



# Mi experiencia en situaciones desesperadas de Linfoma de células grandes B

Matthew Mei, MD

Associate Professor, Hematology/HCT

City of Hope

[mamei@coh.org](mailto:mamei@coh.org)

+1 6267592562



# CONFLICTOS DE INTERÉS

BMS – research

Beigene – research

Incyte – research

Genentech - research

Morphosys – consultancy, speakers' bureau

SeaGen – consultancy, speakers' bureau

AstraZeneca – consultancy

ADC Therapeutics - consultancy

Novartis – consultancy

CTI – consultancy

SyntheKine - consultancy

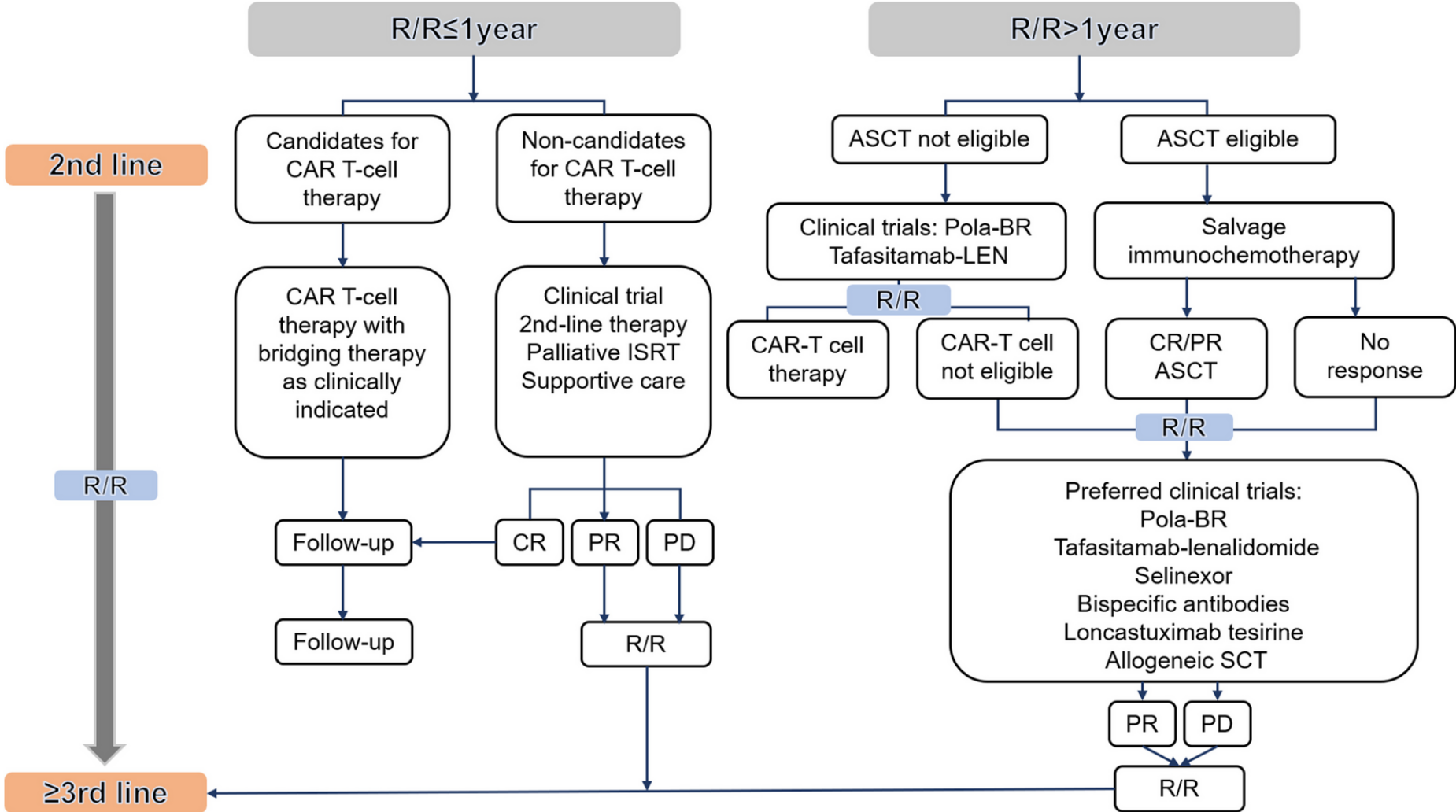
# WHAT IS DESPERATION IN DLBCL?

Some desperate situations:

- 1) Any DLBCL post CAR-T?
- 2) Chemorefractory after 2 lines
- 3) Any SCNSL (?)
- 4) Exhausted all available options



# DLBCL - Where are we today?

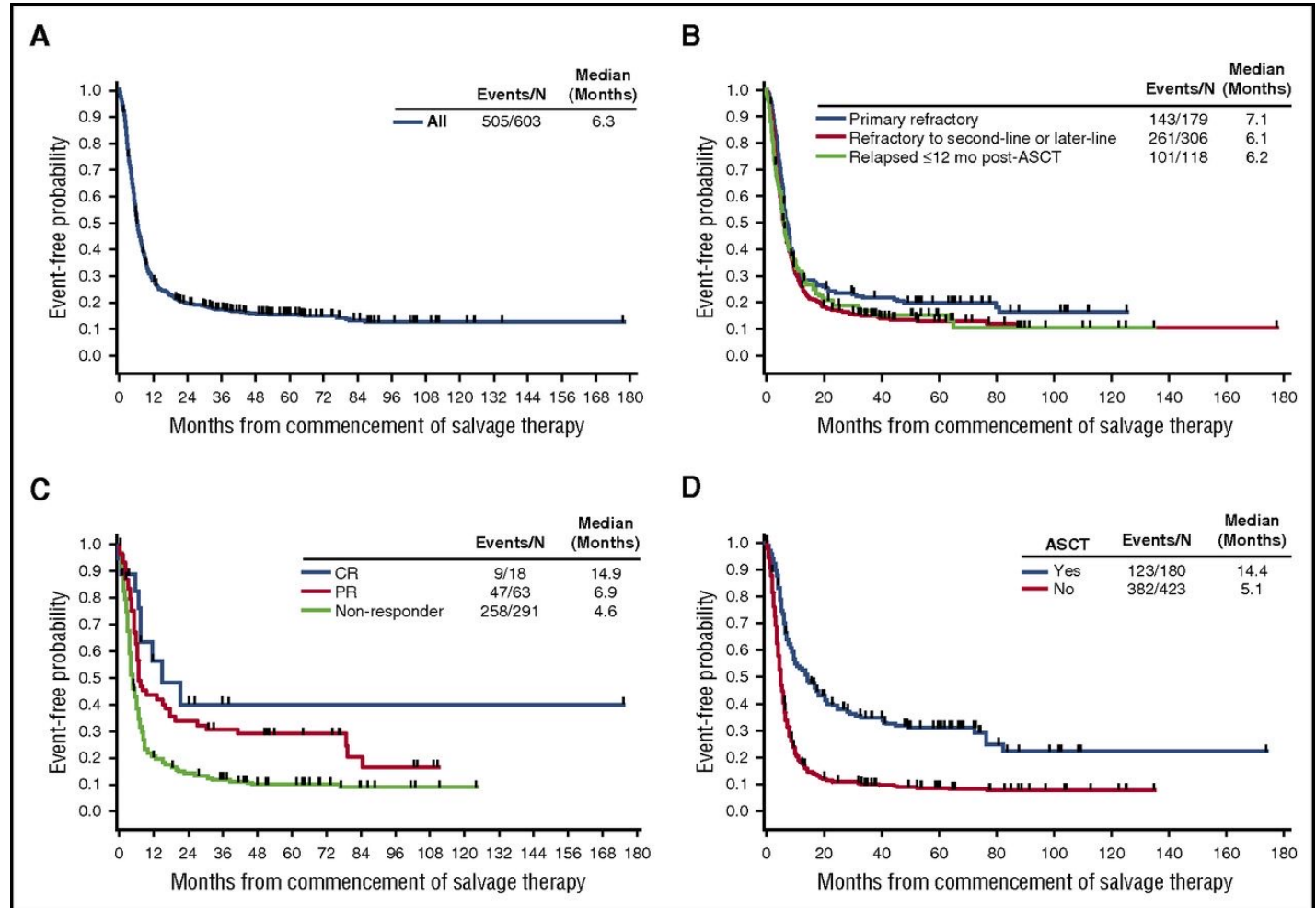


Shi Y, et al. Advances in biology, diagnosis and treatment of DLBCL. Ann Hematol 2024.

# SCHOLAR-1

## Refractory DLBCL (pre CAR-T)

- OS 6.3m
- Next line of therapy:
  - ORR 26%, CR 7%!
  - ORR 20% in primary refractory



Crump M, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017.

# POLATUZUMAB VEDOTIN + BR

Randomized trial of BR + pola vs. BR

In the extension cohort:

ORR 57%

CR 53%

DOR 9.5m

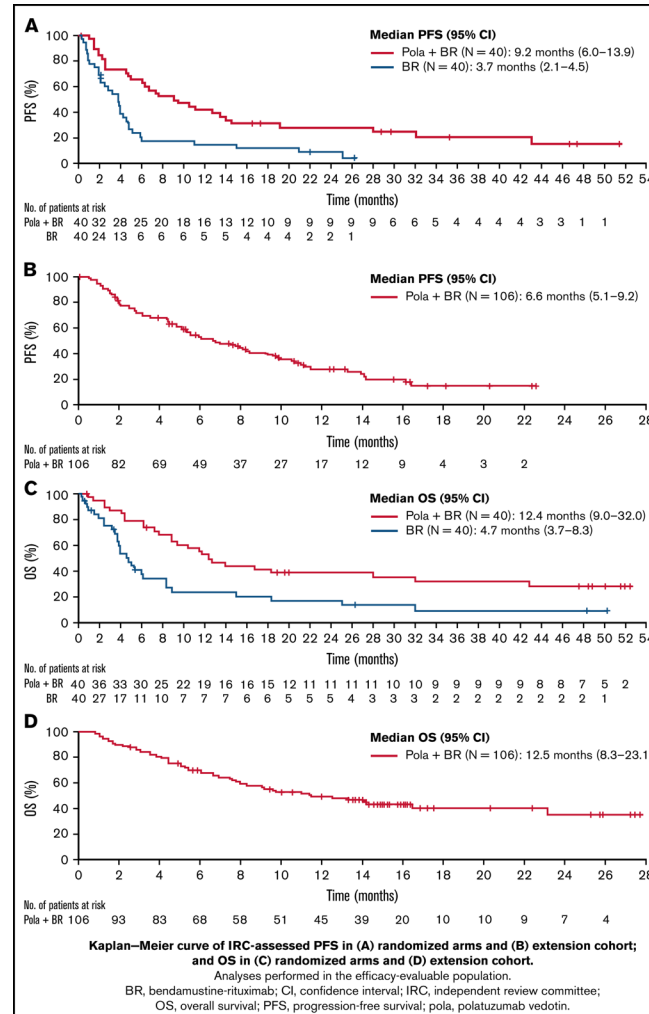
...

Increasing use of pola in 1L

Increasing use as bridging for CAR-T

Benda negatively affects subsequent

CAR-T



Sehn LH, et al. Blood Advances 2022.

# LONCASTUXIMAB TESIRINE

## LOTIS-2 – pivotal trial

Lonca-T in R/R DLBCL


- ORR 48%
- DOR 10m (CR), 5m (PR)

Preserved expression of CD19 post tx  
(Thapa B, et al. Blood Adv 2020)

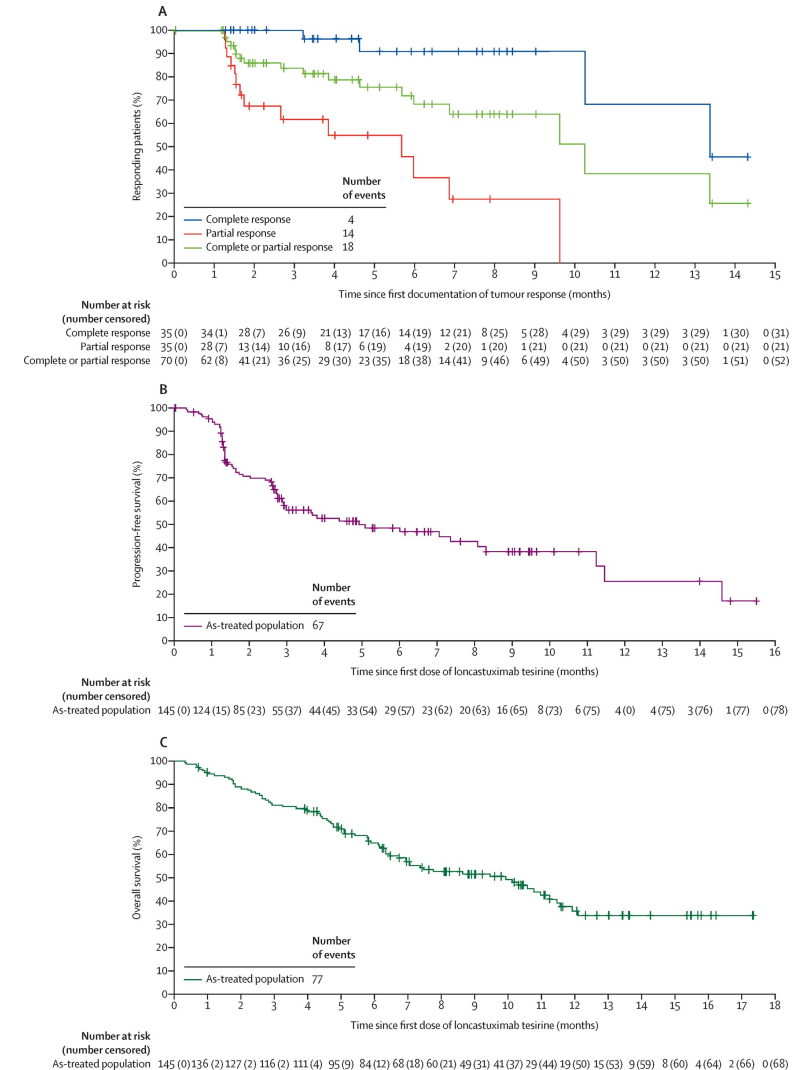
No correlation between activity and CD19  
expression

(Caimi PF, et al. EJHaem 2023)

Neutropenia (26% G3+)

GGT  (17% G3+)

Edema in 28% (3% G3+)



# TAFASITAMAB + LENALIDOMIDE

## L-MIND – Phase 2

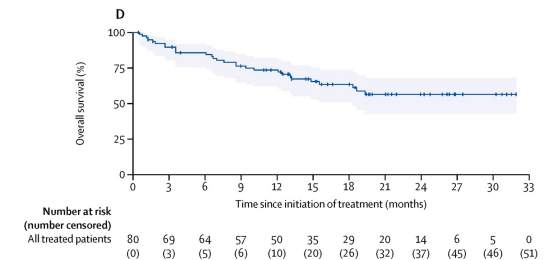
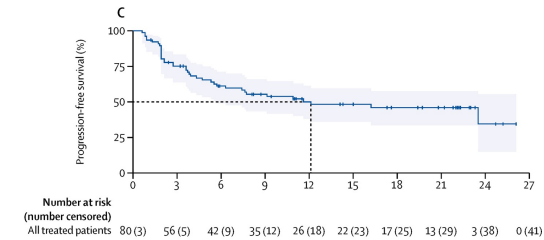
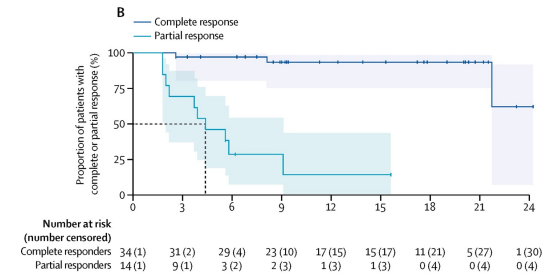
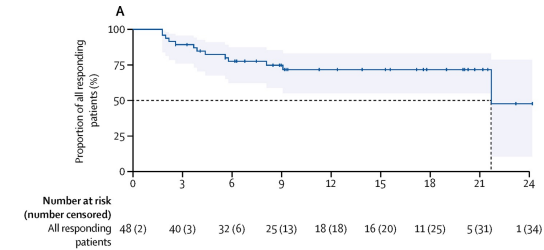
Tafasitamab – anti-CD19 mAb

- 48% ORR
- SLP 12.1m
- DOR 21.7m

“Cherry picked”

Excluido:

- DHL
- primariamente refractario



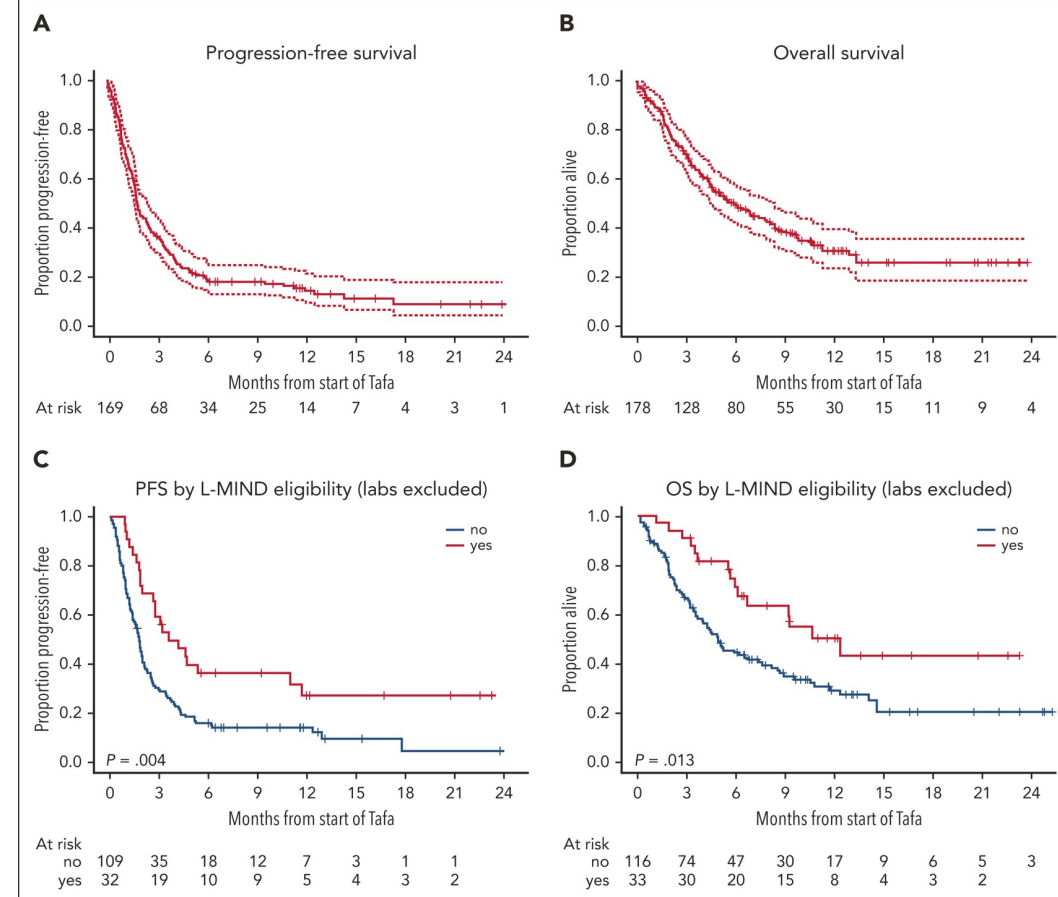
# TAFASITAMAB + LENALIDOMIDE – REAL-WORLD

## Real world analysis

- ORR 31%
- CR 19%
- PFS 1.9m (vs. 12.1m in L-MIND)

\* Most patients would have been ineligible

| Characteristic   | Real world | L-MIND     |
|--|------------|------------|
| Number of patients   | 178        | 81         |
| Female sex   | 87 (49)    | 37 (46)    |
| Age (y), median (range)  | 75 (26-94) | 72 (41-86) |
| <b>Race</b>  |            |            |
| White, all ethnicity   | 161 (90)   | 72 (89)    |
| Asian  | 9 (5)      | 2 (2)      |
| Other or unknown   | 8 (4)      | 1 (1)      |
| <b>Diagnosis</b>   |            |            |
| DLBCL-NOS  | 96 (54)    | 72 (89)    |
| Transformed indolent lymphoma  | 59 (33)    | 7 (9)      |
| HGBCL (nontransformed)   | 19 (11)    | 2 (2)      |
| Other*   | 4 (2)      | 0 (0)      |
| <b>Cell of origin by immunohistochemistry</b>                          |            |            |
| GCB  | 100 (56)   | 38 (47)    |
| Non-GCB  | 62 (35)    | 21 (26)    |
| Unknown  | 16 (9)     | 22 (27)    |
| <b>Risk (IPI)</b>  |            |            |
| 0-2  | 43 (27)    | 40 (49)    |
| 3-5  | 114 (73)   | 41 (51)    |
| <b>Ann Arbor stage</b>   |            |            |
| I-II   | 20 (12)    | 20 (25)    |
| III-IV   | 149 (88)   | 61 (75)    |
| <b>Prior lines of therapy for DLBCL</b>                                |            |            |
| Median (range)   | 2 (0-11)   | 2 (1-4)    |
| 0†   | 12 (7)     | 0 (0)      |
| 1  | 49 (28)    | 40 (49)    |
| 2  | 49 (28)    | 35 (43)    |
| 3  | 27 (15)    | 5 (6)      |
| 4  | 13 (7)     | 1 (1)      |
| ≥5   | 28 (16)    | 0 (0)      |
| Primary refractory (progression within 6 months of first-line therapy) | 87 (49)    | 15 (18)    |
| Refractory to last therapy   | 118 (67)   | 36 (44)    |
| Prior SCT  | 23 (13)    | 9 (11)     |
| Prior CAR-T  | 52 (30)    | 0          |
| L-MIND eligible (not considering laboratory values)                    | 33 (22)    | -          |
| L-MIND eligible (including laboratory values)                          | 16 (11)    | -          |

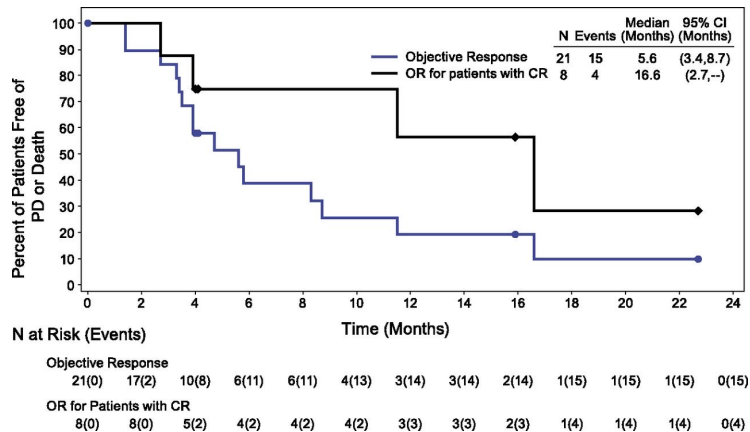


Qualls DA, et al. Blood 2023.

# BRENTUXIMAB VEDOTIN

## BV monox in DLBCL

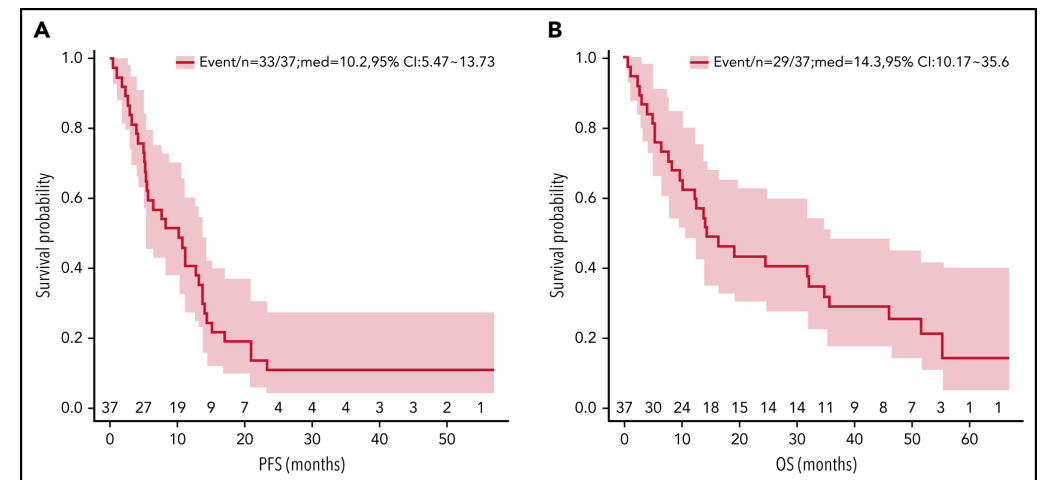
- ORR 44% (Jacobsen ED, et al. Blood 2015)
- Activity independent of CD30 level



Jacobsen ED, et al. Blood 2015

## BV + Len

- BV 1.2 mg/kg + Len 20 mg PO QD q21d
- ORR 57% (CR 35%)
- DOR 13.1m
- PFS 10.2m
- COO not significant

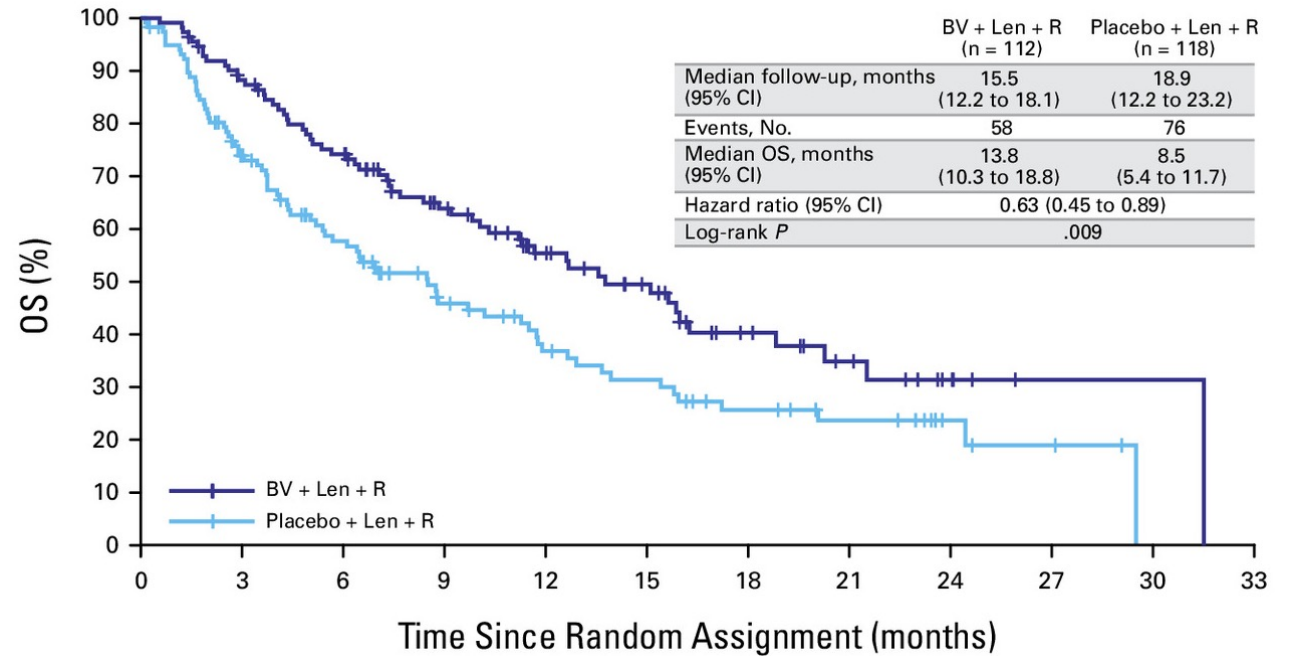
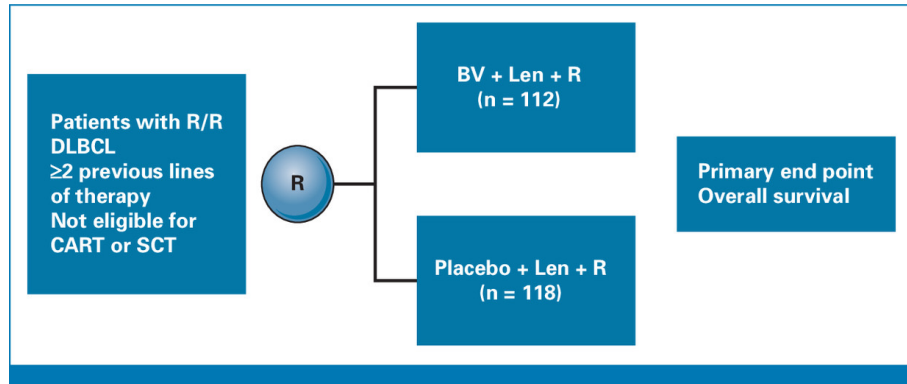


# ECHELON-3

## BV + Len + R vs. R2

N = 230

- 32% CD30+, 46% GC
- > 50% stage IV



Bartlett N, et al. JCO 2025.

**ORR 64.3% vs. 41.5%**

**OS 13.8 vs. 8.5m (p = 0.0085)**

**PFS 4.2m vs. 2.6m**

**PN (27%)**

# BISPECIFIC ANTIBODIES

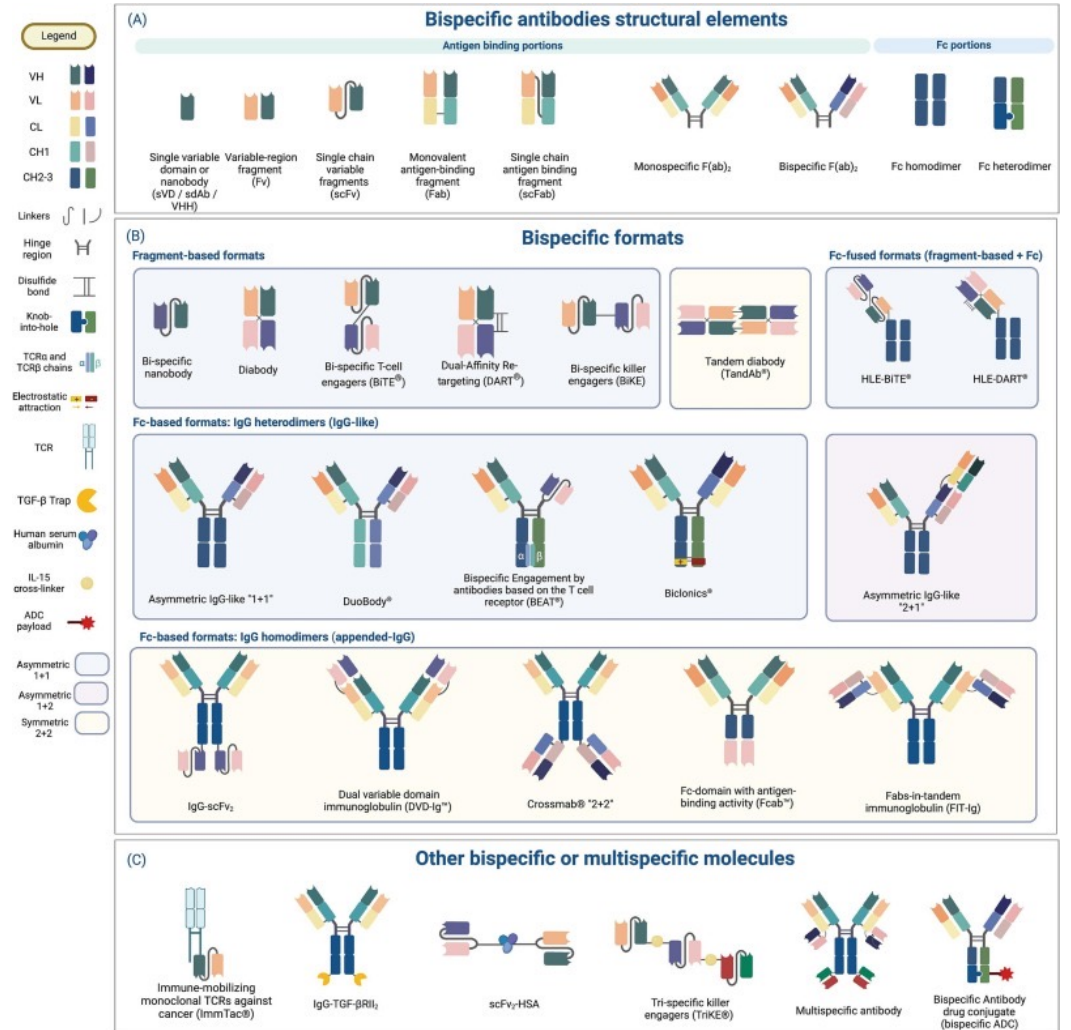
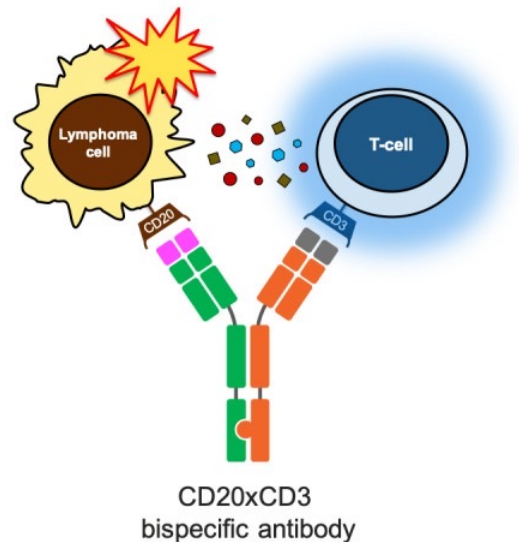
Redirect T-cells to the tumor

Active in many tumors

- Approved in ALL, DLBCL, FL, SCLC
- Highly active in MCL, CLL

All BsAb in B-cell NHL are directed against CD3 / CD20

Many diverse designs



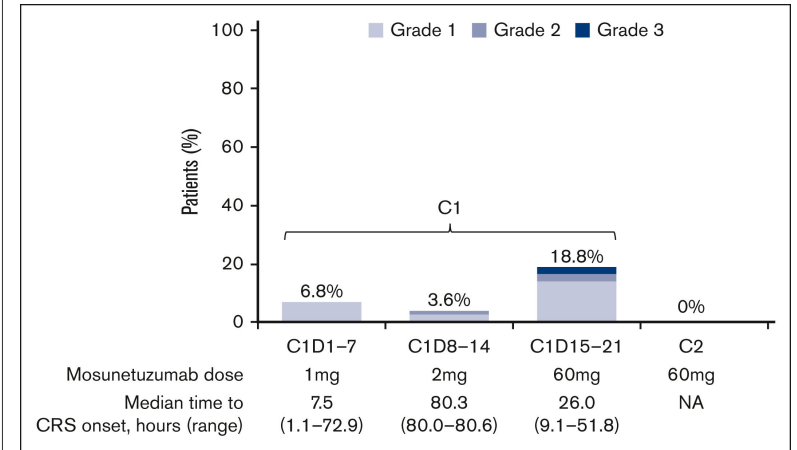
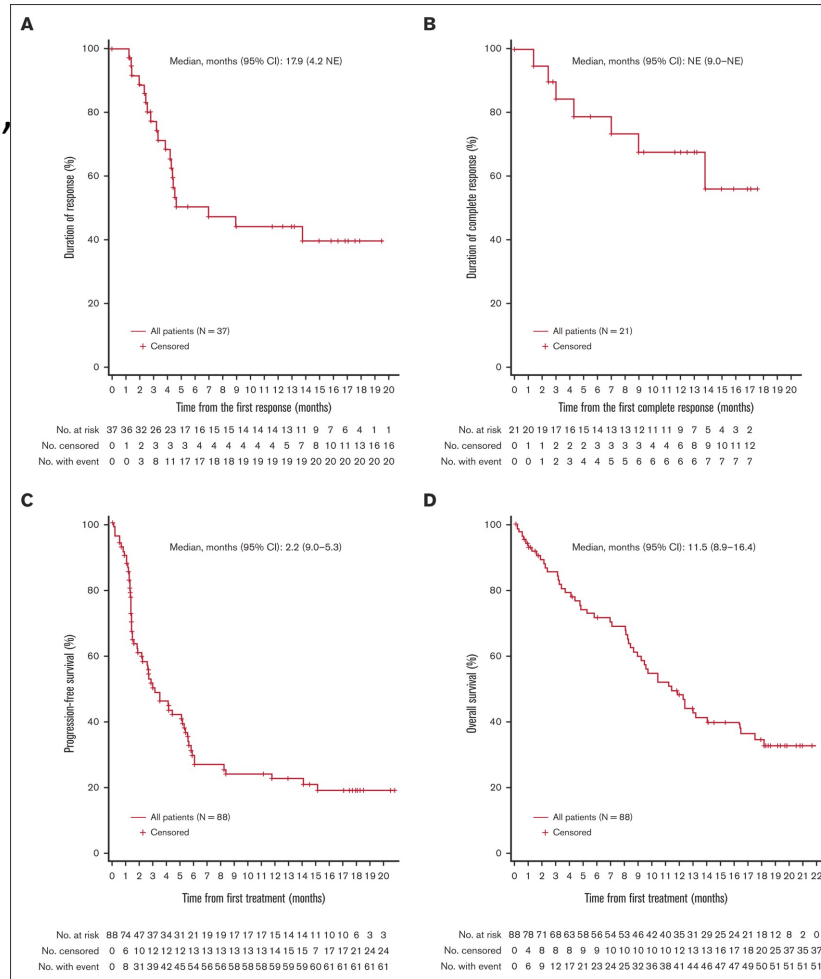
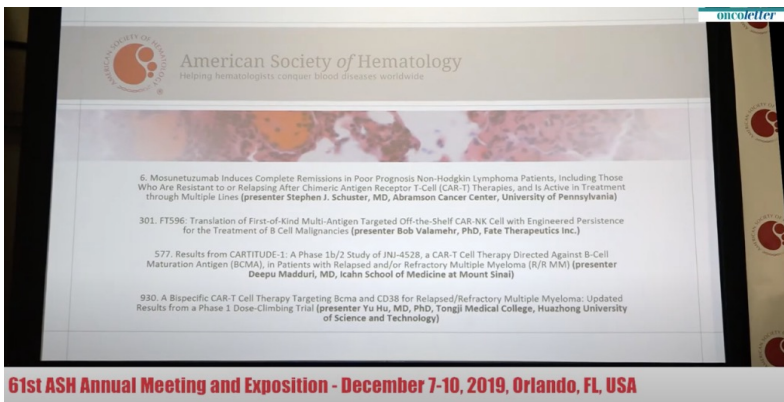
# MOSUNETUZUMAB

## Mosunetuzumab

- In FL: ORR 78%, CR 60%, DOR 36m, median PFS 24m
- In DLBCL: ORR 42%, CR 24% (12% post CAR-T), median PFS 3.2m

3y PFS 10% (Budde LE, JCO 2024).

## Duration of CR not reached in DLBCL

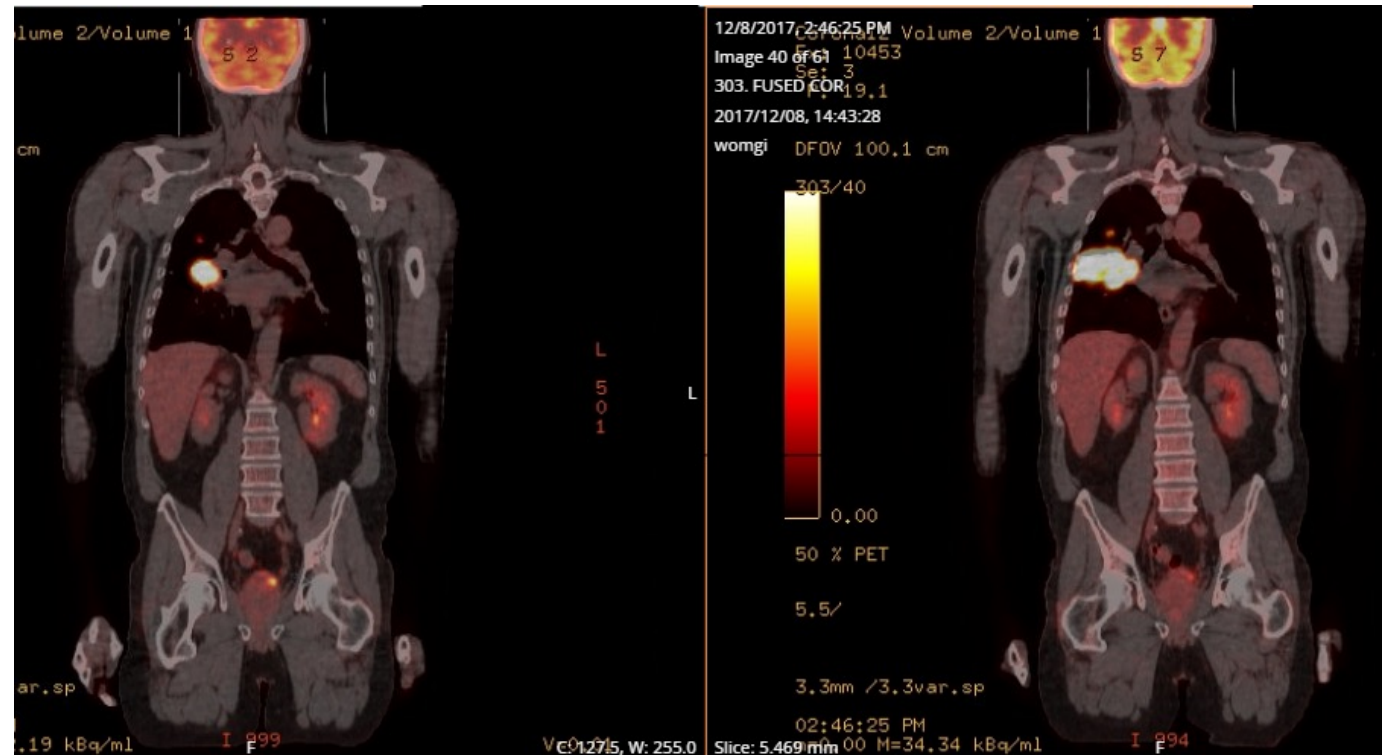


CRS 26% (G3 2%)

Barlett NL, et al. Blood Advances 2023.

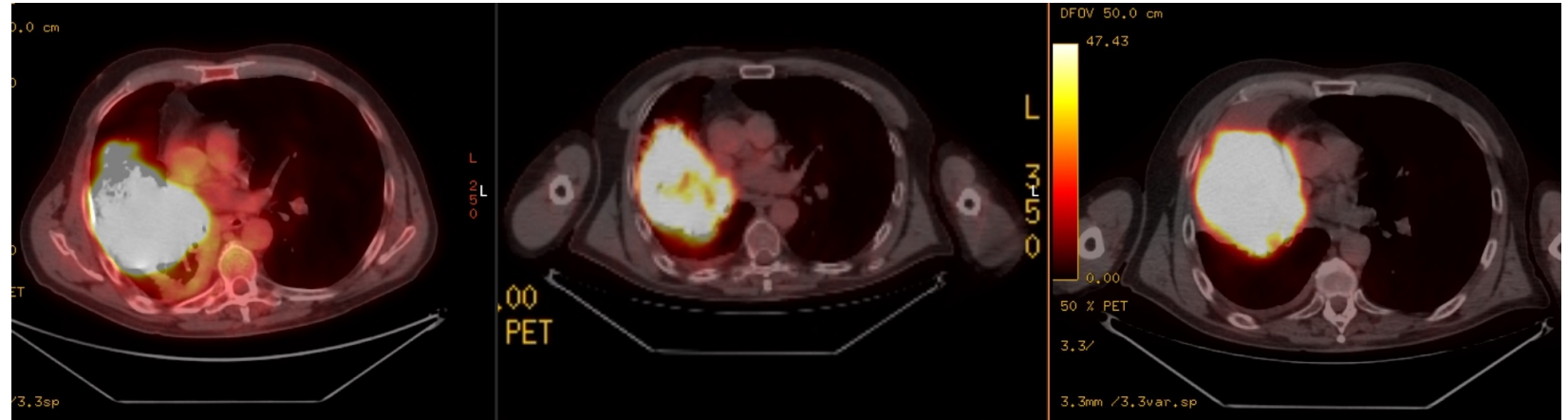
# CLINICAL CASE

- 70yo male with DLBCL, GC subtype with lung primary
  - 2016-12 – 2017-04 – R-CHOP (CR)
  - 2017-09 – Relapse
  - 2017-10– 2017-11 – R-ICE (PD)
  - 2018-02 – Liso-cel



# CLINICAL CASE

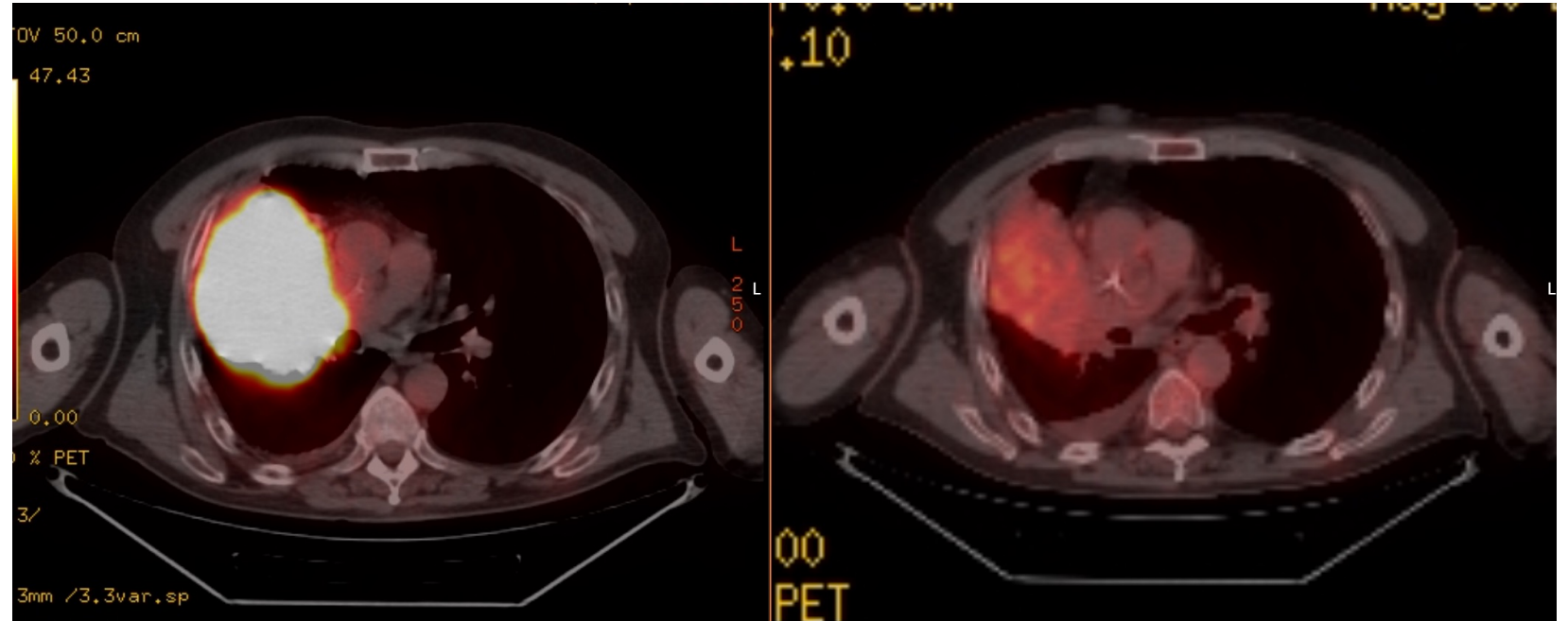
- 1m post CAR-T – no response
- 2m post CAR-T - PD
- Biopsy - DLBCL
  
- 2018-04 – Mosunetuzumab with atezolizumab on trial



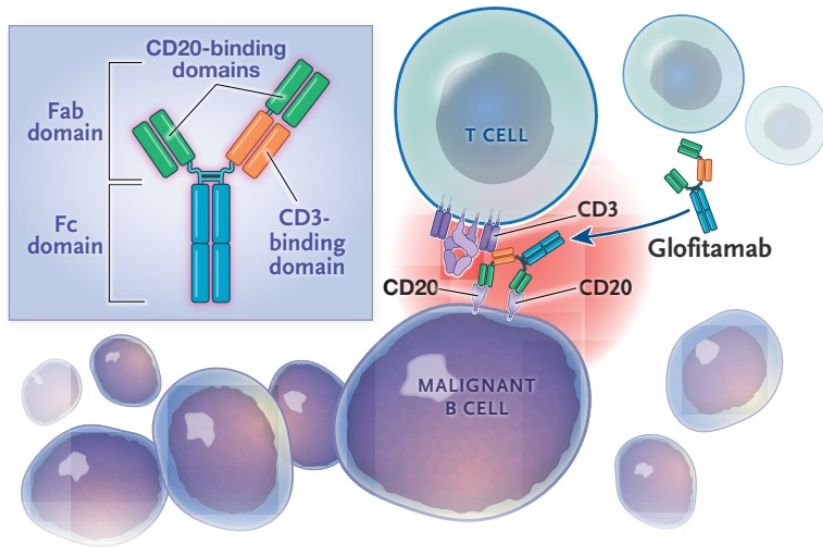
# CLINICAL CASE

- 2018-05 – Biospy – inflammation, no lymphoma
- 2018-12 – Final ciclo de mosunetuzumab – atezolizumab stopped early due to pulmonary toxicity

**2025-01 – Remains in CR!**



# GLOFITAMAB

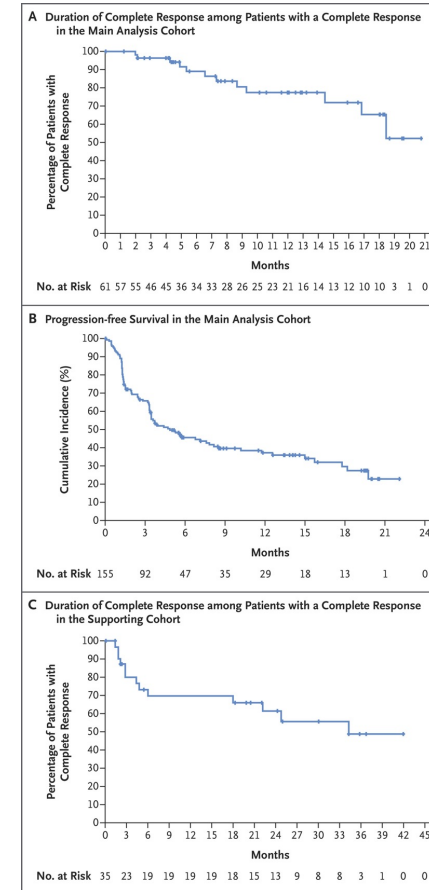


Glofitamab (n=155)

- ORR 52%, CR 39%
- DOR 18.4m

G3+ CRS 4% (all grade 63%)

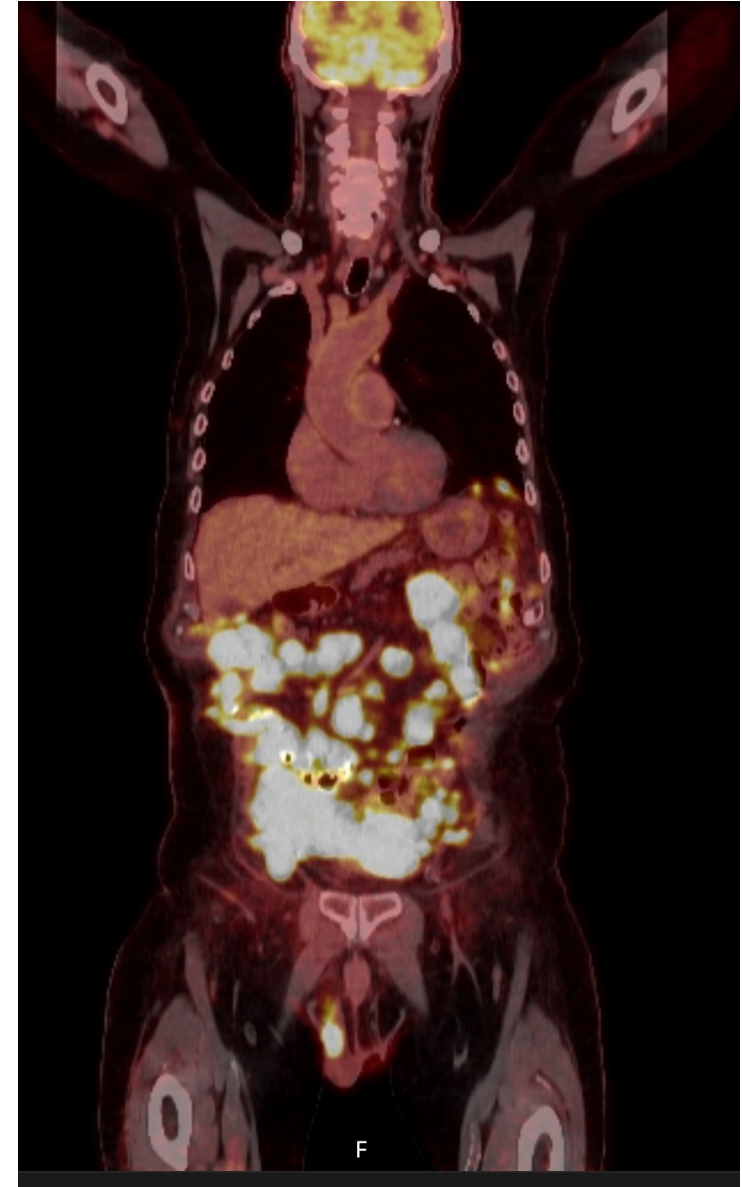
G3+ neurological 3%



Dickinson MJ, et al. NEJM 2022.

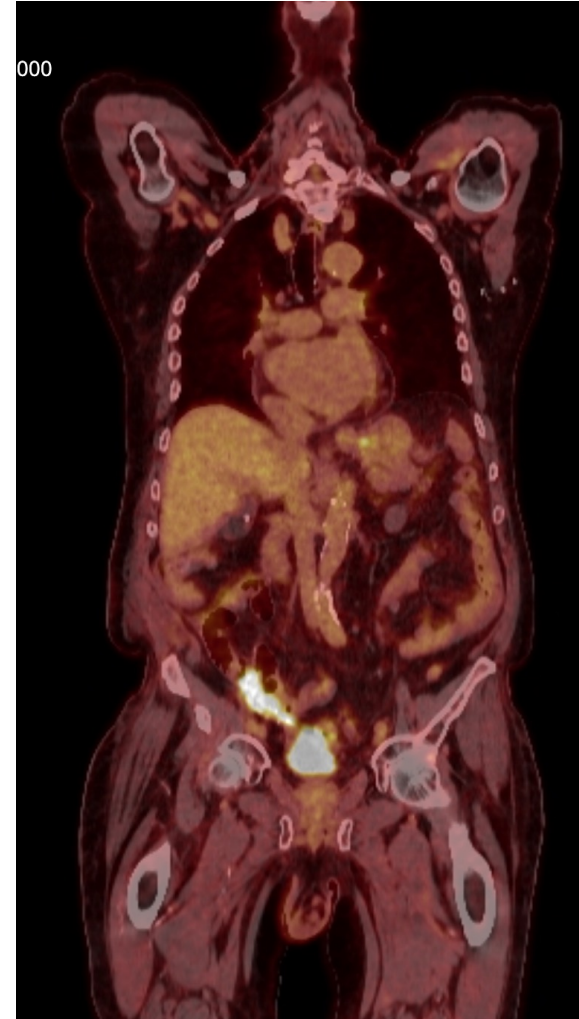
# CLINICAL CASE

- 87yo male with primary gastric DLBCL dx 2018, achieved CR with R-CHOP x 6
- Relapse in 11/2023 with an intestinal perforation
- Consented for a trial of R-GEMOX vs. Mosunetuzumab + polatuzumab vedotin – admitted for tumor lysis syndrome requiring HD.
- Discharged after a few days of cyclophosphamide and high-dose dexamethasone.



# CLINICAL CASE

- 1/24/2024 – Received R-GEMOX
- 2/7/2024 – Received glofitamab with step-up dose #1 (no obinutuzumab priming)
- 4/4/24 – PET/CT scan (PR)
- 10/9/24 – C#12 glofitamab
- 2/12/25 – PET/CT scan (CR)



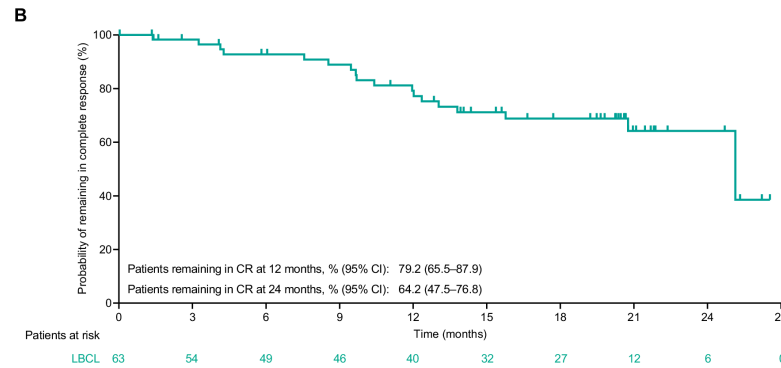
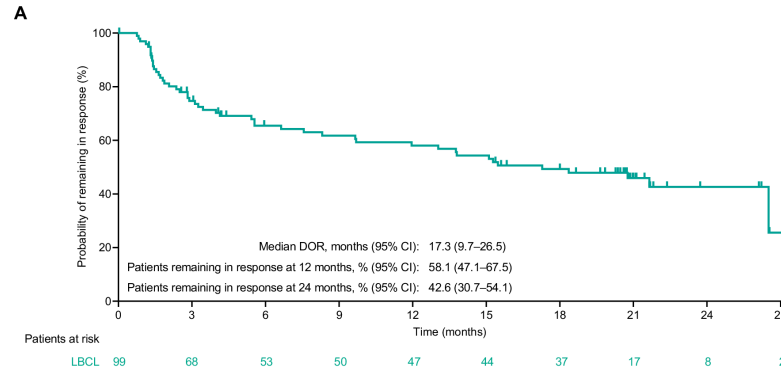
# EPCORITAMAB

## Epcoritamab

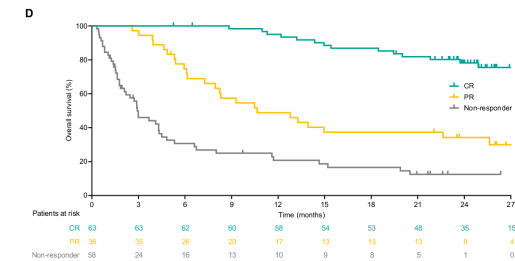
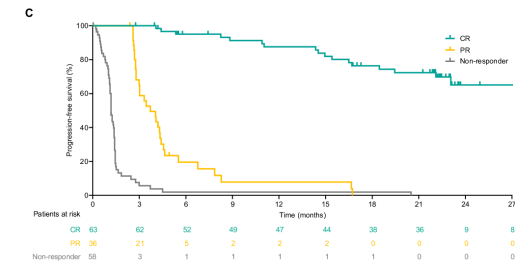
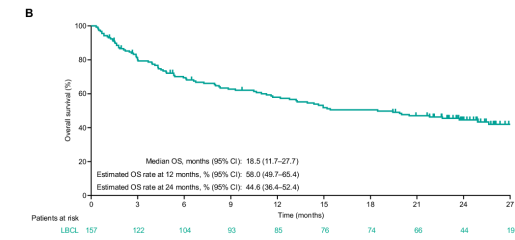
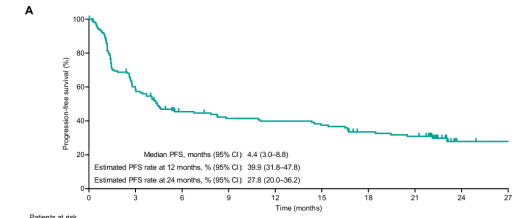
- ORR 63%, CR 40%
- DOR 17.3m

G3+ CRS 3% (all grade 51%)

G3+ ICANS 1%



Thieblemont C, et al. Leukemia 2024.



Thieblemont C, et al. Leukemia 2024.

# MOSUNETUZUMAB + POLATUZUMAB VEDOTIN

Non-overlapping toxicities and distinct mechanisms

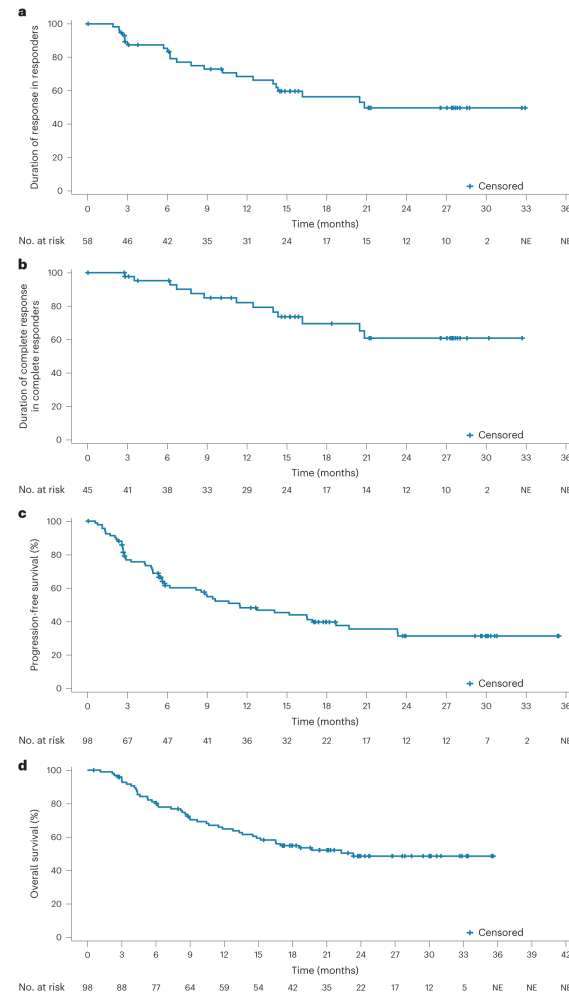
- Both B-cell targeting but in different ways

ORR 59%, CR 46%

CRS 17% (G3 2%)

ICANS 5%

25% G3+ neutropenia



Budde LE, et al. Nature Medicine 2024.

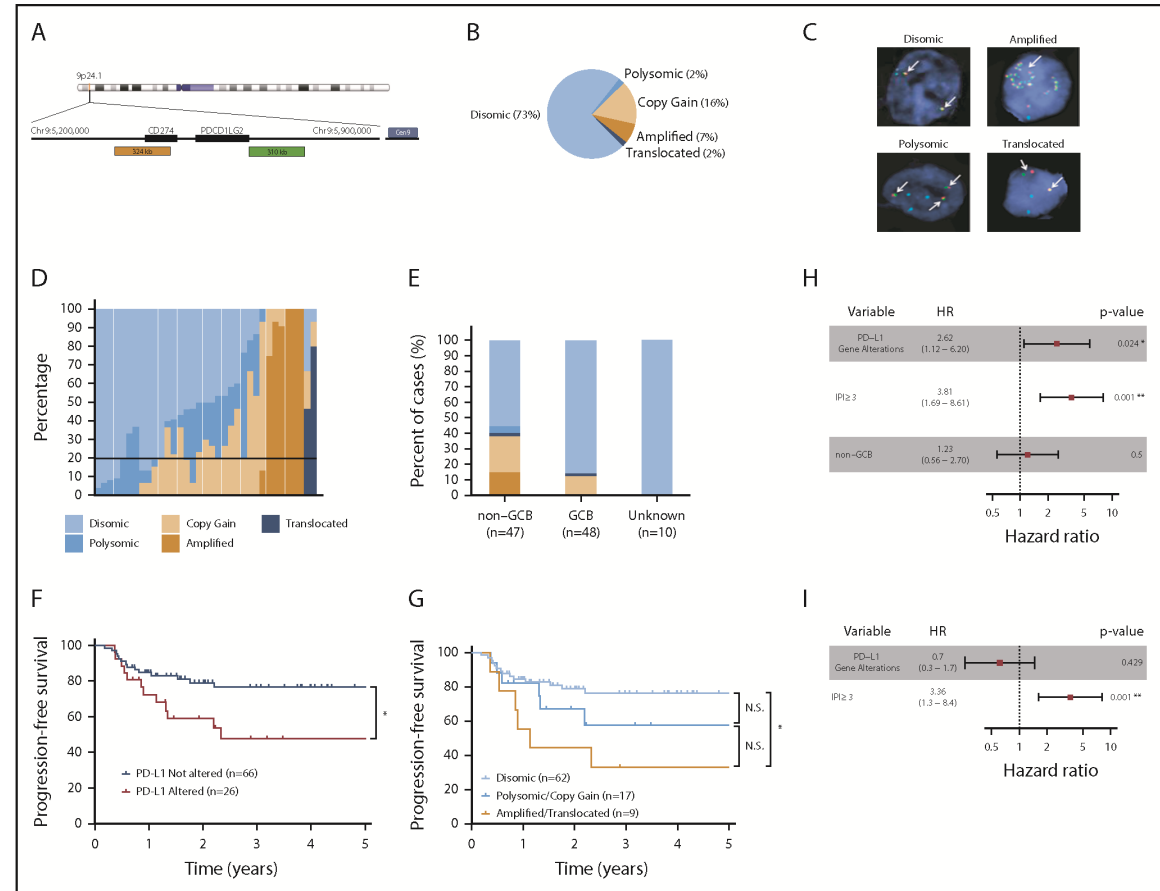
# PD-1 IN DLBCL

## PD-L1 alterations in DLBCL

- 45% in non-GC, 15% in GC
- More aggressive, worse prognosis with R-CHOP
- Over-expression of PD-L1

**Worse response with CAR-T (Jain MD Blood 2021)**

However, these can respond to PD-1 blockade (Godfrey J, Blood 2019).

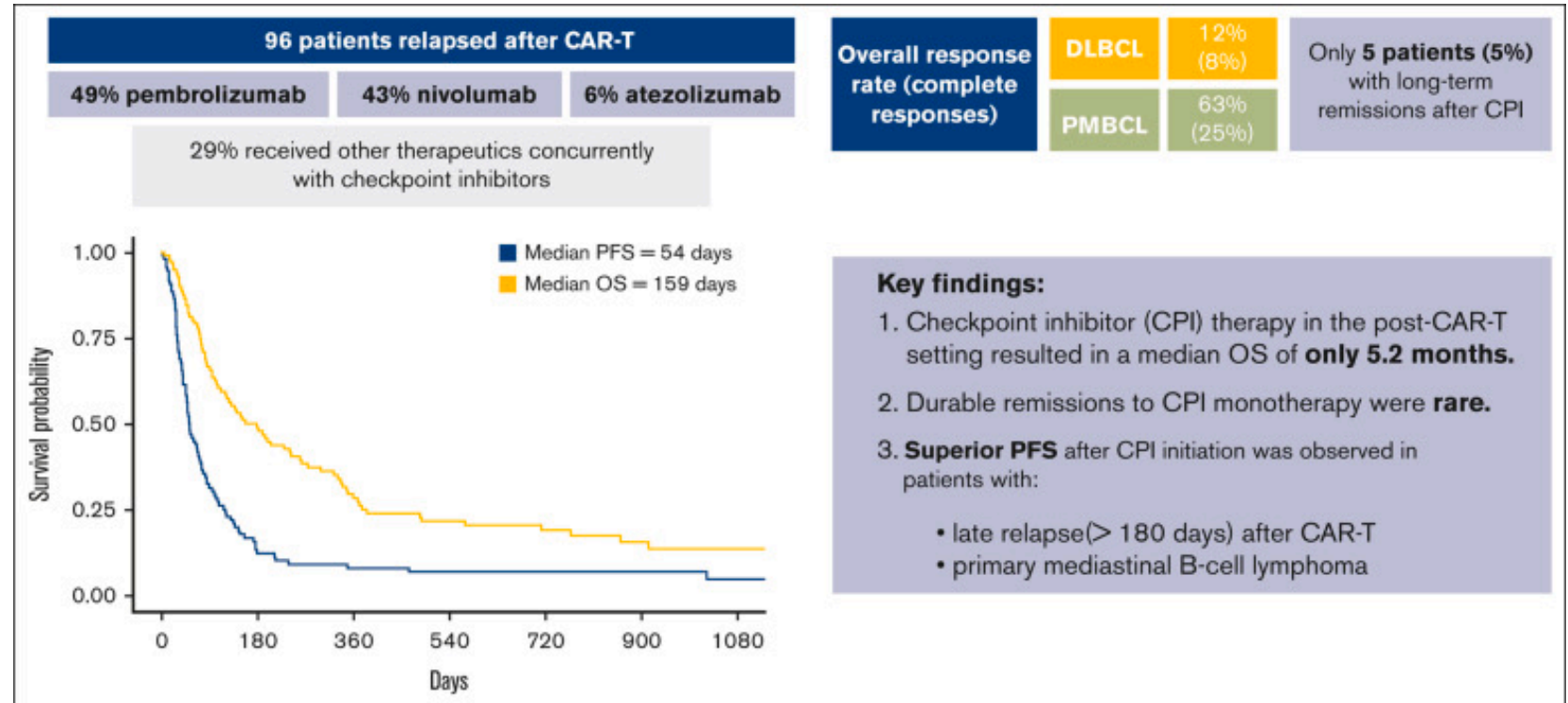


Godfrey J, et al. Blood 2019.

# PD-1 in DLBCL

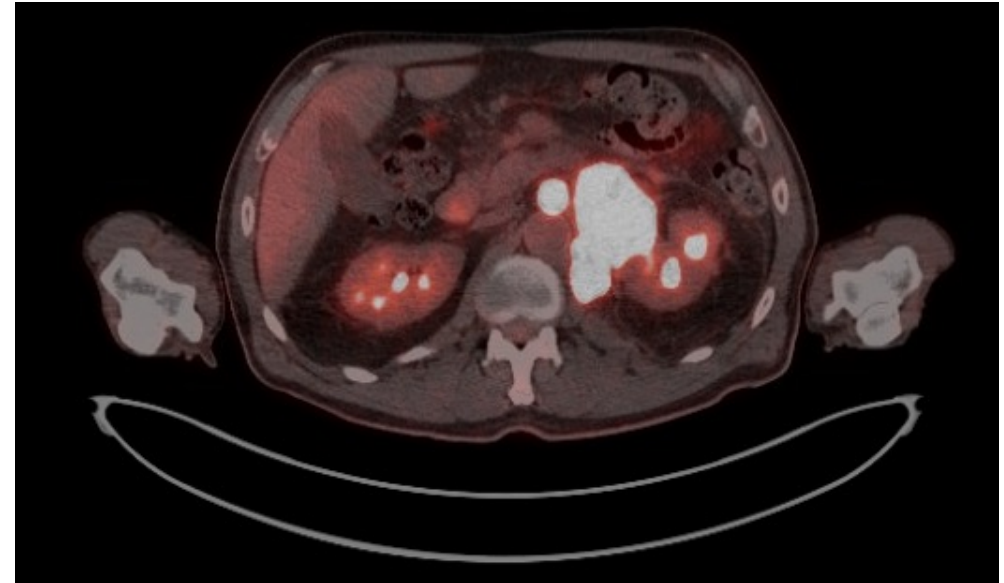
Limited efficacy post CAR-T  
- 12% ORR (8% CR) when given post CAR-T (excluding PMBCL)

But – occasionally patients can be salvaged with this approach!



# CLINICAL CASE

- 69yo male with DLBCL, non-GC subtype
  - 2020-11 – 2021-03 - DA-R-EPOCH x 1 + R-CHOP x 5 (CR)
  - 2021-07 – Relapse
  - 2021-08 – 2021-09 Polatuzumab vedotin + R-ICE x 3 (CR)
  - 2021-11 – Relapse
  - 2021-12 – Apheresis for axi-cel
  - Hospitalized for COVID-19
  - 2022-01 – Ibrutinib bridging (no response)
  - 2022-02– Axi-cel – PR at 1m, PD at 2m



PET-CT 28 Abr 2024, 2m post CAR-T

# CLINICAL CASE

- 2022-05 – IGM-2323 (CD20 BsAb) - progression

## Final Diagnosis

- A. SOFT TISSUE, PERINEPHRIC MASS, CORE NEEDLE BIOPSY FRAGMENTS:  
 - Diffuse large B-cell lymphoma, non-germinal center phenotype (B-DLCL-NOS)

Electronically signed by Karl K Gaal, MD on 5/10/2022 at 1801

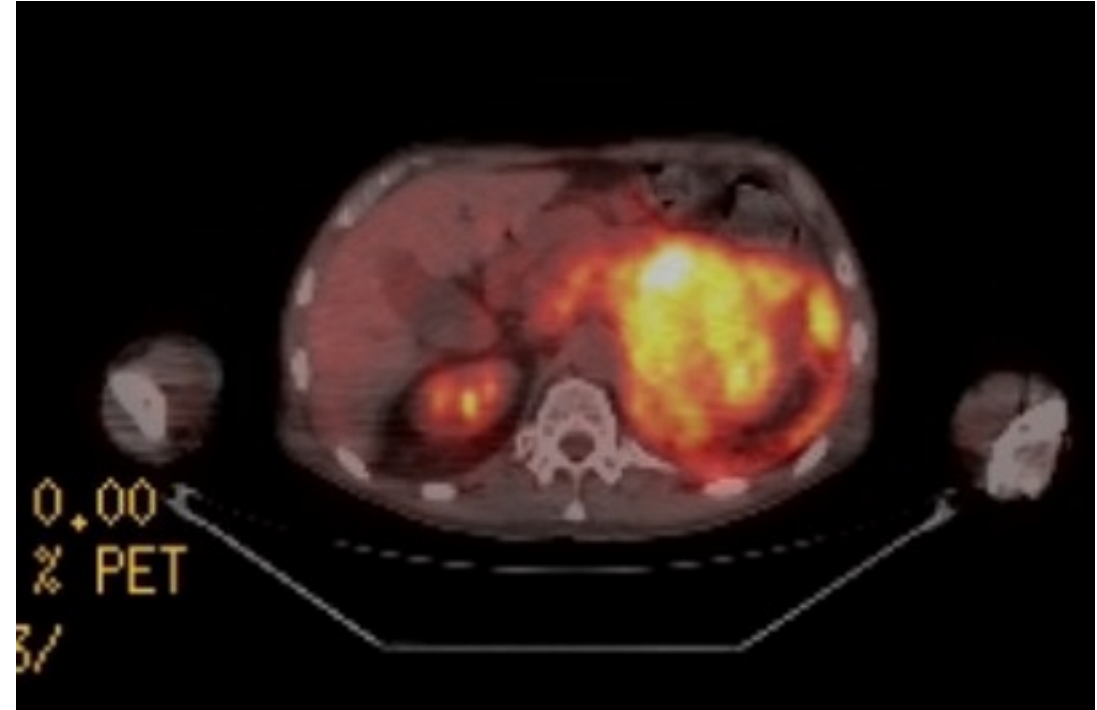
## Microscopic Description

Histologic sections show multiple tissue fragments with infiltration by large atypical lymphocytes with vesicular chromatin, irregular nuclear borders, prominent nucleoli and abundant cytoplasm. There are also increased intracytoplasmic and possibly extracellular dense eosinophilic globular material noted, likely inspissated immunoglobulin.

Immunohistochemistry report:

Lymphoma cells;

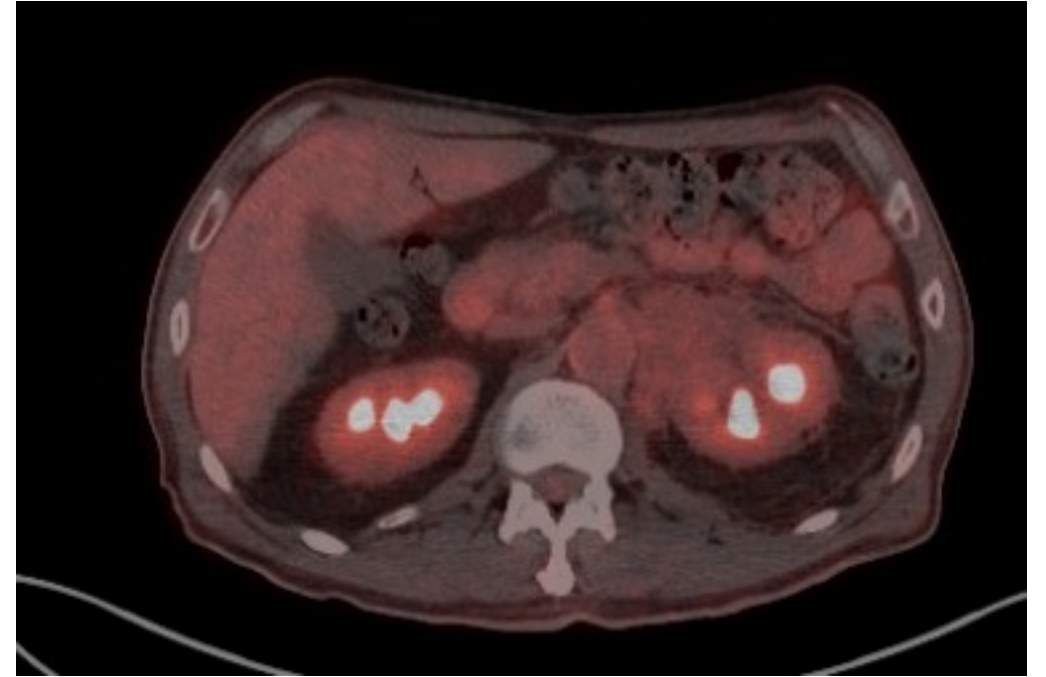
| B cell markers |   | T cell markers |   | Other markers: |                       |
|----------------|---|----------------|---|----------------|-----------------------|
| CD20           | + | CD3            | - | CD10           | -                     |
| CD19           | + |                |   | BCL6           | +                     |
| CD79A          | + |                |   | BCL2           | +                     |
|                |   |                |   | MUM1           | +                     |
|                |   |                |   | Cmyc           | - (<30%)              |
|                |   |                |   | CD30           | - (0%)                |
|                |   |                |   | Ki67           | +, 70%                |
|                |   |                |   | Kappa          | +,                    |
|                |   |                |   |                | eosinophilic globules |
|                |   |                |   | Lambda         | -                     |
|                |   |                |   | PD-L1          | +, 100%, 3+           |



PET-CT 28 Jun 2024 post IgM-2323 x 2 rounds

# CLINICAL CASE

- 2022-06 - 2024-07 – Pembrolizumab 200 mg q21d
- 2024-07-present – Observation.

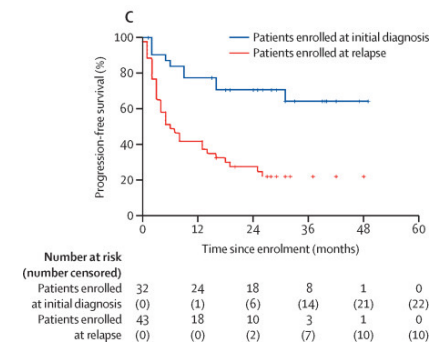
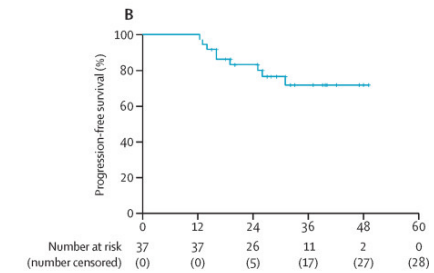
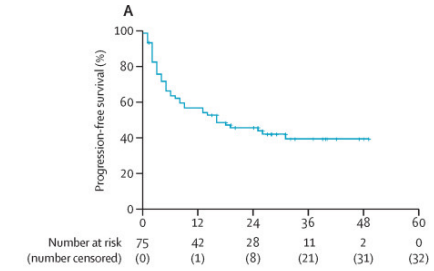
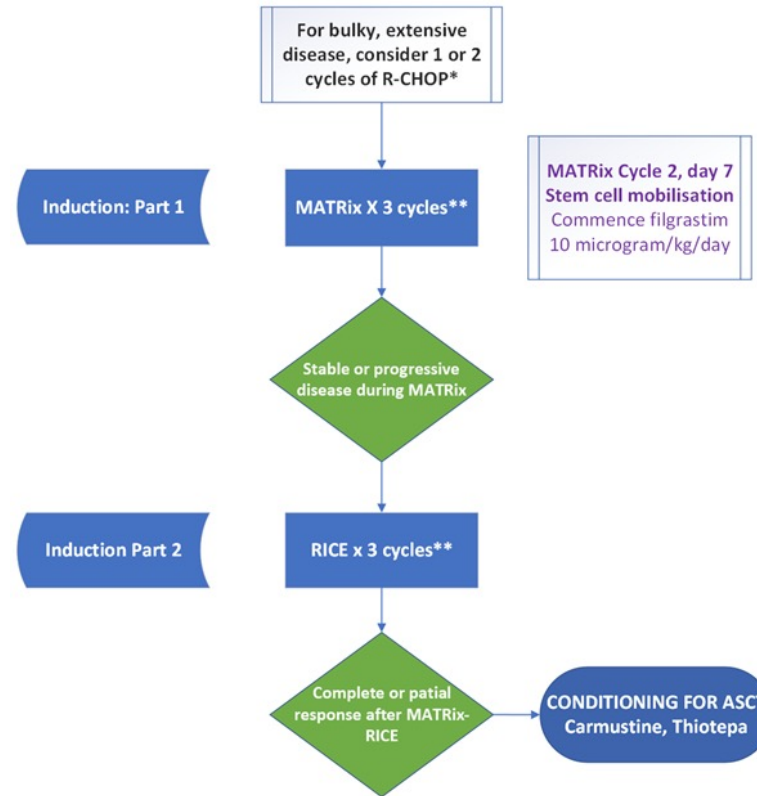


PET-CT 19 OCT 2022

# SCNSL

## Chemo (HD-MTX-based)

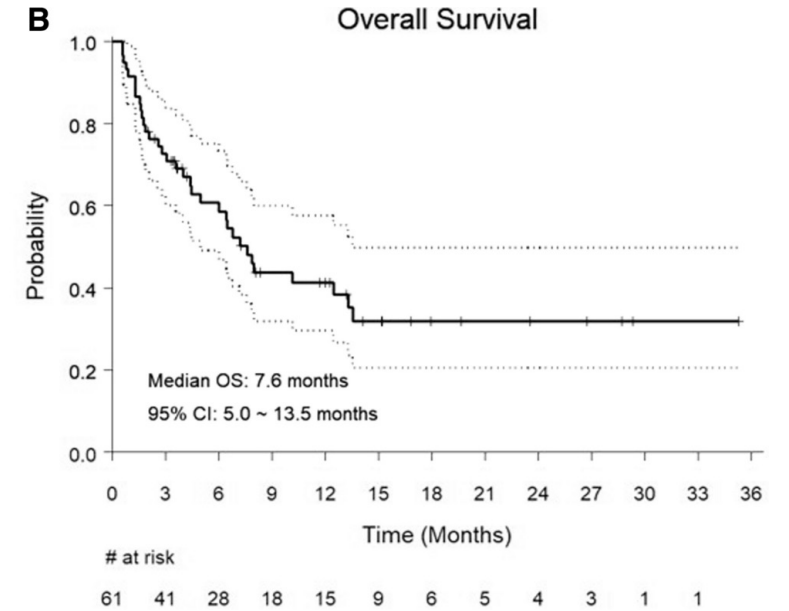
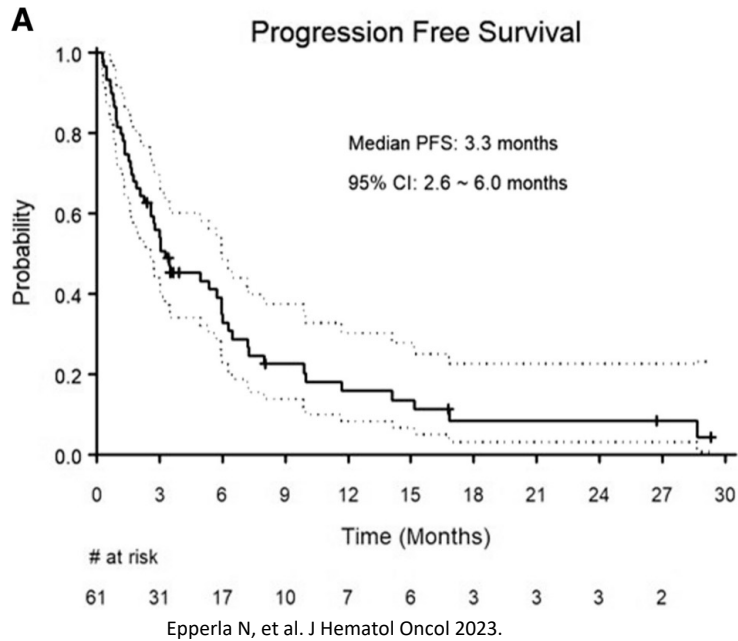
- AutoHCT can be curative
- HD-MTX-based therapy (MATRix, MTR, etc)
- Refractory dz to HD-MTX is very difficult to savage



Ferreri A, et al. Lancet Haem 2021.

# SCNSL

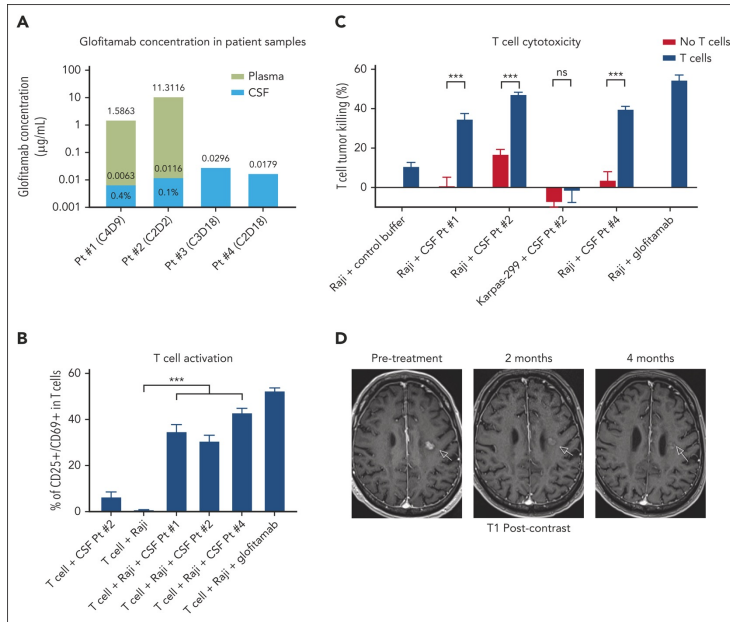
- **CAR-T in SCNSL disappointing**
  - CR 57%
  - 12m PFS 16%
  - Median PFS 3.3m
- Lenalidomide, iBTK with brief responses



# SCNSL

Glofitamab crosses the BBB (CSF concentration 0.1%-0.4% of plasma, similar to R)

Potentially active in SCNSL (Godfrey J et al. Blood 2024).



| Characteristic                | Patient 1  | Patient 2   | Patient 3   | Patient 4   |
|-------------------------------|--|---|---|---|
| Age, y                        | 82   | 56  | 40  | 41  |
| Sex                           | M  | F   | F   | F   |
| No. of lines of prior therapy | 4  | 4   | 4   | 5   |
| Prior therapies               | 1. R-miniCHOP<br>2. Lenalidomide<br>3. Focal RT<br>4. Lisocabtagene maraleucel | 1. R-CHOP<br>2. High-dose MTX<br>3. R-GDP<br>4. Axicabtagene ciloleucel   | 1. R-HyperCVAD<br>2. WBRT<br>3. AVM0703<br>4. Lisocabtagene maraleucel  | 1. R-CHOP<br>2. HyperCVAD<br>3. WBRT<br>4. R-GemOx<br>5. Lisocabtagene maraleucel |
| Sites of disease              | CNS parenchyma   | Bone, leptomeninges, and CSF  | CNS parenchyma  | CNS parenchyma and cranial nerves   |
| Concomitant therapies         | None   | Obinutuzumab pretreatment and intrathecal MTX   | Obinutuzumab pretreatment, focal RT, corticosteroids, and acalabrutinib | Focal RT, corticosteroids, and acalabrutinib                                      |
| Timing of CSF collection      | 9 d after C4D1   | 16 h after C2D1   | 18 d after C3D1   | 18 d after C2D1   |
| CRS or ICANS                  | Gr 2 CRS after C1D1  | Gr 1 CRS after C1D8   | No  | No  |
| No. of glofitamab cycles      | ≥8   | ≥6  | ≥7  | 2   |
| Glofitamab response           | PR   | CR  | PR  | PD  |
| CSF cellular composition      | NA   | Preglofitamab:<br>29 leukocytes/µL<br>12 lymphocytes/µL<br>42% lymphoma cells<br>3 d postglofitamab:<br>366 leukocytes/µL<br>48 lymphocytes/µL<br>3% lymphoma cells | NA  | NA  |

# Thank you!

[mamei@coh.org](mailto:mamei@coh.org)

+1 6267592562