# Eppur si muove...

## La terapia nel MONDO LINFOMI

## *Caso Clinico 3*

***Renato Scalone***
*U.O. Oncoematologia - Programma Trapianto di CSE e Immunoterapia Cellulare*
*Dipartimento Oncologico «La Maddalena», Palermo.*

CATANIA, 11 LUGLIO 2022

# Caratteristiche cliniche all'esordio (I)

- Età: 61 anni.
- Sesso: M.
- Comorbidità: ipertensione arteriosa, diabete mellito, ipercolesterolemia, ipertrofia prostatica benigna, HCV+ (HCV-RNA non rilevato).
- Condizioni cliniche generali: ECOG 0.

- Nell'ottobre 2017 comparsa di linfoadenomegalia inguinale dx in assenza di segni sistemici
- TC t.b.: linfoadenomegalie in sede inguinale bilaterale (dx: 5 x 3,5 cm; sx: 2 x 2 cm).

- Biopsia linfonodo inguinale dx: DLBCL.

# Caratteristiche cliniche all'esordio (II)

- Laboratorio: crasi ematica nella norma; LDH nella norma; funzionalità epatica e renale nella norma.
- Osteomielobiopsia: non localizzazione midollare di malattia.
- PET: captazione in sede ascellare dx (SUV 5) e inguinale bilaterale (SUVmax 15 a dx).
- Conclusioni: DLBCL stadio III A, IPI 2.

# Terapia e valutazione della risposta

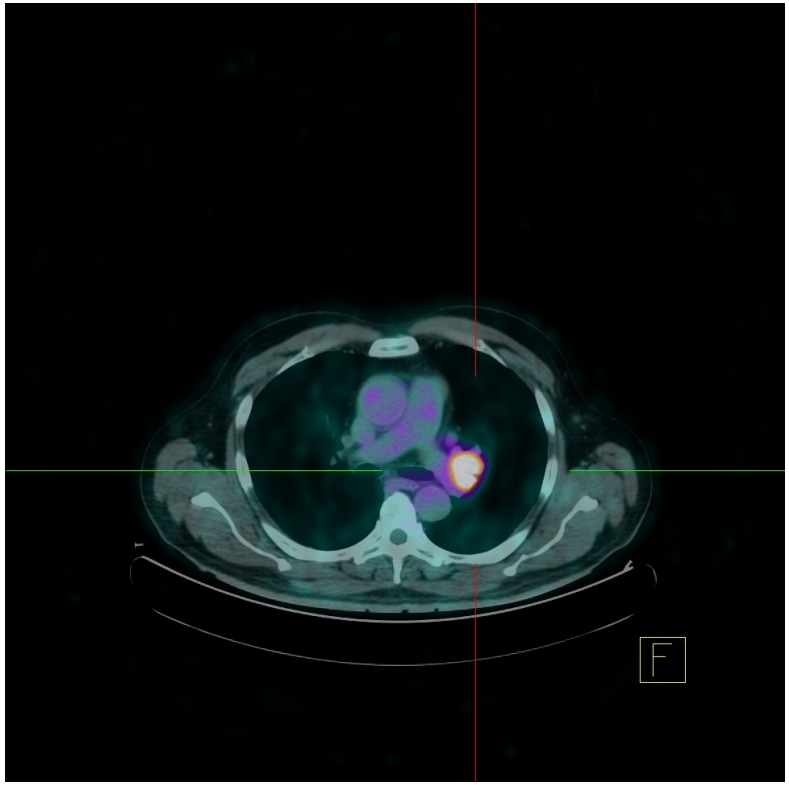
- **Terapia di I linea**: **6 cicli R-CHOP** (inizio 22-11-2017).
- Rivalutazione TC: risposta parziale (residuo linfonodo in sede inguinale dx: 2,5 x 3 cm).
- Rivalutazione PET: risposta metabolica parziale (captazione in sede inguinale dx, SUV 5.5).

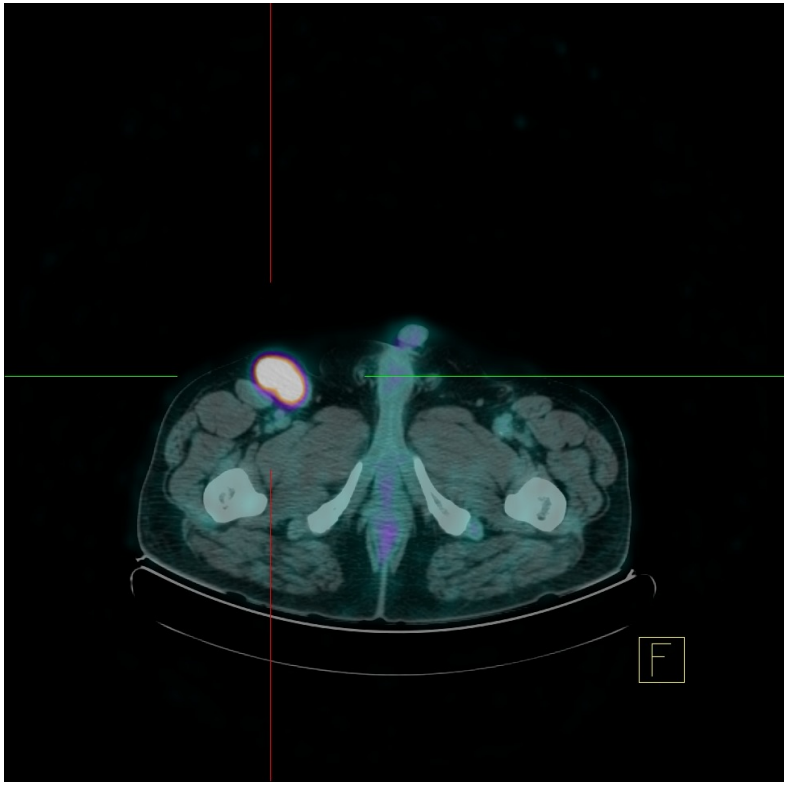
- **Terapia di II linea**: **2 cicli R-DHAOx** (inizio 23-6-2018).
- Rivalutazione TC: residua linfoadenopatia in sede inguinale dx: 2 x 1 cm).
- Rivalutazione PET: minima attività metabolica sede inguinale dx (SUV 2.7).

- Dal 5-10-2018 **FEAM**; il 12-10-2018 **autotrapianto di CSE**.
- Gennaio 2019 rivalutazione con TC (25-1-2019) e PET (28-1-2019): **remissione completa.**

# Recidiva

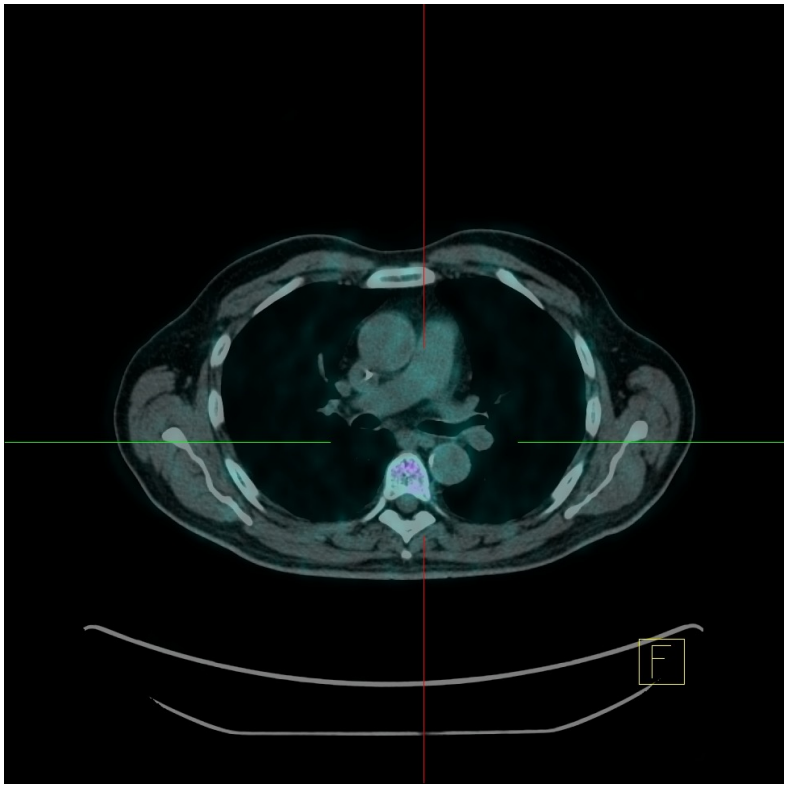
- A luglio 2019 ricomparsa di linfoadenomegalia in sede inguino-femorale dx.
- PET: intenso accumulo del tracciante metabolico all'ilo polmonare sx (SUV 11.1) e in regione inguino-femorale dx (SUV 7.9); ulteriori aree di captazione in sede laterocervicale dx, paratracheale dx e a livello della finestra aortopolmonare.

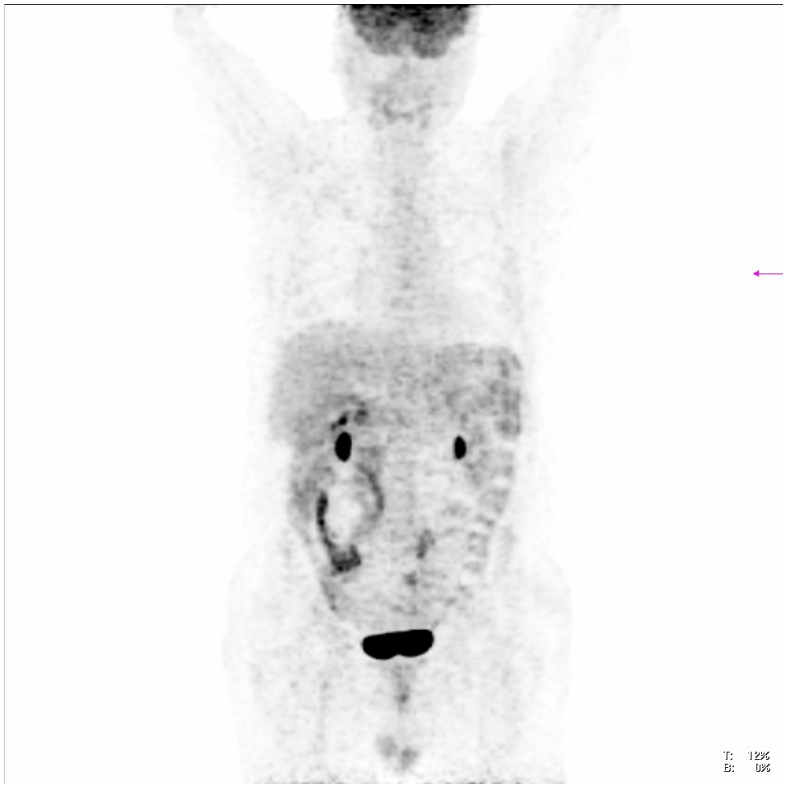


# Terza linea

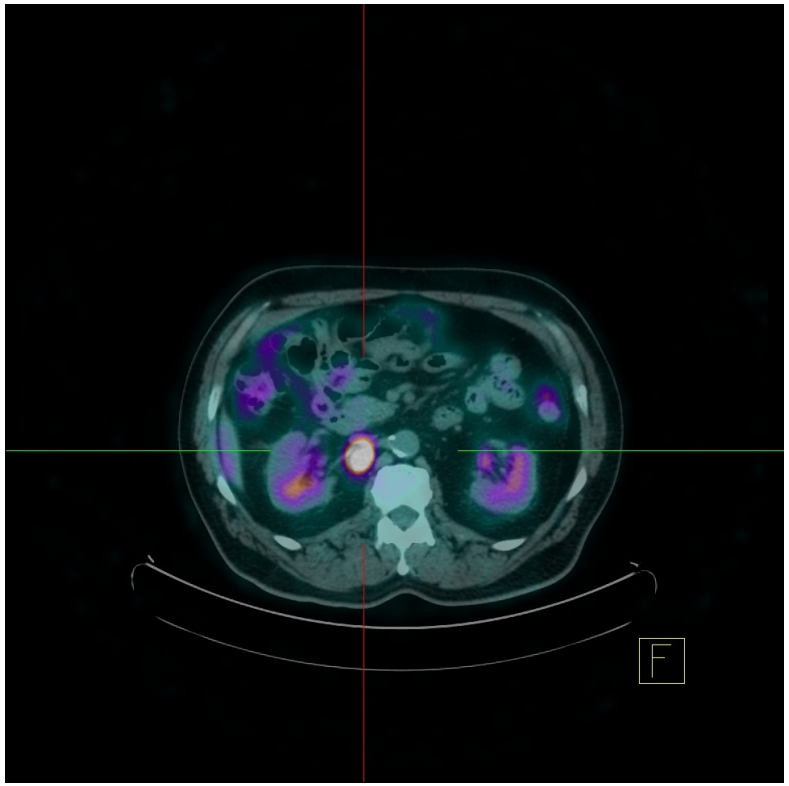
- Richiesto uso compassionevole di Polatuzumab.
- Nell'attesa, somministrati **2 cicli R-GIFOX** (dal 9-8-2019).
- In data 8-10-2019 iniziata terapia con **Polatuzumab-Rituximab-Bendamustina**: 6 cicli.
- PET di rivalutazione 25-3-2020**: remissione completa.**

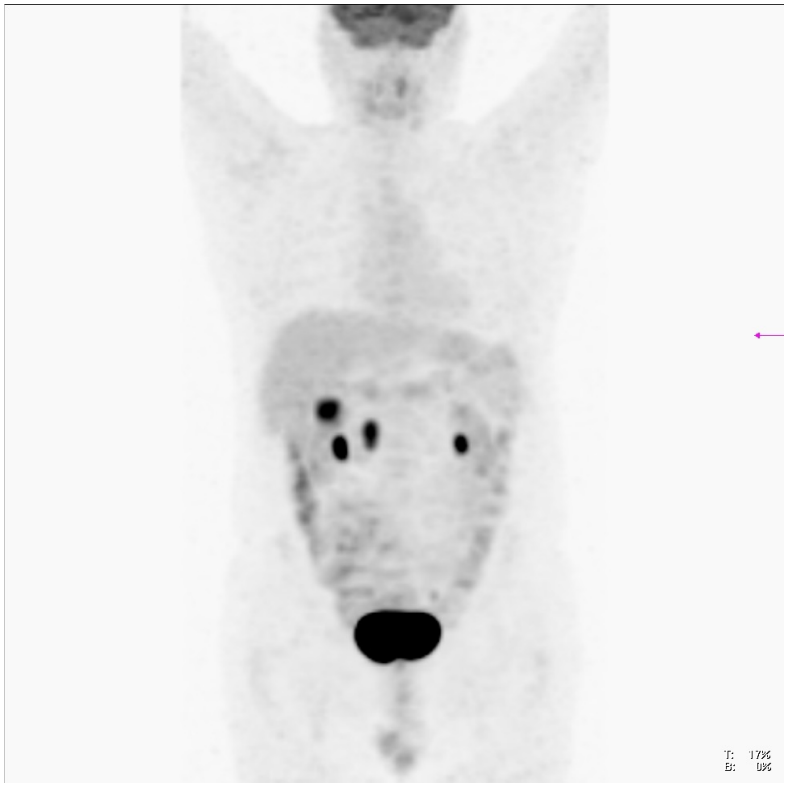




# Seconda recidiva

- PET 16-12-2020: intenso e patologico accumulo del tracciante metabolico in sede paracavale dx alla altezza della vena renale dx, SUV 15.7
- Biopsia TC-guidata (11-1-2021): conferma istologica di DLBCL non-GC, doppio espressore (BCL2 e Myc).





# CAR-T journey

- 15-3-2021: screening per idoneità a terapia CAR-T (Axi-cel).
- 22-3-2021: giudizio di idoneità.
- 1-4-2021: linfocitoaferesi.
- 19-5-2021 → 21-5-2021: linfodeplezione con CTX e Fludarabina.
- 24-5-2021: infusione axi-cel (2 x $10^6$ anti-CD19 CAR-T cells/kg).

**Tossicità**

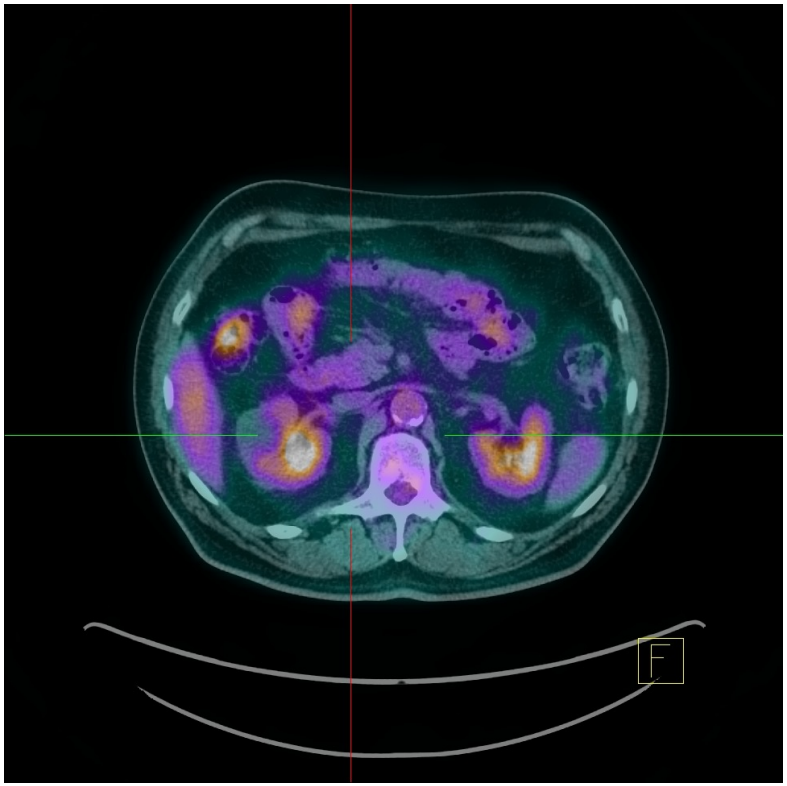
CRS G3 → tocilizumab x 2.

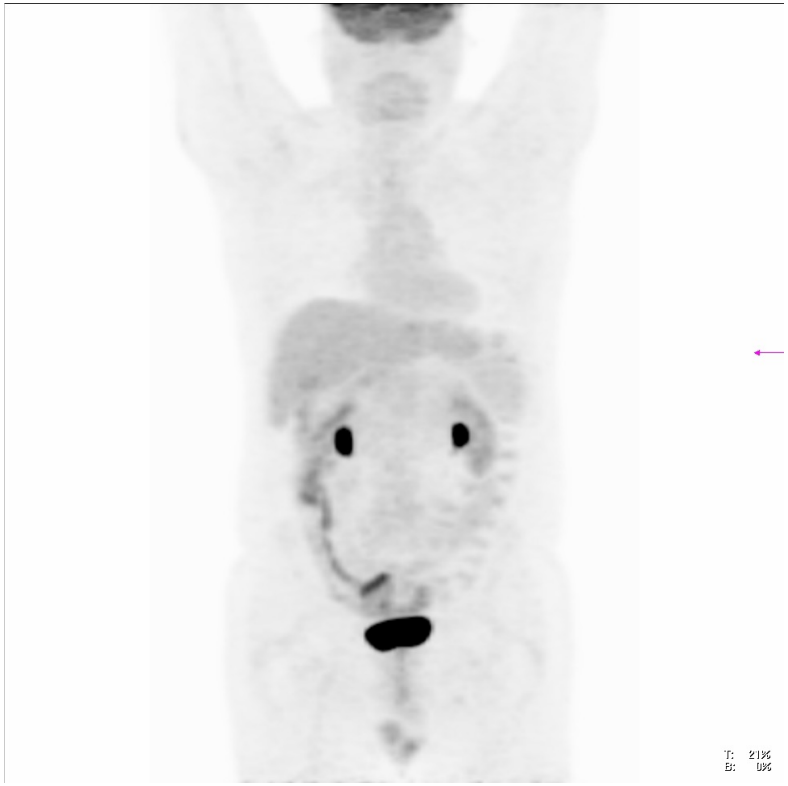
Neutropenia max G4; Piastrinopenia max G2.

N >1000/mmc dal g +77; PLT >100.000/mmc dal g +60.

# Rivalutazione post CAR-T +3 M (24-8-2021)

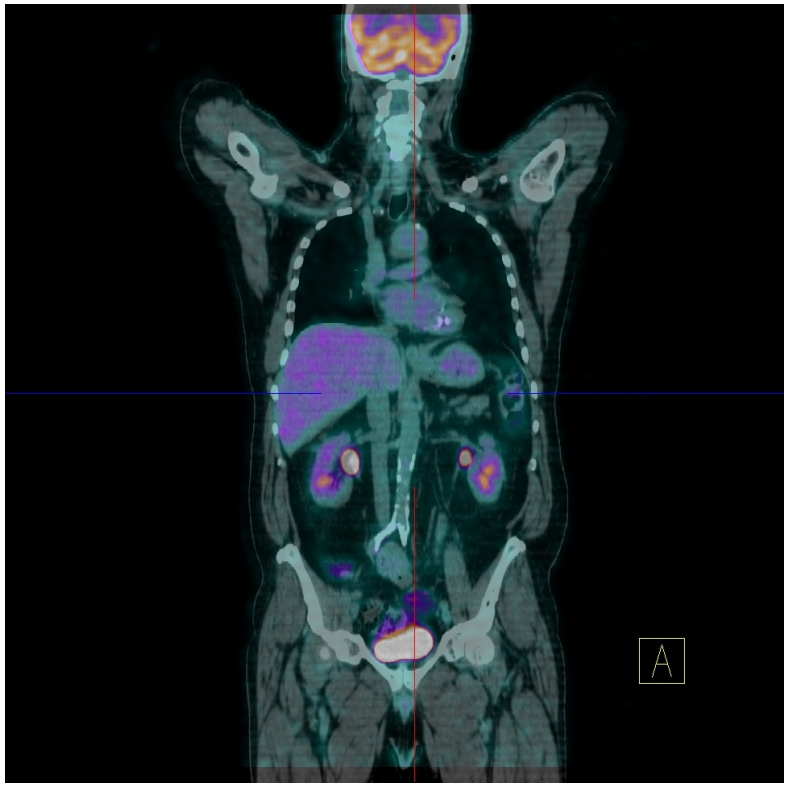
**Remissione completa**

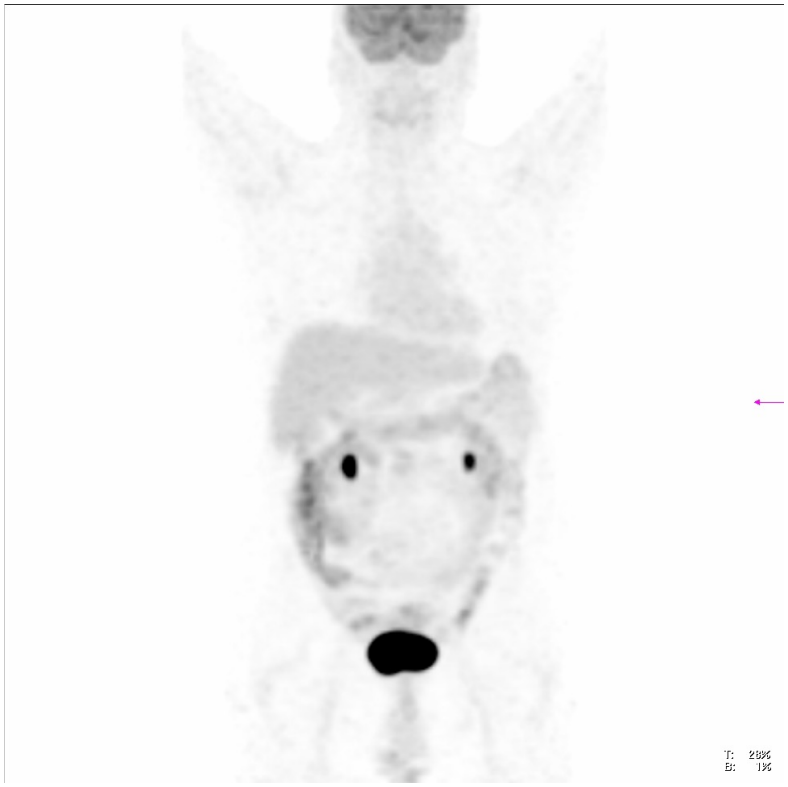




# Rivalutazione post CAR-T +12 M (24-5-2022)

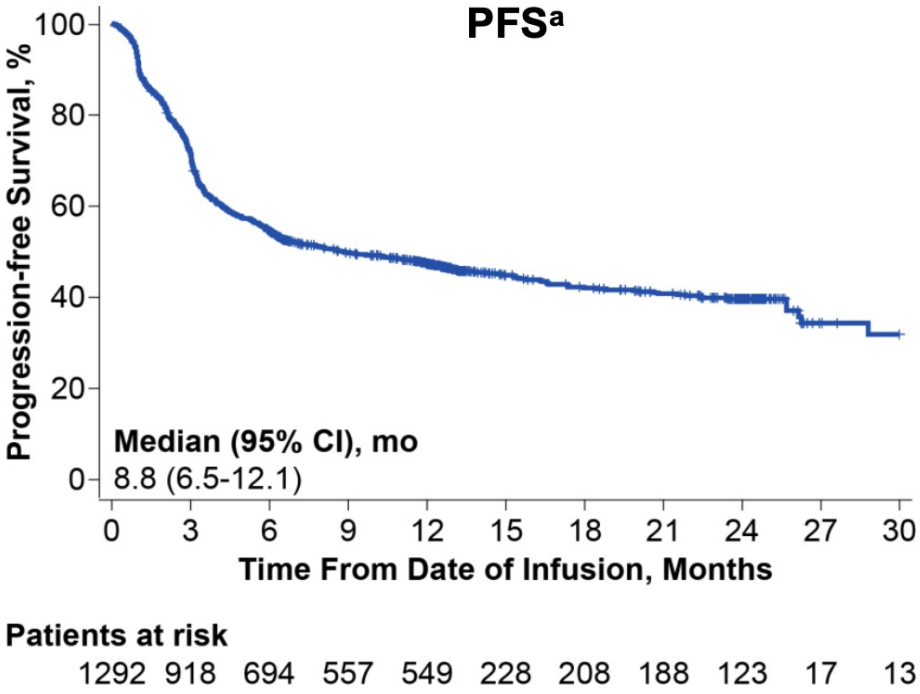
**Remissione completa**

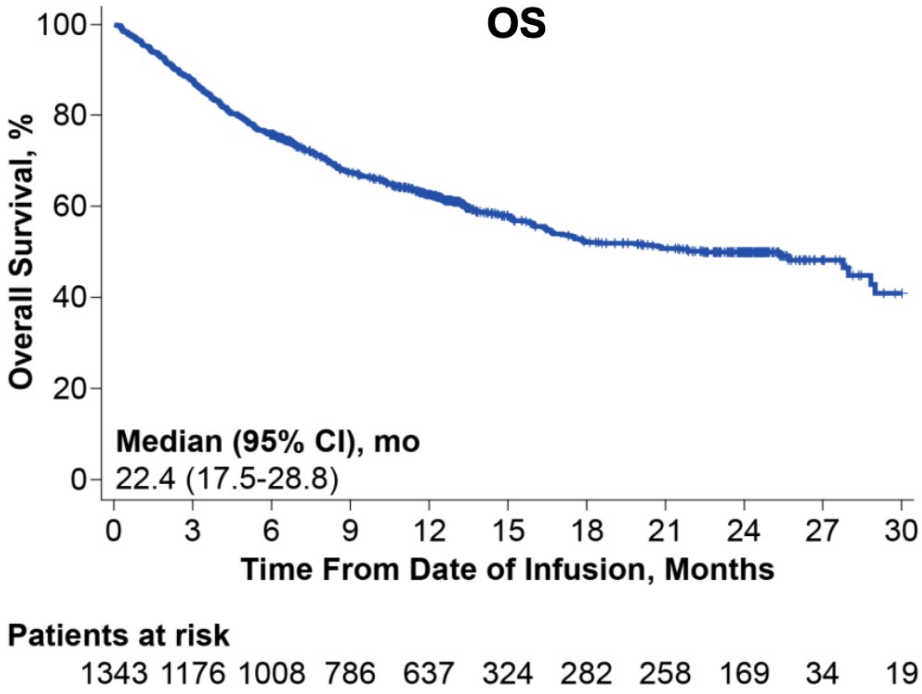




# Survival Outcomes With Axi-Cel (PASS Trial)

1500 LBCL pts enrolled, 1343 pts included in the analysis.

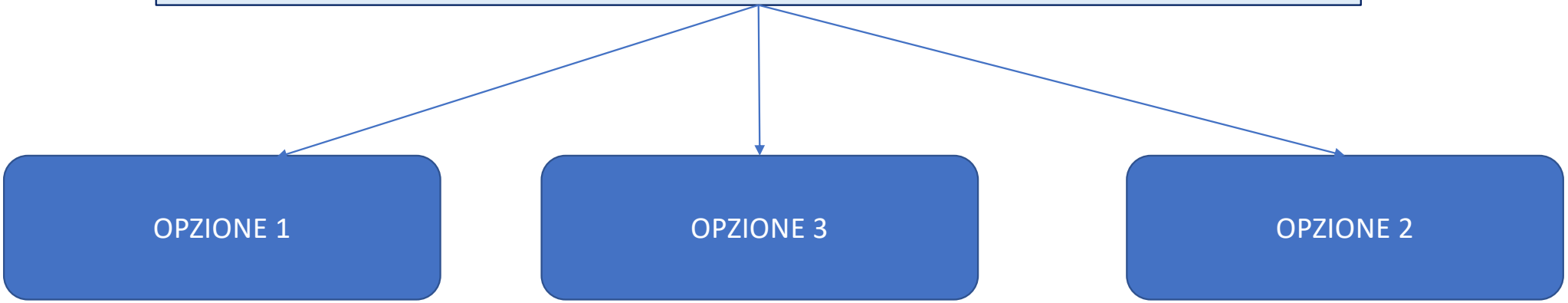


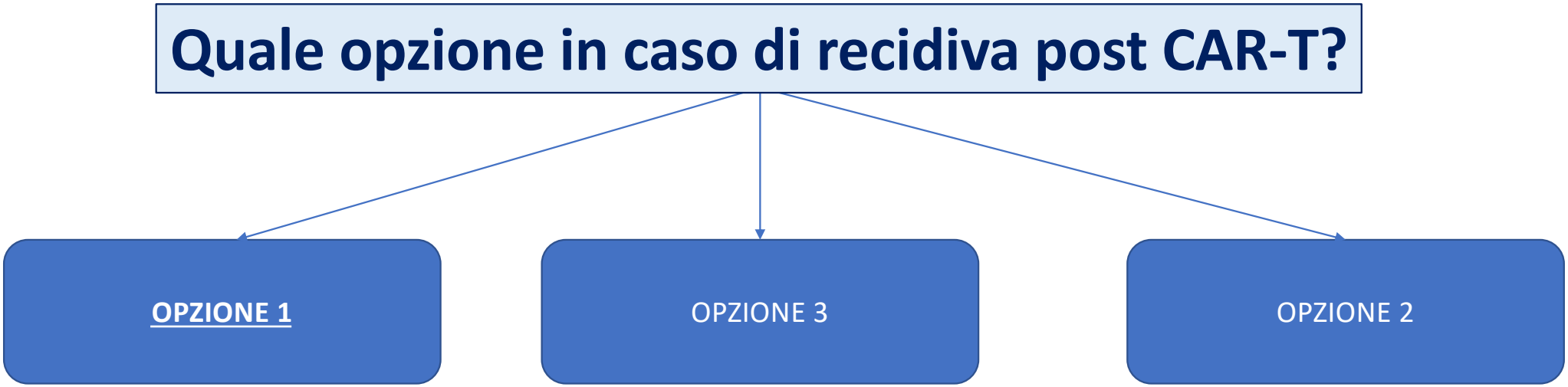




- With a median follow-up of 13 months, median PFS was 8.8 months, and median OS was 22.4 months

*Locke FL et al. Presented at ASH 2021, abstr 530.*

# Quale opzione in caso di recidiva post CAR-T?




Quale opzione in caso di recidiva post CAR-T?
OPZIONE 1
OPZIONE 3
OPZIONE 2

# L-MIND: Phase II Study of Tafasitamab + Len in R/R DLBCL

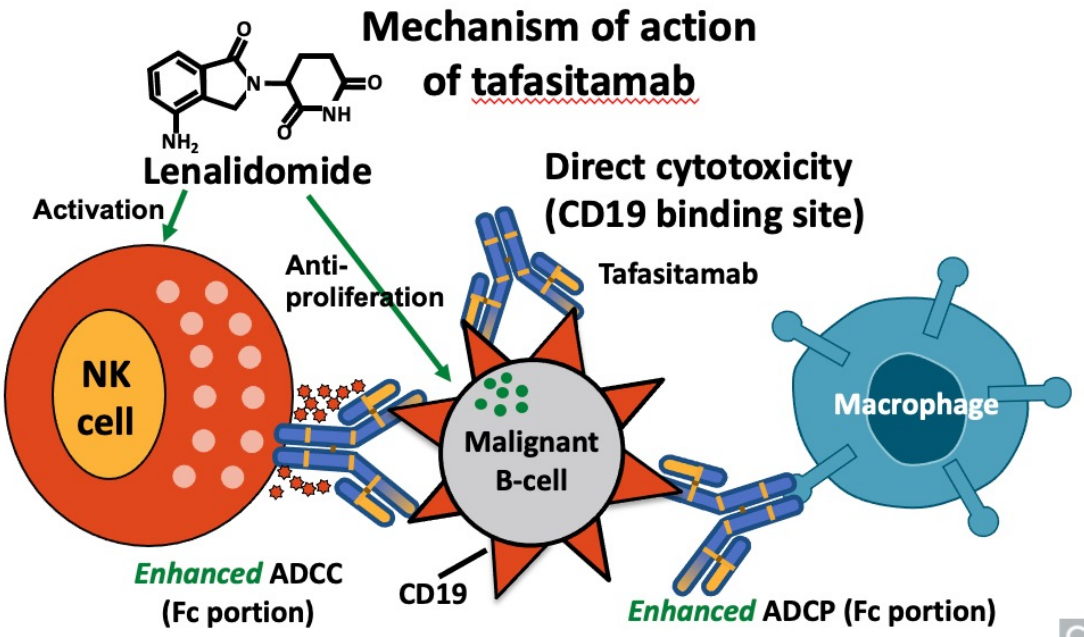
Patients with R/R DLBCL;
1-3 prior regimens
(≥1 anti-CD20); ECOG PS 0-2;
ineligible for HDT/ASCT;
primary refractory excluded
(N = 81)

→ **Lenalidomide** 25 mg/d PO, D1-21 x ≤12 28-d cycles
**Tafasitamab** 12 mg/kg/wk IV, cycles 1-3 (Q4W; D1,8,15,22)
(+ additional loading dose C1, D4) and C4-12 (Q4W, D1,15)

If no PD after 12 cycles →

**Tafasitamab**
12 mg/kg/wk
D1,15 until PD

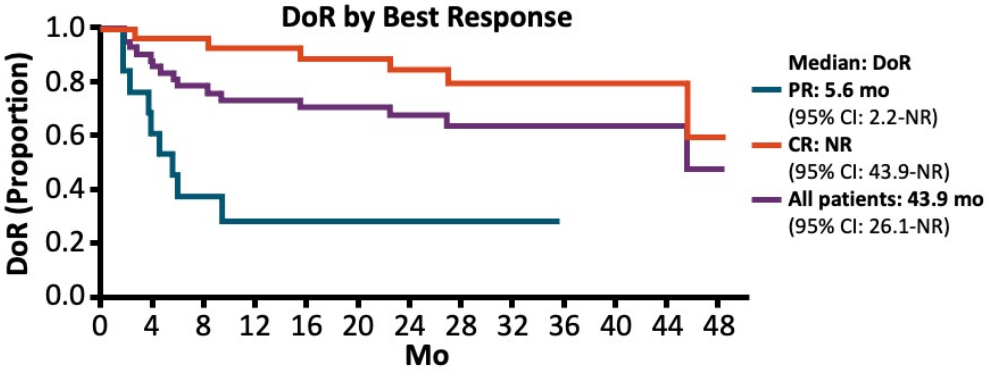
| Baseline Characteristics | N = 81 |
|---|---|
| Median age, yr (range) | 72 (41-87) |
| IPI 3-5, n (%) | 42 (52) |
| Median prior tx, n (range) | 2 (1-4) |
| Refractory to previous line, n (%) | 34 (42) |

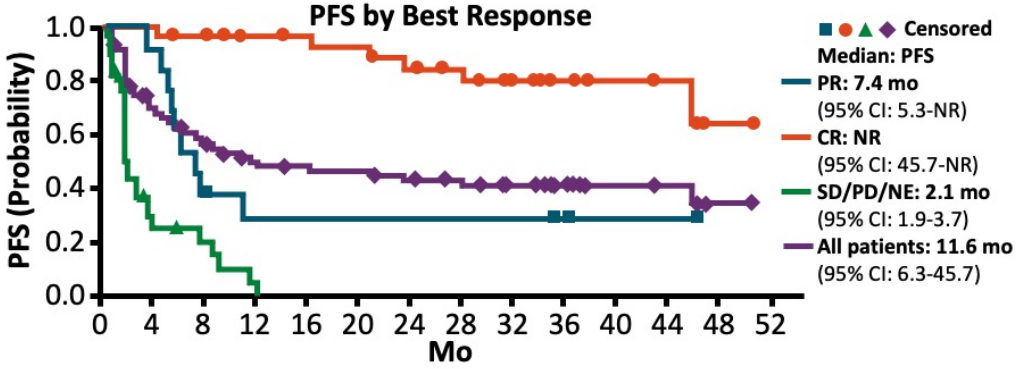


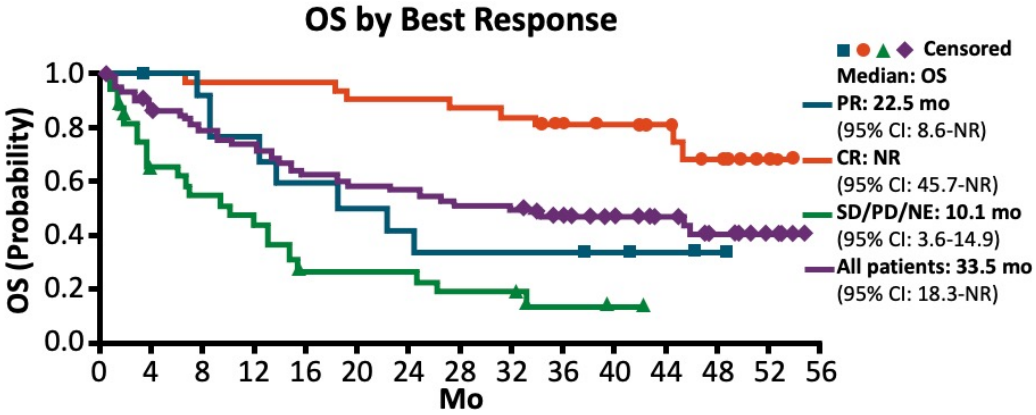

Salles. Lancet Oncol. 2020;21:978.

Slide credit: clinicaloptions.com

# L-MIND 3-Yr Update: Tafasitamab + Lenalidomide in R/R DLBCL




- ORR: 58% (40% CRs)
  - Median DoR: 43.9 mo
- Median PFS: 11.6 mo
- Median OS: 33.5 mo

**Remaining Questions**

- Is it better for non-GCB patients?
- Can this be given before an anti-CD19 CAR T-cell?
- Will it work after failing CAR T-cells? *

Dull. ASCO 2021. Abstract 7513; Duell. Haematologica. 2021;106:2417.

CCO

Slide credit: clinicaloptions.com

* Prior anti-CD19 therapy exclusion criteria in L-MIND

# Tafasitamab/lenalidomide post CAR T-cell therapy in R/R DLBCL: a case study

**Gilles Salles**

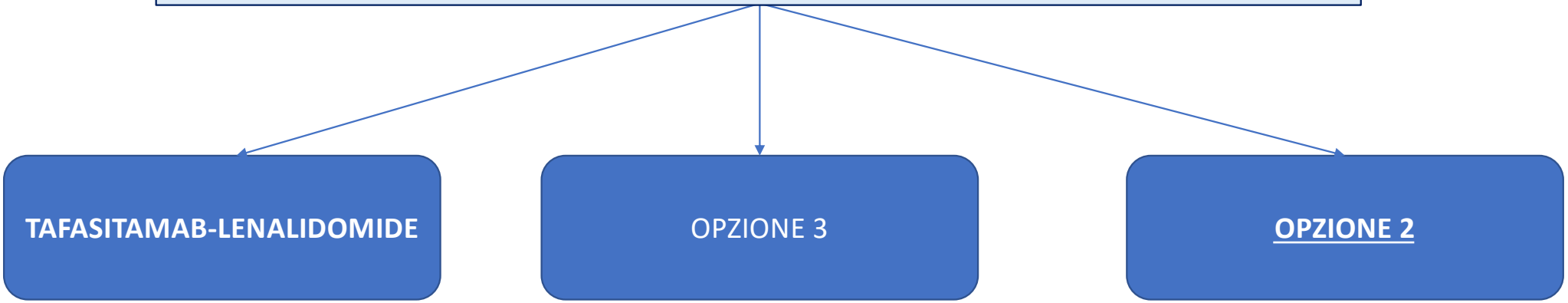
**Important information:**

- The case subject to this presentation deviates from the L-MIND inclusion criteria (previous CD19 treatments was an exclusion criteria of the L-MIND study)

- 2015: MZL stadio IV (BOM+)
- 9/2015: Rituximab QW x 4
- 9/2017: trasformazione in DLBCL double expressor stadio IV (ossa, midollo osseo, linfonodi)
- R-CHOP X 4 -> ICE X 3
- 8/2018: recidiva di DLBCL ABC (ossa, MO, linfonodi) -> R-DHAP/DHAOx -> malattia resistente (BOM+)
- **1/2019: tisagenlecleucel -> CR (2/2019)**
- 1/2020: CR
- **10/2020: recidiva (ossa e midollo osseo)**
- **12/2020: Lenalidomide-Tafasitamab**
- 2/2021: CR
- 6/2021: CR; AEs: tosse G1 e fatigue G1
- ***10/2021: terapia interrotta dopo 11 cicli (scelta concordata tra paziente e medico)***
- **12/2021: COVID-19 -> recidiva (ossa e midollo osseo)**
- 2/2022: Pola-BR -> CR -> allo-SCT

***Presented at EHA 2022***

# Quale opzione in caso di recidiva post CAR-T?



# Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥2 prior therapies: pivotal Phase II expansion results

Pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (NP30179)

## Key inclusion criteria

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

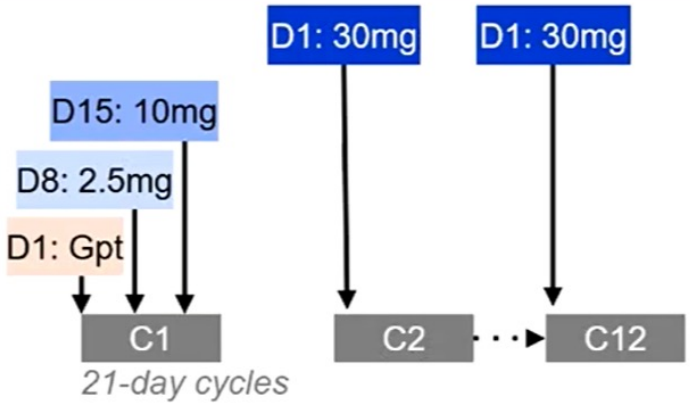
## Glofitamab IV administration

**Fixed-duration treatment**

- max. 12 cycles

**CRS mitigation:**

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




## Endpoints

- **Primary: CR (best response) rate by IRC***
- **Key secondary:** ORR rate,† DoR, DoCR,† PFS, and OS

*Dickinson M et al. Presented at ASCO 2022 (abstr 7500) and at EHA 2022 (abstr 220)*

# Baseline characteristics

| n (%)* | | N=154† |
|---|---|---|
| Median age, years (range) | | 66.0 (21–90) |
| Male | | 100 (64.9) |
| ECOG PS‡ | 0 | 69 (44.8) |
| | 1 | 84 (54.5) |
| Ann Arbor stage | I | 10 (6.5) |
| | II | 25 (16.2) |
| | III | 31 (20.1) |
| | IV | 85 (55.2) |
| NHL subtype | DLBCL | 110 (71.4) |
| | trFL | 27 (17.5) |
| | HGBCL | 11 (7.1) |
| | PMBCL | 6 (3.9) |
| Bulky disease | >6cm | 64 (41.6) |
| | >10cm | 18 (11.7) |

| n (%)* | N=154 |
|---|---|
| Median no. of prior lines, n (range) | 3 (2–7) |
| 2 prior lines | 62 (40.3) |
| ≥3 prior lines | 92 (59.7) |
| Prior anti-CD20 Ab | 154 (100.0) |
| Prior anthracycline | 149 (96.8) |
| Prior CAR-T | 51 (33.1) |
| Prior ASCT | 28 (18.2) |
| Refractory to any prior therapy | 139 (90.3) |
| Refractory to last prior therapy | 132 (85.7) |
| Primary refractory | 90 (58.4) |
| Refractory to prior CAR-T | 46 (29.9) |
| Refractory to any prior anti-CD20 | 128 (83.1) |

**Heavily pre-treated, highly refractory population**

Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients);
‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

*Dickinson M et al. Presented at ASCO 2022 (abstr 7500) and at EHA 2022 (abstr 220)*

# Glofitamab in R/R DLBCL: CR and DoR

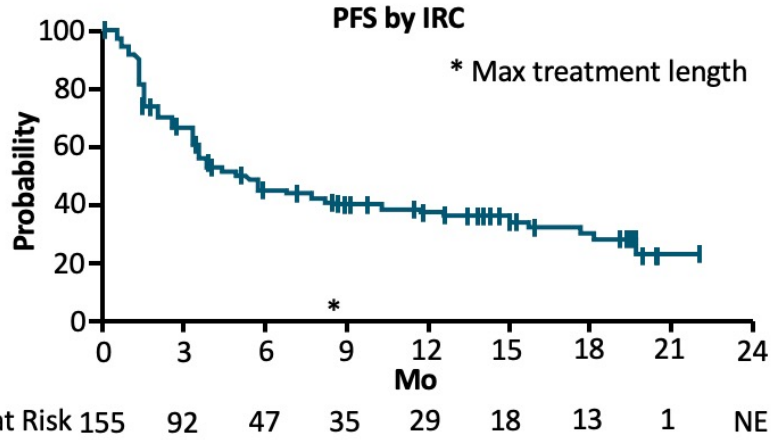
| Parameter | Glofitamab (N = 155) |
|---|---|
| CR rate, % | 39.4 |
| ORR, % | 51.6 |
| Median time to first CR, days (95% CI) | 42 (42-44) |
| Median duration follow-up, mo (range) | 12.6 (0-22) |

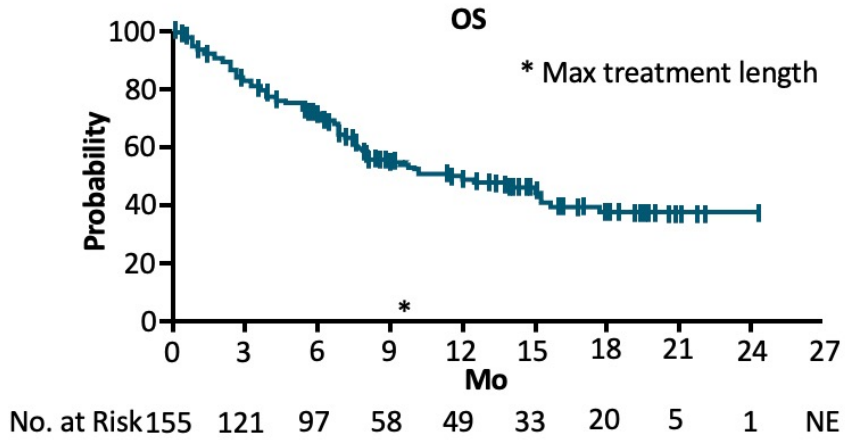
**CR rates were consistent in patients with or without prior CAR T-cell therapy (35% vs 42%)**

| Outcome | Patients With Any Response to Glofitamab (n = 80) | Patients With CR to Glofitamab (n = 61) |
|---|---|---|
| mDoR, mo (95% CI) | 18.4 (13.7-NE) | NE (16.8-NE) |
| mDoR follow-up, mo (range) | 10.6 (0-21) | 10.6 (0-21) |
| 12-mo DoR (or DoCR) | 63.6 | 77.6 |
| OR ongoing at cutoff date, % | 66.3 | 80.3 |

*Dickinson M et al. Presented at ASCO 2022 (abstr 7500) and at EHA 2022 (abstr 220)*

# Glofitamab in R/R DLBCL: PFS, OS




| Outcome, % (95% CI) | Glofitamab (N = 155) |
|---|---|
| Median PFS, mo (95% CI) | 4.9 (3.4-8.1) |
| 6-mo PFS rate | 45.5 (37.2-53.8) |
| 12-mo PFS rate | 37.1 (28.5-45.8) |
| Median OS, mo (95% CI) | 11.5 (7.9-15.7) |
| 12-mo OS rate | 49.8 (41.1-58.5) |

Slide credit: clinicaloptions.com

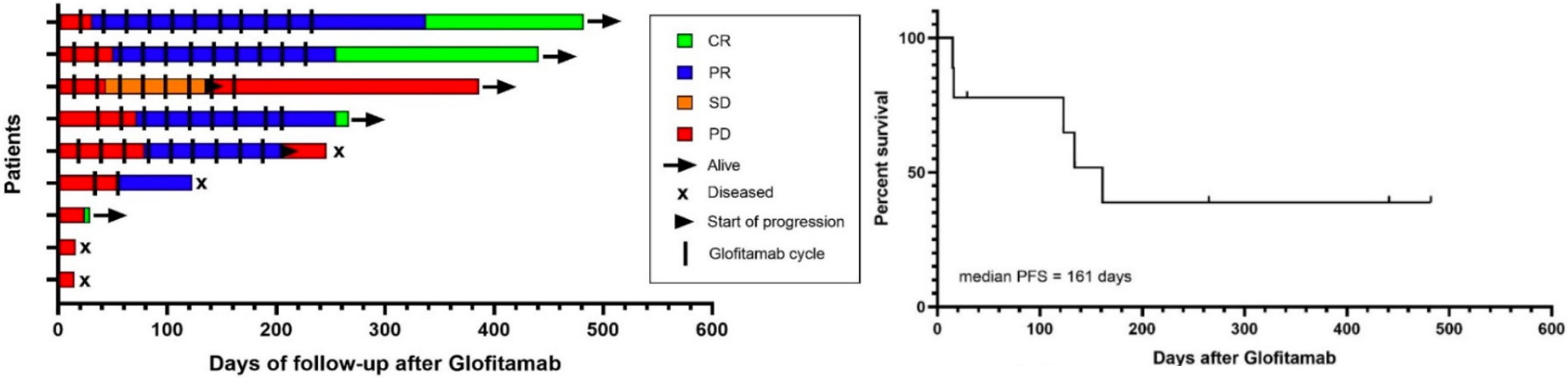
*Dickinson M et al. Presented at ASCO 2022 (abstr 7500) and at EHA 2022 (abstr 220)*

*Article*

# Glofitamab Treatment in Relapsed or Refractory DLBCL after CAR T-Cell Therapy

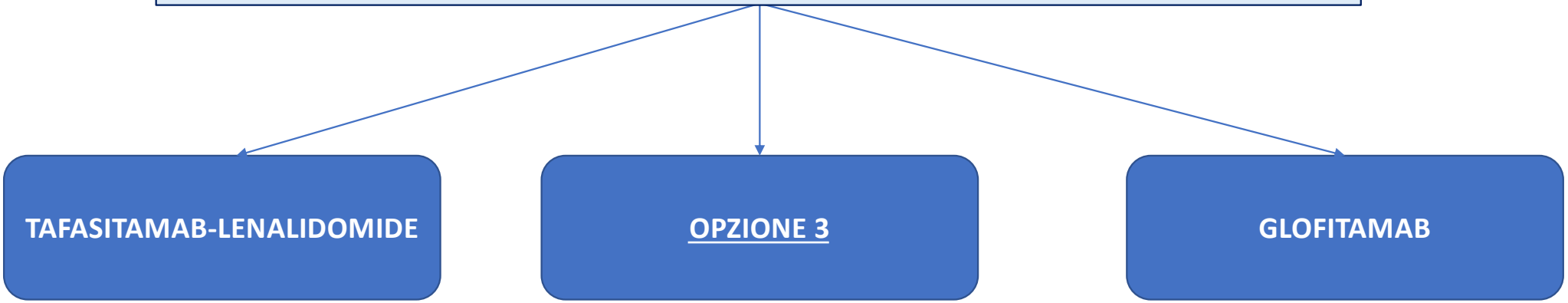
**Vera Rentsch [1], Katja Seipel [2], Yara Banz [3], Gertrud Wiedemann [4], Naomi Porret [4], Ulrike Bacher [5] and Thomas Pabst [1,*]**

- **9 pts,** median age 66 yr (41-75); median time between CAR T and glofitamab 187 d (86-655).
- 4 (44%) pts completed the planned 12 cycles; **premature glofitamab termination due to PD.**
- **CRS in 2 (22%) pts, all G2;** no ICANS; neutropenia G3 in 2 (22%) pts; infections in 4 (44%) pts.
- **ORR: 67% (CR 44%);** median time to CR: 8.3 m.
- Median FU: 246 d (15-482); **PFS 44%, median PFS 161 d; deaths: 4 (44%), all for PD.**




*Cancer 2022*

# Quale opzione in caso di recidiva post CAR-T?

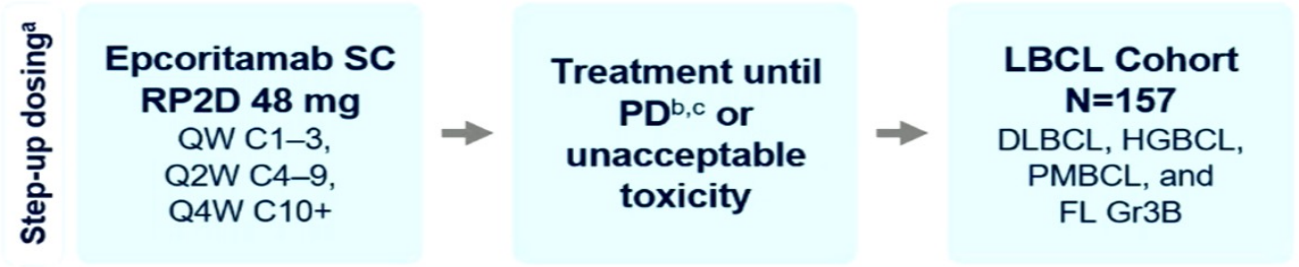


# SUBCUTANEOUS EPCORITAMAB IN PATIENTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA (EPCORE NHL-1): PIVOTAL RESULTS FROM A PHASE 2 STUDY

**Dose expansion data cutoff: January 31, 2022**
**Median follow-up: 10.7 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 allowed




- 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 independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

*Thieblemont C et al. Presented at EHA 2022*

# Patients characteristics

| Demographics | LBCL, N=157 |
|---|---|
| Median age (range), y | 64 (20–83) |
| <65 y, n (%) | 80 (51) |
| 65 to <75 y, n (%) | 48 (31) |
| ≥75 y, n (%) | 29 (18) |
| ECOG PS, n (%) | |
| 0 | 74 (47) |
| 1 | 78 (50) |
| 2 | 5 (3) |
| **Disease Characteristics[a]** | **LBCL, N=157** |
| Disease type, n (%) | |
| DLBCL | 139 (89) |
| De novo | 97/139 (70) |
| Transformed | 40/139 (29) |
| Unknown | 2/139 (1) |
| HGBCL | 9 (6) |
| PMBCL | 4 (3) |
| FL Gr3B | 5 (3) |

| Prior Treatments | LBCL, N=157 |
|---|---|
| Median time from initial diagnosis to first dose, y | 1.6 |
| Median time from end of last therapy to first dose, mo | 2.4 |
| Median prior lines of therapy (range) | 3 (2–11) |
| ≥3 Lines of therapy, n (%) | 111 (71) |
| Primary refractory[b] disease, n (%) | 96 (61) |
| Refractory[b] to last systemic therapy, n (%) | 130 (83) |
| Refractory[b] to ≥2 consecutive lines of therapy, n (%) | 119 (76) |
| Prior ASCT, n (%) | 31 (20) |
| Prior CAR T therapy, n (%) | 61 (39) |
| Progressed within 6 mo of CAR T therapy | 46/61 (75) |

*Thieblemont C et al. Presented at EHA 2022*

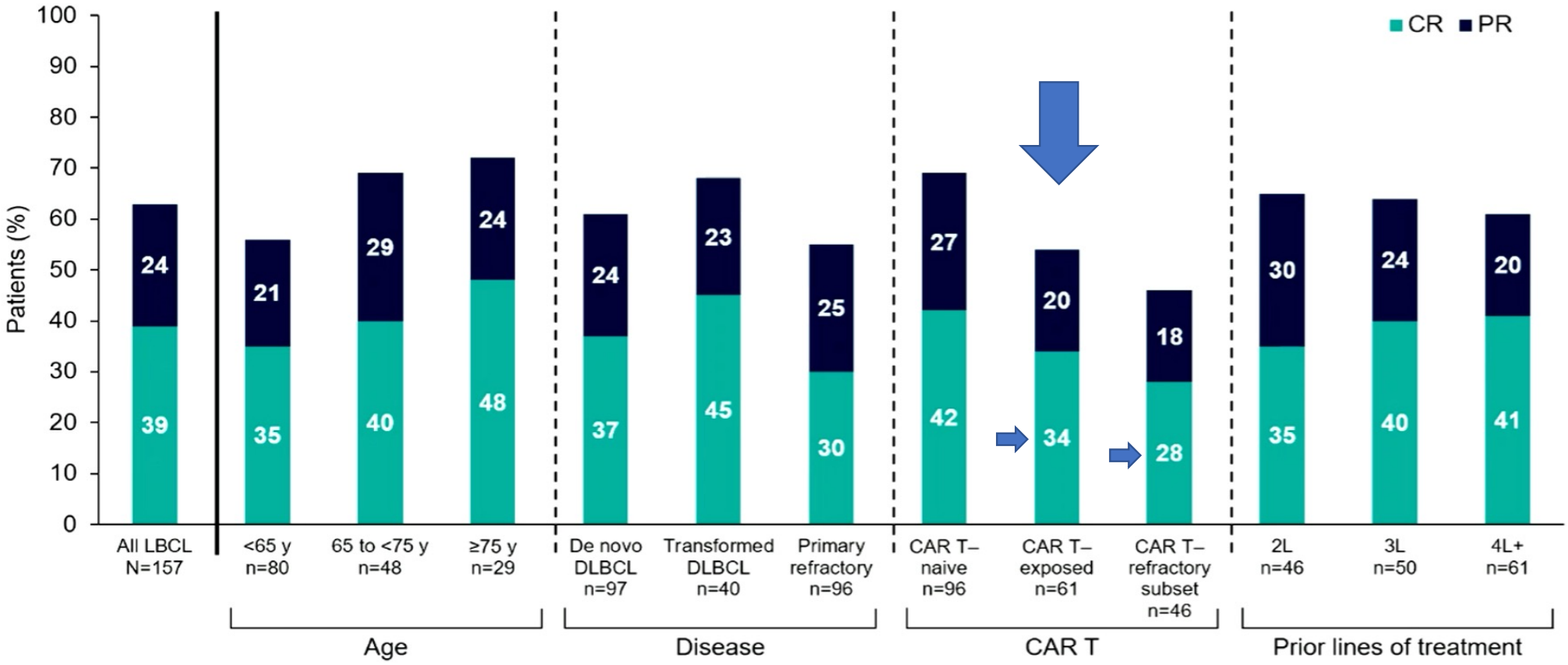
# Epcoritamab (EPCORE NHL-1): Response Rate

| Best Overall Response by IRC, n (%)[a] | LBCL N=157 |
|---|---|
| **Overall response** | **99 (63)** [95% CI: 55–71] |
| **Complete response** | **61 (39)** [95% CI: 31–47] |
| Partial response | 38 (24) |
| Stable disease | 5 (3) |
| Progressive disease | 37 (24) |

[a]Based on Lugano criteria.

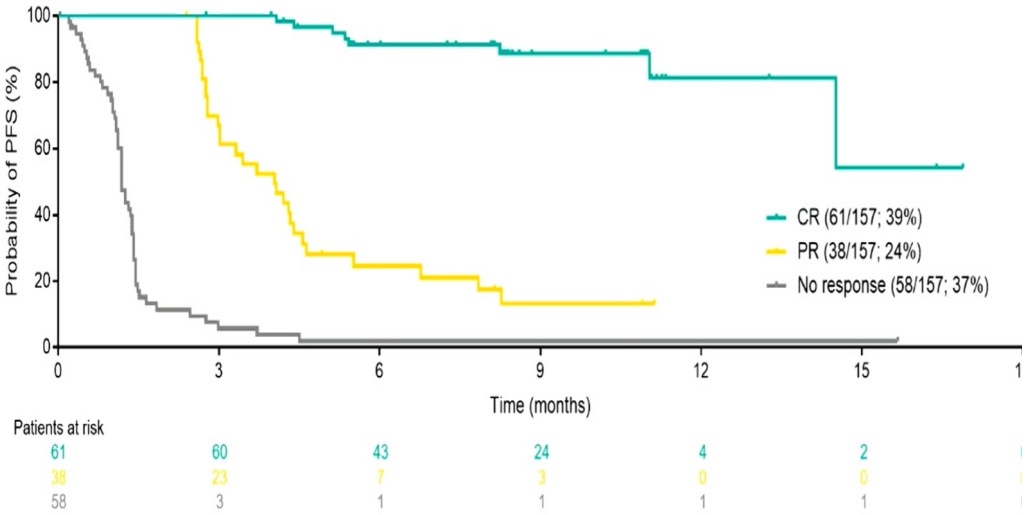
*Thieblemont C et al. Presented at EHA 2022*

# Epcoritamab (EPCORE NHL-1): Response Rate according to Subgroups

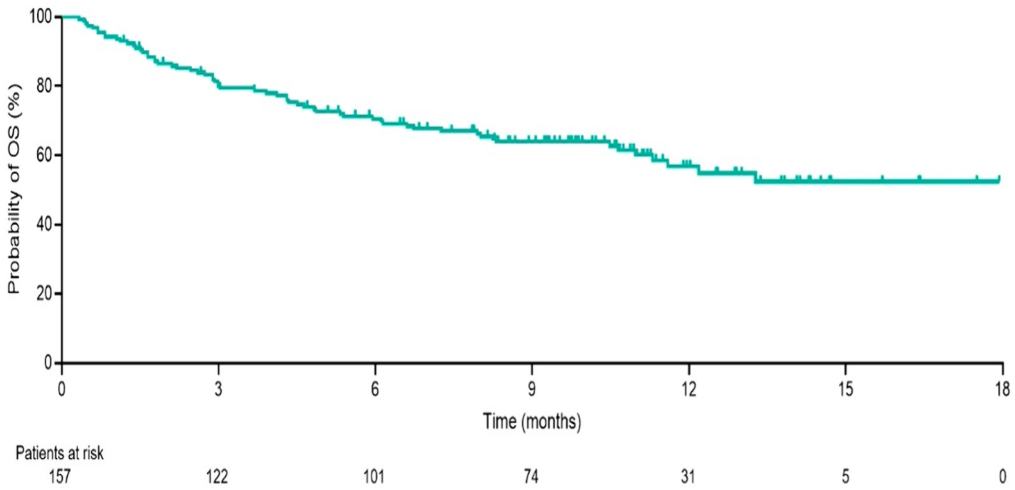



*Thieblemont C et al. Presented at EHA 2022*

# Epcoritamab (EPCORE NHL-1): PFS and OS




| Kaplan–Meier Estimate | |
|---|---|
| **Median PFS for complete responders** | **Not reached** |
| **Complete responders remaining in complete response at 9 mo** | **89%** |
| Median PFS, mo (95% CI) | 4.4 (3.0–7.9) |
| PFS at 6 mo, % (95% CI) | 43.9 (35.7–51.7) |




| Kaplan–Meier Estimate | N=157 |
|---|---|
| **Median OS** | **Not reached** |
| OS at 6 mo, % (95% CI) | 70.6 (62.7–77.2) |
| OS at 12 mo, % (95% CI) | 56.9 (47.3–65.4) |

*Thieblemont C et al. Presented at EHA 2022*


Quale opzione in caso di recidiva post CAR-T?
TAFASITAMAB-LENALIDOMIDE
EPCORITAMAB
GLOFITAMAB
Se in risposta
Allo-SCT?

# Conclusioni

- Per i pazienti con R/R DLBCL dopo almeno 2 linee terapeutiche, **la terapia CAR-T** può considerarsi oggi **il nuovo standard terapeutico**, con ORR attese del 50–80% e CR del 40–50%.

- **La recidiva o refrattarietà dopo CAR-T** è una **nuova sfida terapeutica;** la prognosi per questi pazienti è «very poor» e attualmente non vi sono definitive indicazioni sulla terapia di salvataggio.

- In questo gruppo di pazienti, un **nuovo approccio immunoterapico** con immunoconiugati, anti-CD19, o anticorpi bispecifici, valutando anche il trapianto allogenico, se fattibile, può essere una valida opzione terapeutica.