, et al. ASCO 2024. Abstract #7013; 3. Abramson J, et al. Blood 2023;141;1675-84; 4. Cheson BD, et al. J Clin Oncol 2014;32;3059–68.*

# Algorithm for Second-line Therapy for LBCL

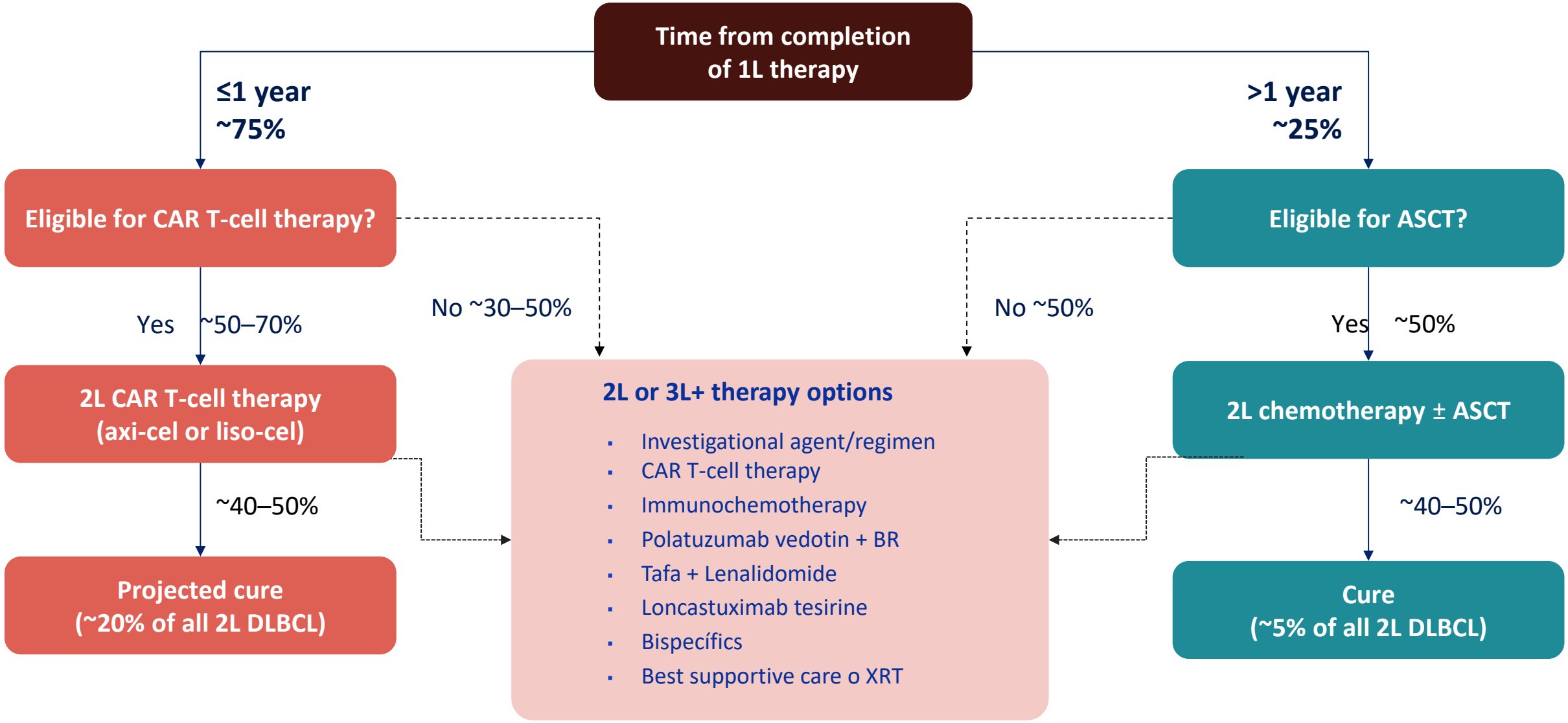
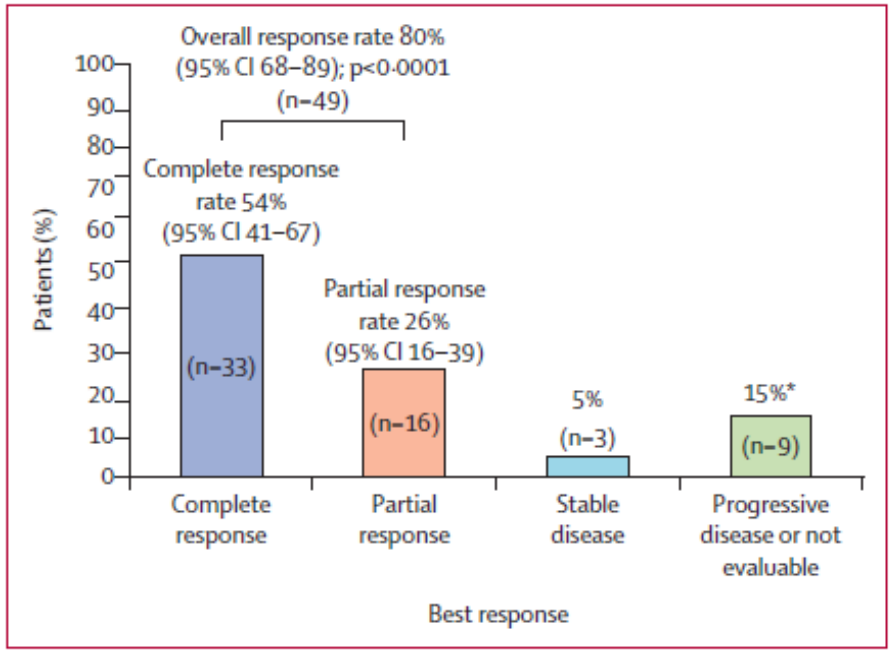
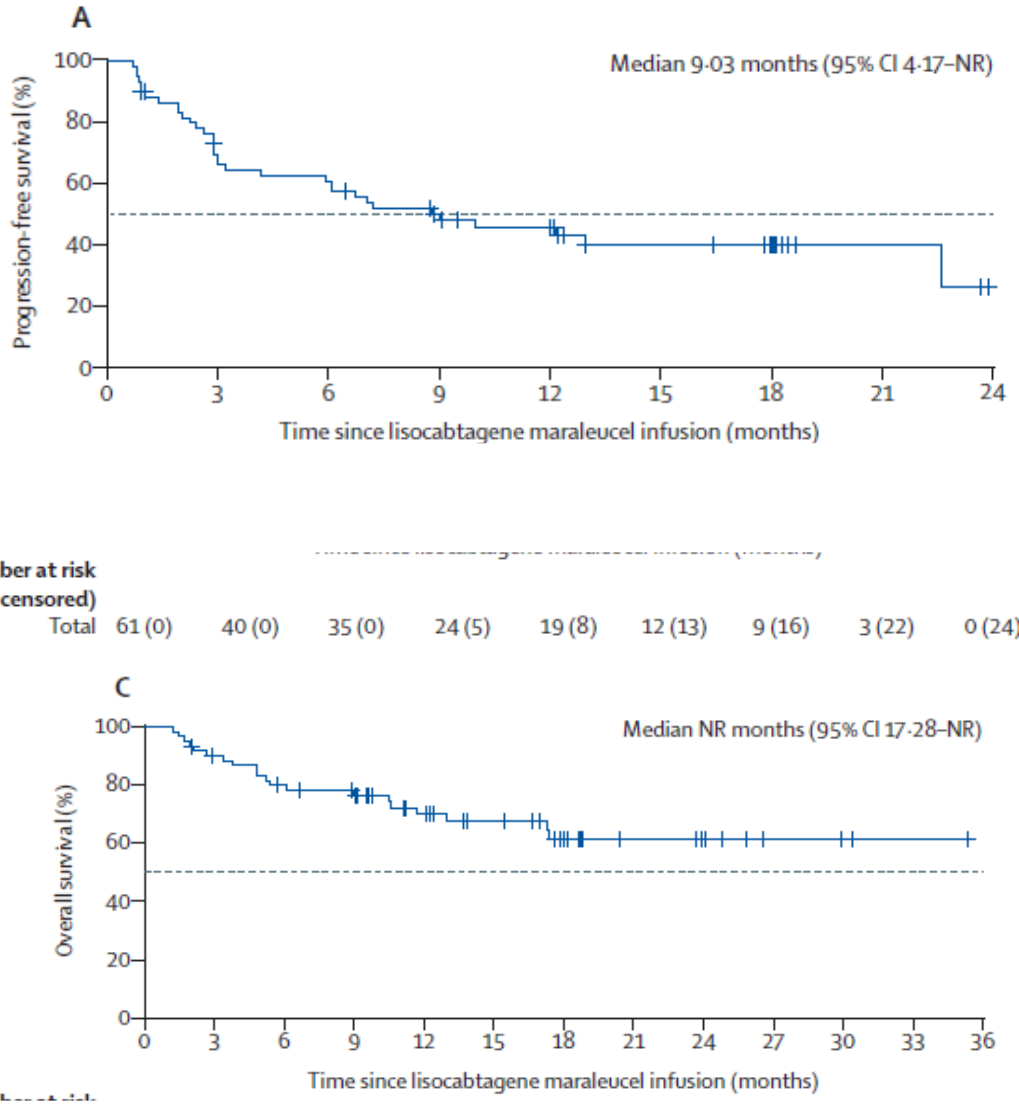



*Figure adapted from Westin J & Sehn LH. Blood 2022;139:2737-46*

# Lisocel as 2L in R/R LBCL who were not intended for HSCT

*PILOT: open phase 2 study*

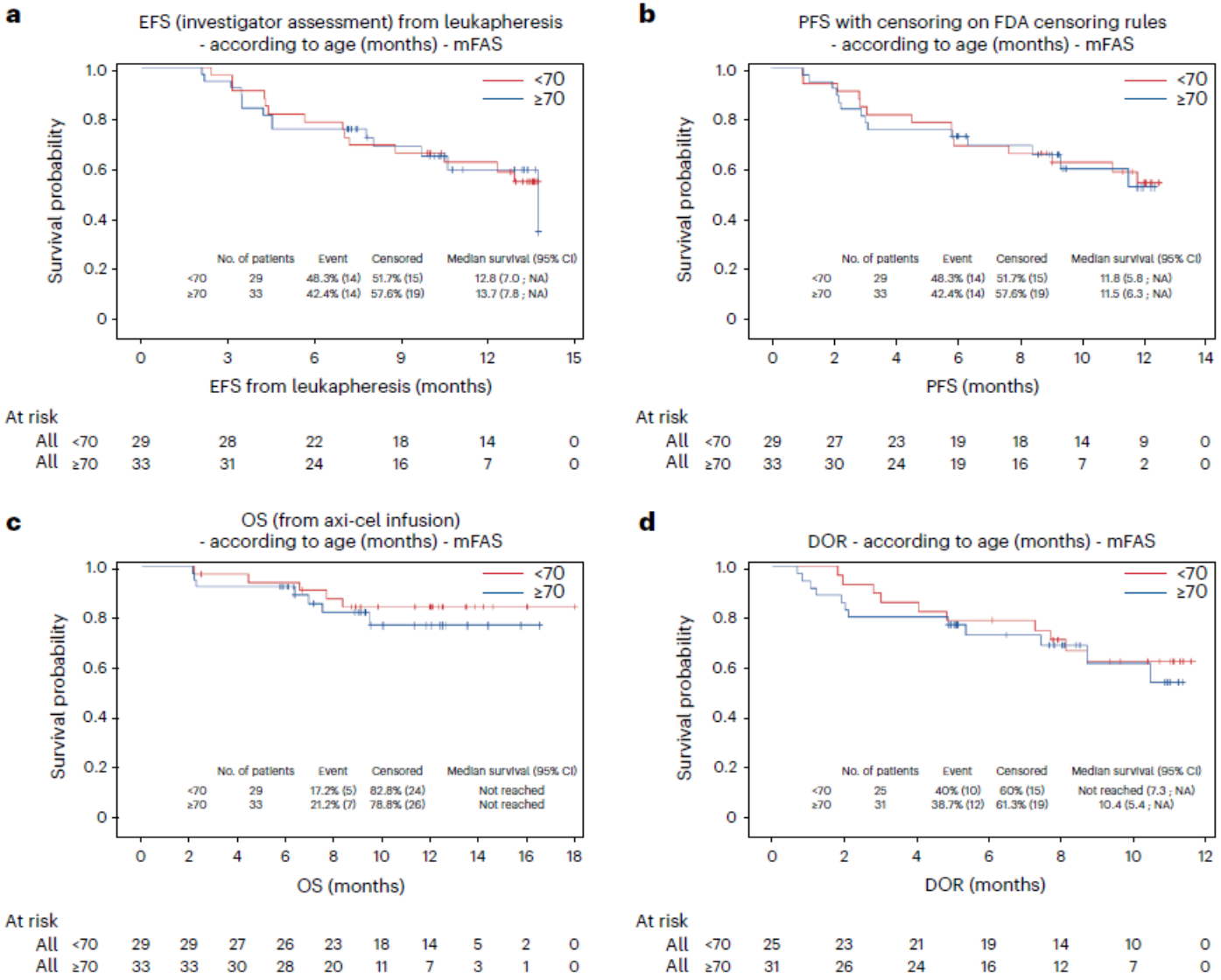



*1. Shegal A, et al. Lancet Oncol 2022; 23: 1066-77*

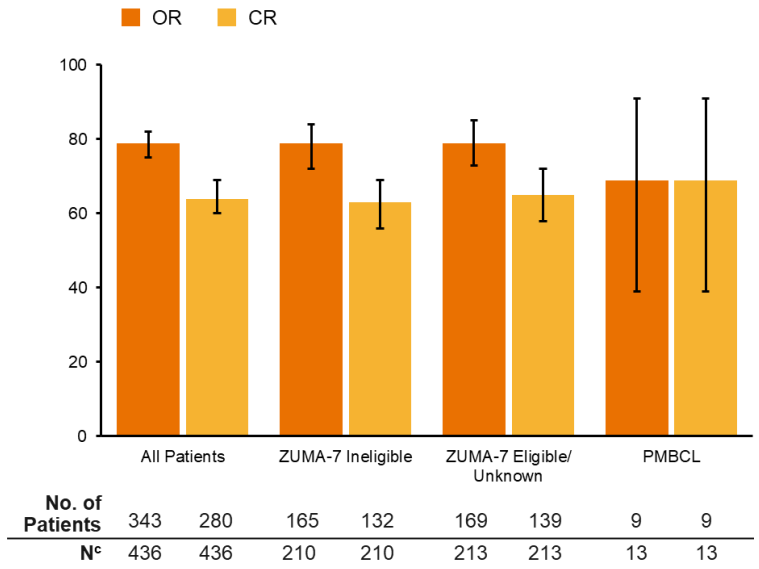
# Axicel 2L in R/R LBCL who were not intended for HSCT

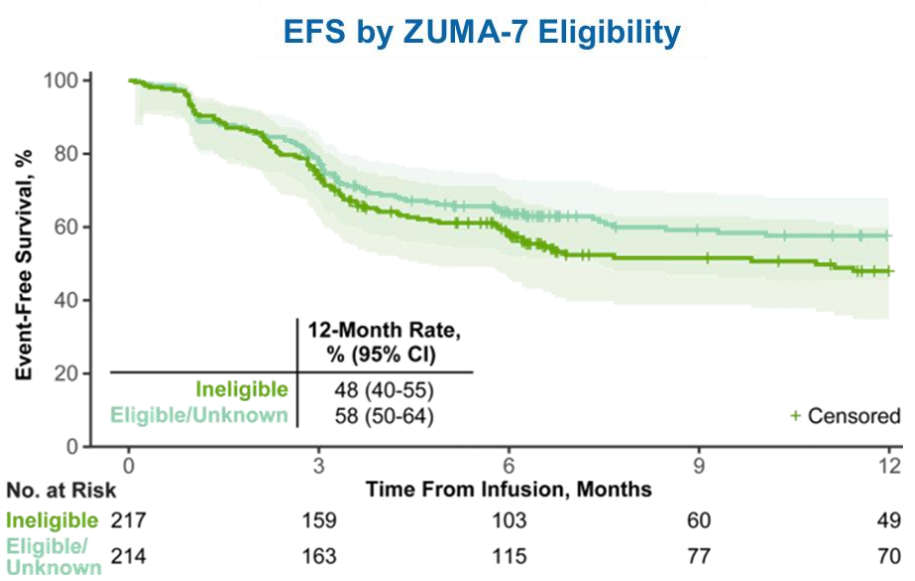
## *ALYCANTE: Open phase 2 study*

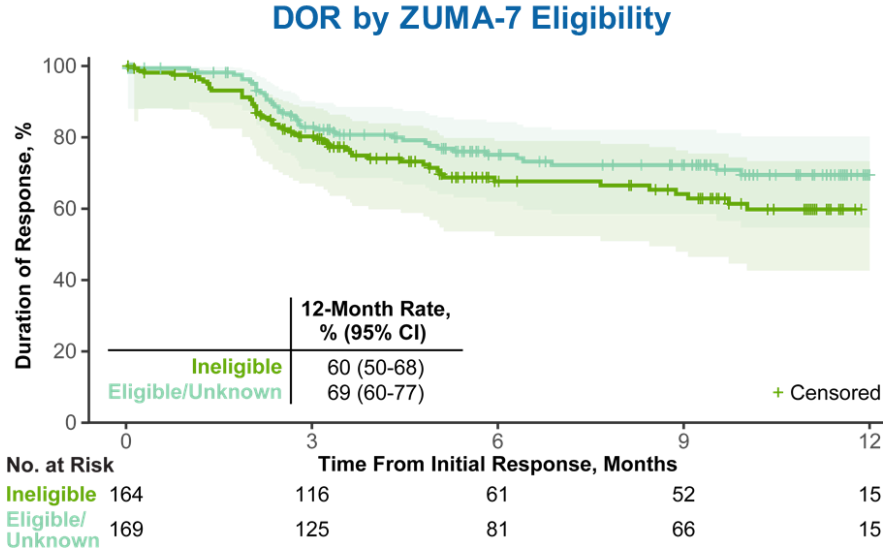


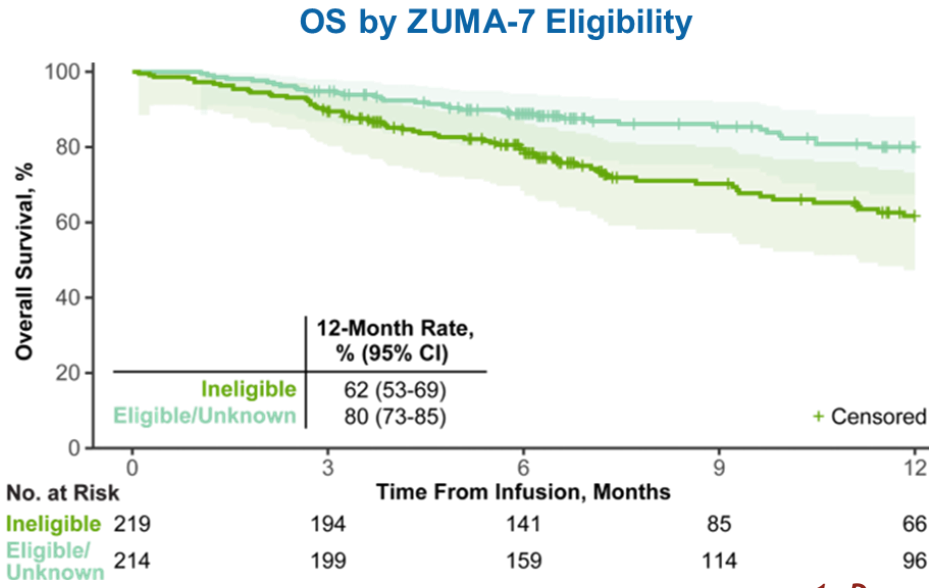

*1. Houot R, et al. Nature Medicine 2023*

# Real-World Early Outcomes of 2L Axicel in R/R LBCL



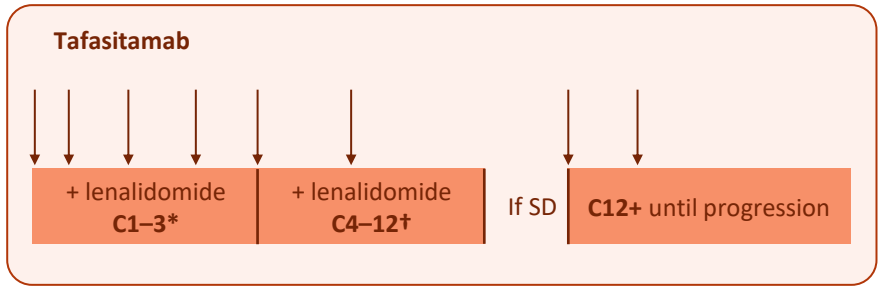

*1. Dasom CL, et al. ASH 2024.*

# Tafasitamab-lenalidomide in R/R LBCL

*Phase II L-MIND study*

N=80

- ✓ ASCT-ineligible R/R DLBCL
- ✓ ECOG PS 0–2
- ✓ 1–3 prior systemic regimens, including ≥1 anti-CD20 targeting therapy




**Primary endpoint:**
ORR by IRC
(per Lugano criteria[2])

## Efficacy outcomes[3] (N=80)

| ORR | CR rate | Median OS | Median DOR, |
|---|---|---|---|
| 57.5% | 41.3% | 33.5 months | NR |
| (95% CI: 45.9–68.5) | (95% CI: 30.4–52.8) | (95% CI: 18.3–NR) | (95% CI: 33.8–NR) |

## Safety (N=81)[3]

**Most common Gr ≥3 TEAEs**

**48% neutropenia**
**16% thrombocytopenia**
**12% febrile neutropenia**

The ORR was 57.5%, with a CR rate of 41.3% (n=33)
A manageable safety profile was observed with no new safety signals


*1. NCT02399085. Available at: https://clinicaltrials.gov; 2. Cheson BD, et al. J Clin Oncol 2007;25:579-86;*
*3. Duell J, et al. Haematologica 2024;109:553–66.*

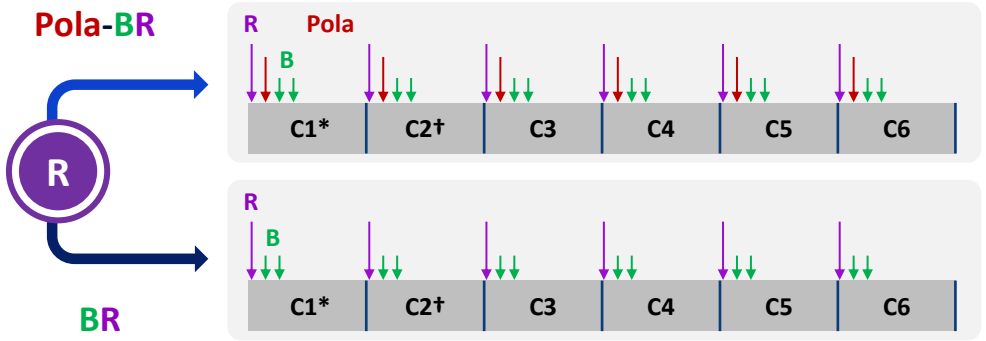
# Pola-BR in R/R DLBCL

## *Phase Ib/II GO29365 study*

Transplant-ineligible patients

- ✓ R/R DLBCL
- ✓ ECOG PS 0–2
- ✓ ≥1 prior therapy

**Pooled Pola-BR cohort: N=152**
Safety run-in: Pola-BR (n=6)
Randomized arms:
Pola-BR (n=40) versus BR (n=40)
Extension cohort: Pola-BR (n=106)




**Primary endpoint (randomized arm):**
CR (IRC-assessed by modified Lugano)[2]

### Efficacy outcomes for Pola-BR[3,4]

| | CR rate, % (95% CI) | Median OS, months (95% CI) | Median DOCR, months (95% CI) |
|---|---|---|---|
| **Randomized cohort:** | 42.5 (27.0–59.1) | 12.4 (9.0–32.0) | 10.9 (5.7–40.7) |
| **Extension cohort:** | 39.6 (30.3–49.6) | 12.3 (8.3–17.0) | 13.4 (8.6–20.0) |

### Safety (n=151‡)[4]

**Common Gr ≥3 AEs**

**32.5% neutropenia**
**20.5% thrombocytopenia**

**Peripheral neuropathy**

**Any grade: 31.1%**
**Gr ≥3: 2.0%**

The **Phase III POLARGO** study of **Pola + R-GemOx versus R-GemOx** in patients with 2L transplant-ineligible DLBCL is ongoing[5]


*1. NCT02257567. Available at: https://clinicaltrials.gov; 2. Cheson BD, et al. J Clin Oncol 2014;32:3059-68;*
*3. Sehn LH, et al. ASH 2022. Poster #4260; 4. Sehn LH, et al. Blood Adv 2022;6:533-43;*
*5. Matasar M, et al. J Clin Oncol 2022;40:7551*

# Loncastuximab tesirine

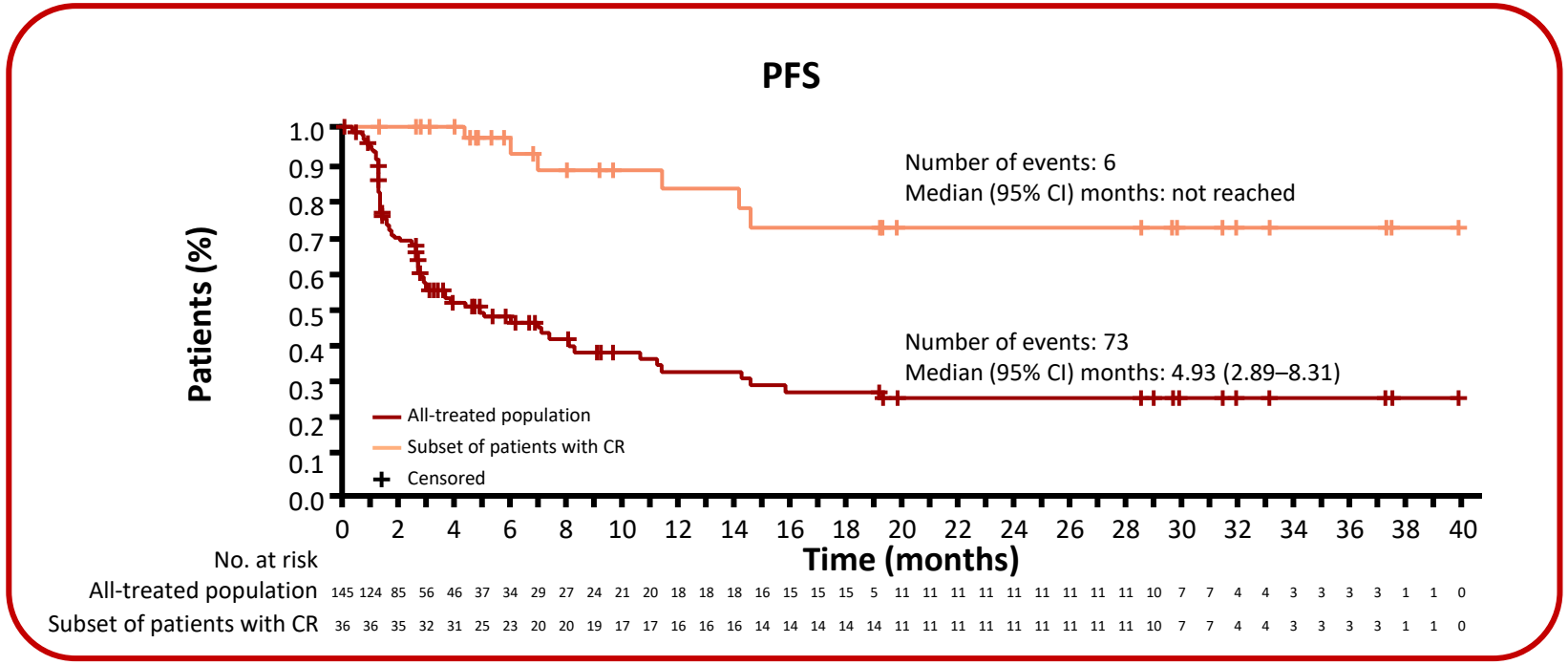
## *Phase II LOTIS-2 study*

**Eligibility criteria**

- R/R DLBCL (including DLBCL NOS, HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, or PMBCL)
- ECOG PS 0–2
- ≥2 prior multi-agent systemic regimens

**(N=145)[1]**


21-day cycles for up to 1 year*




**ORR:[2] 48%**

**CR:[2] 25%**

**Median PFS:[2] 4.9 mo**
**Median OS:[2] 9.5 mo**

**Most common Gr 3/4 AEs:[1]**

- Neutropenia (26%)
- Thrombocytopenia (18%)

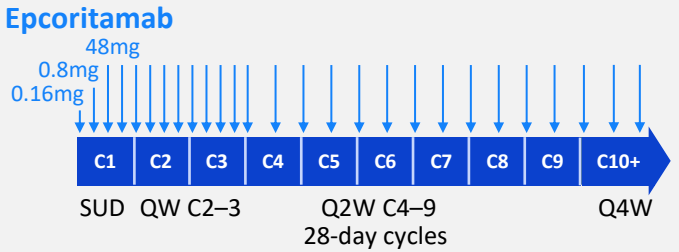
*1. Caimi PF, et al. Lancet Oncol 2021;6:790-800; 2. Caimi PF, et al. EHA 2023. Abstract #P1132.*

# Epcoritamab: EPCORE NHL-1

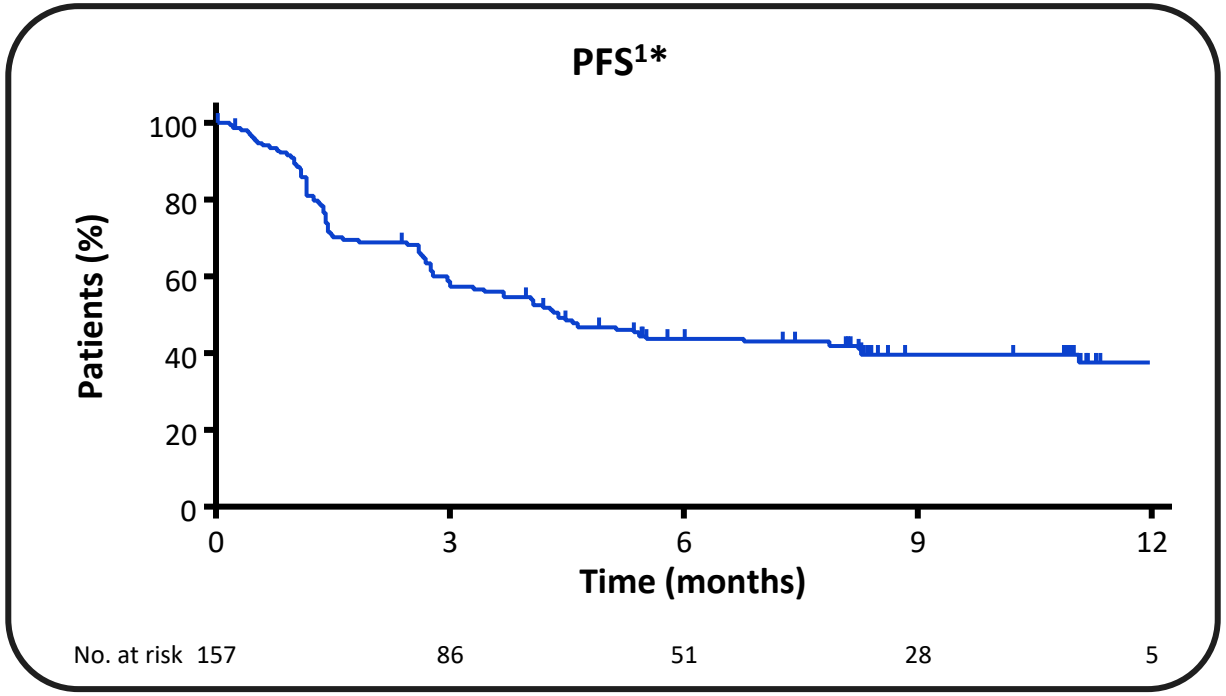
**Eligibility criteria**

- R/R CD20-positive B-cell neoplasm (DLBCL, HGBCL, PMBCL or FL Gr 3B)
- ≥1 measurable lesion
- ECOG PS 0–2
- Received ≥2 prior therapies, including ≥1 anti-CD20 antibody-containing regimen

**(N=157)** [1–3]




Treatment until progression or unacceptable toxicity




**Key AEs, any Gr (≥Gr3)[1,4]***

| | |
|---|---|
| CRS§ | 51% (3%) |
| ICANS | 6% (1%) |
| Neutropenia | 24% (15%) |
| Infections | (29%) |

**ORR:[4]*‡ 59%**

**CR:[4]*‡ 41%**

**Median PFS:[1] 4.4 mo**
**Median OS:[3]*† 18.5 mo**

**Most common Gr ≥3 AEs:[1]***

- Neutropenia (15%)
- Anemia (10%)

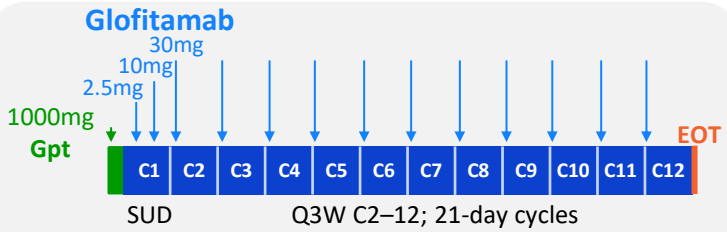

1. Thiebelmont C, et al. J Clin Oncol 2023;41:2238-47;
2. NCT03625037. Available at: https://clinicaltrials.gov/ct2/show/NCT03625037;
3. Jurczak W, et al. EHA 2023. Abstract #P1118; 4. Karimi Y, et al. ASCO 2024. Poster #7039.

# Glofitamab: Phase I/II NP30179 study

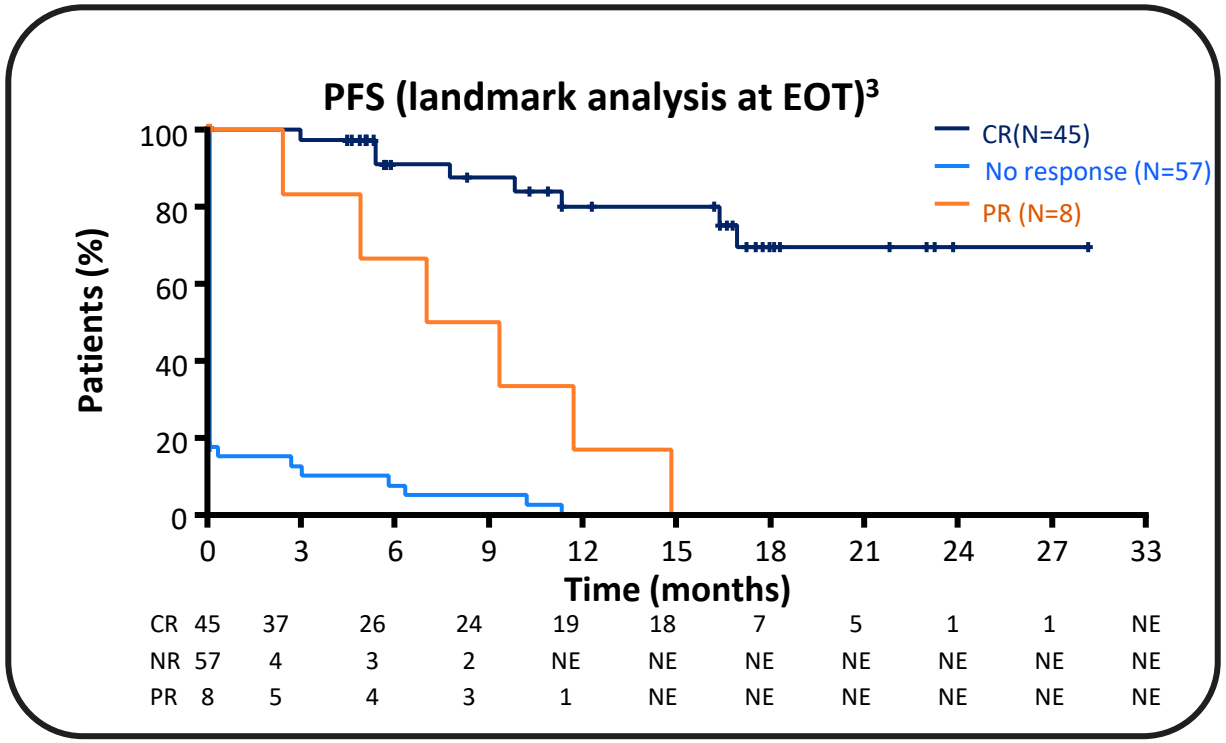
**Eligibility criteria**

- R/R DLBCL, DLBCL NOS, PMBCL, trFL, HGBCL NOS, HGBCL with *MYC* and *BCL2* rearrangements
- ECOG PS 0 or1
- ≥2 prior therapies including an anti-CD20 antibody and anthracycline-based regimen

**(N=155)[1–3]**




**Fixed duration:** 14 doses (including Gpt) over ~8.3 months




**Key AEs, any Gr (≥Gr3)[2]**

| | |
|---|---|
| CRS† | 63% (4%) |
| ICANS | 8% (3%) |
| Neutropenia | 38% (27%) |
| Infections | 38% (15%) |

**ORR:[3,4] 52%**

**CR:[3,4] 40%**

**Median PFS in pts with CR:[4*] 24 mo**

**Median OS in pts with CR:[4*] NE**

**Most common Gr ≥3 AEs:[1,2]**

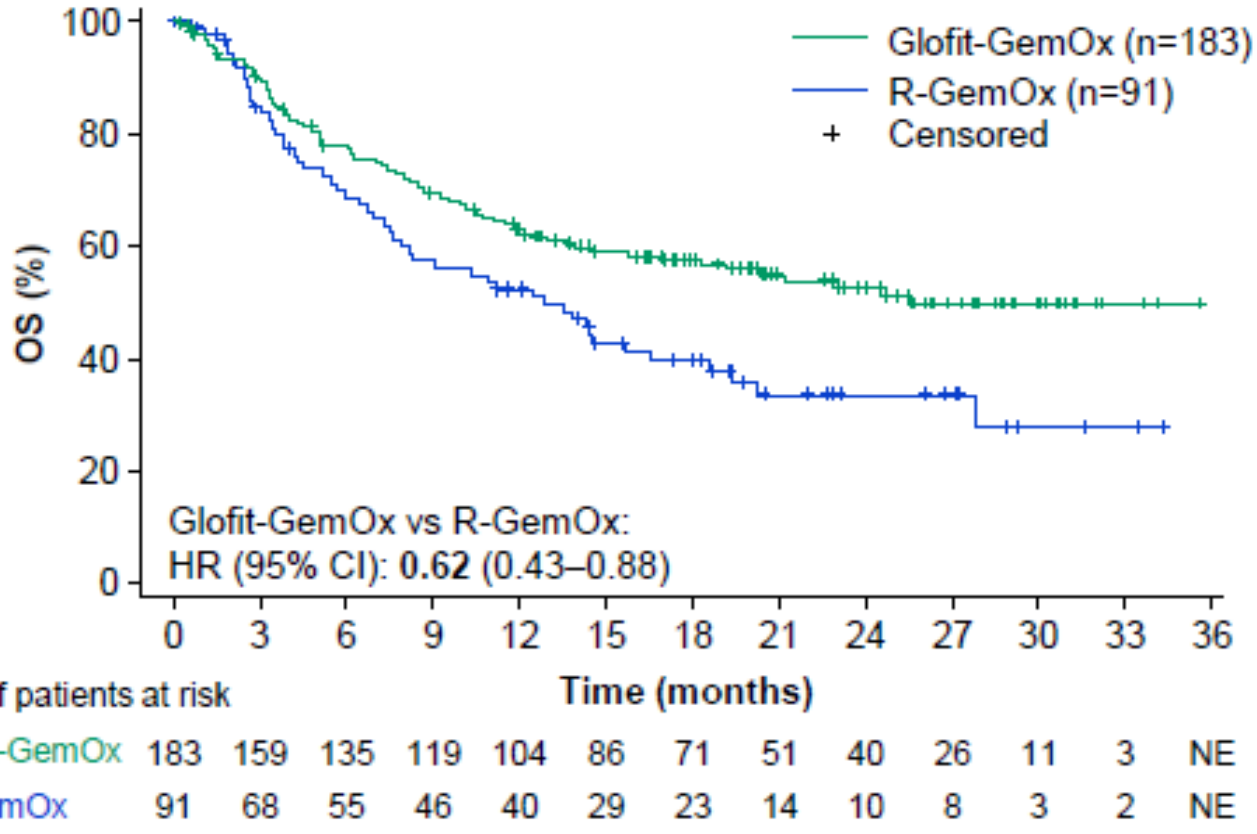
- Neutropenia (27%)
- Thrombocytopenia (8%)


*1. Dickinson M, et al. N Engl J Med 2022;387:2220-31; 2. Dickinson M, et al. ASCO 2022. Poster #7500;*
*3. Falchi L, et al. ASCO 2023. Poster #7550; 4. Hutchings M, et al. ASH 2023. Oral #433;*
*5. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-38*

# Glofit-GemOx for R/R LBCL

*Randomized Phase III Trial (STARGLO)*

**Updated analysis**

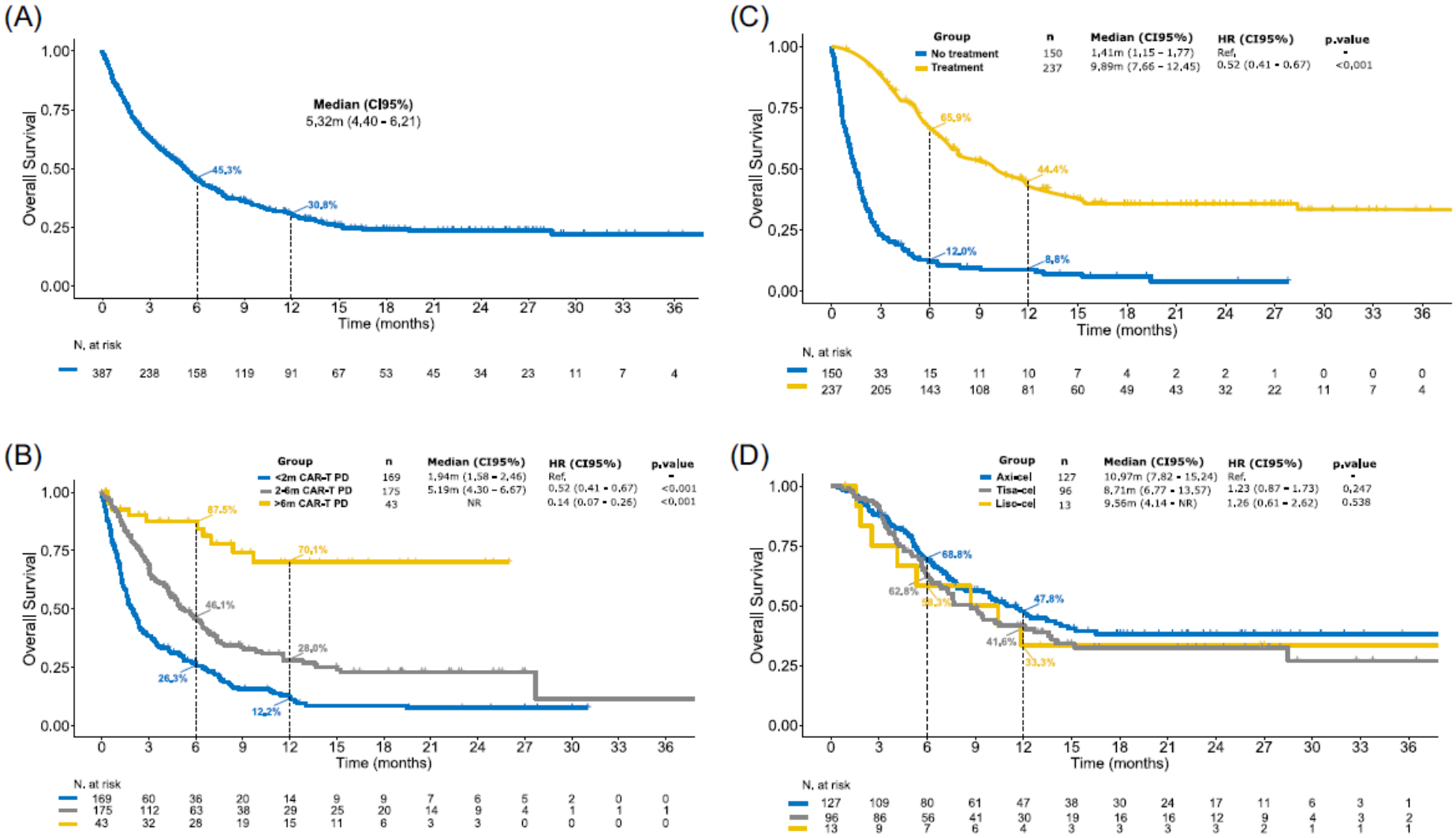



| | R-GemOx (n=91) | Glofit-GemOx (n=183) |
|---|---|---|
| **Primary analysis** (median follow-up: 11.3 months) | | |
| OS, median (95% CI); months | 9 (7.3–14.4) | NE (13.8–NE) |
| HR (95% CI) | 0.59 (0.40–0.89) | |
| p-value* | 0.011 | |
| **Updated analysis** (median follow-up: 20.7 months) | | |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

Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** vs R-GemOx

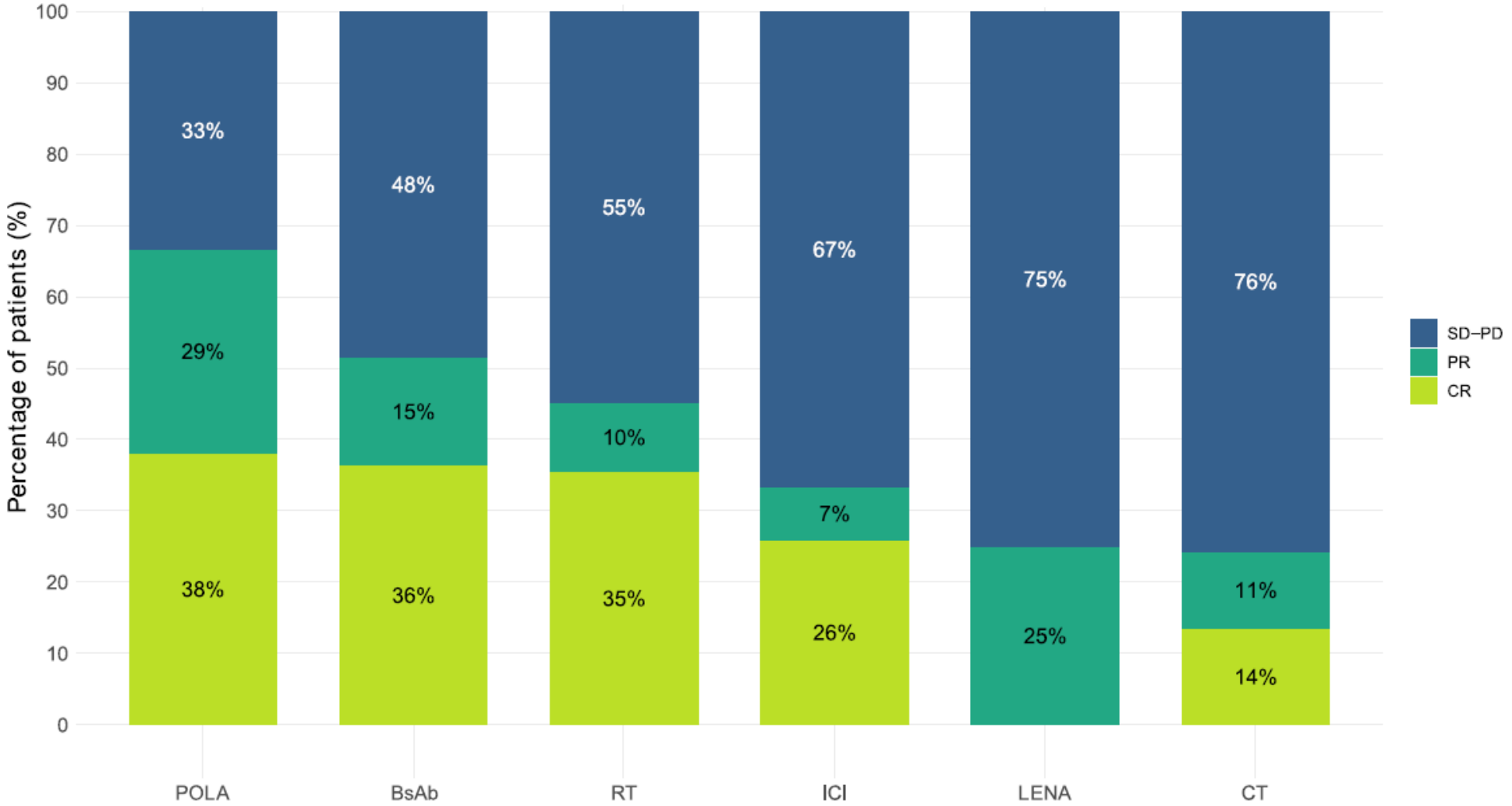
*1. Jeremy S. Abramson. EHA 2024*

# Treatment outcomes after progression to CAR-T



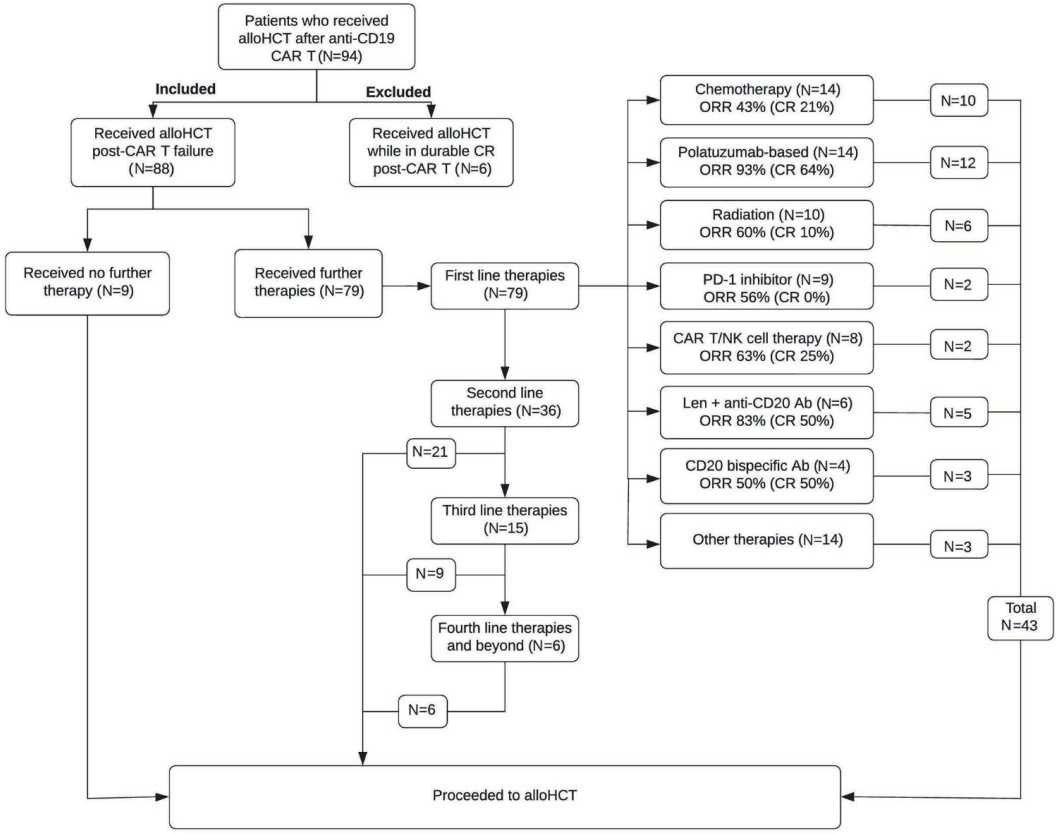

*1. Iacoboni G, et al. Hemasphere 2024;8:e62*

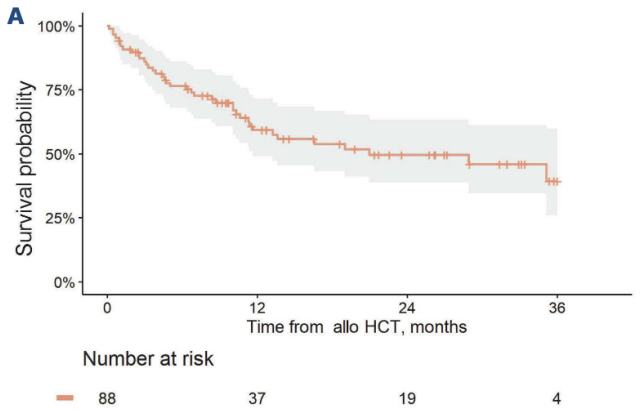
# Response rates for first-line regimens given after CAR-T failure

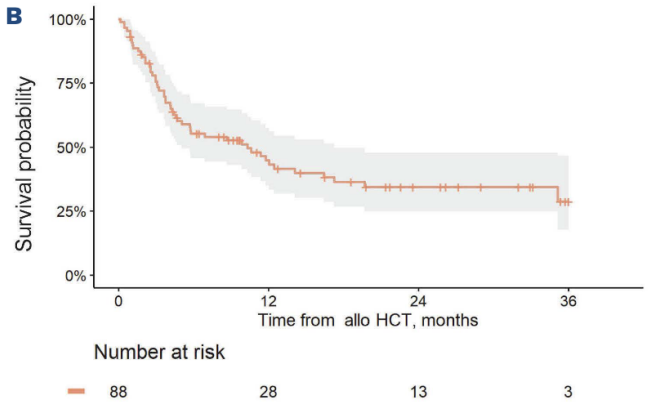


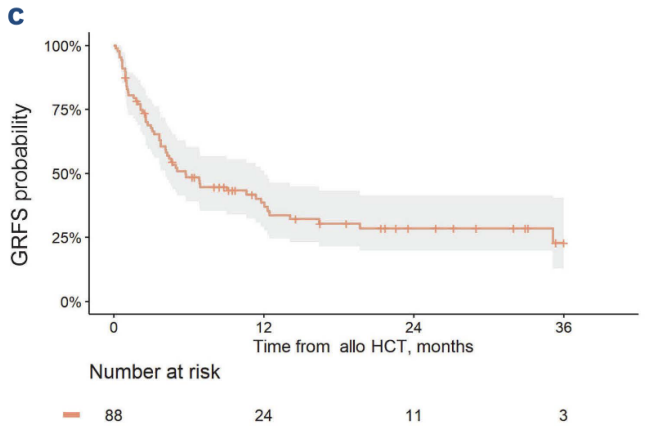

*1. Iacoboni G, et al. Hemasphere 2024;8:e62*

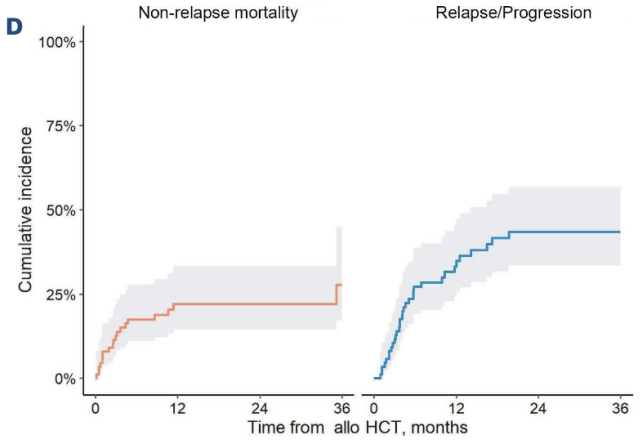
# Is there still room for allogeneic transplantation following CAR-T failure?



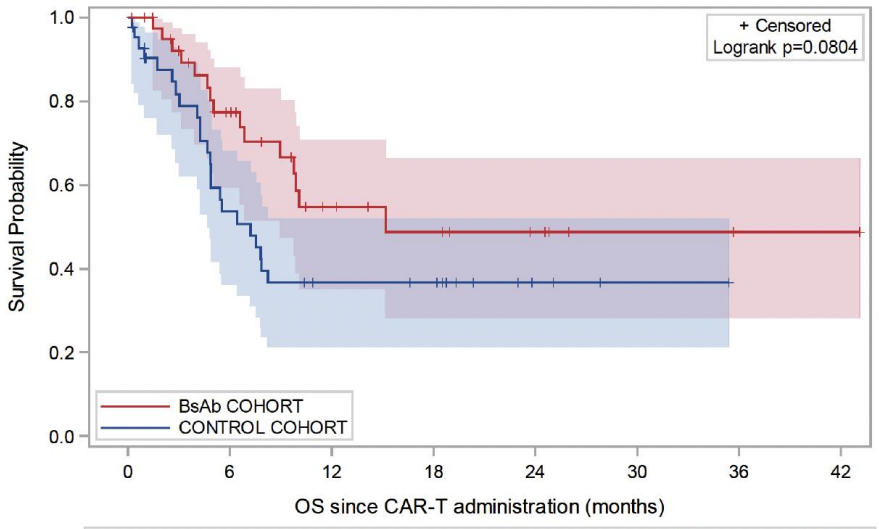




MVA
- 1 line between CART and alloSCT
- CR at time of alloSCT

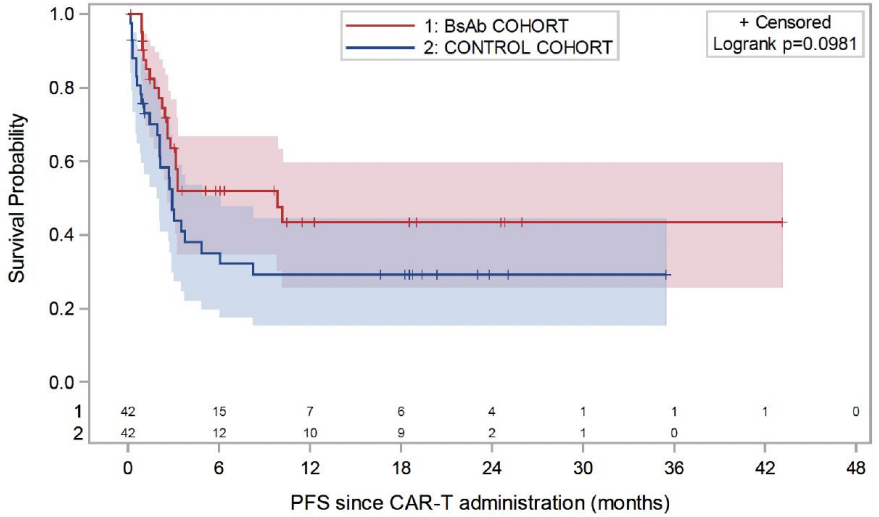
*1. Zurko J, et al. Haematologica 2023;108:98-109*

# CAR T-cells after BsAbs in DLBC

1) Prior BsAb exposure does not appear to impair subsequent CAR-T efficacy
2) Response to prior BsAbs may not be a reliable predictor of respond to CAR-T
3) Interval between the last dose of BsAb and leukapheresis (50 days) does not seem to influence outcomes
4) BsAb exposure was not associated with an increased incidence of CRS / ICANS



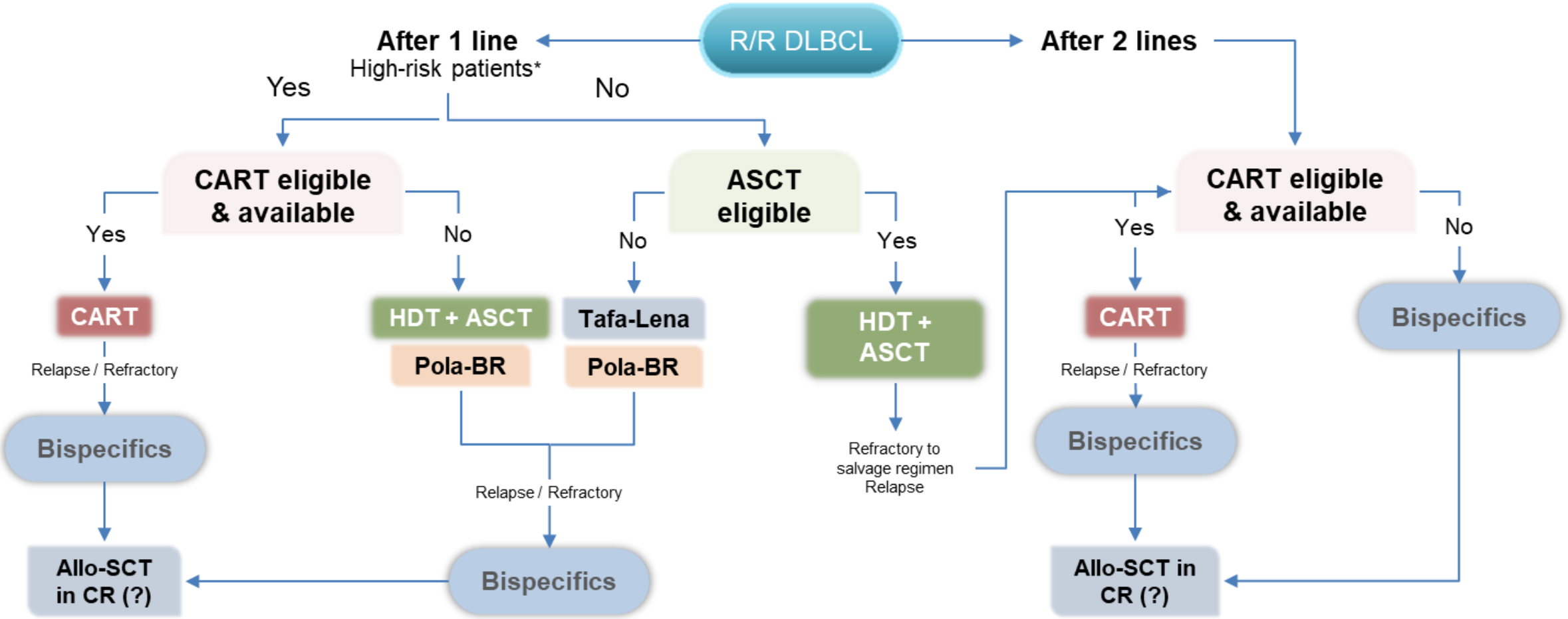

| | No. of Subjects | Event | Censored | Median Survival (95%CL) |
|---|---|---|---|---|
| BsAb COHORT | 42 | 35.7 % (15) | 64.3 % (27 ) | 15.2 (9 ; NA) |
| CONTROL COHORT | 42 | 54.8 % (23) | 45.2 % (19 ) | 7.2 (4.9 ; NA) |




| | No. of Subjects | Event | Censored | Median Survival (95%CL) |
|---|---|---|---|---|
| BsAb COHORT | 42 | 47.6 % (20) | 52.4 % (22 ) | 9.9 (2.6 ; NA) |
| CONTROL COHORT | 42 | 61.9 % (26) | 38.1 % (16 ) | 2.9 (2.1 ; 6) |

*1. Crochet G, et al. Blood 2024;144:334-8*

# Relapsed and refractory DLBCL: An evolving paradigm

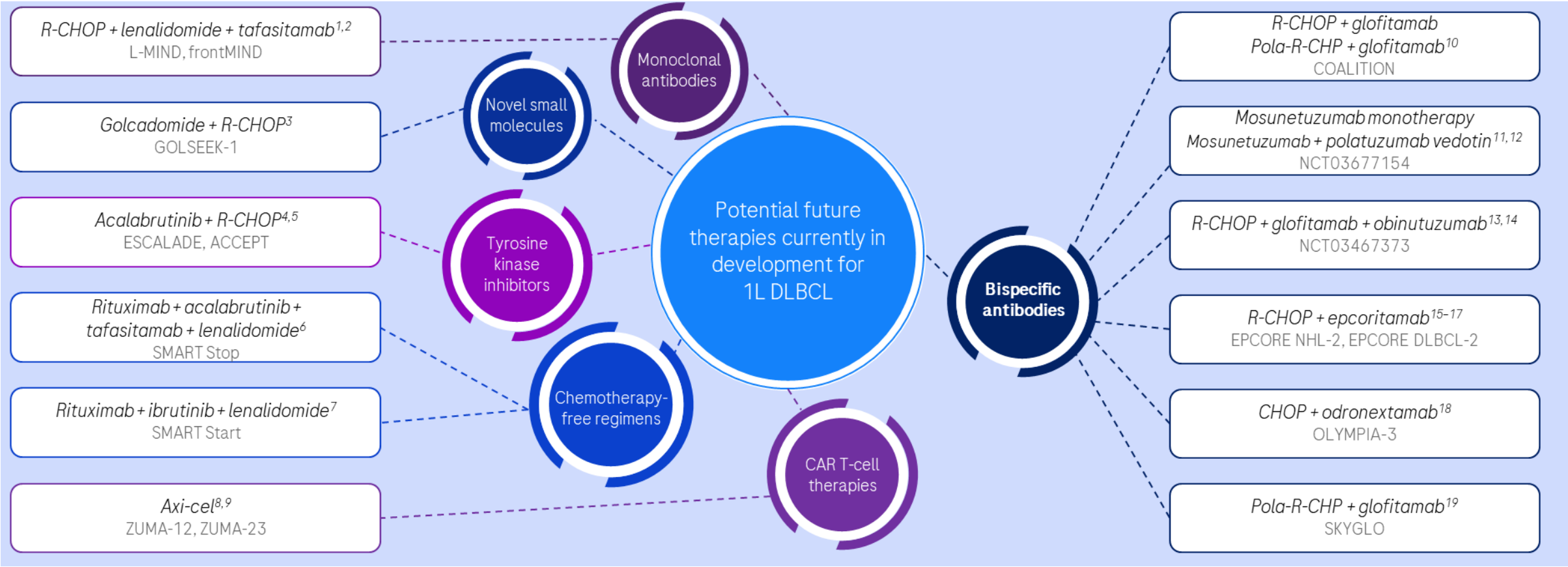



* High-risk patients: primary refractory, relapsed <12 months after initial therapy

*Cortesía Dr. M. Ángel Canales*

*Adapted from*
*Westin J, Sehn LH. Blood 2022;139:2737-46*
*Major A, Kamdar M. Hematology 2023;2023:370-381*
*Melody M, Gordon LI. Haematologica 2024;109:3138-45*

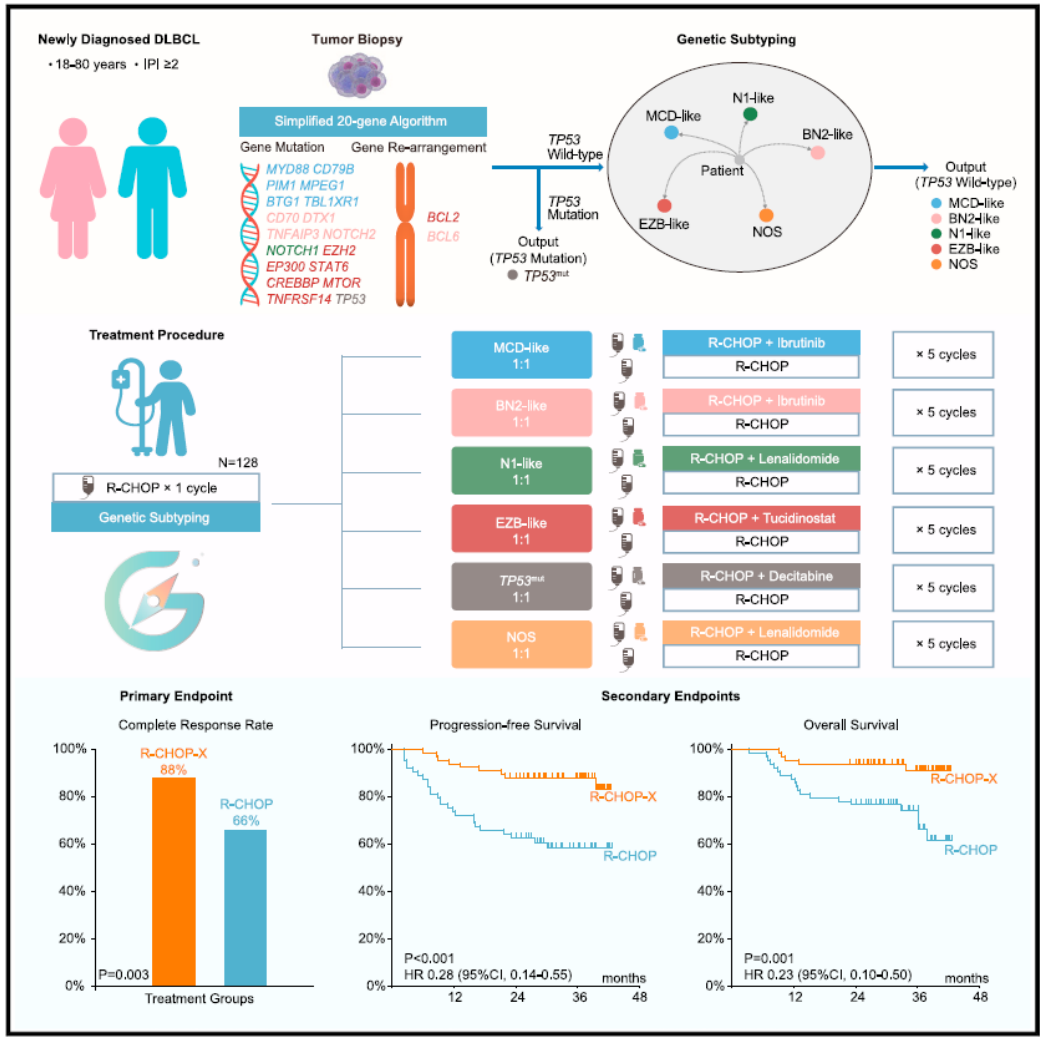
# Potential future 1L therapies for DLBCL




*1. Salles G, et al. Lancet Oncol 2020;21:978-88; 2. Vitolo U, et al. Hemasphere 2022;6(Suppl.):1984-5; 3. NCT06356129. Available at: https://clinicaltrials.gov/study/NCT06356129; 4. Sehn L, et al. J Clin Oncol 2021;39:TPS7572; 5. Davies A, et al. Blood 2020;136(Suppl. 1):38-9; 6. Westin JR, et al. Blood 2023;142(Suppl. 1):856; 7. Westin JR, et al. Blood 2019;134:1581; 8. Neelapu SS, et al. Nat Med 2022;28:735-42; 9. Westin J, et al. J Clin Oncol 2023;41(Suppl.):TPS7578; 10. Minson A, et al. Blood 2021;138(Suppl. 1):3571; 11. NCT03677154. Available at: https://clinicaltrials.gov; 12. Olszewksi A. et al. Blood 2023;142(Suppl. 1):613-15 ; 13. NCT03467373. Available at: https://clinicaltrials.gov; 14. Topp MS, et al. ASH 2023. Poster #3085; 15. Clausen MR, et al. Hemasphere;7(Suppl.): e55140cd; 16. NCT05578976. Available at: https://clinicaltrials.gov/study; 17. Tessoulin B. et al. Hemasphere 2023;7(Suppl.):e06798be; 18. NCT06047080. Available at: https://clinicaltrials.gov.*

# Genetic subtype-guided immunochemotherapy in DLBCL

*The randomized GUIDANCE-01 trial*




*1. Zhang et al., 2023, Cancer Cell 41, 1705-1716*

# Mensajes finales

R-CHOP sigue siendo la base del tratamiento para la mayoría de los pacientes con LDCGB en primera línea, pero avanzamos hacia tratamientos personalizados.

El algoritmo de tratamiento actual para el LDCBG R/R prioriza la administración de CAR-T para gran parte de los casos, tanto en segunda, como en tercera línea.

Los anticuerpos biespecíficos son de elección como línea de tratamiento posterior a la terapia CAR-T. Los estudios apuntan hacia un uso más precoz en la secuencia terapéutica.

Los tratamientos guiados por subtipo genético podrían ser más eficaces y es probable que se desarrollen en un futuro próximo.

La indicación de la terapia CAR-T y de los biespecíficos en primera línea probablemente cambie el paradigma terapéutico de esta enfermedad.

Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

# HEMATOLOGÍA EN 48H

[LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

# Gracias

cgrandeg@unav.es