LYMPHOMA Forum of Ireland

# Management of relapsed and refractory diffuse large B-cell lymphoma

UNIVERSITY OF COPENHAGEN

**20th Lymphoma Forum of Ireland Plenary Meeting**

**County Meath, 09 November 2024**

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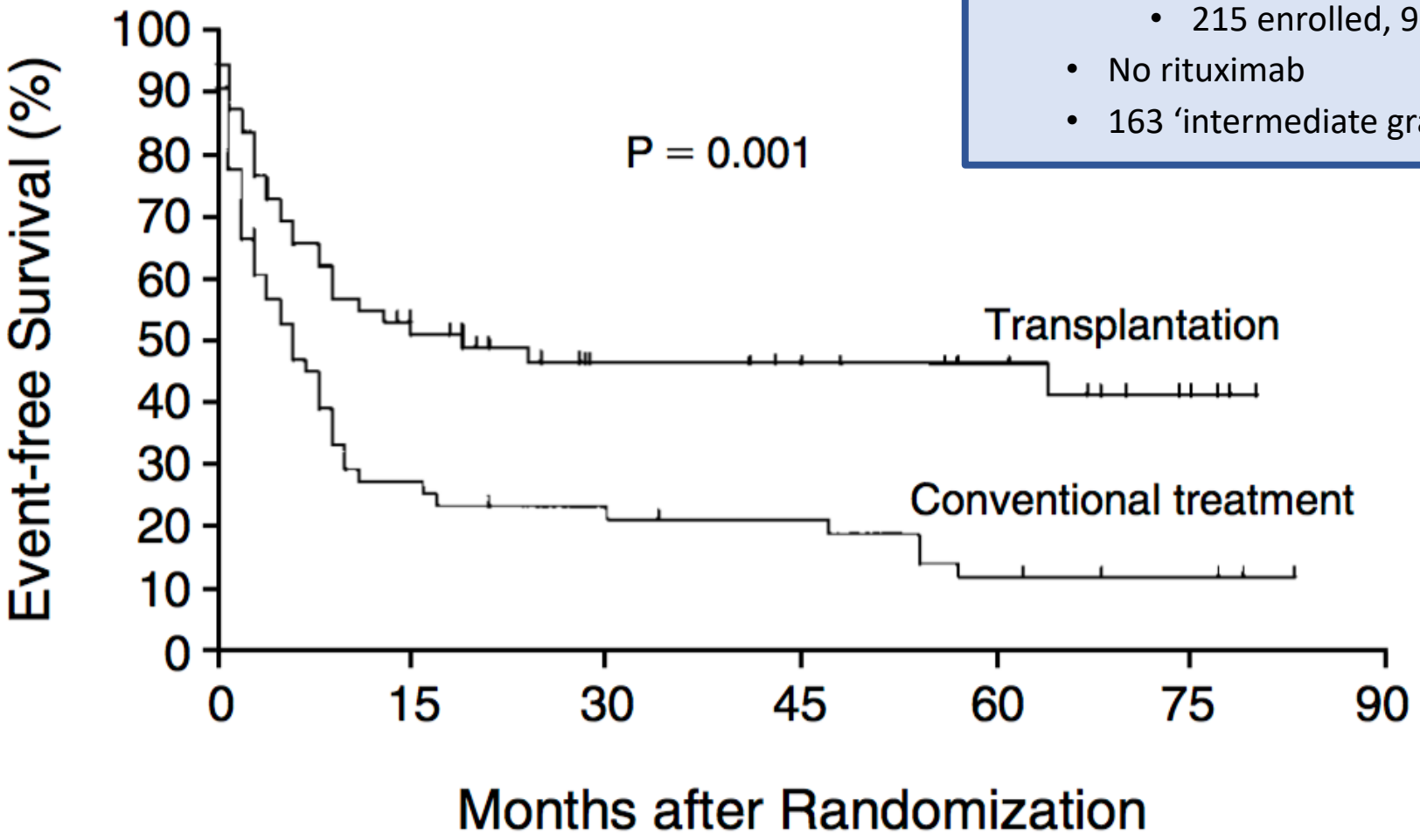
# Disclosures

- **Scientific advisory boards:**
  - AbbVie, AstraZeneca, Genmab, Johnson&Johnson, Merck, Roche, Takeda
- **Research support (institution):**
  - AbbVie, Arvinas, AstraZeneca, Bristol Myers-Squibb, Celgene, Genentech, Genmab, Incyte, Johnson&Johnson, Merck, Novartis, Pfizer, Roche, Takeda

# Conventional chemotherapy for relapsed and refractory DLBCL

# Parma trial

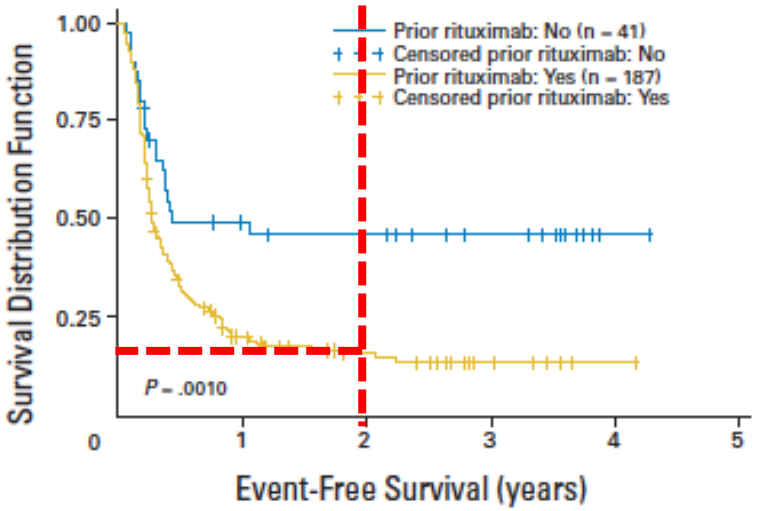
- This trial is no longer relevant in 2024:
  - Only chemo sensitive patients
    - 215 enrolled, 90 excluded after DHAP failure
  - No rituximab
  - 163 ‘intermediate grade lymphoma’, 52 ‘high grade’



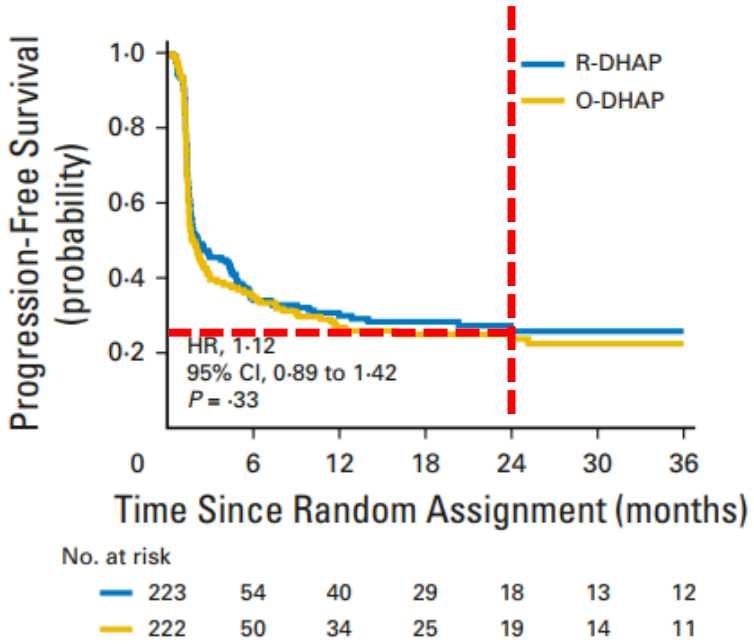

Philip T, et al. N Engl J Med 1995; 333:1540-1545

# CORAL – ORCHARRD – LY.12

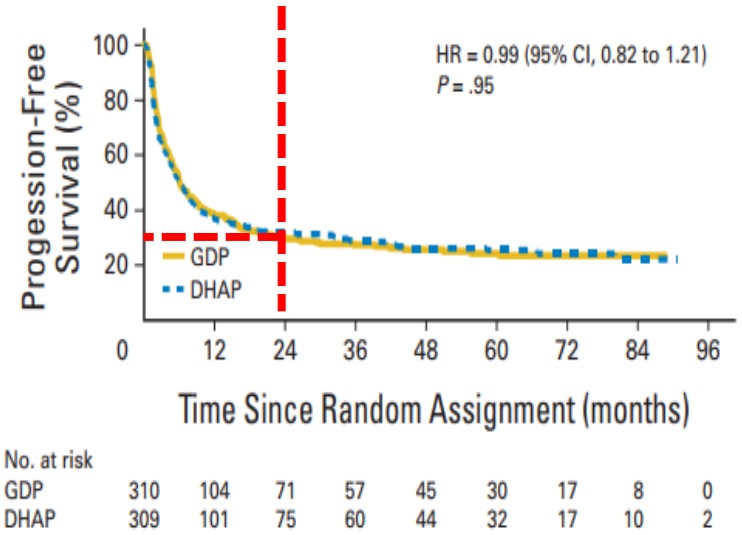
## CORAL




## ORCHARRD




## NCIC-CTG LY.12




So for patients planned for HDCT and ASCT
(which already means they are fit, not too old and co-morbid):

- The chance of cure is 25% incl. late relapses
- 10% (at best) in patients with < 1 year in remission


1. Gisselbrecht C, et al. J Clin Oncol 2010; 28(27): 4184-90.
2. Van Imhoff GW, et al. J Clin Oncol 2017; 35(5): 544-551.
3. Crump M, et al. J Clin Oncol 2014; 32(31): 3490-3496.

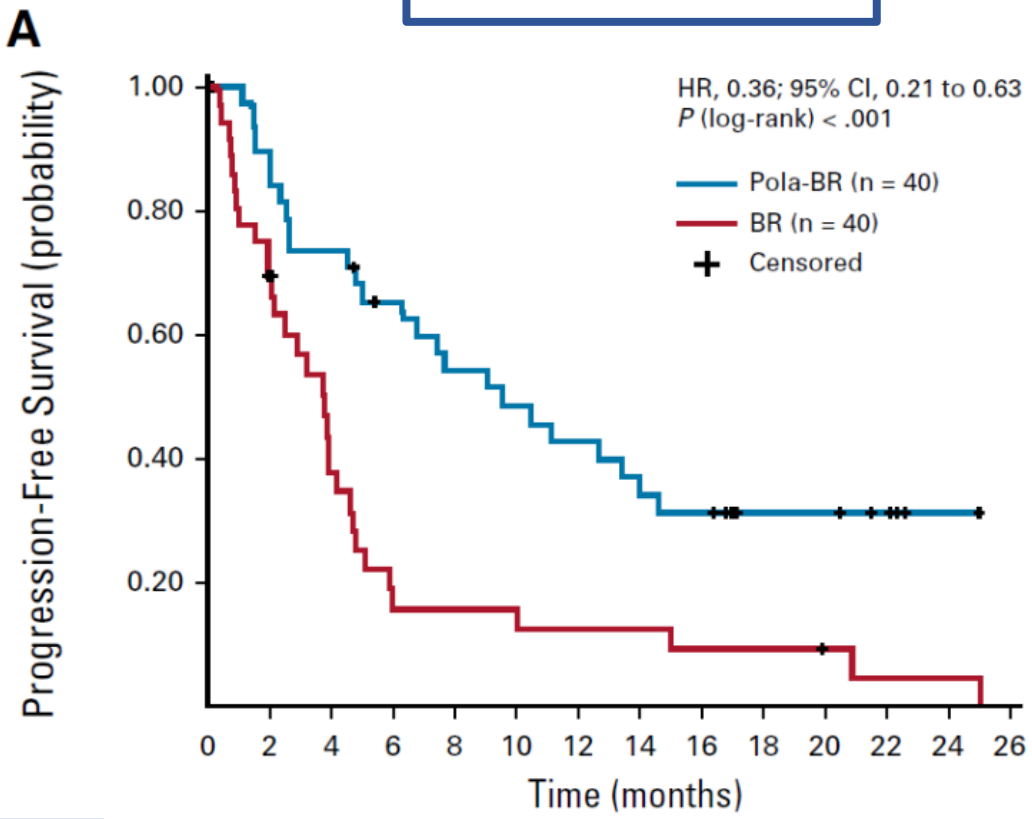
# Newer treatment options in r/r DLBCL

# Pola + R-Benda vs. R-Benda in transplant-ineligible r/r DLBCL
## (Polatuzumab vedotin: anti-CD79b ADC)

**CR rate: 40% vs. 17%**

### Inclusion

- Age ≥ 18
- Biopsy-confirmed R/R DLBCL[a]
- ≥ 1 prior line of therapy
- ECOG PS 0-2
- Grade ≤ 1 peripheral neuropathy
- Transplant ineligible or treatment failure with prior ASCT

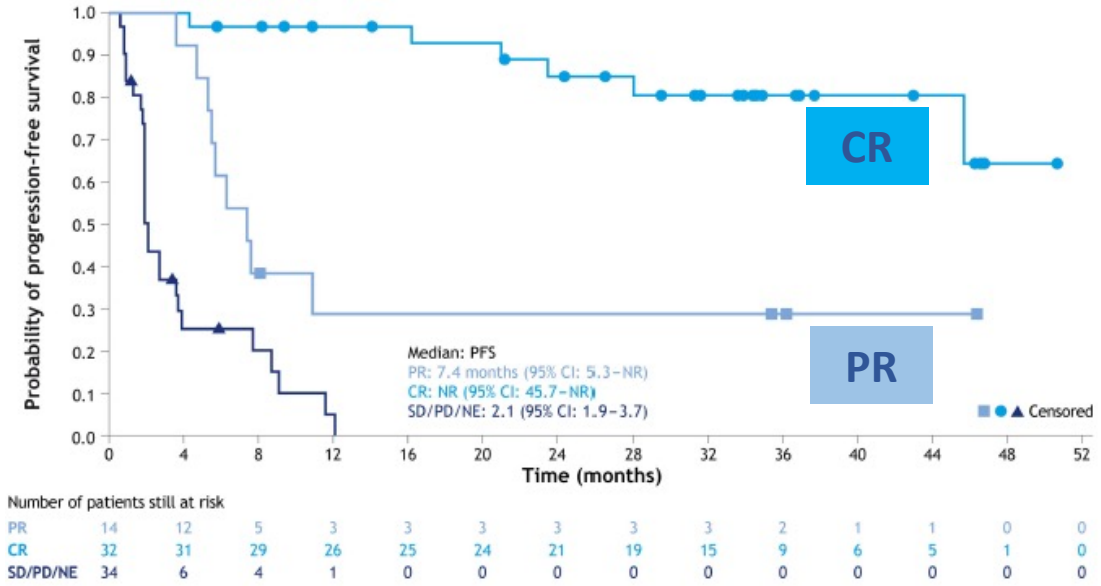



Small randomised phase 2 study with 40+40 patients
- 50% ASCT-ineligible because of age
- 20% failing prior ASCT

Sehn LH, et al. J Clin Oncol 2020; 38(2): 155-165.

# L-MIND: Phase 2 study of Tafasitamab + Lenalidomide in r/r DLBCL (Tafasitamab: Fc-enhanced, anti-CD19 mAb)

| Characteristic | Patients (n=81) |
|---|---|
| Median age (range), years | 72 (41-86) |
| Median prior LOT (range) | 2 (1-4) |
| No. Prior Lines, % (1/2/3/4) | 50/43/6/1 |
| Primary refractory, % (Y/N) | 19/81 |
| Refractory to last prior therapy, % (Y/N) | 44/56 |
| Prior SCT, % (Y/N) | 11/89 |

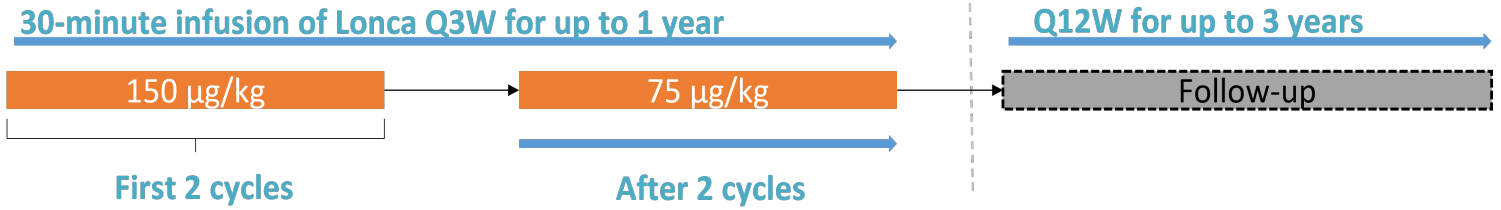



| | Tafa + Len (N = 80) |
|---|---|
| **Best Response (≥ 35 Mo)** | |
| CR | **40% (32)** |
| PR | 17.5% (14) |
| SD | 16.3% (13) |
| PD | 16.3% (13) |
| NE | 10% (8) |
| **ORR** | 57.5% (46) |
| **Median DOR** | **43.9 mo** |

Salles G, et al. Lancet Oncol 2020;21(7):978-988.

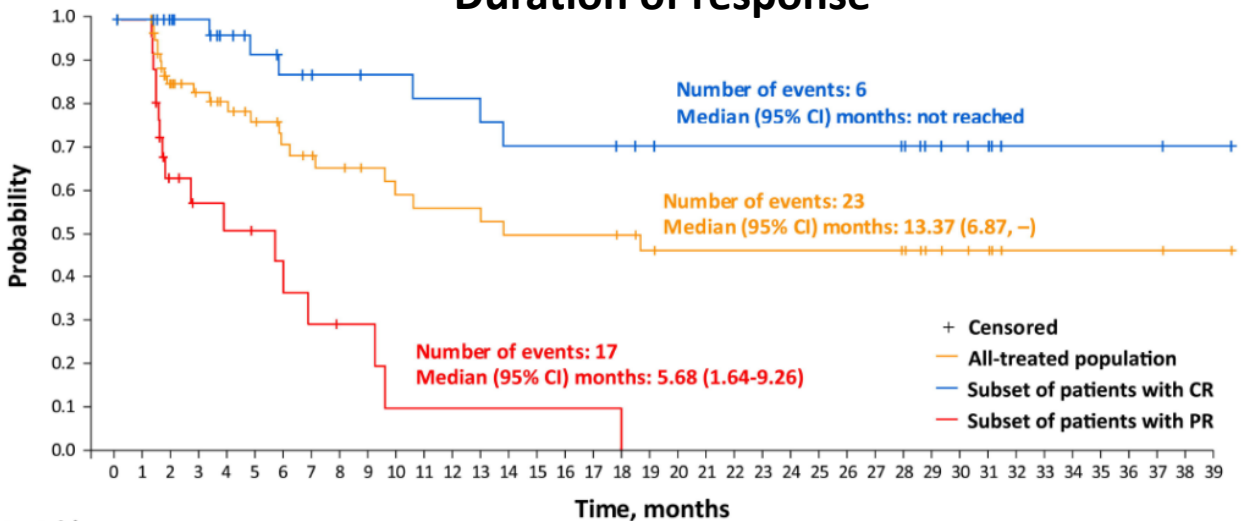
# LOTIS-2: Phase 2 study of Loncastuximab tesirine for r/r DLBCL
## (Loncastuximab tesirine-T: anti-CD19 ADC)

**Eligibility:** Adults with R/R DLBCL after 2 or more lines of systemic therapy, CD19+ biopsy if prior anti-CD19 therapy received, ECOG PS 0-2, ASCT 30+ days prior or alloSCT 60+ days prior permitted

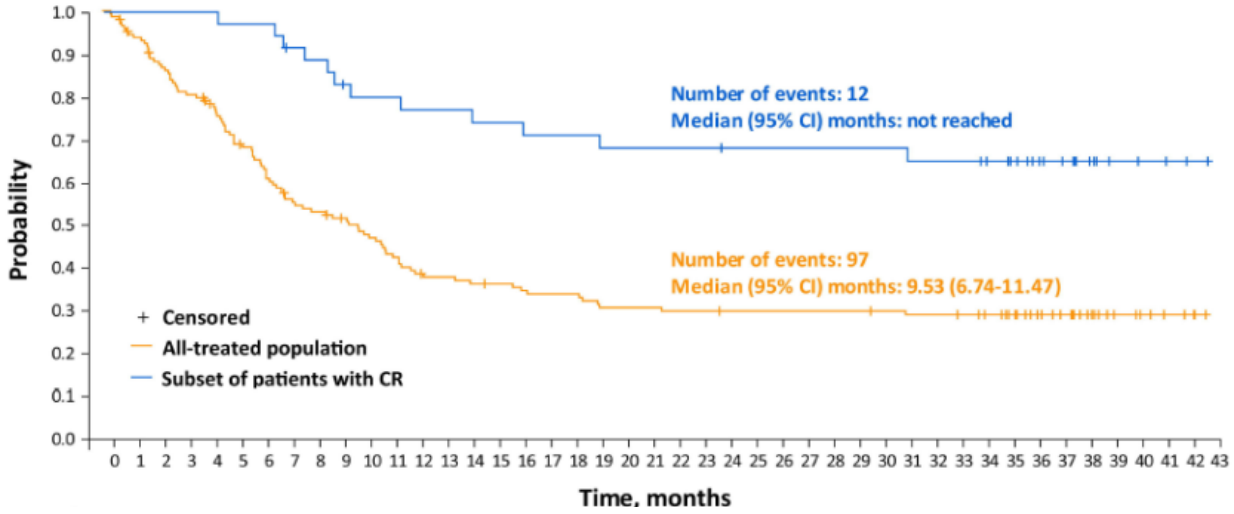



**N = 145, median 3 prior lines**
**ORR 48%**
**CRR 24%**

### Duration of response




### Progression-free survival

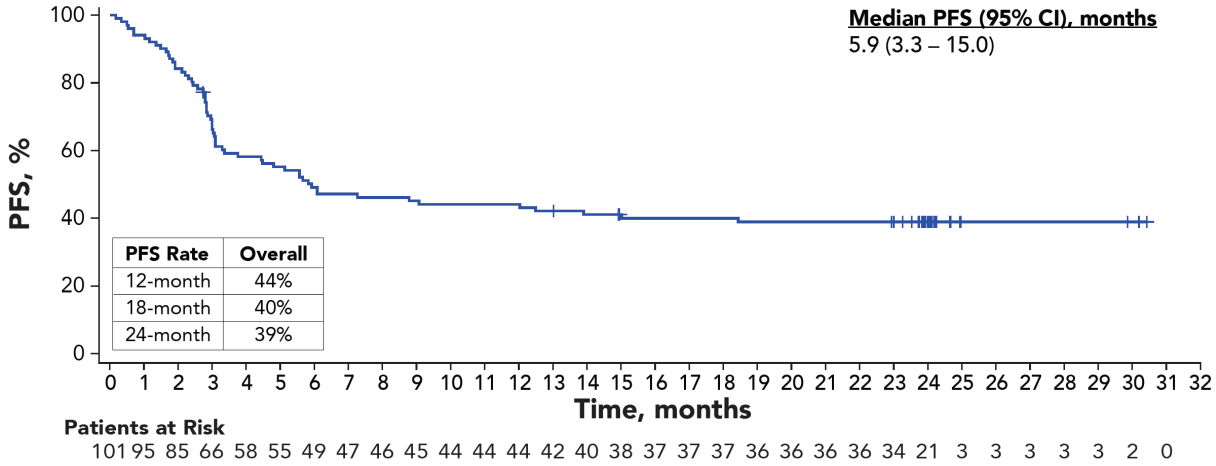




1. Caimi PF, et al. Lancet Oncol. 2021;22:790-800.
2. Caimi PF, et al. Haematologica 2024; 109(4): https://doi.org/10.3324/haematol.2023.283459.

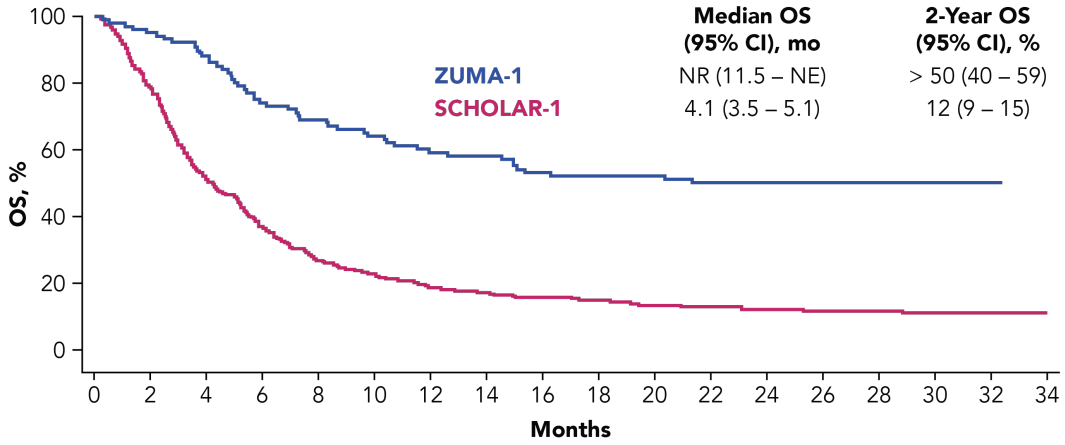
# ZUMA-1: Phase 1-2 study of Axicabtagene Ciloleucel in r/r DLBCL

## PFS: 39% progression-free at 27.1 mo




N= 145
70% with ≥ 3 prior therapies
65% refractory to most recent therapy

## Standardized OS Comparison: ZUMA-1 vs. SCHOLAR-1




**Similar results were seen in:**

**TRANSCEND[2] (Lisocabtagene maraleucel in r/r DLBCL with ≥ 3 prior therapies**
**JULIET[3] (Tisagenlecleucel in r/r DLBCL with ≥ 3 prior therapies)**


1. Neelapu S, et al. N Eng J Med 2017;377(26):2531-2544.
2. Abramson JS, et al. Lancet 2020; 396(10254): 839-852.
3. Schuster SJ, et al. N Engl J Med 2019; 380(1):45-56.

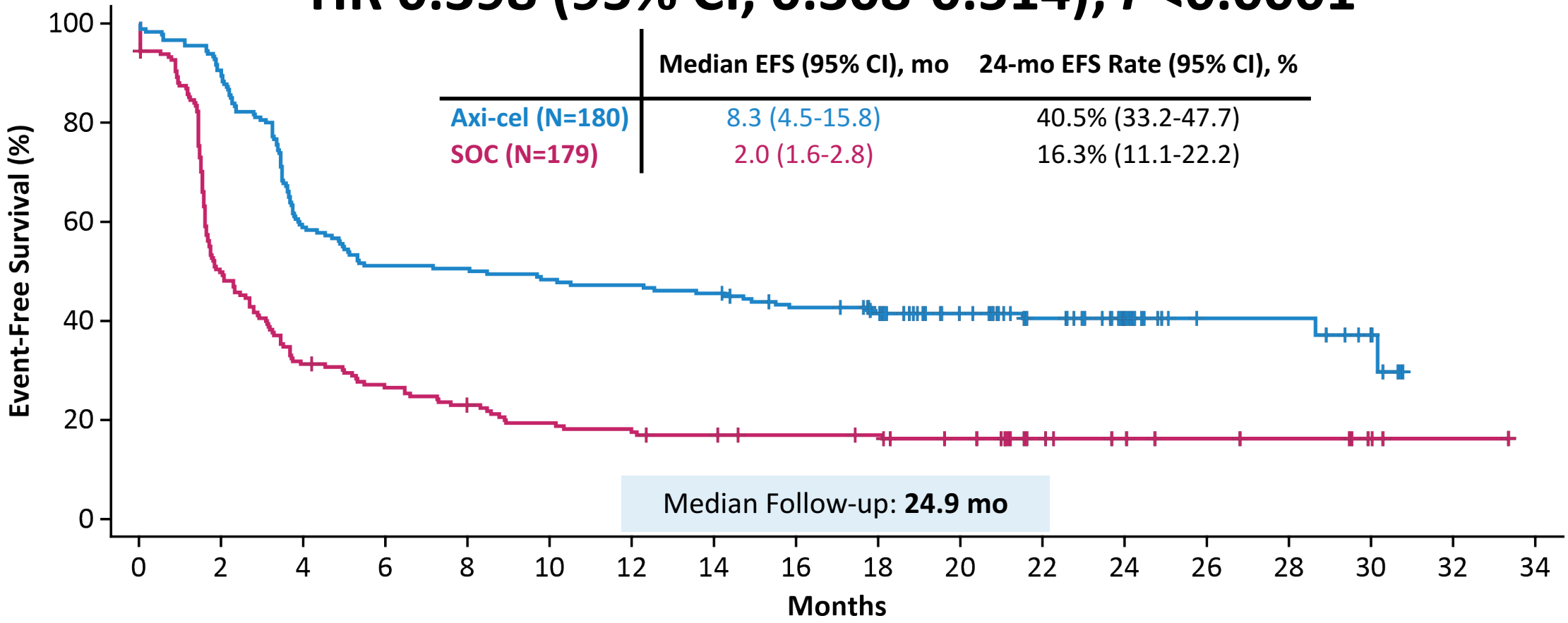
# CAR-T in 2nd line treatment of DLBCL

# ZUMA-7: Phase 3 study of Axi-cel vs. SOC in 2nd line treatment of DLBCL

## Primary endpoint: EFS

**HR 0.398 (95% CI, 0.308-0.514); *P*<0.0001**

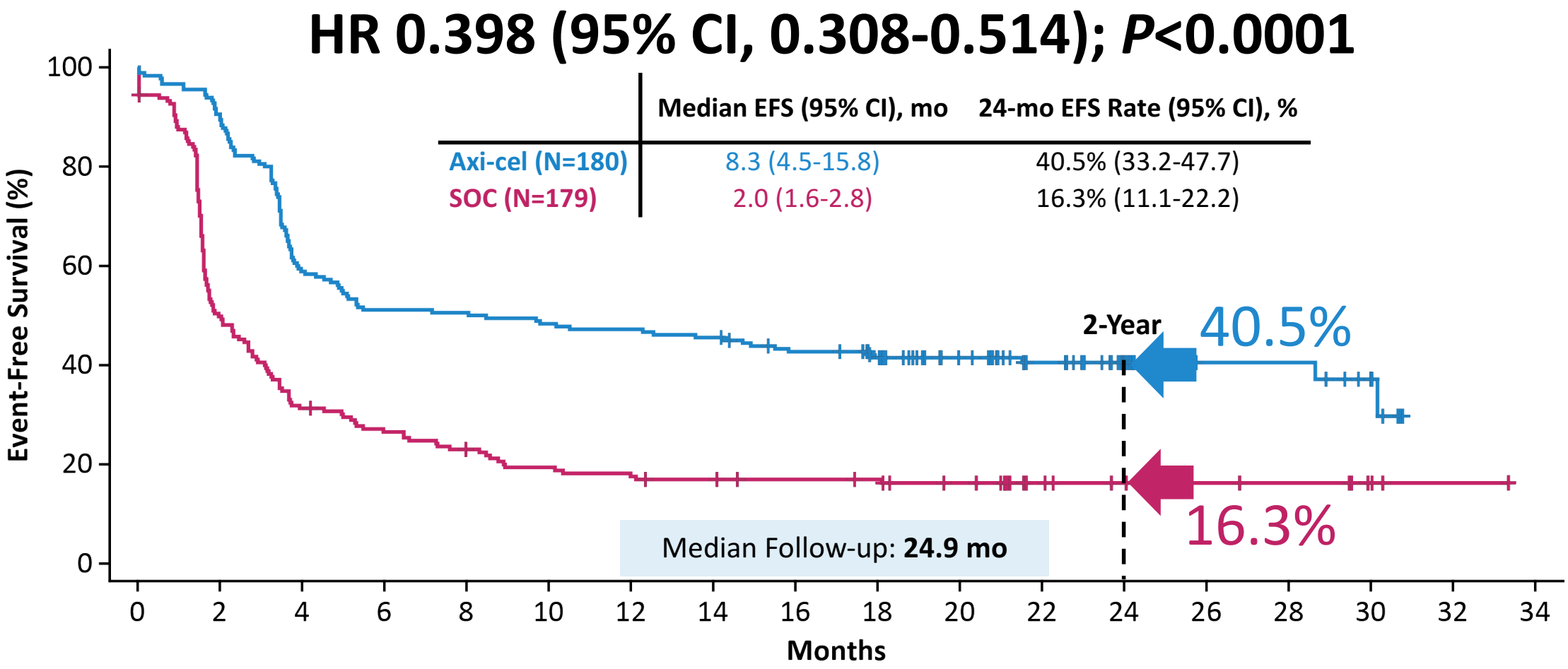
| | Median EFS (95% CI), mo | 24-mo EFS Rate (95% CI), % |
|---|---|---|
| Axi-cel (N=180) | 8.3 (4.5-15.8) | 40.5% (33.2-47.7) |
| SOC (N=179) | 2.0 (1.6-2.8) | 16.3% (11.1-22.2) |




Locke FL, et al. N Engl J Med 2022; 386:640-654

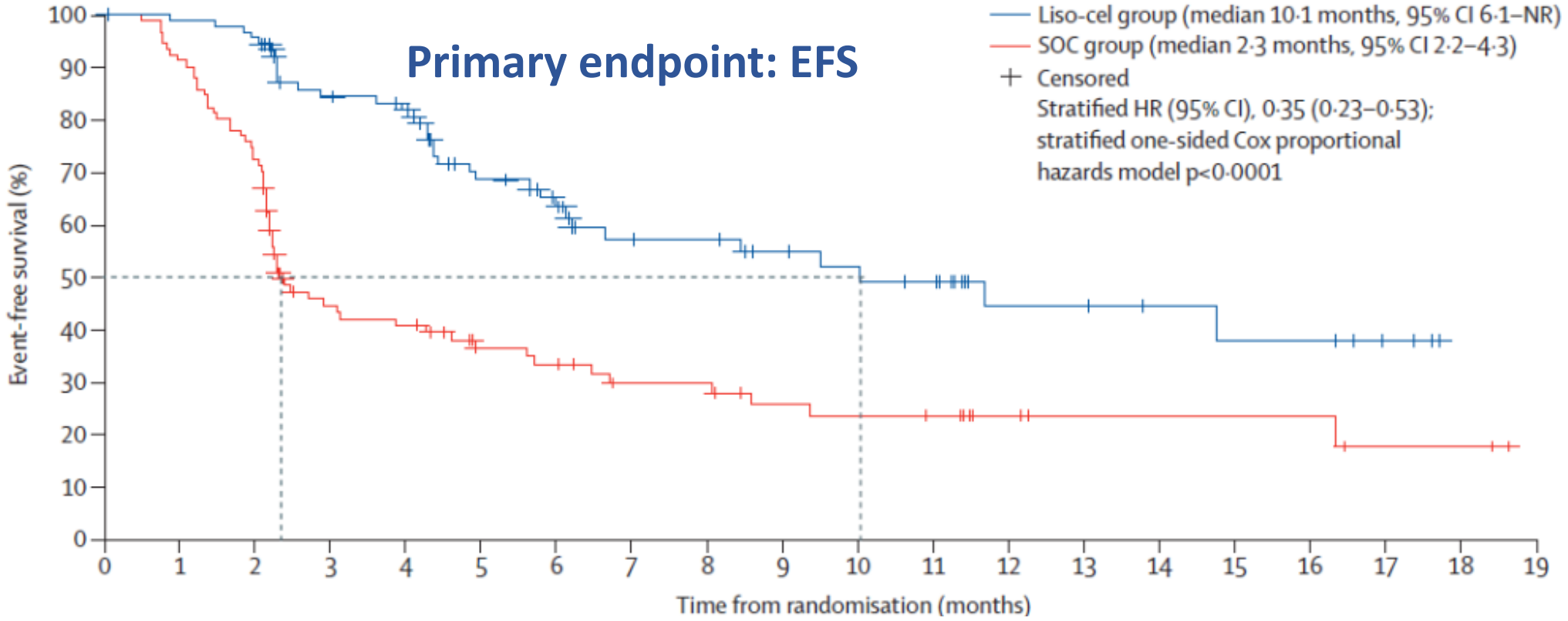
# ZUMA-7: Phase 3 study of Axi-cel vs. SOC in 2nd line treatment of DLBCL

## Primary endpoint: EFS




Locke FL, et al. N Engl J Med 2022; 386:640-654

# TRANSFORM: Phase 3 study of Lisocabtagene maraleucel vs. SOC in 2nd line treatment of DLBCL




**June 2022 FDA approved Liso-cel for 2nd line treatment of LBCL (primary refractory or relapse <12 months)**

Kamdar M, et al. Lancet 2022; 399(10343: 2294-2308.

# CD20xCD3 antibodies for r/r DLBCL after 2 or more prior treatment lines

# Studies of CD20xCD3 bispecific antibodies for R/R DLBCL after ≥2 lines of treatment: prior therapies at enrollment

| | Trial | Number of patients | Median (range) prior therapies | Primary refractory, n (%) | Refractory to most recent line, n (%) | Prior CAR T-cell therapy, n (%) | Prior ASCT, n (%) |
|---|---|---|---|---|---|---|---|
| Mosunetuzumab[1] | GO29781 | 88 | 3 (2–13) | – | 70 (80) | 26 (30) | 15 (17) |
| Odronextamab[2] | ELM-2 | 140 | 2 (2–8) | 80 (57) | – | – | – |
| Glofitamab[3] | NP30179 | 154 | 3 ( 2–7) | 90 (58) | 132 (86) | 51 (33) | 28 (18) |
| Epcoritamab[4] | EPCORE NHL-1 | 157[†] | 3 (2–11) | 96 (61) | 130 (83) | 61 (39) | 31 (20) |

1. Bartlett NL, et al. Blood Adv 2023;7(17):4926-4935.
2. Walewski J, et al. EHA 2023. Abstract P1115.
3. Dickinson M, et al. N Engl J Med 2022;387:2220–31.
. 4. Thieblemont C, et al. J Clin Oncol 2023; 41(12):2238-2247.

# Phase II dose expansion of mosunetuzumab in patients with R/R DLBCL after ≥2 therapies

ASCT-ineligible R/R DLBCL
ECOG PS 0–1
R/R to ≥2 prior systemic regimens, including, including ≥1 anti-CD20 MAb and anthracycline
(N=88)

**Cycles 1–2**
**Mosunetuzumab** IV step-up dosing: C1D1 1 mg, C1D8 2 mg, C1D15, C2D1 60 mg

**Cycles 3–8**
**Mosunetuzumab** IV D1 30 mg

**Cycles 8+**
**Mosunetuzumab** IV D1 30 mg
Complete treatment after C17 if PR or stable disease

**Primary endpoint:**
CR (IRF-assessed)

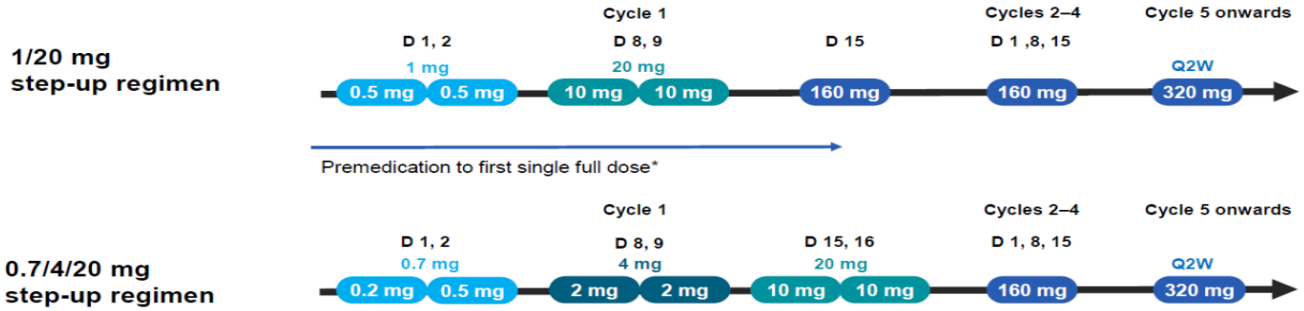
| Efficacy outcomes (95% CI)* | N=88 |
|---|---|
| **CR rate, %** | **24 (15–34)** |
| ORR, % | 42 (32–53) |
| Median DOCR, months | NR (9.0–NE) |
| Median DOR, months | 7.0 (4.2–NE) |
| Median PFS, months | 3.2 (2.2–5.3) |
| Median OS, months | 11.5 (9.0–16.4) |

**Safety (N=88)**

**Most common Grade ≥3 AEs:**
- Neutropenia (22%)
- Hypophosphatemia (11%)
- Anemia (9%)

Bartlett NL, et al. Blood Adv 2023;7(17):4926-4935.

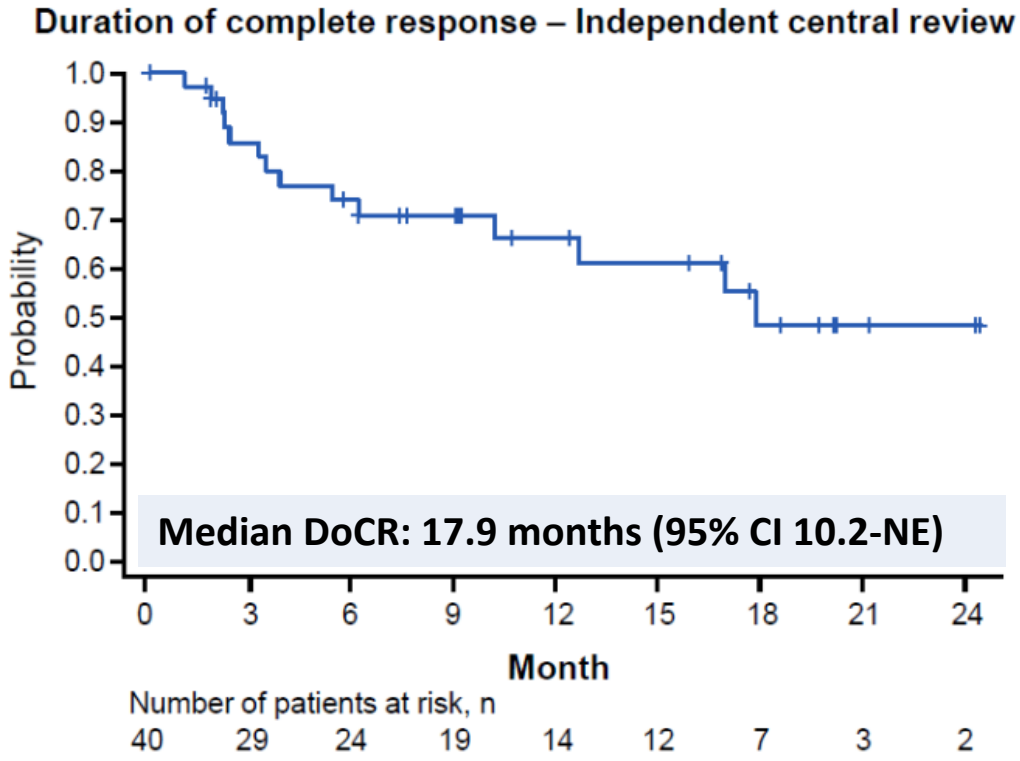
# Phase II study of odronextamab in patients with R/R DLBCL




| n, (%) | 1/20 regimen N=67 | 0.7/4/20 regimen N=73 |
|---|---|---|
| CRS any Grade | 38 (56.7%) | 39 (53.4%) |
| Grade 1 | 21 (31.3%) | 28 (38.4%) |
| Grade 2 | 12 (17.9%) | 10 (13.7%) |
| Grade 3 | 5 (7.5%) | 1 (1.4%) |
| Grade 4 | 0 | 0 |

| Best overall response | Independent central review N=130* |
|---|---|
| Objective response rate (ORR)† | **49.2%** [95% CI 40.4%–58.1%] |
| Complete response | **30.8%** |

Median follow-up: 21.3 months (range 2.6–29.8)



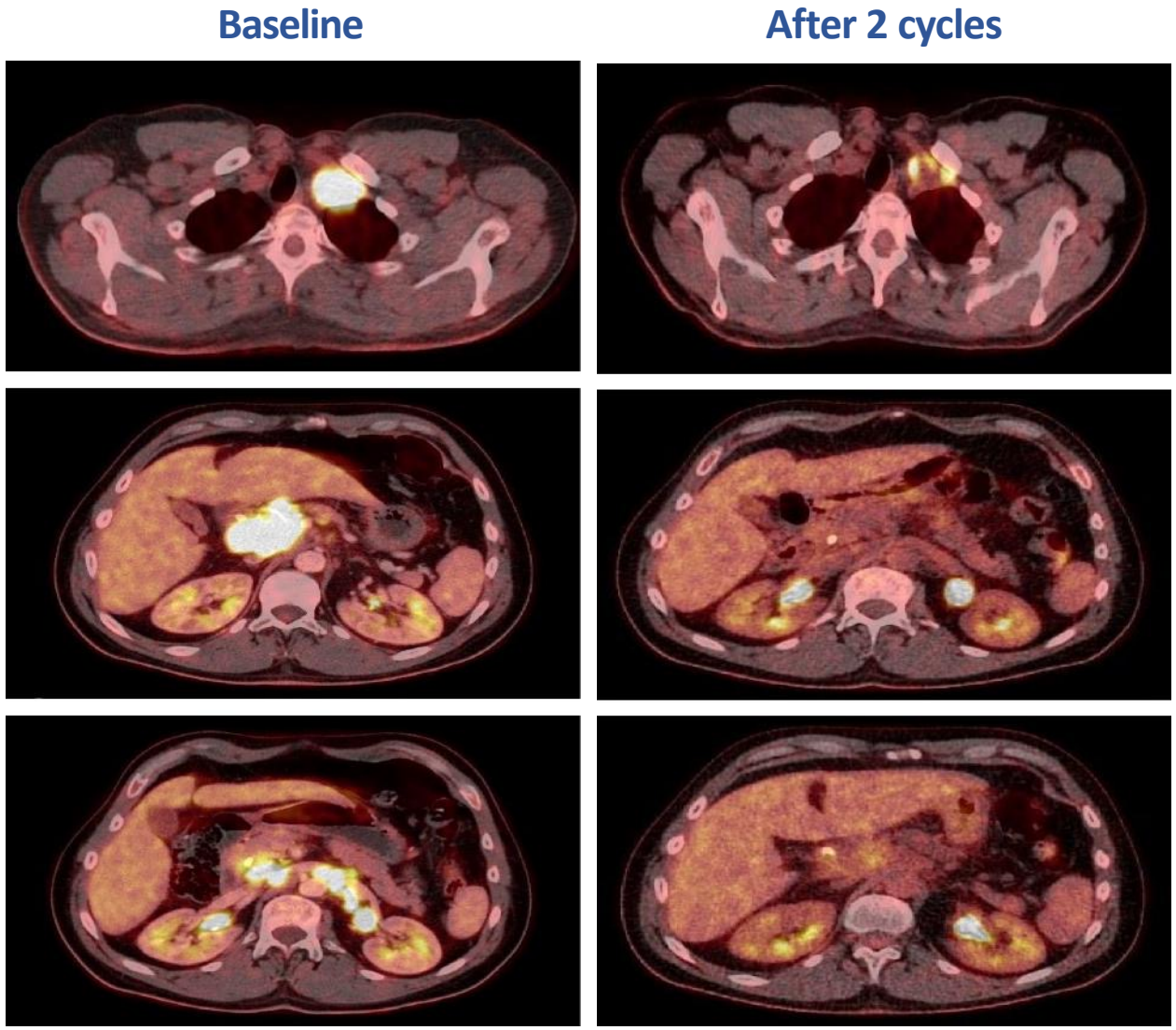

**Median DoCR: 17.9 months (95% CI 10.2-NE)**

- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

Poon M, et al. ICML 2023, abstract #93.

# *Patient case #1 – DLBCL treated with glofitamab during dose-escalation*

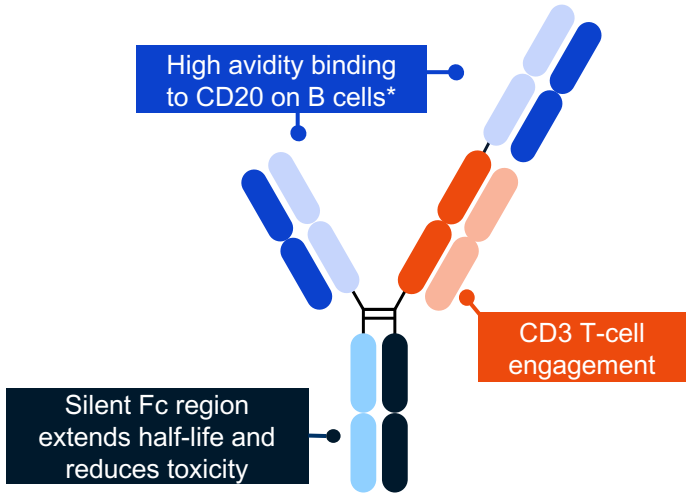
- 42-year old male with DLBCL
- Failure of R-CHOP and HD+ASCT
- Severe tumor pain and Horner's syndrome due to tumor flare within 12 hours of first glofitamab dose
- Very deep PR after 2 cycles of glofitamab
- Consolidation RT after 8 cycles
- Still in CR 5 years after last treatment



# NP30179: Phase II dose expansion study of glofitamab in R/R DLBCL after ≥2 therapies – study design and patients

## Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline



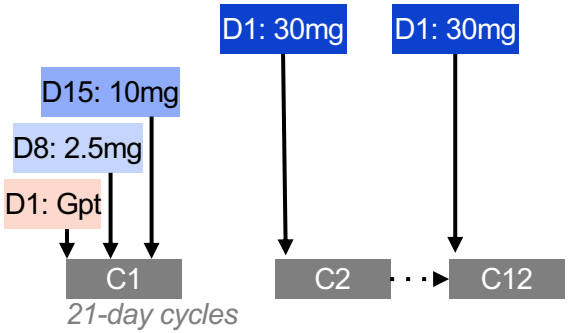

## Glofitamab IV administration

**Fixed-duration treatment**

- max. 12 cycles

**CRS mitigation:**

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



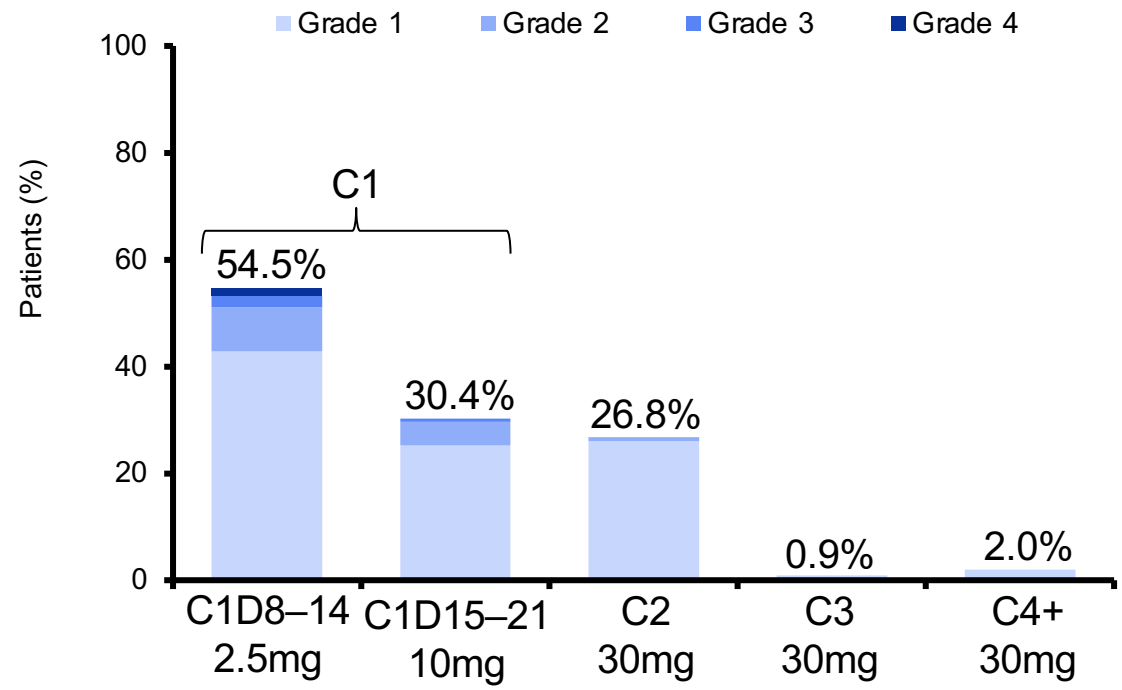

| n (%) | N=155 |
|---|---|
| **Median no. of prior lines of therapy, n (range)** | 3 (2–7) |
| 2 prior lines | 61 (39) |
| ≥3 prior lines | 94 (61) |
| **Prior anti-CD20 therapy** | 155 (100) |
| **Prior anthracycline therapy** | 152 (98) |
| **Prior CAR-T** | 52 (34) |
| **Prior ASCT** | 29 (19) |
| **Refractory to any prior therapy** | 139 (90) |
| **Refractory to first prior therapy** | 91 (59) |
| **Refractory to last prior therapy** | 131 (85) |
| **Refractory to prior CAR-T** | 46/52 (88) |
| **Refractory to any prior anti-CD20** | 129 (83) |

Dickinson M, et al. N Engl J Med. 2022 Dec 15;387(24):2220-2231.
Hutchings M, et al. ASH 2023 (Abstract #179)

# Phase II dose expansion study of glofitamab in R/R DLBCL after ≥2 therapies – cytokine release syndrome

| n (%) | N=154 |
|---|---|
| CRS (any grade)* | 97 (63.0) |
| Grade 1 (fever) | 73 (47.4) |
| Grade 2 | 18 (11.7) |
| Grade 3 | 4 (2.6) |
| Grade 4 | 2 (1.3) |
| Median time to CRS onset from C1D8 dose, hours (range) | 13.6 (6.2–51.8) |
| Corticosteroids for CRS management | 27/97 (27.8) |
| Tocilizumab for CRS management | 31/97 (32.0) |

## CRS by cycle and grade†

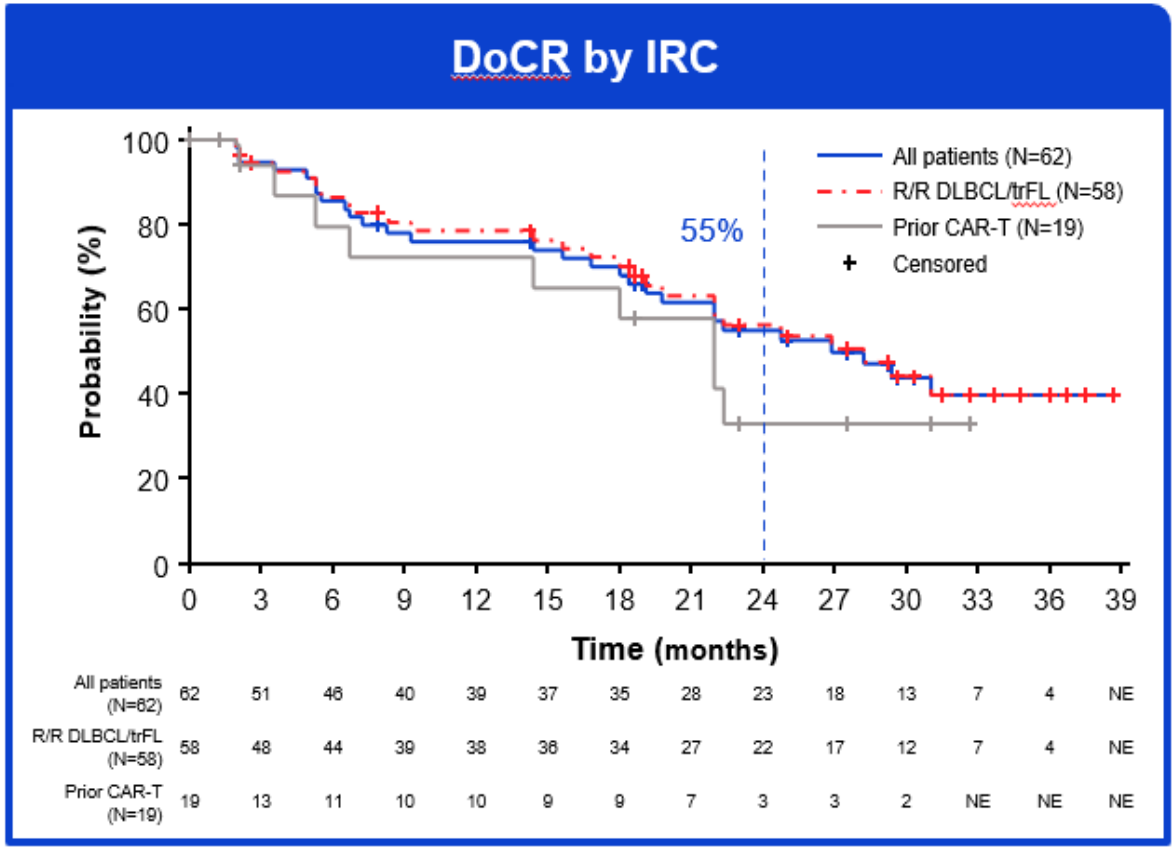



**CRS was mostly low grade, time of onset was predictable, and most events occurred during C1**

Dickinson M, et al. EHA 2022 oral presentation

# Phase II dose expansion study of glofitamab
# Response rates and duration of CR

| | All patients (N=155)* | R/R DLBCL/ trFL (N=132)[1†‡] | Prior CAR-T (N=52)† |
|---|---|---|---|
| **ORR**, n (%) [95% CI] | 80 (52) [43.5–59.7] | 74 (56) [47.2–64.7] | 26 (50) [35.8–64.2] |
| **CR rate**, n (%) [95% CI] | 62 (40) [32.2–48.2] | 58 (44) [35.3–52.8] | 19 (37) [23.6–51.0] |
| **Median DoCR**, months (95% CI) | 26.9 (19.8–NR) | 28.3 (19.8–NR) | 22.0 (6.7–NR) |
| **24-month DoCR**, % (95% CI) | 55.0 (41.1–68.8) | 56.2 (41.9–70.4) | 33.1 (7.2–59.0) |
| **Median CR follow-up**, months (range) | 29.6 (0–39) | 29.6 (0–39) | 23.0 (0–33) |
| **Ongoing CRs**, n/N (%) | 34/62 (55) | 32/58 (55) | 10/19 (53) |



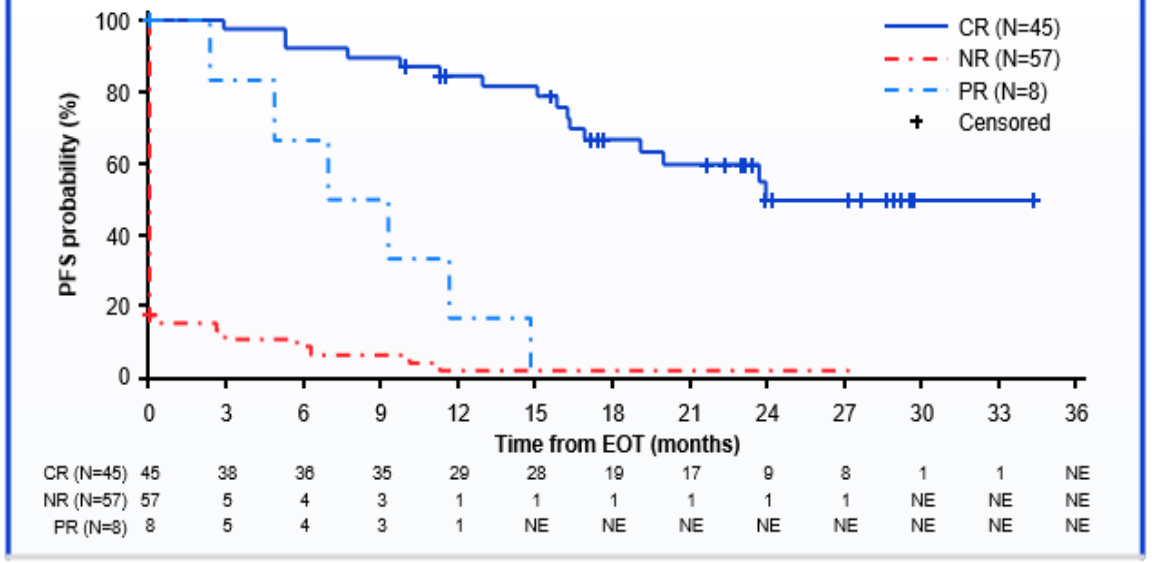

- Median time on study: 32.1 months (range: 0–43)

**With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups**

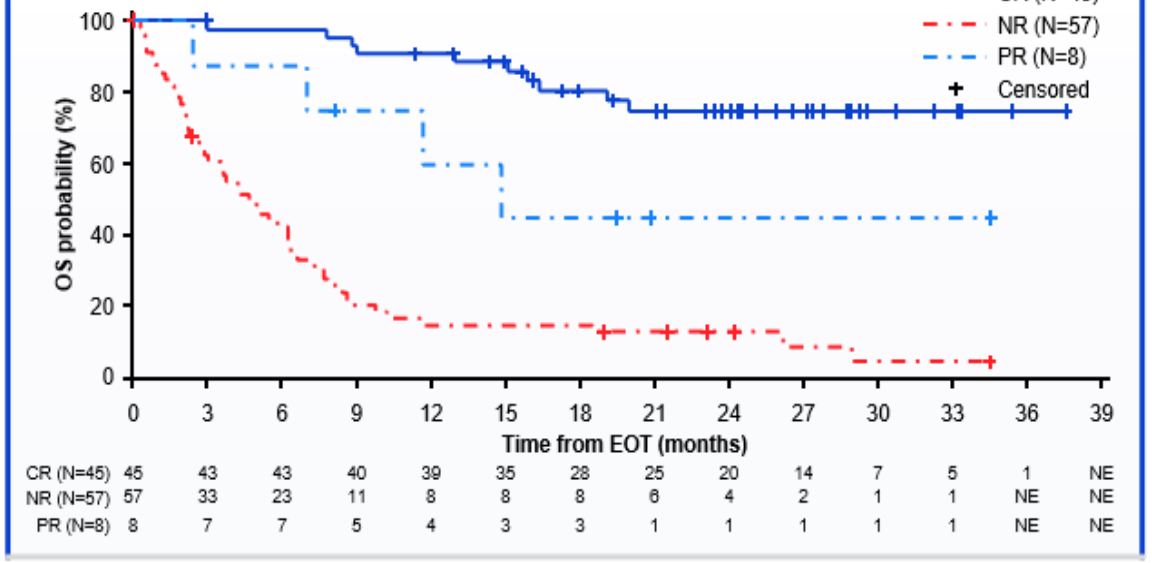
Hutchings M, et al. ASH 2023 (Abstract #179)

# Phase II dose expansion study of glofitamab in R/R DLBCL after ≥2 therapies – ASH 2023 update

## PFS




## OS




| Landmark PFS from EOT in patients with CR at EOT* | N=45 |
|---|---|
| Median PFS, months (95% CI) | 24.0 (19.1–NE) |
| 18-month PFS rate, % (95% CI) | 66.6 (51.0–82.2) |

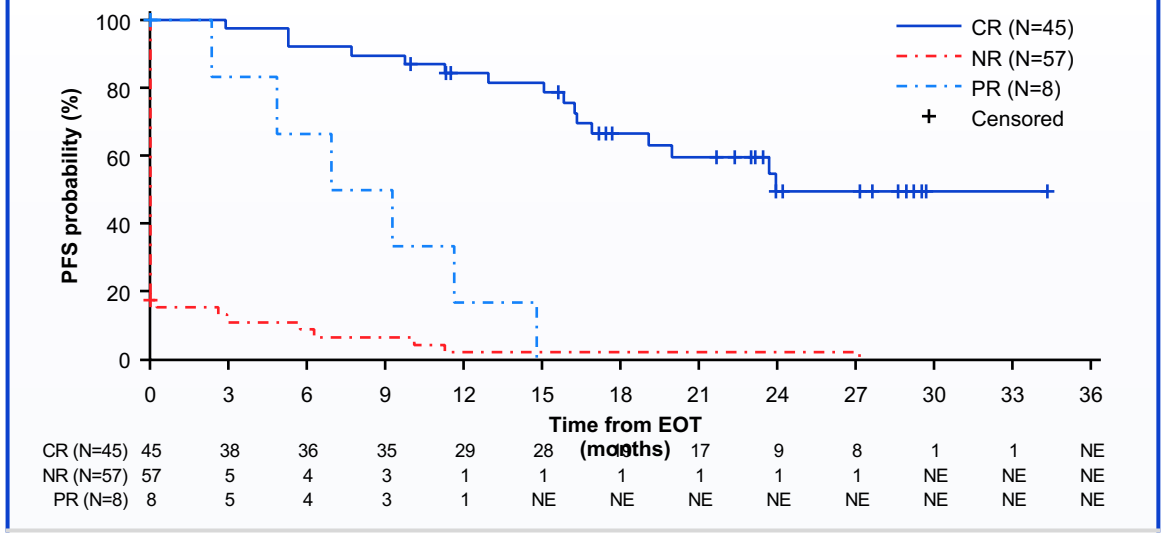
| Landmark OS from EOT in patients with CR at EOT* | N=45 |
|---|---|
| Median OS, months (95% CI) | NE (NE) |
| 18-month OS rate, % (95% CI) | 80.7 (68.6–92.8) |

**Majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT**

Hutchings M, et al. ASH 2023 (Abstract #179)

# Landmark analysis by response at EOT

## PFS

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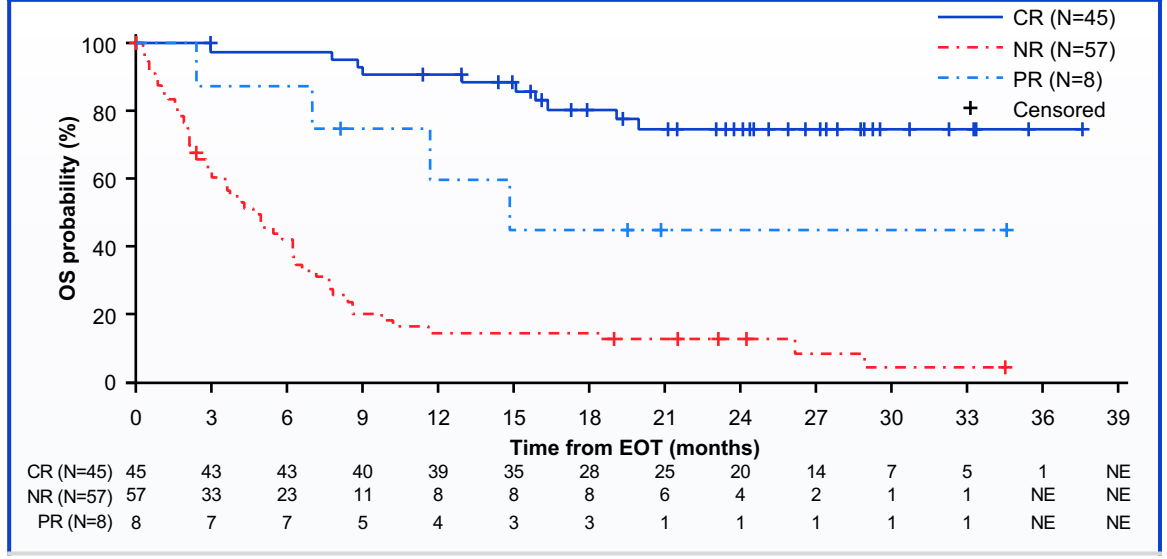


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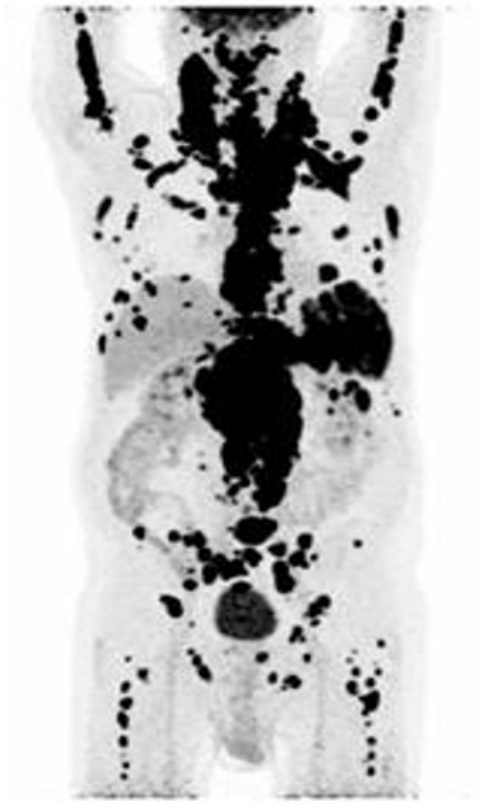
Hutchings M, et al. ASH 2023 (Abstract #179)

# *Patient case #2 – DLBCL (transformed FL) treated with glofitamab*

- 69 y.o. man with a transformed FL
- 3 prior lines of treatment
- Refractory to the 2 most recent lines
- Begins glofitamab in late 2018
- CRS grade 1 during C1
- PR after 2 cycles and CR after 5 cycles
- Still in CR at the end of 12 cycles of glofitamab in June 2019
- Remained in CR for more than 2 years after last treatment
- Died from a chemotherapy-related MDS/AML in 2021

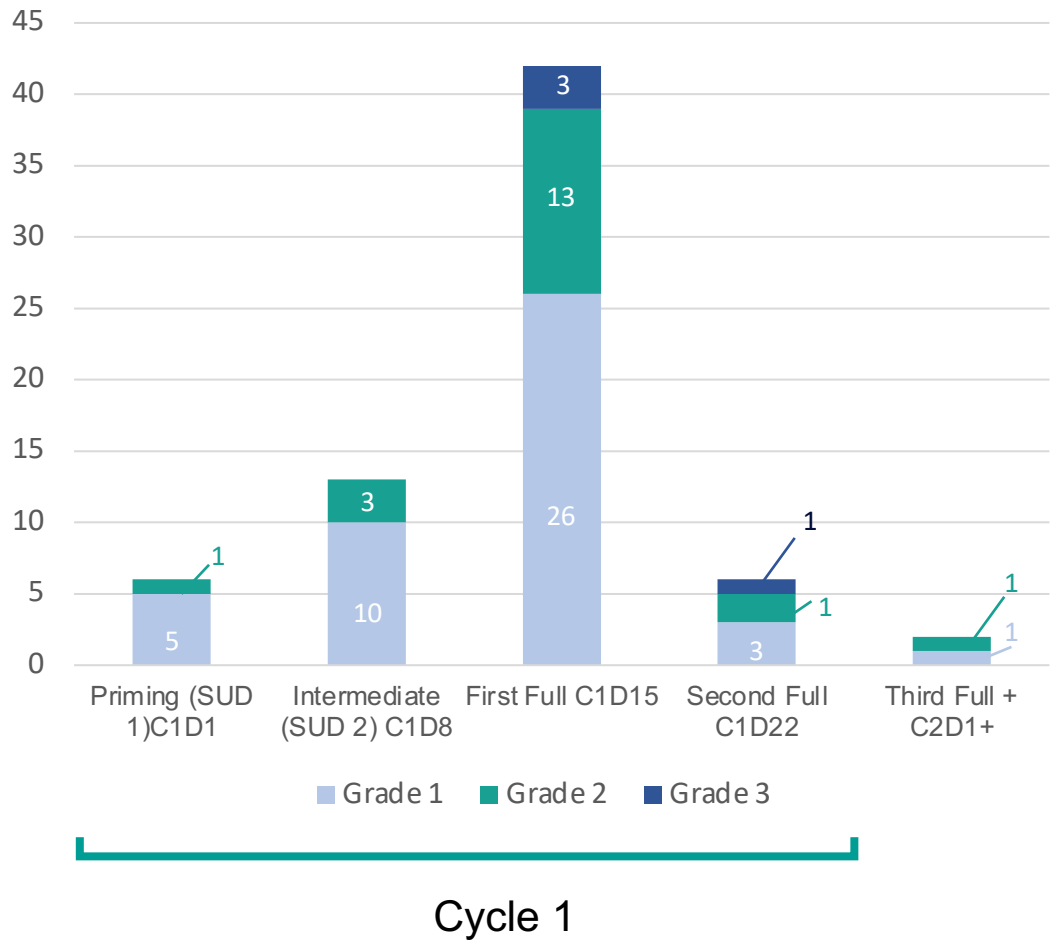
**Before treatment**



**After 2 cycles = PR**

# Phase II dose expansion study of epcoritamab in patients with R/R LBCL – patients and safety

| Prior Treatments | DLBCL, n=139 | LBCL, N=157 |
|---|---|---|
| Median time from initial diagnosis to first dose, mo | 19 | 19 |
| Median time from end of last therapy to first dose, mo | 2.4 | 2.4 |
| Median prior lines of therapy (range) | 3 (2–11) | 3 (2–11) |
| ≥3 Lines of therapy, n (%) | 97 (70) | 110 (70) |
| Primary refractory[b] disease, n (%) | 81 (58) | 95 (61) |
| Refractory[b] to last systemic therapy, n (%) | 114 (82) | 130 (83) |
| Refractory[b] to ≥2 consecutive lines of therapy, n (%) | 103 (74) | 118 (75) |
| Prior ASCT, n (%) | 26 (19) | 31 (20) |
| Prior CAR T therapy, n (%) | 53 (38) | 61 (39) |
| Refractory[b] to CAR T therapy | 39/53 (74) | 46/61 (75) |

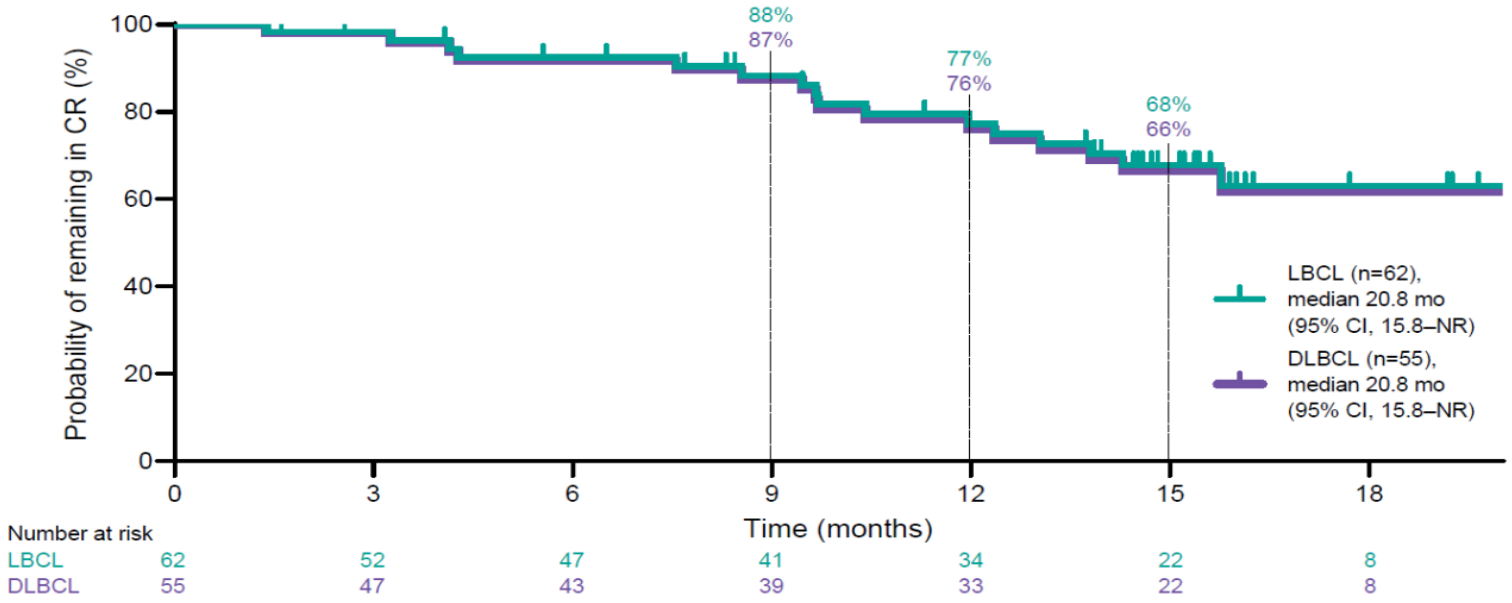



Thieblemont C, et al. J Clin Oncol 2022; 41(12): 2238-2247.

# Phase II dose expansion study of epcoritamab in patients with R/R LBCL - response data

| Best Overall Response, n (%) | LBCL N=157[a] | DLBCL n=139[a] | HGBCL n=9 | PMBCL n=4 | FL G3B n=5 |
|---|---|---|---|---|---|
| Overall response | 99 (63) | 86 (62) | 4 (44) | 4 (100) | 5 (100) |
| Complete response | 62 (39) | 55 (40) | 2 (22) | 2 (50) | 3 (60) |

## Durable Complete Responses

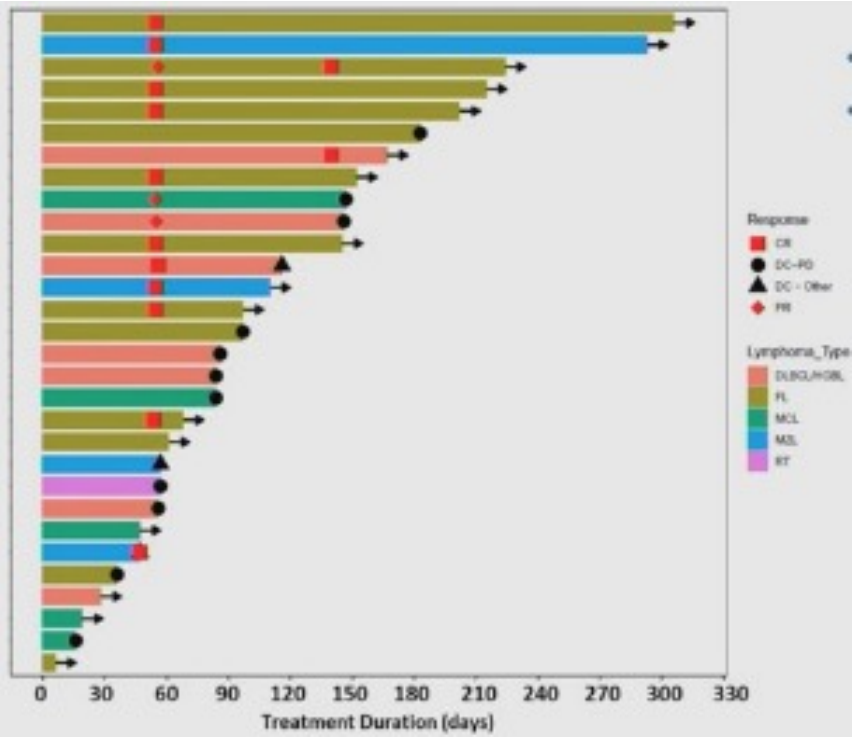



Karimu Y, et al. ASCO 2023 #7525 (poster).
Jurczak W, et al. EHA 2023 #P1118 (poster).
Thieblemont C, et al. ICML 2023 #94 (oral).

# Phase 1 Study of Tnb-486, (CD19xCD3) in R/R B-NHL

**Key Results**
- DLBCL: ORR 75%; CR 50%
- FL: ORR 87.5% (all CR)

## Durable Responses with No Relapses from CR




## Cytokine Release Syndrome (CRS)

- All CRS events occurred during Cycle 1, **all rapidly resolved**
- CRS events were predominantly **low-grade** and short in duration (1 day)
- No Grade 3 CRS in patients with FL

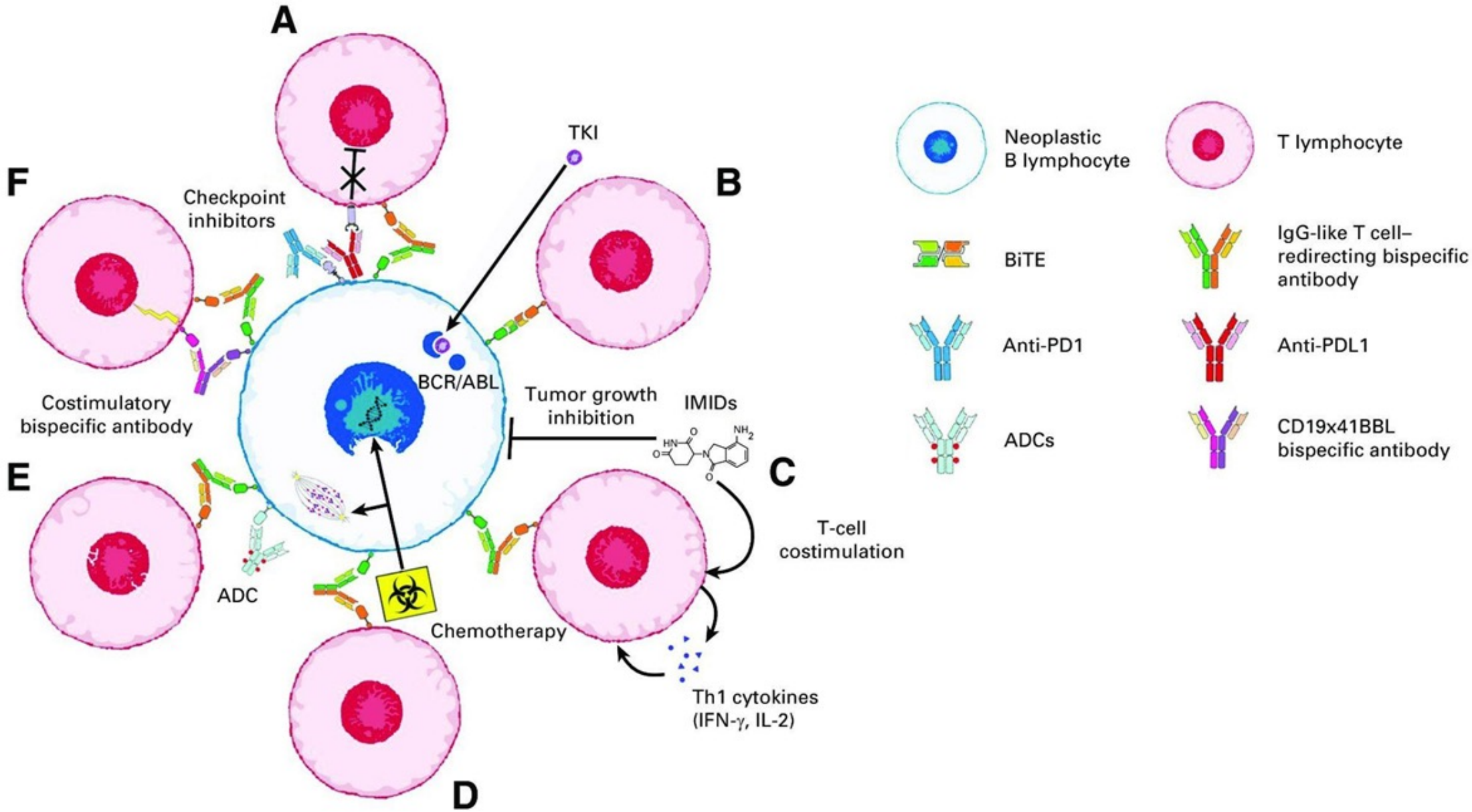
| | N = 30 |
|---|---|
| Patients that experienced CRS | 18 (60%) |
| Grade 1 | 11 (37%) |
| Grade 2 | 6 (20%) |
| Grade 3 | 1 ( 3%) |
| Onset, median days (range) | 2 (0 - 2) |
| Duration, median days (range) | 2 (0 - 7) |
| Tocilizumab use for CRS | 9 (30%) |
| Resolved | 18 (100%) |

- 16 of 30 patients remained on treatment
- Loss of CD19 expression could not be examined because no relapses from CR have been observed to date

*Tnb-486 is not indicated for use in DLBCL. Safety and efficacy have not been established*

Hou J-Z, et al. ASH 2022, abstract #612.

# Selected combination studies


A
B
C
D
E
F
TKI
Checkpoint inhibitors
BCR/ABL
Tumor growth inhibition
IMIDs
Costimulatory bispecific antibody
ADC
Chemotherapy
T-cell costimulation
Th1 cytokines (IFN-γ, IL-2)
Neoplastic B lymphocyte
T lymphocyte
BiTE
IgG-like T cell–redirecting bispecific antibody
Anti-PD1
Anti-PDL1
ADCs
CD19x41BBL bispecific antibody

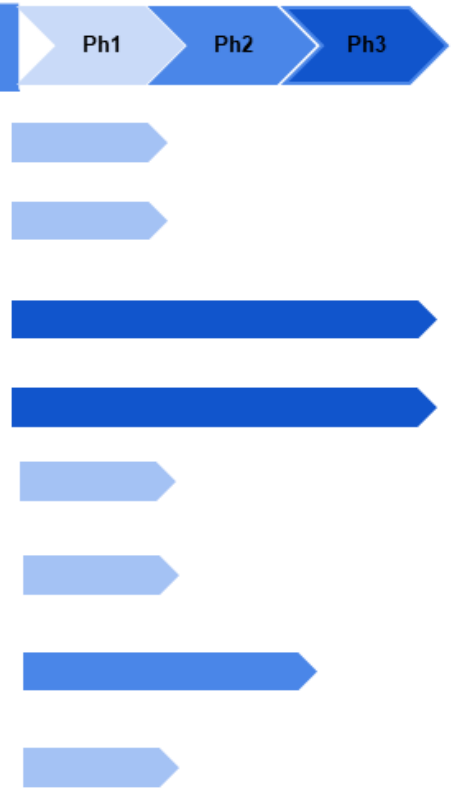
# Glofitamab clinical development plan

## Roche Sponsored studies

| Study No Name | Combination | Indication |
|---|---|---|
| NP30179 | *Glofit mono, Glofit + Gazyva* | R/R DLBCL, R/R FL, R/R MCL |
| YO42610 (GLOSHINE) | *Glofit mono* | R/R DLBCL (China) |
| BP43015 (SC study) | *Glofit mono* | R/R DLBCL |
| GO41943 | *Glofit-GemOx* | R/R DLBCL |
| NP39488 | *Glofit+Pola* | R/R NHL |
| GO41944 (STARGLO) | *Glofit-GemOx* | R/R DLBCL |
| GO43693 | *Glofit+R-ICE* | R/R DLBCL |
| CO43805 | *Glofit+CELMoDs* | R/R NHL |


## Roche Sponsored studies

| CT.gov ID | Combination | Indication |
|---|---|---|
| NP40126 | *Glofit+R-CHOP/ R-CHP-Pola* | 1L DLBCL |
| GO43075 | *Glofit+R-CHOP* | 1L DLBCL (ctDNA) |
| GO44145 (SKYGLO) | *Glofit+ R-CHP-Pola* | 1L DLBCL |
| GO43878 (GLOBRYTE) | *Glofit mono* | R/R MCL |
| *BP41072* | *Glofit+CD19x41BBL* | R/R NHL |
| *BP43131* | *Glofit+CD19xCD28* | R/R NHL |
| C4971006 (Pfizer) | *Glofit + CD47* | R/R DLBCL |
| LOTIS7 (ADC Thera.) | *Glofit + Lonca* | R/R NHL |



# Epcoritamab clinical development plan

| TRIAL NAME | LOT | POPULATION/SETTING | INTERVENTION | PHASE |
|---|---|---|---|---|
| EPCORE NHL-1 | 3L | DLBCL/FL/MCL | Epcor monotherapy | 1b |
| EPCORE NHL-2 | 1L | DLBCL High-risk (IPI 3-5) | Epcor + R-CHOP (Arm 1) | 1/2 |
| | 2L | FL 2L+ | Epcor + R$^2$ (Arm 2) | |
| | 1L | FL 1L | Epcor + BR (Arm 3) | |
| | 2L | DLBCL Salvage (SCT eligible) | Epcor + R-DHAX (Arm 4) | |
| | 2L | DLBCL SCT ineligible/failed | Epcor + GemOx (Arm 5) | |
| | 1L | FL 1L | Epcor + R$^2$ (Arm 6) | |
| | 1L 2L | FL Maintenance | Epcor monotherapy (Arm 7) | |
| | 1L | DLBCL Elderly/frail | Epcor + R-miniCHOP (Arm 8) | |
| | 2L | FL POD24 | Epcor + Len (Arm 9) | |
| | 2L | DLBCL Salvage (SCT eligible) | Epcor + R-ICE (Arm 10) | |
| EPCORE NHL-5 | 2L | DLBCL 2L+ | Epcor + Len (Arm 1) | 1/2 |
| | 2L | DLBCL post-CART | Epcor + Len + Ibr (Arm 2) | |
| | 1L | DLBCL 1L | Epcor + Pola-R-CHP (Arm 3) | |
| | 2L | DLBCL Not CAR-T refractory | Epcor + CC-99282 (CELMoD) (Arm 4) | |
| | 2L | FL Not CAR-T refractory | Epcor + CC99282 (CELMoD) (Arm 5) | |
| | 2L | MCL Not CAR-T refractory | Epcor + Ibr ± Ven (Arms 6A,B) | |
| | 1L | MCL 1L | Epcor + Ibr + Ven (Arm 7) | |
| EPCORE NHL-6 | 3L | DLBCL/FL | Epcor monotherapy (outpatient) | 2 |
| EPCORE DLBCL-1 | 2L | DLBCL SCT ineligible/failed | Epcor monotherapy vs R-GemOx or BR | 3 |
| EPCORE DLBCL-2 | 1L | DLBCL 1L High-risk (IPI 2-5) | Epcor + R-CHOP vs R-CHOP | 3 |
| EPCORE DLBCL-3 | 1L | DLBCL Anthracycline-ineligible | Epcor; Epcor ± Len | 2 |
| EPCORE DLBCL-4 | 2L | DLBCL SCT & CAR T ineligible | Epcor + Len (12C) vs R-GemOx | 3 |
| EPCORE FL-1 | 2L | FL 2L+ | Epcor + R$^2$ vs R$^2$ | 3 |
| EPCORE FL-2 | 1L | FL 1L | Epcor + R$^2$ vs CITs | 3 |
| EPCORE CLL-1 | 3L | CLL 3L | Epcor monotherapy (Arm 1) | 1/2 |
| | 1L 2L 3L+ | RT CIT ineligible | Epcor monotherapy (Arm 2A) | |
| | 1L 2L 3L+ | RT CIT ineligible | Epcor + Len (Arm 2B) | |
| | 1L | RT 1L | Epcor + R-CHOP (Arm 2C) | |

| TRIAL NAME | LOT | POPULATION/SETTING | INTERVENTION | PHASE |
|---|---|---|---|---|
| EPCORE NHL-3 | 3L | DLBCL/FL | Epcor monotherapy (Arm 1) | 1/2 |
| | 2L | FL 2L+ | Epcor + R$^2$ (Arm 2) | |
| | 1L | DLBCL 1L High-risk (IPI 3-5) | Epcor + R-CHOP (Arm 3) | |
| | 2L | DLBCL SCT ineligible/failed | Epcor + GemOx (Arm 4) | |
| | 1L 2L | FL Maintenance | Epcor monotherapy (Arm 5) | |
| EPCORE NHL-4 | 3L | DLBCL/FL | Epcor monotherapy (Cohort 1) | 1/2 |
| | 1L | DLBCL High-risk (IPI 2-5) | Epcor + R-CHOP → Epcor (Cohort 2) | |
| | 2L | FL 2L+ | Epcor + R$^2$ (Cohort 3) | |

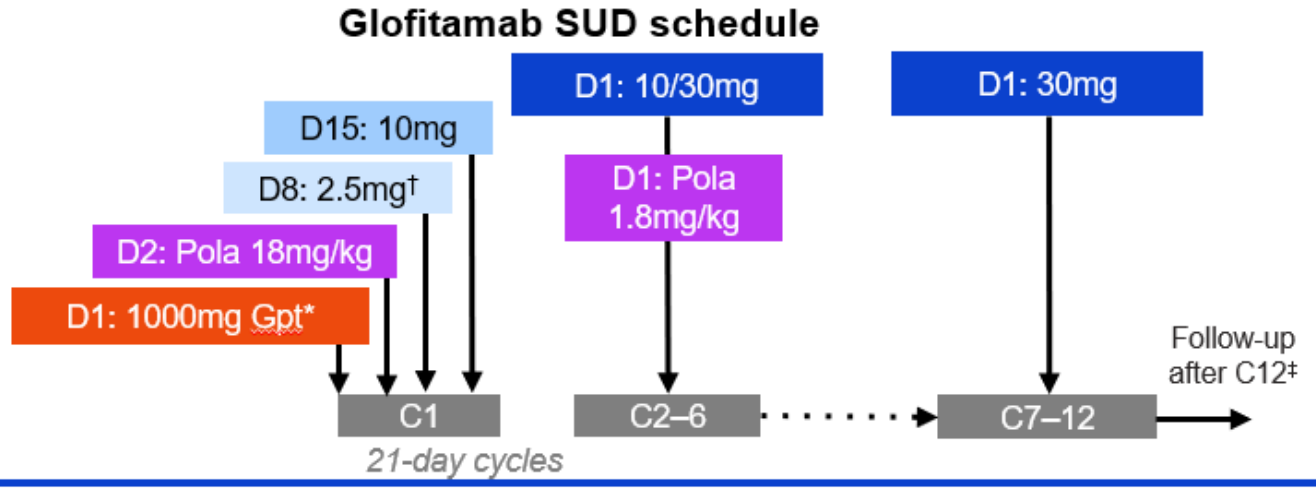
## ISTs / COLLAB STUDIES

| TRIAL NAME | LOT | POPULATION/SETTING | INTERVENTION | PHASE |
|---|---|---|---|---|
| IST (MDACC) | 1L | DLBCL Elderly/frail/anth-ineligible | Epcor + R-miniCVP | 2 |
| IST (ACCRU) | 2L | DLBCL Post-CAR T | Epcor monotherapy | 2 |
| IST (Karmanos) | 2L | DLBCL Salvage (SCT/CAR T eligible) | Epcor + GDP | 1/2 |
| IST (UPenn) | 2L | DLBCL Bridge/consolidation to CAR T | Epcor monotherapy | 2 |
| ALLG NHL38 | 2L | DLBCL Salvage (SCT eligible) | Epcoritamab + R-DHAX | 2 |
| IST (CoH) | 1L | FL 1L | Epcor + Len | 2 |
| IST (DFCI) | 1L | FL 1L | Epcor + Rituximab | 2 |
| IST (Beth Israel) | 2L | FL 2L+ | Epcor monotherapy | 2 |
| REFRACT | 2L | FL 2L | Epcor + Len vs CIT | 2 |
| AETHER | 2L | CLL 2L+ | Epcor + Ven | 1/2 |

1. https://classic.clinicaltrials.gov/ct2/show/NCT05206357; 2. https://classic.clinicaltrials.gov/ct2/show/NCT05451810; 3. https://classic.clinicaltrials.gov/ct2/show/NCT04663347; 4. https://classic.clinicaltrials.gov/ct2/show/NCT05578976; 5. https://classic.clinicaltrials.gov/ct2/show/NCT05283720; 6. https://clinicaltrials.gov/study/NCT06045247; 7. https://classic.clinicaltrials.gov/ct2/show/NCT05660967; 8. https://classic.clinicaltrials.gov/ct2/show/NCT04628494; 9. https://clinicaltrials.gov/study/NCT06508658; 10. https://clinicaltrials.gov/study/NCT06238648; 11. https://clinicaltrials.gov/study/NCT05852717; 12. https://clinicaltrials.gov/study/NCT06458439; 13. https://clinicaltrials.gov/study/NCT06287398; 14. https://classic.clinicaltrials.gov/ct2/show/NCT03625037; 15. https://classic.clinicaltrials.gov/ct2/show/NCT06191744; 16. https://clinicaltrials.gov/study/NCT06112847; 17. https://clinicaltrials.gov/study/NCT05783609; 18. https://classic.clinicaltrials.gov/ct2/show/NCT05409066; 19. https://clinicaltrials.gov/study/NCT05848765; 20. https://classic.clinicaltrials.gov/ct2/show/NCT04623541; 21. https://clinicaltrials.gov/study/NCT05791409?term=aether&intr=epcoritamab&rank=1

# Glofitamab and Polatuzumab vedotin in DLBCL – study design

## Glofit-Pola administration in R/R DLBCL




## Key inclusion criteria

- R/R DLBCL
- Aged ≥18 years
- ECOG PS 0–2
- ≥1 prior therapy

## Endpoints

- **Primary:** RP2D (identified as 30mg from Part I of the study)
- **Secondary:** safety, efficacy, pharmacokinetics
- **Exploratory:** biomarker evaluation

## Treatment period

- **Fixed treatment duration**: maximum 12 cycles of glofitamab plus six cycles of Pola (21-day cycles)
- As of September 4, 2023 (CCOD), 125 patients had received ≥1 dose of study drug
- **Median follow-up:** 20.4 months (range: 17.5–23.2)

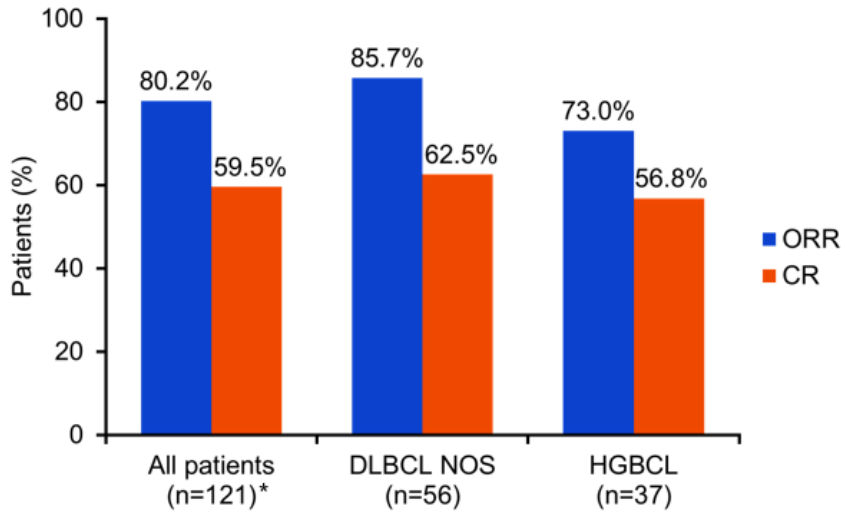
Hutchings M, et al. ASH 2023 (Abstract #4460)

*Glofit + Pola is not indicated for use in DLBCL. Safety and efficacy have not been established*

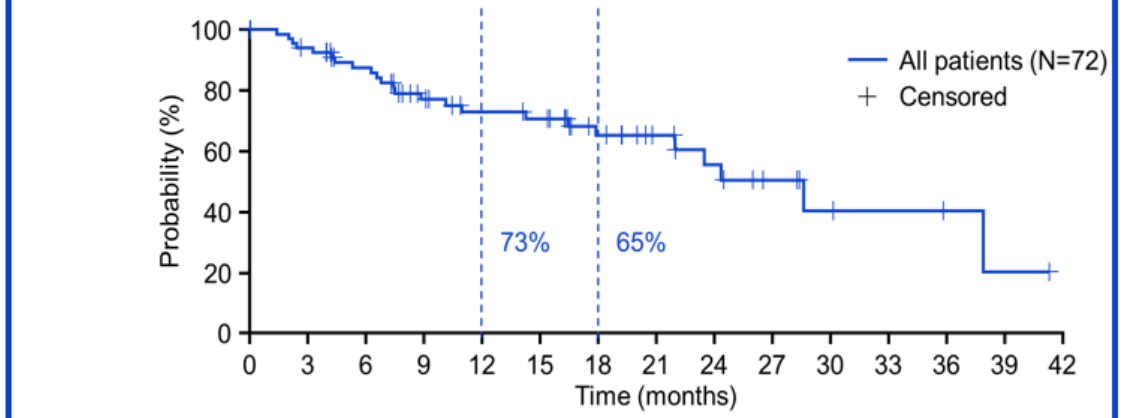
# Glofitamab and Polatuzumab vedotin in DLBCL – response data

| | N=72 |
|---|---|
| **Median CR follow-up**, months (range) | 16.6 (0–41) |
| **Median DoCR**, months (95% CI) | 28.6 (21.9–NE) |

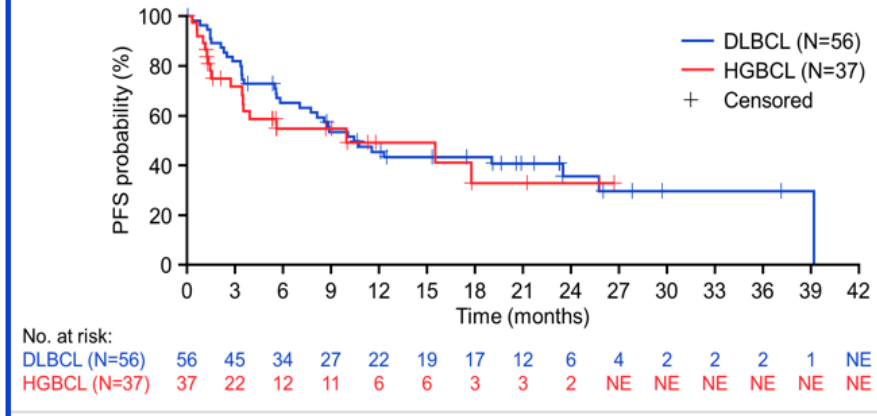
## Best overall response by histology




## Glofit-Pola DoCR




## PFS by histology†




Median PFS was 10.4 months (95% CI: 7.7–25.7) for DLBCL and 9.9 months (95% CI: 3.4–NE) for HGBCL

*Glofit + Pola is not indicated for use in DLBCL. Safety and efficacy have not been established*

Hutchings M, et al. ASH 2023 (Abstract #4460)

# BP41072: Glofitamab + Englumafusp alfa (CD19/4-1BBL) – design

*Open-label Phase I study investigating escalating IV englumafusp alfa dose levels in combination with IV glofitamab in patients with R/R B-NHL*

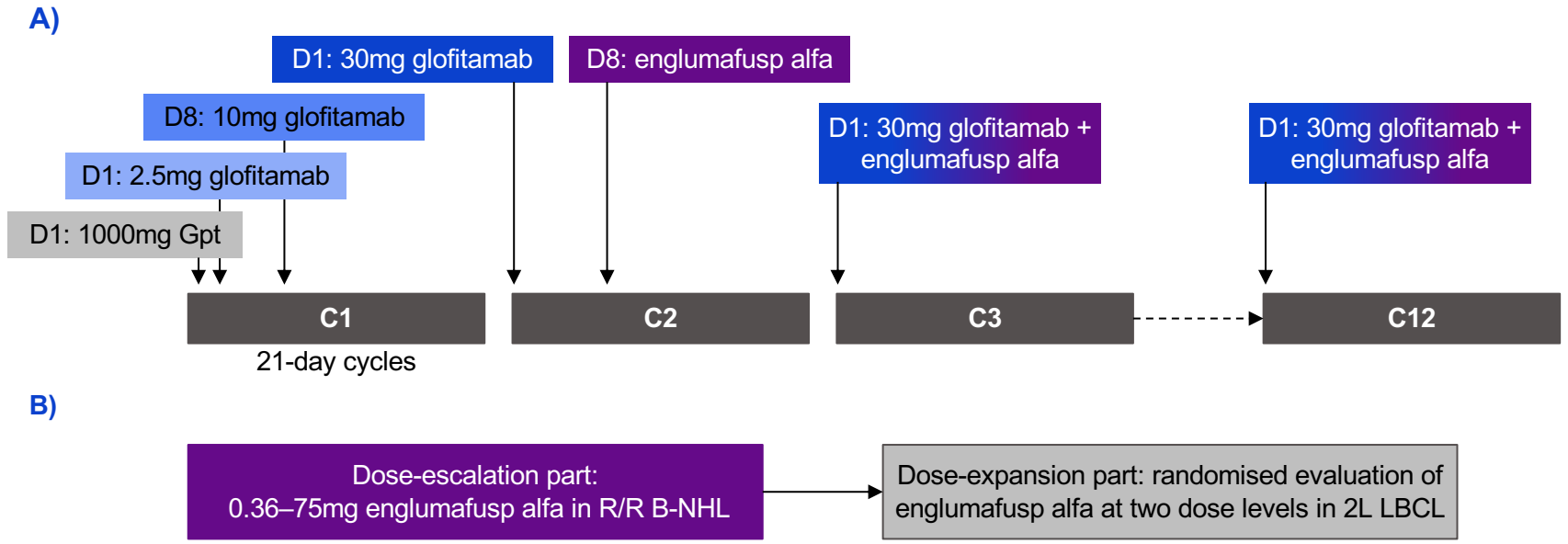
## Patients

- Age ≥18 years
- R/R B-NHL
- ≥1 measurable lesion
- ≥2 prior therapies
- ECOG PS ≤1

## Primary objectives

- Safety and tolerability
- RP2D
- PK

## Treatment schedule (A) and dose escalation (B)




Englumafusp alfa is initiated after glofitamab step dosing on C2D8, and is co-administered with glofitamab on the same day from C3 onwards

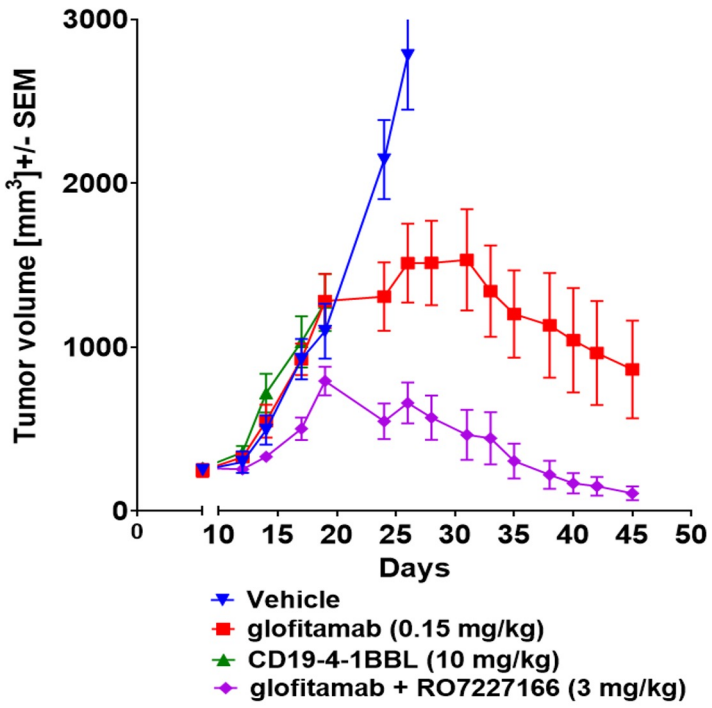
*Glofit + Englumafusp alfa is not indicated for use in DLBCL. Safety and efficacy have not been established*

Morschhauser F, et al. EHA 2024. Abstract S237.

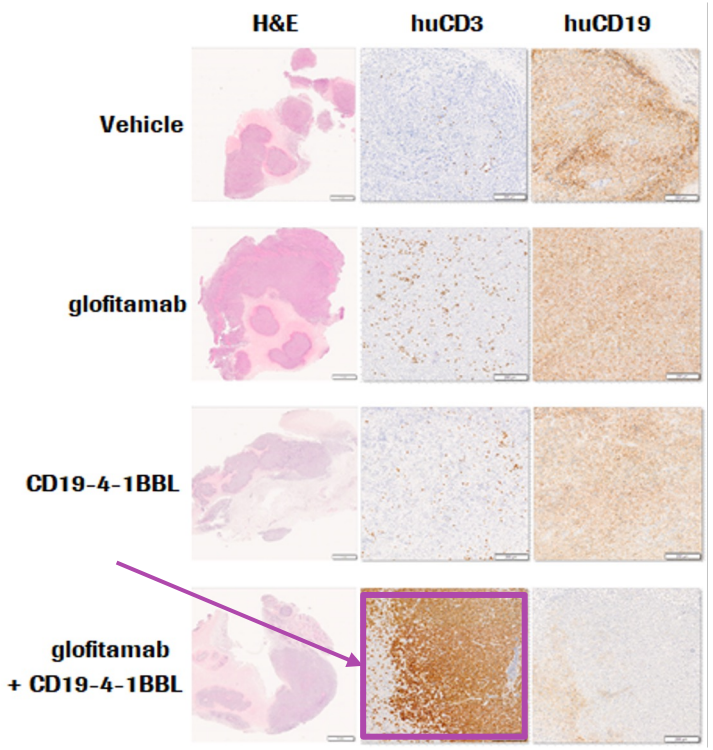
# Glofitamab + Englumafusp alfa – preclinical data

## CD19 4-1BBL plus glofitamab is superior to glofitamab single-agent in vivo

### Improved tumor growth inhibition

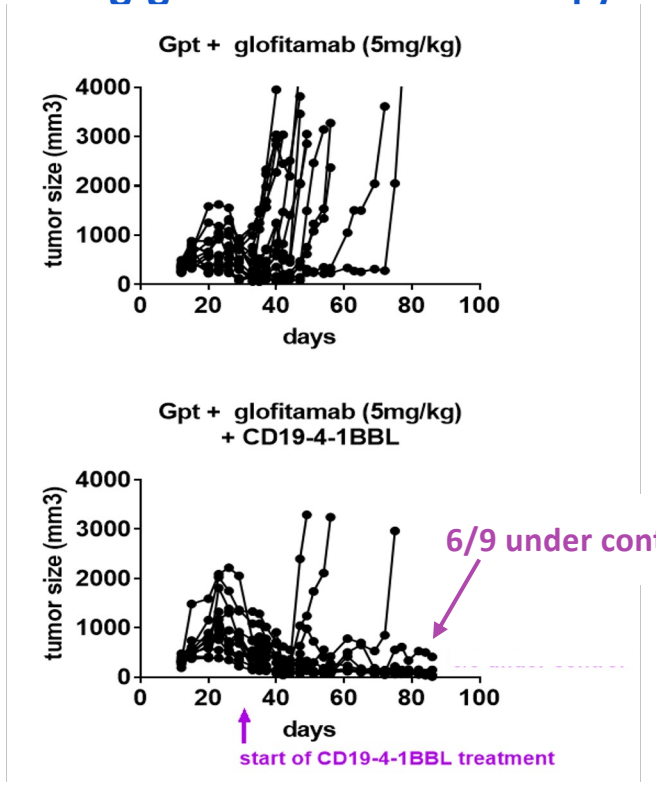



### Significantly enhanced T cell infiltration




WSU DLCL2 s.c. in humanized mice

### Prevention of tumor outgrowth during glofitamab monotherapy




OCILY18 s.c. in humanized mice

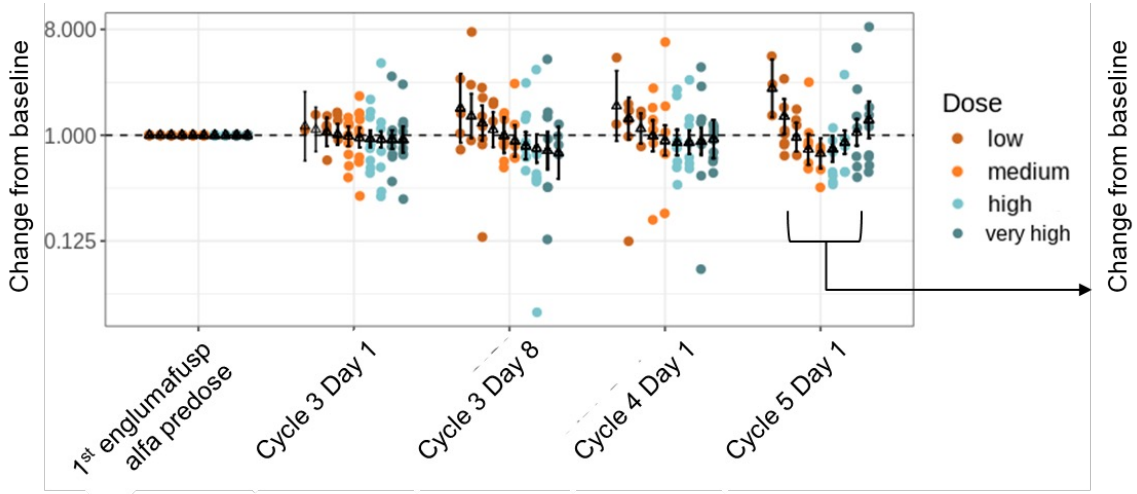
*Glofit + Englumafusp alfa is not indicated for use in DLBCL. Safety and efficacy have not been established*

Hutchings M, et al. ASH 2020. Abstract 3269.

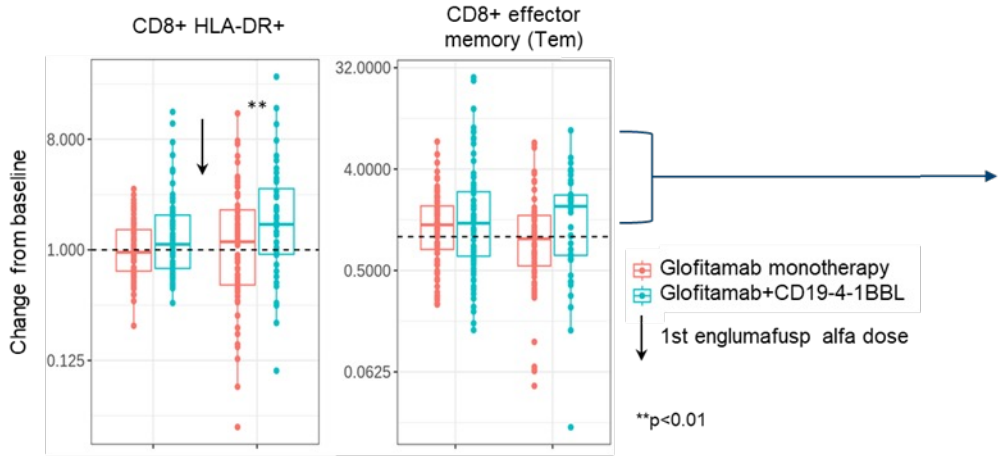
# Activity of glofitamab + englumafusp alfa in r/r aNHL

| n (%) | BOR | CR |
|---|---|---|
| R/R aNHL | | |
| 2L+ | 56 (67.0) | 47 (57.0) |
| 3L+ | 46 (65.7) | 37 (52.8) |
| R/R aNHL with prior CAR-T | 26 (61.9) | 20 (47.6) |

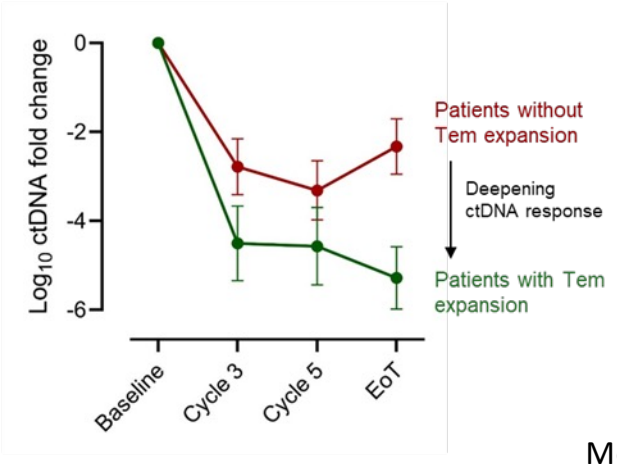
**Englumafusp alfa prevents T-cell terminal differentiation/exhaustion**




***Boosting activated and effector memory T-cell expansion***




***Tem expansion deepens molecular (ctDNA) response***



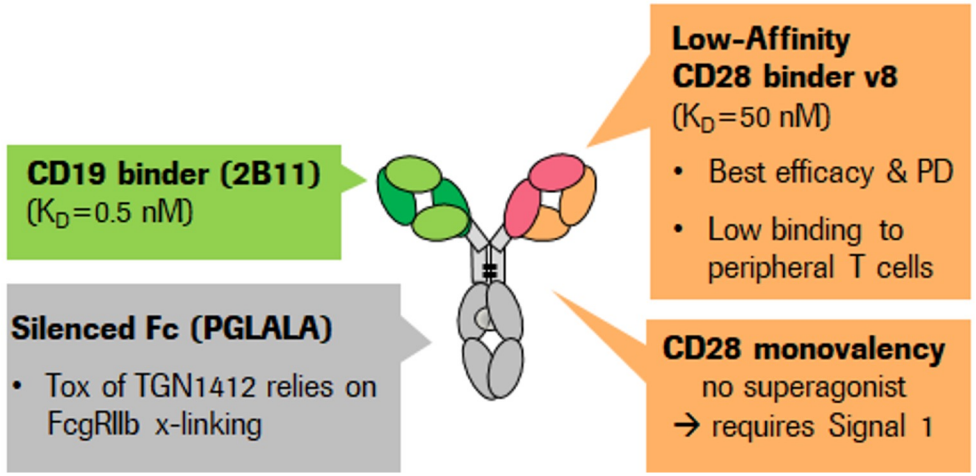

Morschhauser F, et al. EHA 2024. Abstract S237.

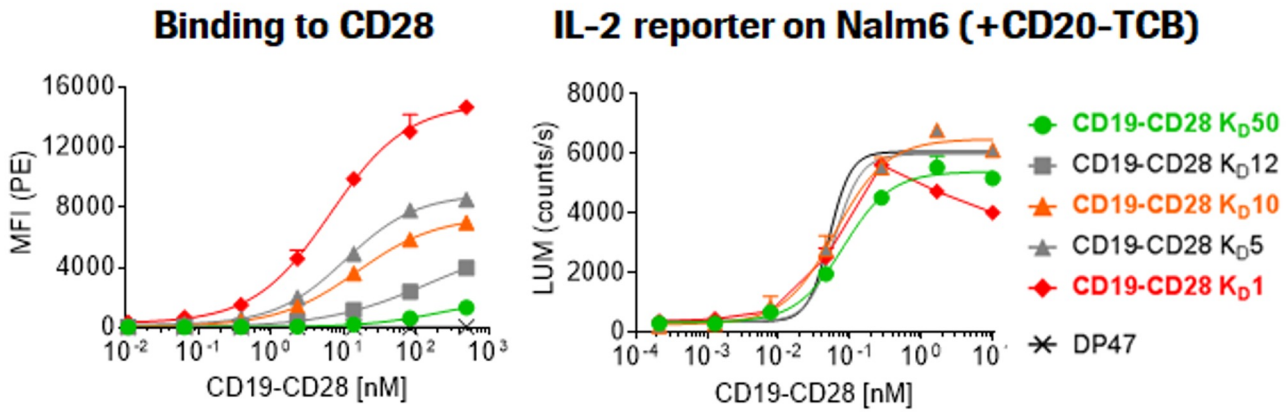
*Glofit + Englumafusp alfa is not indicated for use in DLBCL. Safety and efficacy have not been established*

# BP43131: Glofitamab + CD19-targeted CD28 agonist

**Providing safe agonistic CD28 targeting w/o autonomous T cell activation**

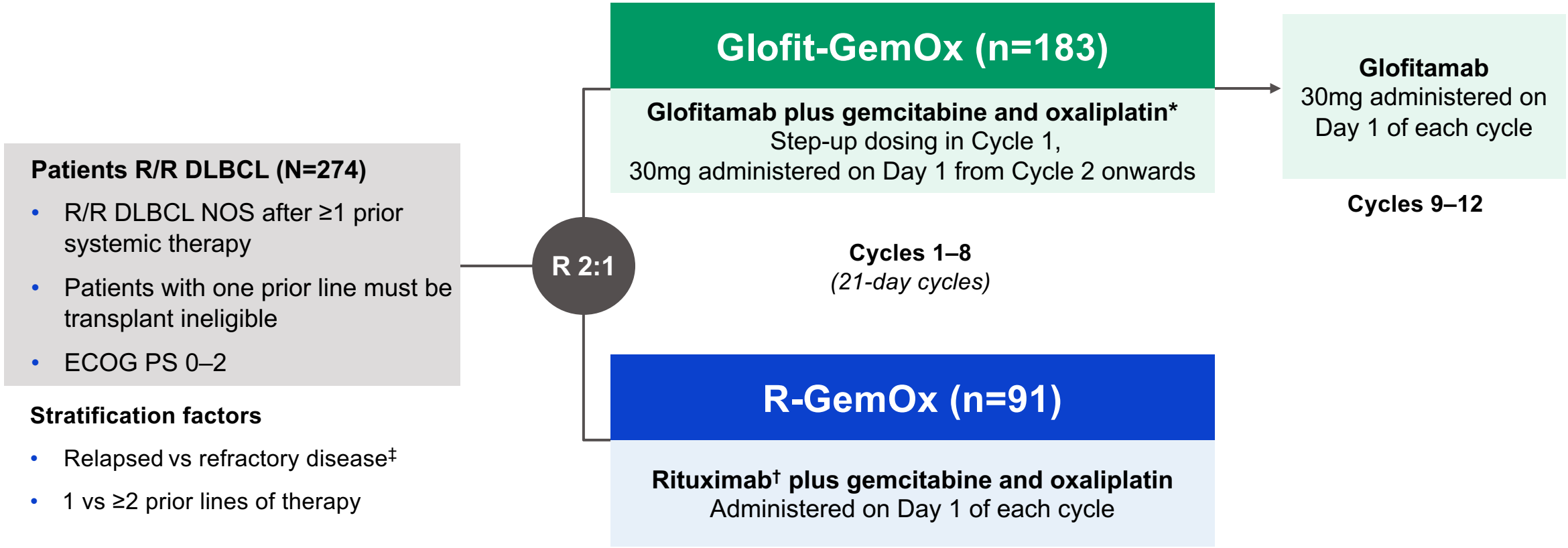
**Reduce peripheral binding to CD28 w/o losing potency**




**Study design and preclinical data presented at ASH 2022: Dickinson M, et al. P1659 – program now discontinued**

# STARGLO: randomized Phase III trial in ASCT-ineligible patients with R/R DLBCL

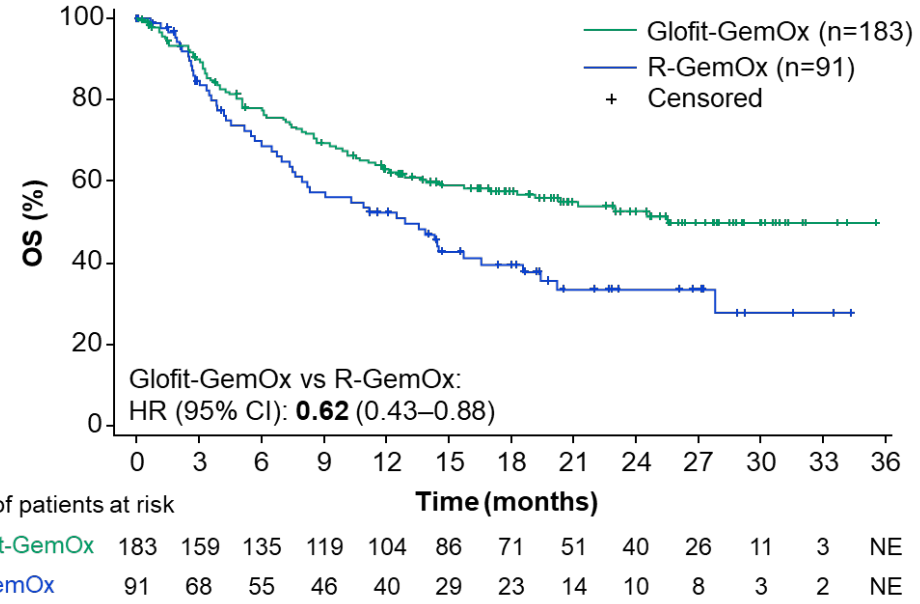



*Glofit + GemOx is not indicated for use in DLBCL. Safety and efficacy have not been established*

Abramson J, et al. EHA 2024. Abstract LB3438.

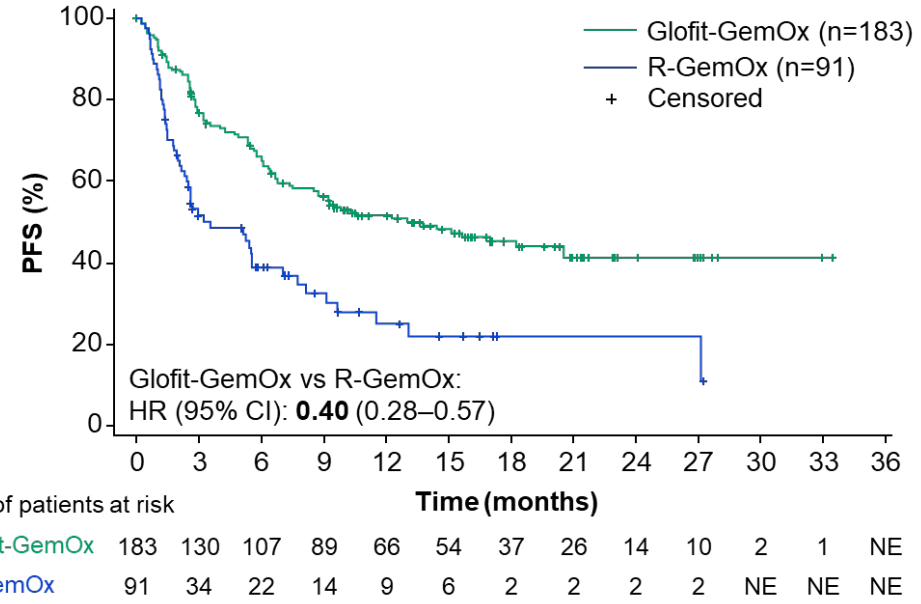
# STARGLO: Overall survival (primary endpoint) and PFS

**Updated analysis**




| | R-GemOx (n=91) | Glofit-GemOx (n=183) |
|---|---|---|
| **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) |

**Updated analysis**




| | R-GemOx (n=91) | Glofit-GemOx (n=183) |
|---|---|---|
| **Updated analysis** (median follow-up: 16.1 months) | | |
| PFS, median (95% CI); months | 3.6 (2.5–7.1) | 13.8 (8.7–20.5) |
| HR (95% CI) | **0.40** (0.28–0.57) | |
| p-value* | <0.000001* | |
| 12-month PFS (95% CI) | 25.2% (13.6–36.9) | 51.7% (44.0–59.4) |

*Glofit + GemOx is not indicated for use in DLBCL. Safety and efficacy have not been established*

Abramson J, et al. EHA 2024. Abstract LB3438.

# STARGLO: COVID-19 AEs

| COVID-19 AE, n (%) | R-GemOx (n=88) | Glofit-GemOx (n=180) |
|---|---|---|
| **Any grade COVID-19 AE** | 8 (9.1) | 33 (18.3) |
| Grade ≥3 AE | 2 (2.3) | 11 (6.1) |
| Grade 5 (fatal) AEs associated with COVID-19* | **0** | **7 (3.9)** |
| AE leading to treatment discontinuation† | 5 (5.7) | 22 (12.2) |

*Glofit + GemOx is not indicated for use in DLBCL. Safety and efficacy have not been established*

Abramson J, et al. EHA 2024. Abstract LB3438.

# NP40126: R-CHOP (or Pola-R-CHP) + glofitamab in DLBCL 1st line

**Glofit + R-CHOP administration in 1L DLBCL**

- **R-CHOP**
  - A total of six to eight 21-day cycles of R-CHOP were given
- **Glofitamab IV**
  - Step-up dosing 2.5/10/30mg
  - Hospitalization at investigator's discretion for patients enrolled in the expansion stage

| n (%) of patients unless otherwise stated | | N=56* |
|---|---|---|
| Median age, years (range) | | 68.0 (21–84) |
| Male | | 27 (48.2) |
| ECOG PS | 0 | 28 (50.0) |
| | 1 | 19 (33.9) |
| | 2 | 8 (14.3) |
| | 3 | 1(1.8) |
| Ann Arbor stage at study entry | Stage I–II | 2 (3.6) |
| | Stage III | 10 (17.9) |
| | Stage IV | 44 (78.6) |
| Bulky disease | >6cm | 34 (60.7) |
| | >10cm | 19 (33.9) |
| IPI score | 1 | 2 (3.6) |
| | 2 | 19 (33.9) |
| | 3 | 20 (35.7) |
| | 4 | 13 (23.2) |
| | 5 | 2 (3.6) |
| Extranodal disease† | | 42 (75.0) |

| n (%) of patients unless otherwis | N=56* |
|---|---|
| CRS (any grade) | 6 (10.7) |
| Grade 1 | 4 (7.1) |
| Grade 2 | 2 (3.6) |
| Grade ≥3 | 0 |
| Serious AE of CRS (any grade) | 2 (3.6) |
| Median time to first CRS event, hrs | 10.2 (8.0–35.9) |
| Tocilizumab for CRS management‡ | 2/6 (33.3) |
| CRS resolved | 6/6 (100) |

| Efficacy endpoint, n (%) \| | EOT patients dosed with glofitamab (N=53)† |
|---|---|
| EOT response | |
| CMR rate | **40 (75.5)** [61.7–86.2] |
| Overall response rate | **46 (86.8)** [74.7–94.5] |

Topp MS, et al. ASH 2023. Abstract #3085.

# Look out for the following studies

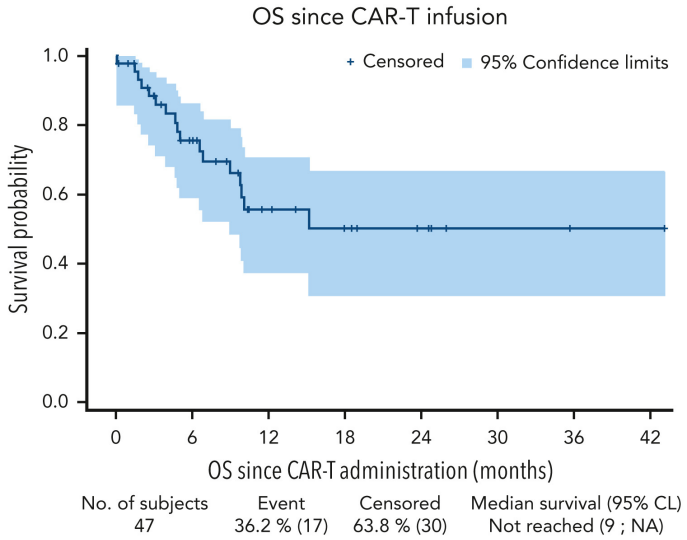
- EPCORE DLBCL-1:
  - Phase 3 trial of **epcoritamab** Vs R-Benda or R-GemOx in patients with r/r DLBCL (transplant-ineligible or failing transplant)
- EPCORE DLBCL-2:
  - Phase 3 trial of **epcoritamab** + R-CHOP Vs R-CHOP in previously untreated DLBCL (IPI 2-5)
- SKYGLO:
  - Phase 3 study of Pola-R-CHP +/- **glofitamab** in newly diagnosed LBCL IPI 2-5

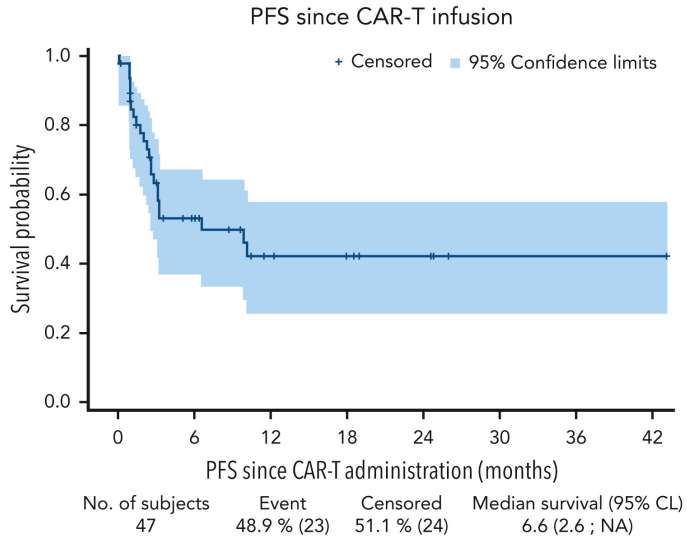
# A few questions I would like to address if time allows:

1. What is the optimal sequencing of CART and bispecifics in DLBCL?
2. Which criteria should be taken into consideration before giving a CART or a bispecific?
3. Does prior bendamustine exposure (e.g. transformed FL patient) impact the efficacy of CART or bispecific antibodies?
4. What are the recommendations about vaccination and infection management?

# What is the optimal sequencing in DLBCL with all the new options (CAR-T and Bispecifics)?

- The phase 2 studies of glofitamab and epcoritamab show more or less the same response rates, the same complete response rates, and the same durability of responses in patients with and withour prior CART exposure
- Retrospective analysis from the French DESCARTES database show that the opposite is also true:




- The chronology of the development (CART with longer FU and a demonstrated curative potential) speaks in favour of CART before BsAbs
- This may change when we have randomised data on BsAbs in 1st and perhaps 2nd line

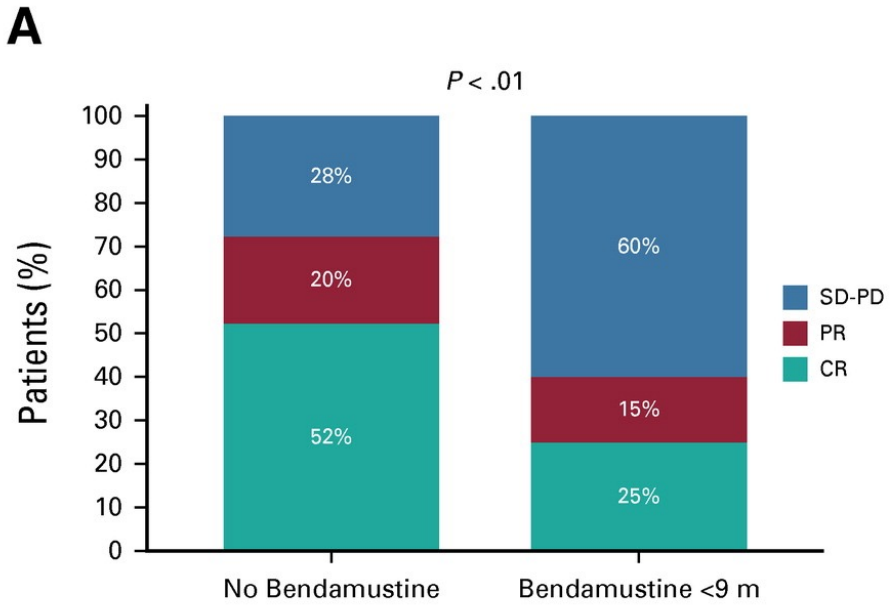
Crochet G, et al. Blood 2024; 144(3): 334-338.

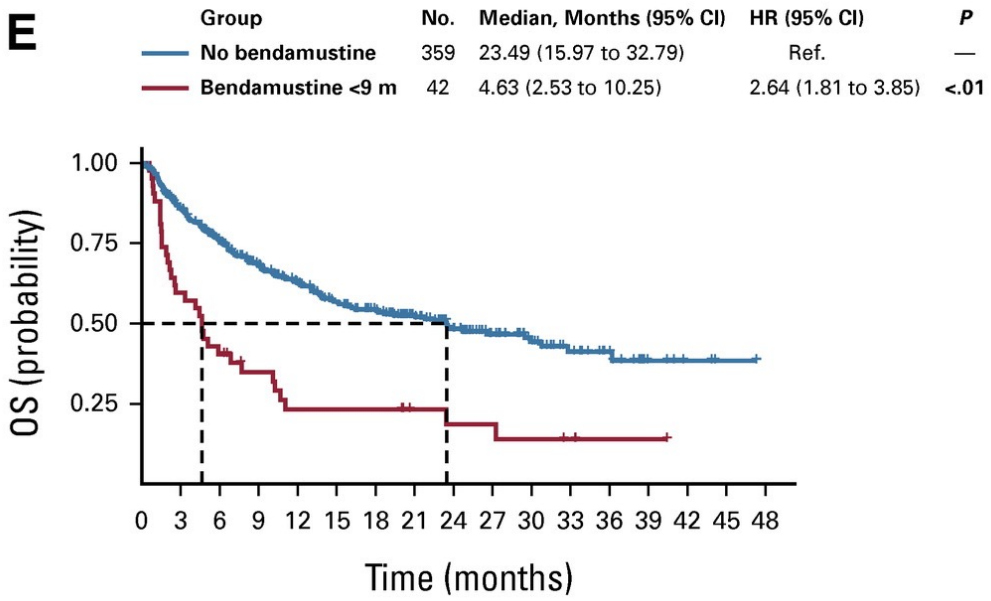
# Which criteria do you take into consideration while choosing a bispecific antibody for treatment?

- Expression of the target (CD19, CD20, CD22, CD79)
- Reasonable performance status and organ function
  - Cardiac and pulmonary function should be good enough to support pressors and assisted ventilation in case of severe CRS
- Risk factors for severe CRS should be assessed (tumor volume, leukemic and/or extranodal disease, etc.)
- Risk factors for tumor flare should be assessed
- Consider hospitalisation in high-risk cases and in patient living alone and/or far from the hospital

# If patient was treated with bendamustine (eg transformed FL patient), do you prefer CAR-T or bispecific antibody?

- Recent Bendamustine before apheresis is associated with poor outcomes after CD19 CART therapy:

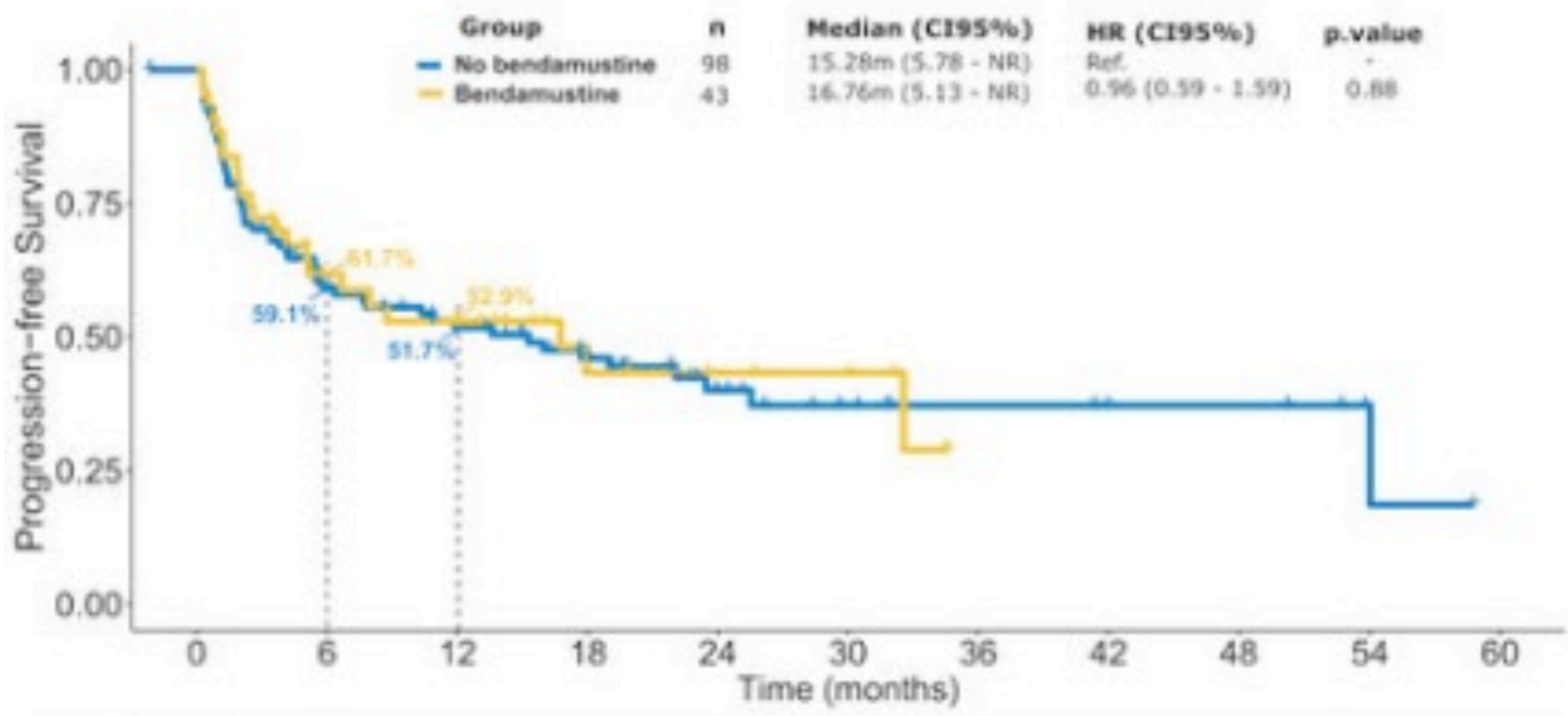



Iacoboni G, et al. J Clin Oncol 2024; 42(2): 205-217.

# If patient was treated with bendamustine (eg transformed FL patient), do you prefer CAR-T or bispecific antibody?

- Recent Bendamustine before BsAb therapy, on the other hand, is not associated with poor outcomes




Iacoboni G, et al. ASH 2023; abstract #310.

# Recommendation regarding vaccination and infection management?

## A. Anemia and thrombocytopenia:

- No clear recommendations can be made about EPO or TPO
- Transfusions should be administered as per clinical indication

## B. Lymphopenia and hypogammaglobulinemia:

- Monthly monitoring and replenishing IgG to ≥ 400mg/dL
- In case of repetitive infections replenishing to ≥ 600mg/dL should be considered

## C. Neutropenia:

- Use G-CSF in case of neutropenia <1000/mm³ while avoiding dosing delays

## D. Prophylactic antibiotics:

- Prophylactic broad-spectrum antibiotics considered in individual cases but not generally recommended
- Antifungal prophylaxis should be considered in cases of neutropenia < 500/mm³ for more than 7-14 days (and in patients with recent invasive fungal infections or recent, long term high dose corticosteroid use)
- HSV/VZV prophylaxis and prophylaxis against Pneumocystis jirovecii both recommended, during treatment and until total lymphocyte and CD4 counts approach normal levels

Hutchings M. ASH 2023; educational.

# Recommendation regarding vaccination and infection management?

- All inactivated vaccines are considered safe
- Vaccinations against COVID19 and influenza are recommended
- Despite profound lymphopenia and complete B-cell depletion, COVID19 mortality was close to zero in a well-vaccinated population
- Most fatal COVID19 infections across the different studies of the bispecifics occurred in less well-vaccinated populations

Kyvsgaard ER, et al. Br J Haematol 2024;204(1):356-360.

# Summary

- The T-cell engaging bispecific antibodies show an antitumor activity which is unprecedented in heavily pretreated r/r DLBCL
- Data from DLBCL phase 2 expansion cohorts (35-40% with prior CAR-T):
  - Glofitamab: ORR 52%, CRR 40% *(FDA and EMA approved in 2023 for LBCL 3+ line)*
  - Epcoritamab: ORR 63%, CRR 39% *(FDA and EMA approved in 2023 for LBCL 3+ line)*
- Complete responses are highly durable (for glofitamab also beyond EOT)
  - Suggests a curative potential even when given as single agents
- The toxicity profile is favourable:
  - Very little CRS > grade 2
  - Very little treatment-related CNS toxicity
- The toxicity profile and mechanism of action make the bispecifics ideal for combination strategies (chemotherapy, ADCs, costimulatory antibodies, etc.)
- Recent data show OS superiority of Glofitamab-GemOx over R-GemOx in r/r LBCL
- Waiting for outcome of 1$^{st}$ line studies and for a randomised study against CART….