SESSION IV: NEW PERSPECTIVES IN R/R DLBCL

Chairmen: C. Califano (Pagani-SA), M. Picardi (Napoli)

COACHES

Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

Emerging drugs in RR-DLBCL

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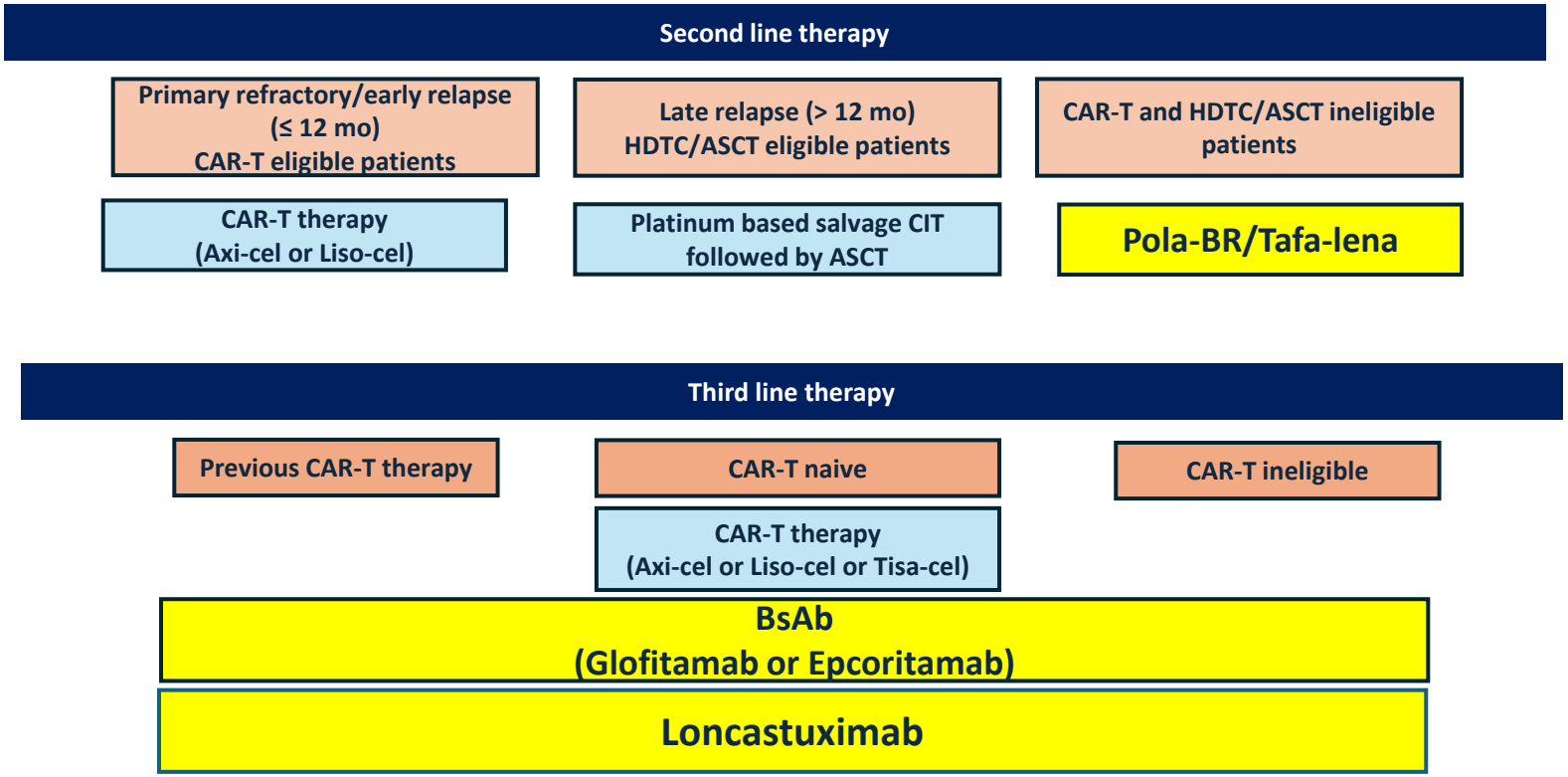
Ematologia Università Sapienza Roma

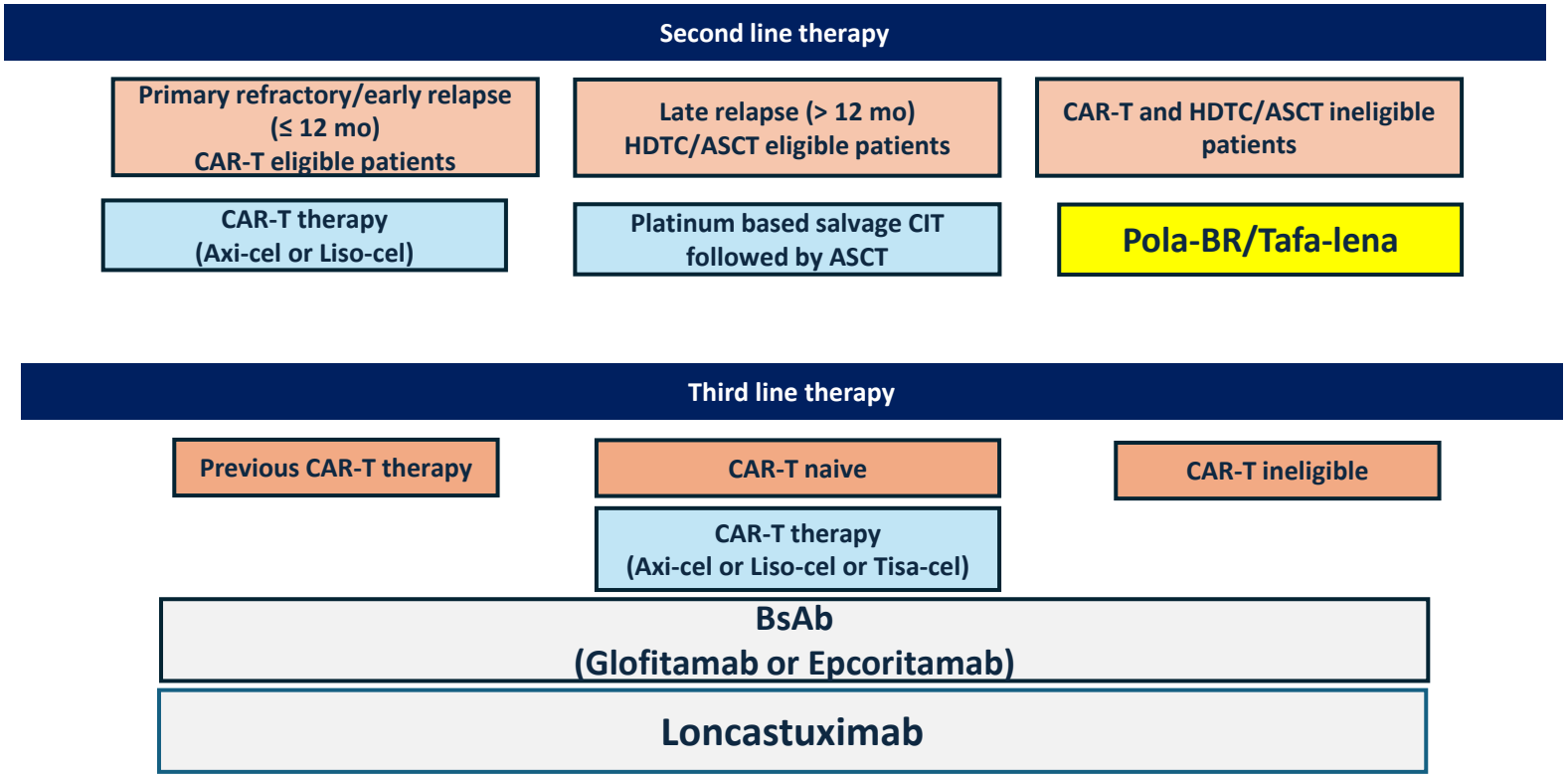
Disclosures of Maurizio Martelli

Company name	Researh support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Gilead					X	X	
Novartis					X	X	
Takeda					X	X	
Abbvie					X	X	
Incyte	X				X	X	
Janssen					X	X	
BMS					X	X	
Beigene					X	X	
Eli Lilly					X	X	

RR- DLBCL: patients journey in the era of novel drug

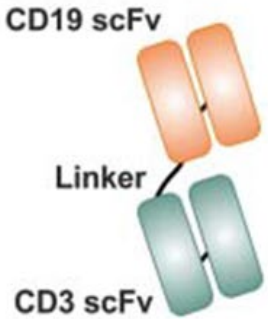


RR- DLBCL: patients journey in the era of novel drug

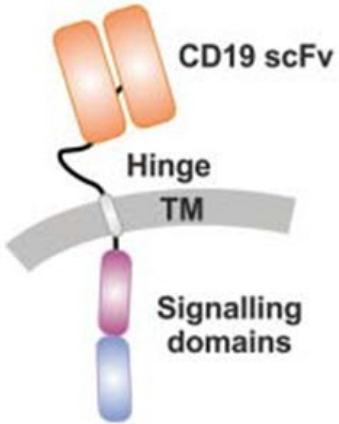


Multiple Targeting anti CD19 strategies

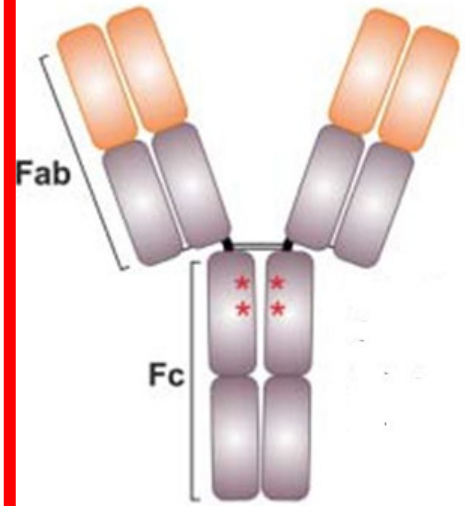
BLINATUMOMAB (BITE)



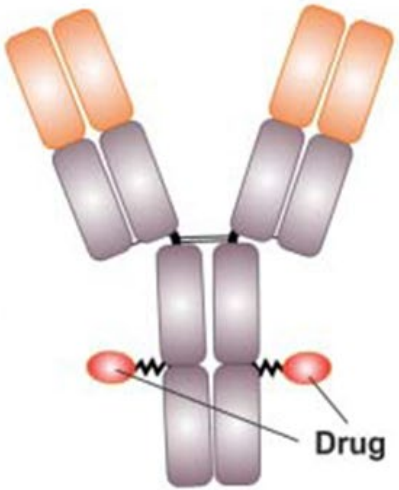
CAR-T cells



TAFASITAMAB (engineered Ab)

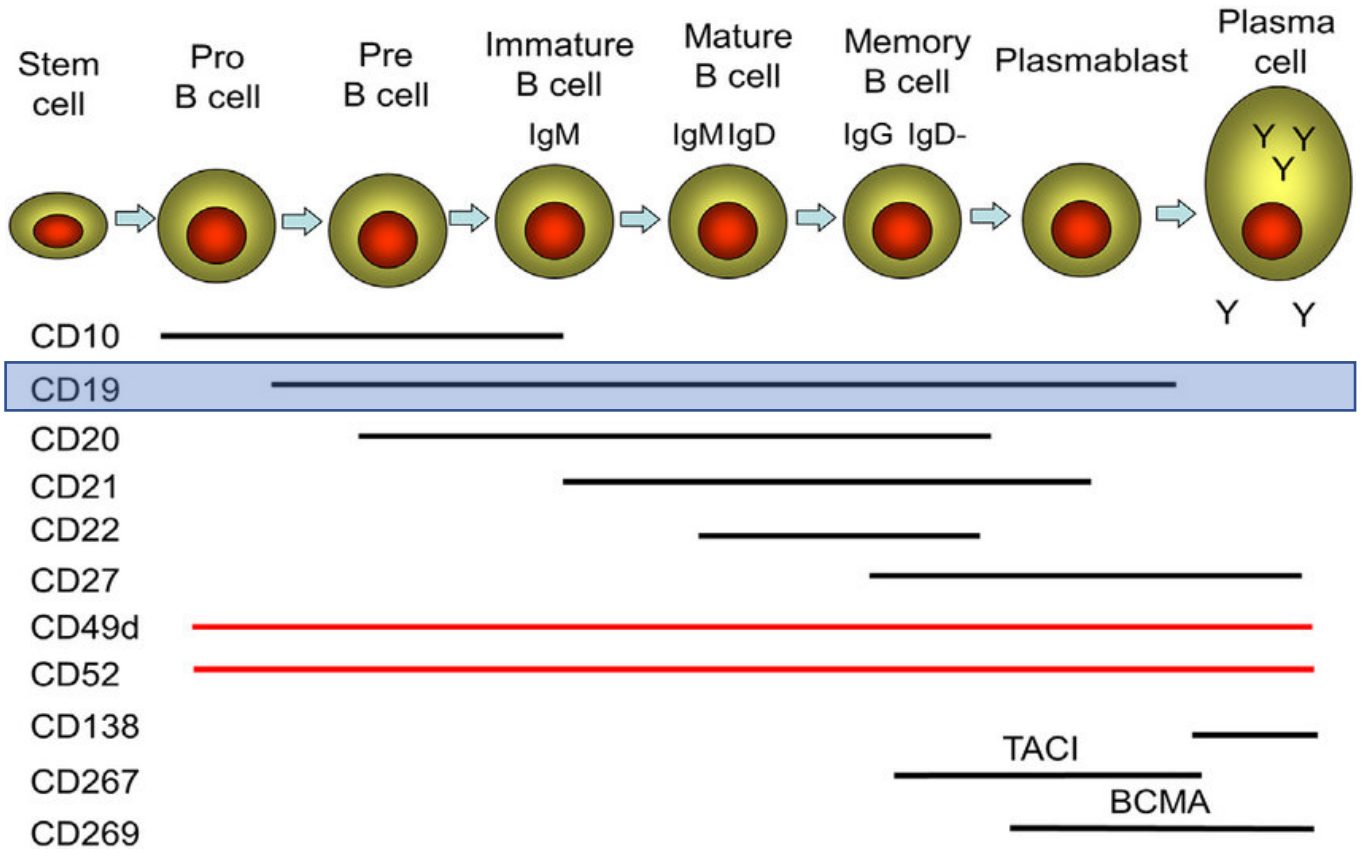


LONCASTUXIMAB TESIRINE (ADC)



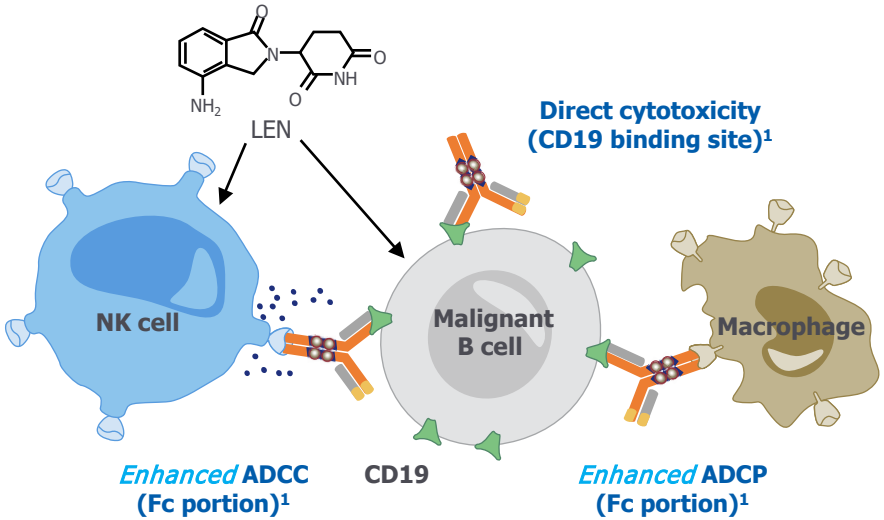
Kellner et al., Oncoimmunol 2018.

CD19 expression in B cells



Baker et al, Lancet Disc Sci 2017

Tafasitamab & lenalidomide : rationale for a sinergistic activity



Tafasitamab (Fc-enhanced, anti-CD19 mAb)[1–3]

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

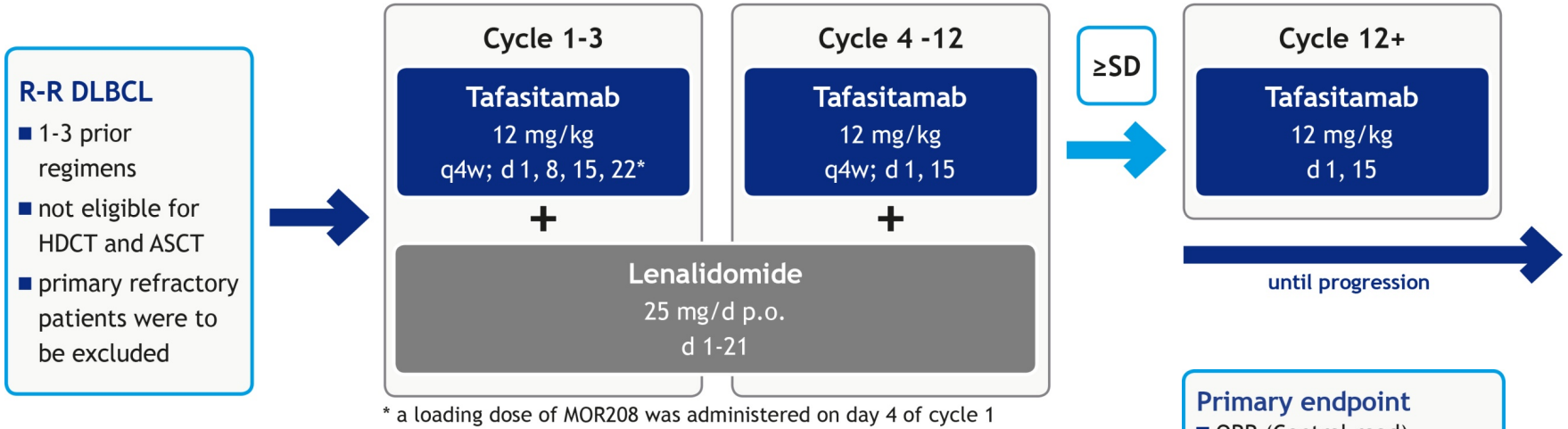
LEN[4,5]

- T-cell and NK-cell activation/expansion
- Direct cell death
- Well-studied as an antilymphoma agent, alone or in combination

The L-MIND trial provided clinical evidence supporting the efficacy and synergy of the combination of tafasitamab and lenalidomide in which **the affinity of tafasitamab for both effector and target cells is magnified by the immunomodulating effects of lenalidomide** (such as stimulation of NK cell proliferation, as well as activation and enhancement of NK-mediated ADCC)[6]

L-MIND: study design

phase 2 single arm open label multicenter study (NCT 02399085)



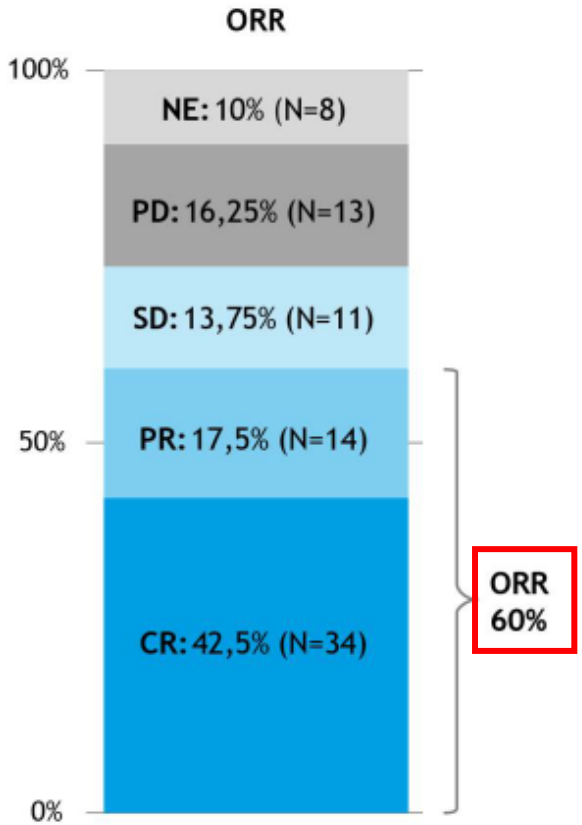
- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

Primary endpoint
- ORR (Central read)

Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

Salles G et al. Lancet Oncology 2020

Primary end point: ORR by IRC (81pts)



- ORR 60.0% (95% CI 48.4% - 70.8%)
- CR-rate 42.5%
  - 82% of CRs PET-confirmed
  - 18% of CRs based on CT only

N=80: full analysis set → patients receiving at least one dose of tafasitamab and LEN

NE due to missing post-baseline tumor assessment

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

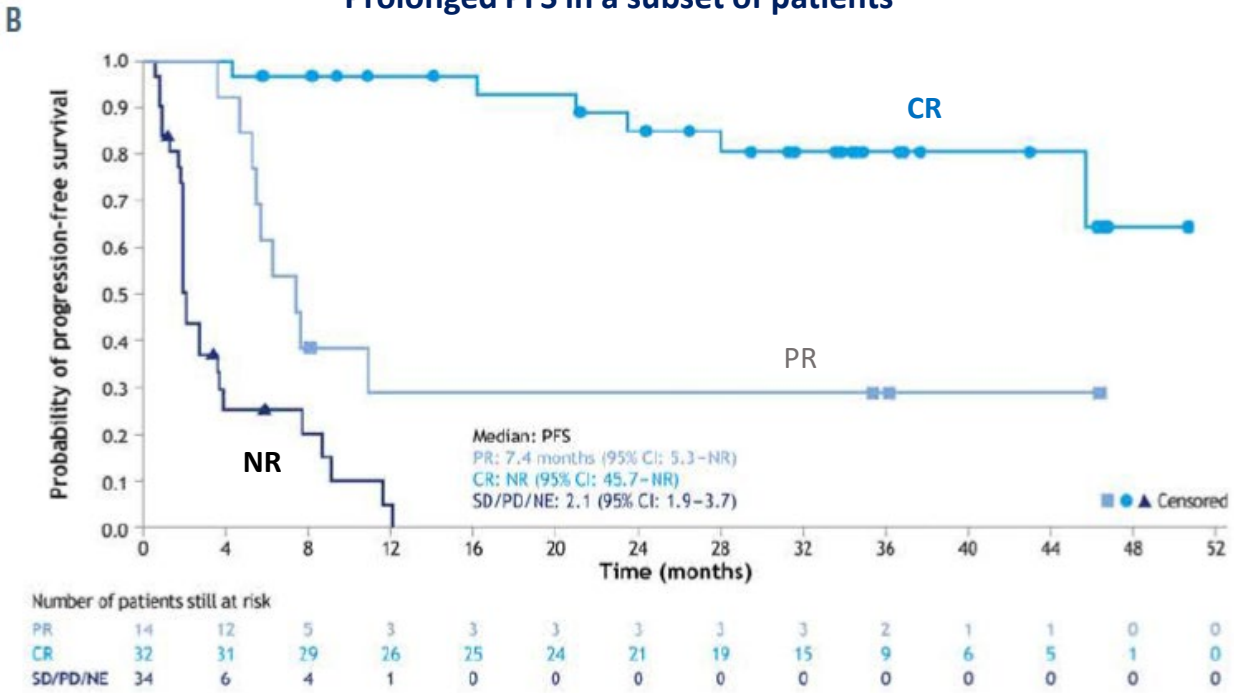
Salles G et al. Lancet Oncology 2020

Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma

Ferrata Storti Foundation

Haematologica 2021
Volume 106(9):2417-2426

Prolonged PFS in a subset of patients



Duell J. et al Haematologica 2021

blood

LETTER | SEPTEMBER 22, 2023

Tafasitamab and lenalidomide in large B cell lymphoma: real-world outcomes in a multicenter retrospective study

Clinical Trials & Observations

David A Qualls, Nicholas Lambert, Paolo F. Caimi, Mwanasha H Merrill, Priyanka Pullarkat, Richard C. Godby, David A Bond, Graham T Wehmeyer, Jason T. Romancik, Behzad Amoozgar, Lori A. Leslie, Loretta J Nastoupil, Jennifer L. Crombie, Jeremy S Abramson, Arushi Khurana, Grzegorz S. Nowakowski, Kami J Maddocks, Sarah C. Rutherford, Brad S Kahl, Michelle Okwali, Michael J Buege, Venkatraman E Seshan, Connie L. Batlevi, Gilles A. Salles

Patients characteristics and prior treatments

Patient and Disease

Characteristic	TLOC cohort	L-MIND trial
Number of patients	157	81
Female sex	51%	46%
Age (yrs), median (range)	75 (26-94)	72 (41-86)
Race		
White, all ethnicity	89%	89%
Asian	6%	2%
Other/Unknown	5%	1%
Diagnosis		
DLBCL, NOS	59%	89%
Transformed	23%	9%
HGBCL (Double/Triple Hit)	15%	2%
Other	3%	0%
Cell of Origin (Hans)		
GCB	57%	47%
non-GCB	34%	26%
Unknown	10%	27%
Risk (IPI)		
0-2	28%	49%
3-5	72%	51%
Ann Arbor Stage		
I-II	10%	25%
III-IV	90%	75%

Prior Treatment

Characteristic	TLOC	L-MIND
Prior lines of therapy for DLBCL		
Median (range)	2 (0-11)	2 (1-4)
0	4%*	0%
1	29%	49%
2	30%	43%
3	16%	6%
4	6%	1%
≥5	16%	0 (0)
Primary Refractory	51%	18%
Refractory to last therapy	66%	44%
Prior SCT	13%	11%
Prior CAR T	28%	0%

*5 patients with transformed lymphoma; all had received prior treatment for indolent lymphoma.

L-MIND Eligible: 11%

Reasons for L-MIND ineligibility:

- EGFR < 60 ml/min 33%
- Prior anti-CD19 therapy 28%
- >3 prior lines of therapy 23%
- ECOG PS 3-4 18%
- High-grade B cell lymphoma 15%

131 (89%) were ineligible, and 116 (78%) were still ineligible if laboratory values were not considered.

All about patient selection

✓ 90% did not meet L-mind eligibility criteria

→ Patient related outcome

a) more lines of therapy
b) prior CAR T
c) ECOG>3
d) GFR

→ Disease related outcome

a) higher IPI
b) >Stage III/IV
c) Primary refractory
d) HGBL

L-MIND Eligible: 11

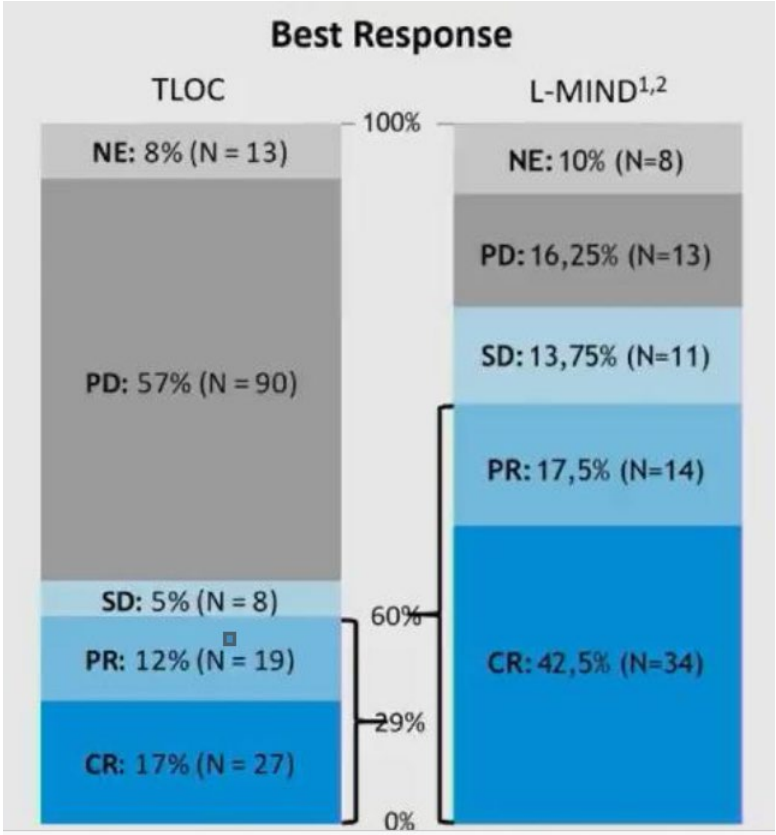
Reasons for L-MIND ineligibility:

- EGFR < 60 ml/min
- Prior anti-CD19 therapy
- >3 prior lines of therapy
- ECOG PS 3-4
- High-grade B cell lymphoma

Quall D. A.et al ASH 2022, Blood 2023

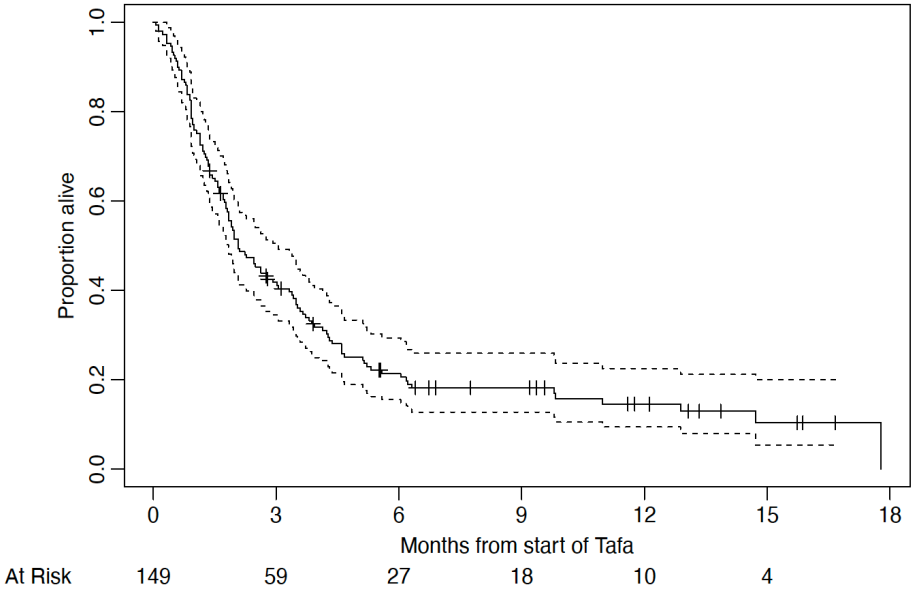
Treatment exposure and response

Treatment	
Time on treatment	
Median (IQR), days	59 (28 - 118)
Lenalidomide treatment timing	
Patients with delay in initiation	46%
Median delay time, days (IQR)	7 (4-20)
Starting daily lenalidomide dose (L-MIND: 25 mg)	
Patients with dose reduction at initiation	66%
Median starting dose, mg (IQR)	20 (10-25)
Reasons for initial lenalidomide reduction	
Frailty/Performance status	43%
Renal dysfunction	35%
Cytopenias	10%
Other/unknown	12%

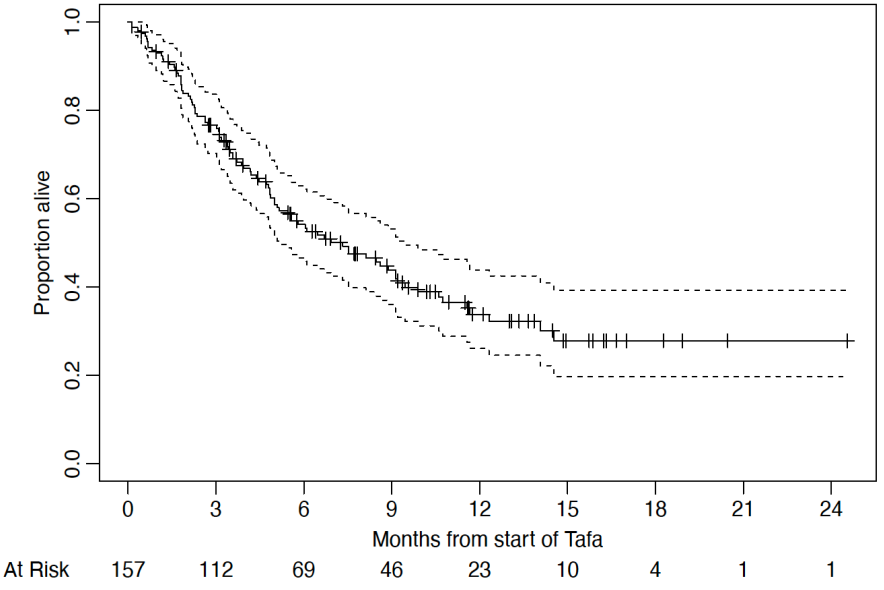


Quall D. A.et al ASH 2022, Blood 2023

Tafa-Lena US Real World Survival



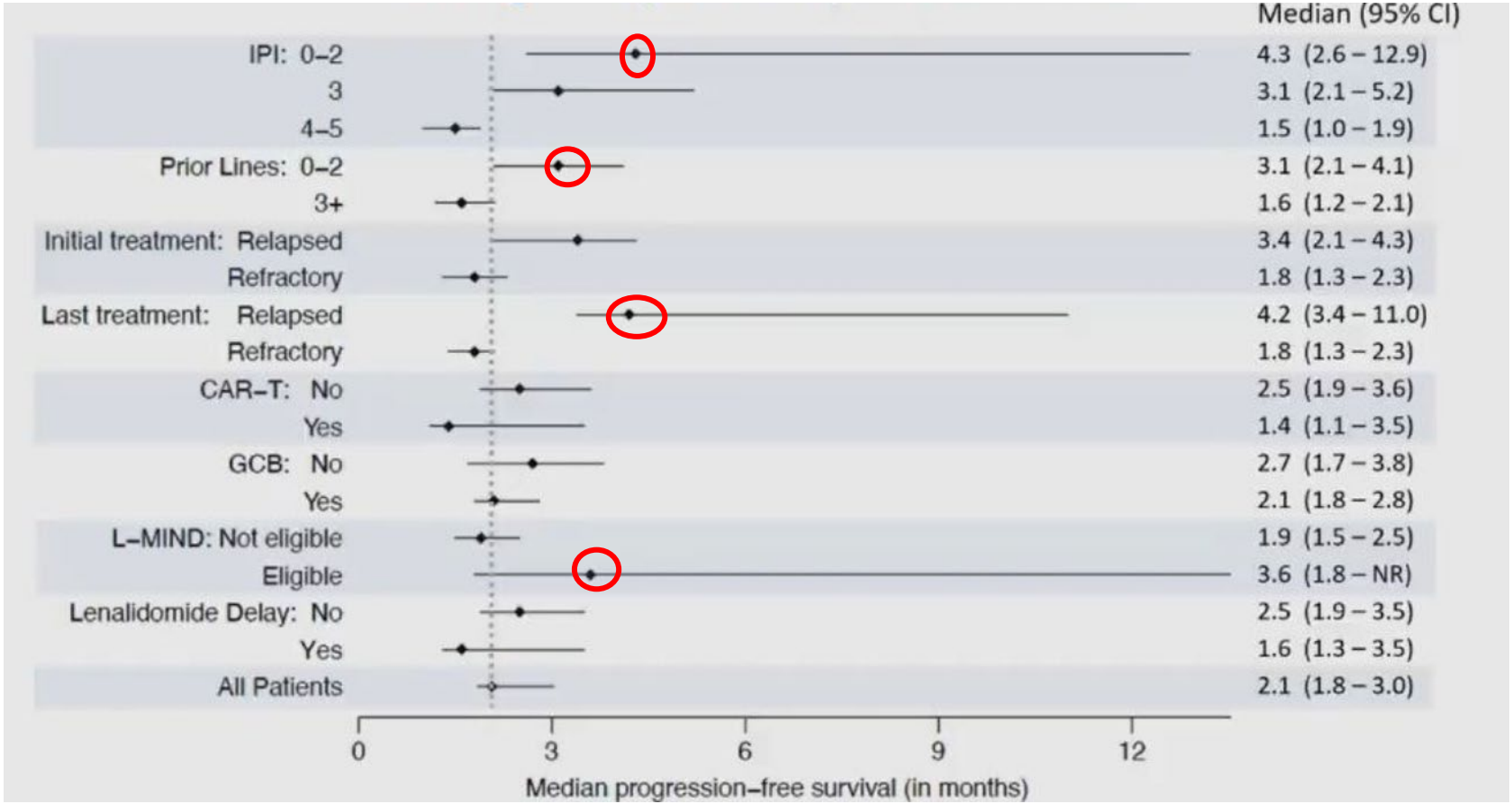
Median PFS: 2.1 months (95% CI 1.8 – 3.0)
Median follow-up: 5.2 months



Median OS: 7.3 months (95% CI 5.2 – 9.5)
Median follow-up: 5.2 months

Quall D. A.et al ASH 2022, Blood 2023

Subgroup analysis of PFS



Tafasitamab for the Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the US Real-World Setting

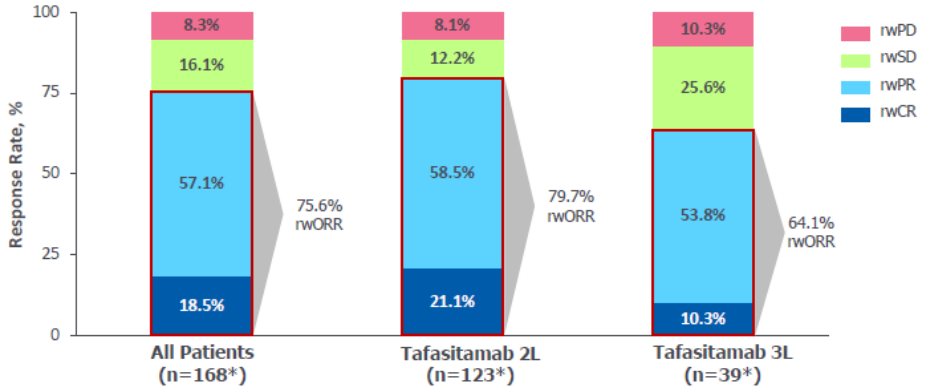
US RWE (Saverno et al. ASH 2023 ORAL 265)

Patients characteristics

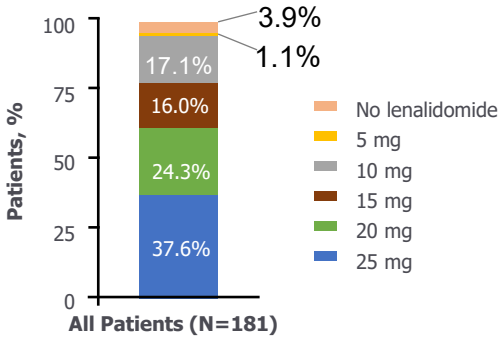
Characteristics		All patients (N=181)	Tafasitamab 2L (n=130)	Tafasitamab 3L (n=43)
ECOG PS at tafasitamab initiation, n (%)	0-1	95 (52.5)	69 (53.1)	21 (48.8)
	≥2	86 (47.5)	61 (46.9)	22 (51.2)
Ann Arbor stage at tafasitamab initiation, n (%)	Stage I/II	10 (5.5)	9 (6.9)	1 (2.3)
	Stage III	58 (32.0)	50 (38.5)	7 (16.3)
	Stage IV	111 (61.3)	70 (53.8)	35 (81.4)
	Unknown	2 (1.1)	1 (0.8)	0
R-IPI at tafasitamab initiation, n (% patients with data available)*	1-2 (good prognosis)	33 (19.5)	22 (18.3)	8 (19.0)
	3-5 (poor prognosis)	136 (80.5)	98 (81.7)	34 (81.0)
Double-hit or triple-hit at tafasitamab initiation, n (%)	Yes, double-/triple-hit	22 (12.2)	14 (10.8)	8 (18.6)
	Tested, found to be negative	130 (71.8)	103 (79.2)	26 (60.5)
	Unknown	29 (16.0)	13 (10.0)	9 (20.9)
Cell of origin information, n (%)	GCB	81 (44.8)	60 (46.2)	17 (39.5)
	Non-GCB/ABC	39 (21.5)	28 (21.5)	9 (20.9)
	Unknown	61 (33.7)	42 (32.3)	17 (39.5)
Refractory to line prior to tafasitamab†		59 (32.6)	33 (25.4)	19 (44.2)

US real-world: clinical benefits when used earlier lines

Median follow-up time: 6.5 months [1]



Lenalidomide Starting dose



Median follow-up time: 14.7 months [2]

ORR: 73% CR: 23% PR: 50%

mDOR: 9.6 months

mPFS: 11.3 months

mOS: 24.8 mesi

1. Saverno K.et al. ASH, 2023 Saverno K.et al. ASH, 2024

French real-world: 2 Line (56%) with primary refractory (61%)

Study design and patients:

- Data were retrospectively collected from the medical record of patients treated within the EAP between January 2022 and March 2023 in France
- Patients were included into 2 cohorts based on the line of therapy in which T-L was received:
  - **Cohort A**: T-L as second line (**2L**)
  - **Cohort B**: T-L as third- or fourth line (**3L/4L**)

Study outcomes:

- The primary endpoint was the best objective response in the overall population, assessed locally
- Secondary endpoints included BOR in each cohort, event-free survival (EFS), duration of response (DOR), PFS, OS, disease control rate (DCR), and time to next treatment (TTNT)
- Exploratory subgroup analyses were performed by primary refractory status, ECOG PS and IPI scores, DLBCL subtypes, and response type

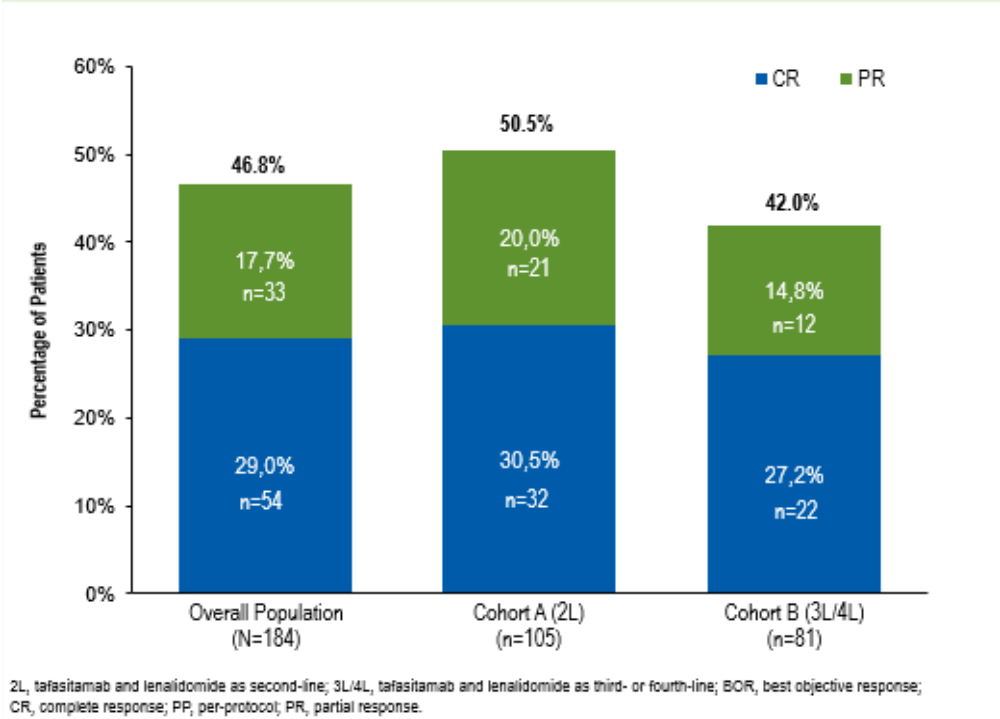
Herbaux et al. EHA, 2024 P 1214

Table 1. Baseline Clinical and Disease Characteristics (PP Set) *

Characteristics	Cohort A (2L) (n=105)	Cohort B (3L/4L) (n=81)	Total (N=186)
Age at T-L initiation, median (range), years	81 (56-93)	74 (32-90)	78 (32-93)
ECOG PS ≥2, n (%)	35 (33.3)	26 (32.1)	61 (32.8)
IPI score ≥3, n (%)	72 (68.5)	61 (75.3)	133 (71.5)
Histology, n (%)			
DLBCL, NOS	76 (72.4)	51 (63.0)	127 (68.3)
GC-DLBCL	35 (46.1)	22 (43.1)	57 (44.9)
Non GC-DLBCL	32 (42.1)	24 (47.1)	56 (44.1)
Unknown	9 (11.8)	5 (9.8)	14 (11.0)
Transformed indolent DLBCL	14 (13.3)	13 (16.0)	27 (14.5)
THRLBCL	1 (1.0)	4 (4.9)	5 (2.7)
HGBCL	14 (13.3)	13 (16)	27 (14.5)
Refractory status,* n (%)			
Primary refractory disease	60 (57.7)	52 (65.0)	112 (60.9)
Refractory to last therapy	74 (70.5)	60 (74.1)	134 (72)
Time of first relapse, n (%)			
Late (≥12 months)	32 (30.8)	21 (26.3)	53 (28.8)
Early (<12 months)†	72 (69.2)	59 (73.8)	131 (71.2)

French real life:29% CR in high risk patient population

Figure 1. BOR in the Overall (PP) Population and in Each Cohort



2L, tafasitamab and lenalidomide as second-line; 3L/4L, tafasitamab and lenalidomide as third- or fourth-line; BOR, best objective response; CR, complete response; PP, per-protocol; PR, partial response.

Herbaux et al. EHA, 2024 P 1214

- mFU: 8.2 months
- The mOS, mPFS and mDOR were not significantly different between the cohorts

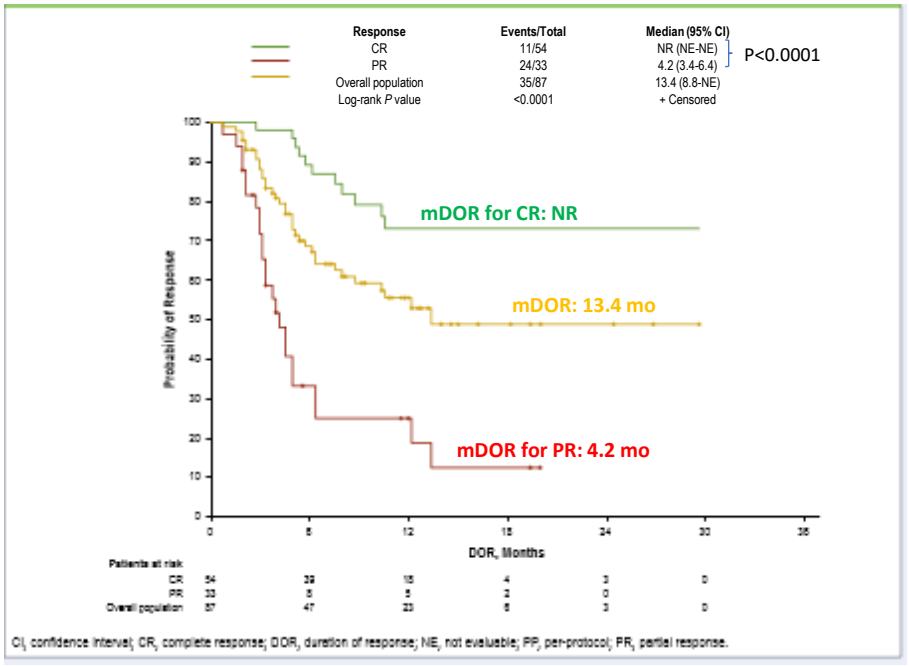
  mOS: **10.0 mo**
  - Cohort A: 10.6 mo
  - Cohort B: 8.2 mo

  mPFS: **4.7 mo**
  - Cohort A: 5.4 mo
  - Cohort B: 3.6 mo

  mDOR: **13.4 mo**
  - Cohort A: 12.2 mo
  - Cohort B: not reached

- The **median time to best response** to T-L was **4.0 cycles** in both cohorts

Long lasting DoR in patients achieving CR (59% are in 2L)



Characteristics of patients with CR

- Median age: 79 years
- ECOG PS 0-1: 81.3%

- Histology:
  - DLBCL NOS: 56.0%
  - THRLBCL: 7.4%
  - transformed indolent: 18.5%
  - HGBCL: 18.5%

- IPI 3-5: 63.0%
- Primary refractory: 55.6%

- Line of treatment for T-L:
  - **2L: 59.3%**
  - 3L: 25.9%
  - 4L: 14.8%

RWE: efficacy in early lines (2L/3L)

	TALOs N = 83 EAP	Qualls et al. 2023 N = 178	Saverno et al. 2023 N = 173	Herbaux et al. 2024 N = 186	Gutierez et al. 2024 N = 99
Primary refractory %	48	49	26	61	56
2L, %	39	35	72	56	72
ORR, %	47	31	73	46.8	61.0
CRR, %	29	19	23	29	42.0
mPFS, months	4.5	1.9	11.3	4.7	10.9
mOS, months	8.6	6.5	24.8	10.0	26.4
mFU, months	16	12	14.7	8.2	16

Qualls et al. *Blood 2023;* Saverno et al. ASH 2024; Herbaux et al. *EHA* 2024; Gutierez et al ASH 2024 TALOs, Italian EAP SIE 2024

Tafa+Lena : Take home messages

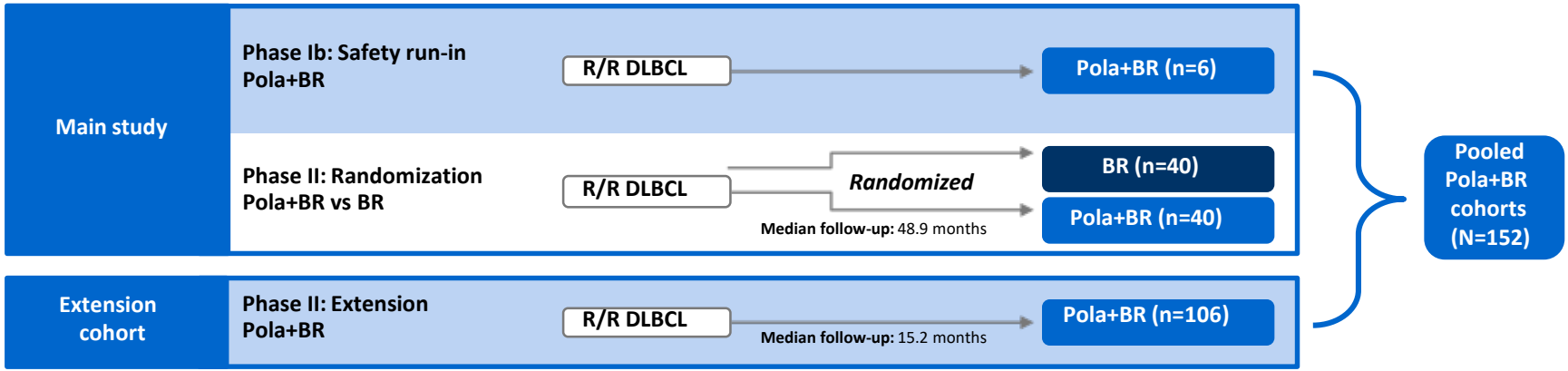
- Clinical benefits when tafa-Lena are used in earlier lines
- Patients achieving CR have favorable PFS, OS and DoR
- Similar safety, despite more comorbidities and high-risk features
  - lenalidomide dose reductions
  - earlier discontinuation
  - undereporting due to retrospective collection of toxicity data

Randomised Phase II study of pola-BR versus BR (GO29365): study design

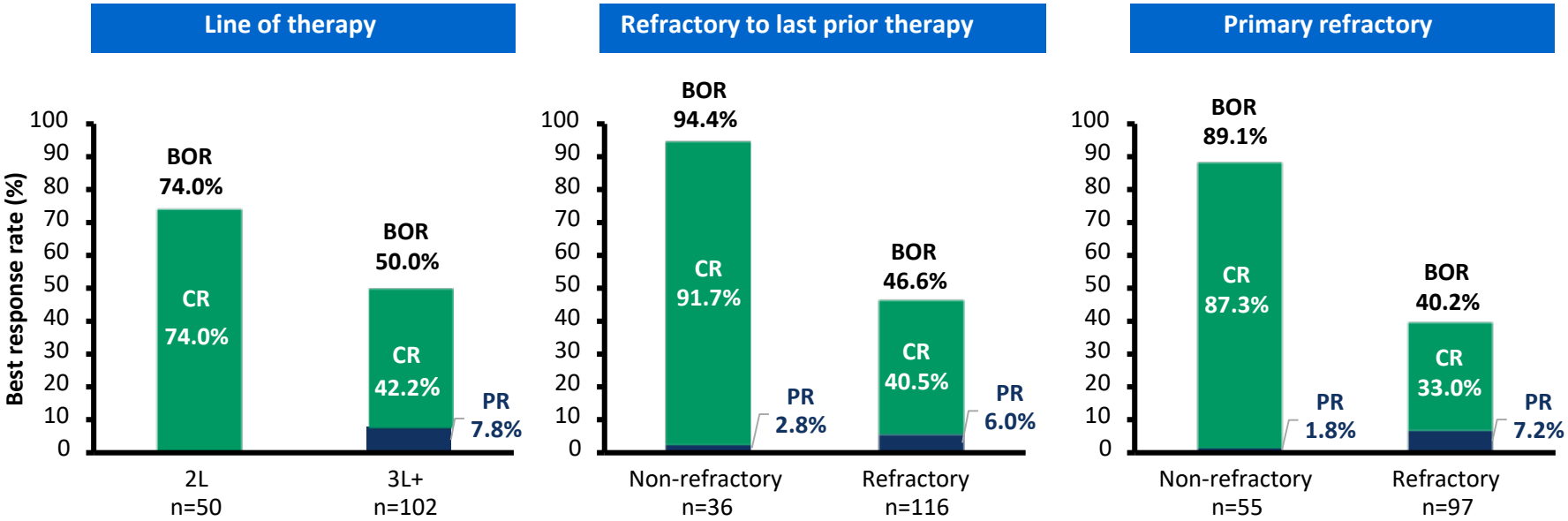
Key eligibility criteria

Inclusion: transplant-ineligible DLBCL, after at least 1 line of therapy

Exclusion: prior allogeneic SCT; history of transformation from indolent disease; current Grade >1 PN



Best objective response in the pooled Pola+BR cohort (152 pts) according to line of therapy and refractory status

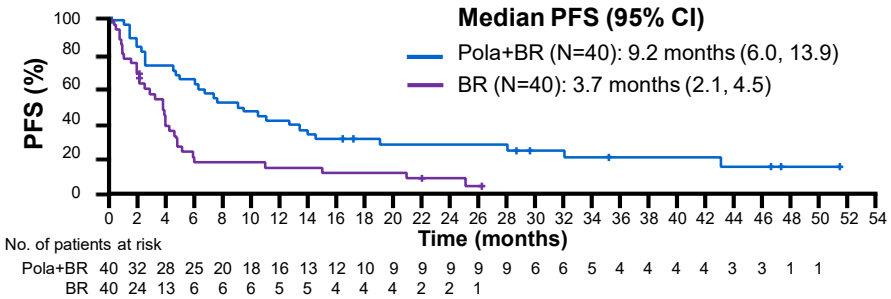


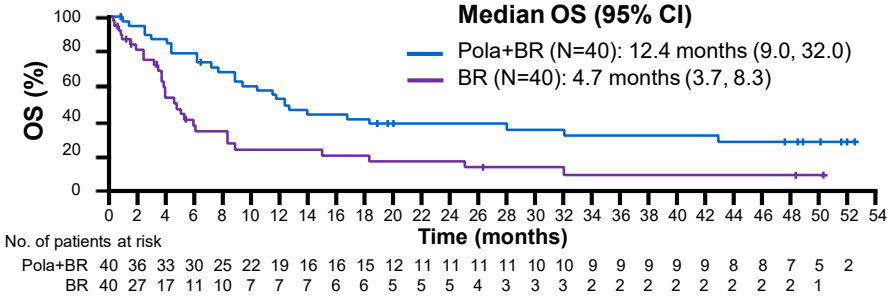
Responses were observed regardless of line of therapy and refractory status. The vast majority of responding patients achieved a CR

Sehn LH, et al. Blood advances 2021

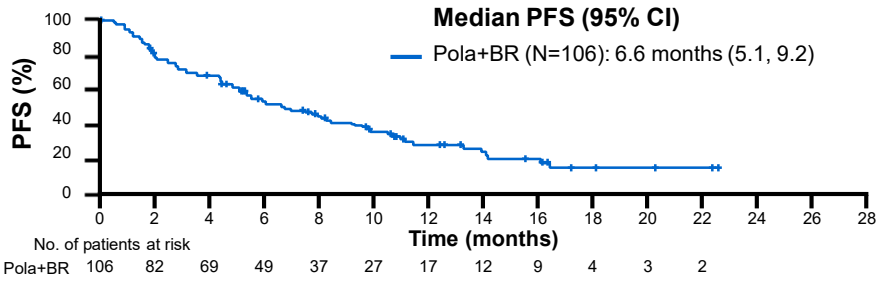
PFS and OS in randomized and extension cohorts

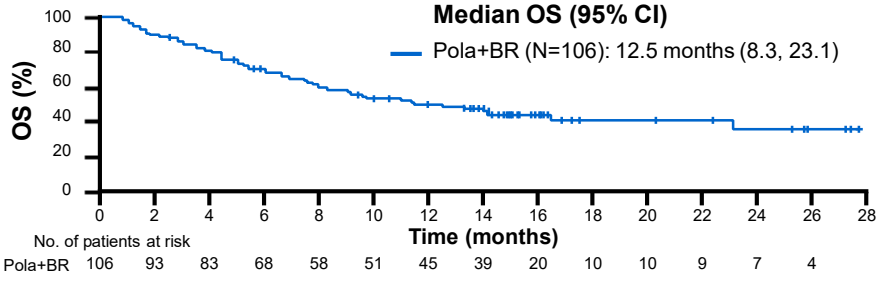
Randomized





Extension cohort





Sehn LH, et al. Blood advances 2021

Pola-BR RWE: German experience

REGULAR ARTICLE

blood advances

Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas

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- ✓ 105 pts with r/r DLBCL, age 22-87
- ✓ Most refractory to last treatment , 12 failed CART
- ✓ Pola containing regimen (mainly PolaBR)
- ✓ Median previous line: 3
- ✓ 54 salvage: ORR 48%
- ✓ 51 bridge to CART or to alloSCT

Characteristic	Salvage cohort (n = 54)	Bridging cohort (n = 51)
Pola treatment		
Chemotherapy backbone		
pola-BR	32 (59.3%)	27 (52.9%)
pola-B	1 (1.85%)	1 (1.96%)
pola-R-CHP	0	1 (1.96%)
pola-R-gemcitabine	1 (1.85%)	0
No chemotherapy backbone		
pola-R	20 (37.0%)	19 (37.3%)
pola-monotherapy	0	3 (5.9%)
Median number of pola cycles (range)	4 (1-9)	2 (1-6)

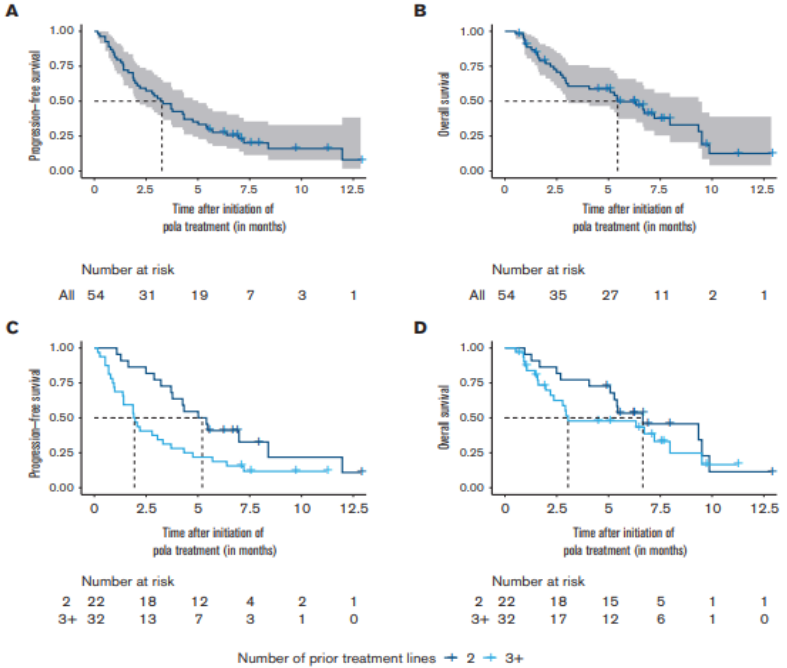
Table 5. Most frequently recorded adverse events during polatuzumab vedotin treatment

	Salvage cohort (n = 52)*		Bridging cohort (n = 49)*	
Adverse event	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Blood disorders				
Anemia	41 (78.8)	14 (26.9)	35 (71.4)	14 (28.6)
Thrombocytopenia	33 (63.5)	17 (32.7)	25 (51.0)	10 (20.4)
Neutropenia	31 (59.6)	20 (38.5)	17 (34.7)	12 (24.5)
Febrile neutropenia	12 (23.1)	8 (15.4)	3 (6.1)	3 (6.1)
Infections†	20 (38.5)	10 (19.2)	14 (28.6)	11 (22.4)
Polyneuropathy	11 (21.2)	0	7 (14.3)	0
Tumor lysis	2 (3.8)	2 (3.8)	4 (8.2)	4 (8.2)

*For 2 patients per cohort, no adverse events were reported and patients were

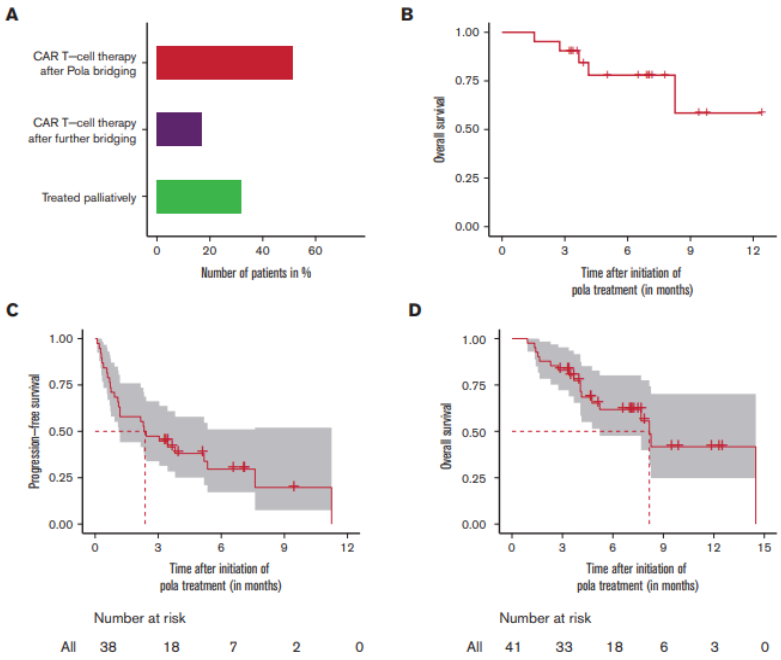
Pola-BR RWE: German experience

Salvage cohort N= 54



ADVERSE INDEPENDENT PROGNOSTIC FACTORS
- ✓ ≥ 3 previous treatment lines
- ✓ Refractoriness to last treatment

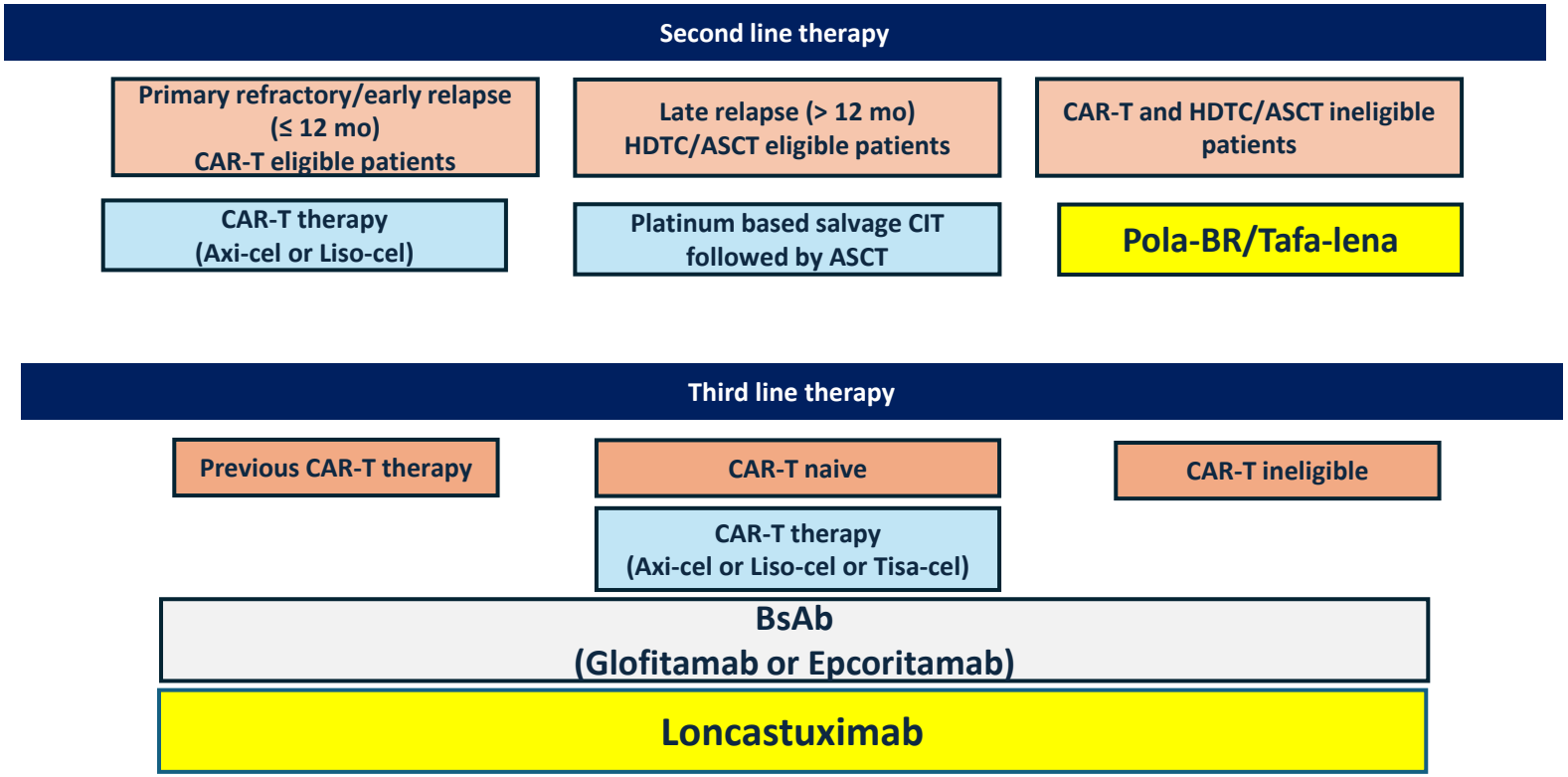
Bridging cohort N= 51



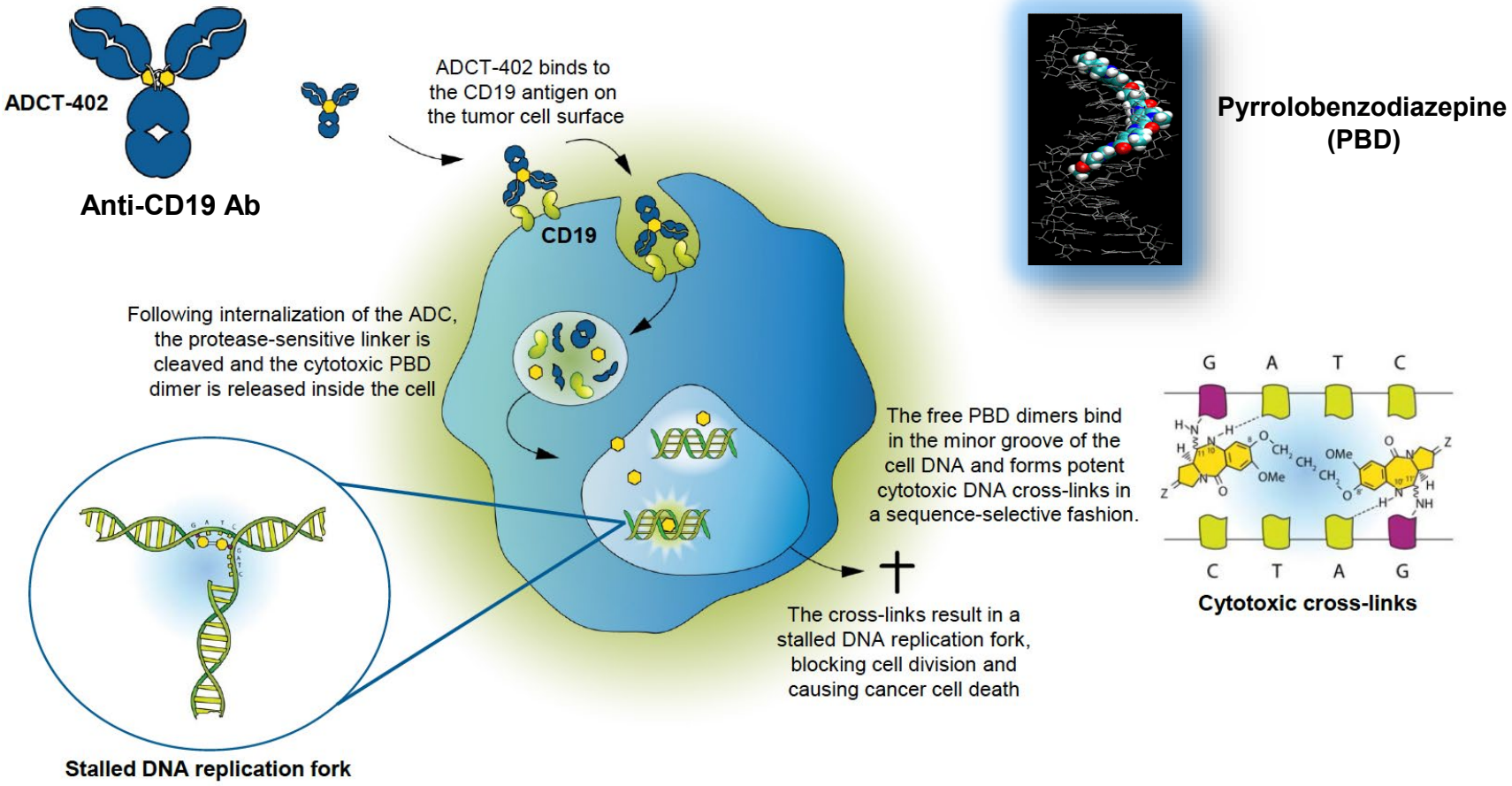
- ✓ 51% successful bridge
- ✓ Pola – R ORR 40%, possible pre-apheresis bridge in CART pts
- ✓ 7 out of 12 pts failing CART responded to pola

Liebers, Blood Advance 2021

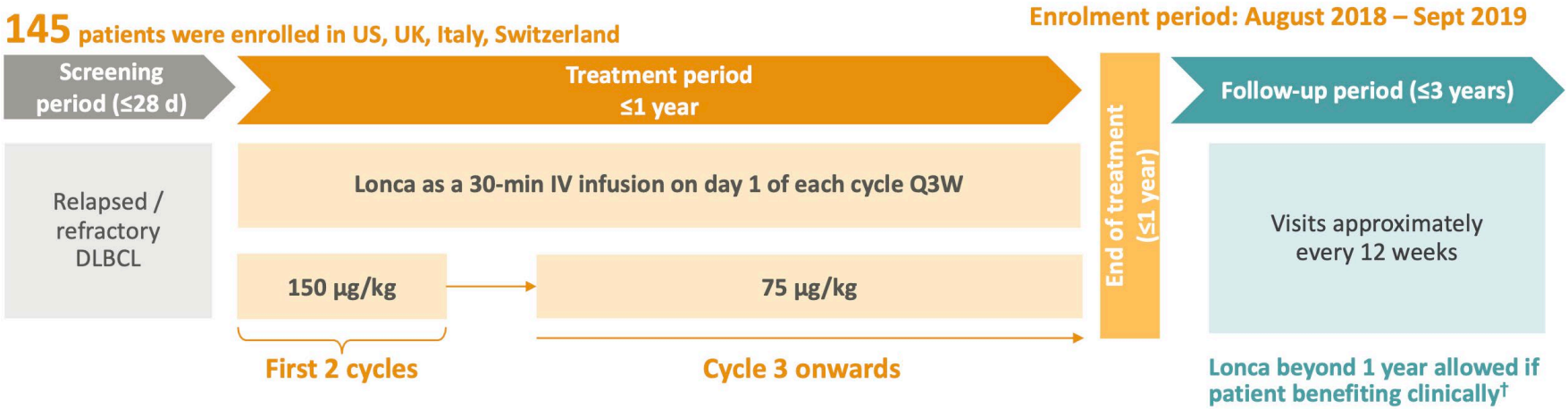
RR- DLBCL: patients journey in the era of novel drug



Loncastuximab Tesirine (ADCT-402)



LOTIS-2 trial: study design



- **Patients received oral dexamethasone premedication per protocol**
- **Disease assessment by central independent review using PET-CT at baseline, W6, W12, then Q9W until EOT**
  During the follow-up period, patients who discontinued Lonca for reasons other than PD or initiation of other anti-cancer therapy except SCT had imaging performed every 12 weeks until 1 year from EOT, then every 6 months, until progression up to 3 years from EOT
- **Data cut-offs:**
  - **Primary analysis:** April 6, 2020 , median follow-up of 7.3 months
  - **Follow-up analysis:** March 1, 2021, median follow-up of 7.8 months
  - **Final analysis:** September 15, 2022, median follow-up of 7.8 months

Caimi PF *et al*, Lancet Oncol 2021; 22:790; Caimi PF *et al*, Haematologica 2024; 109:1184

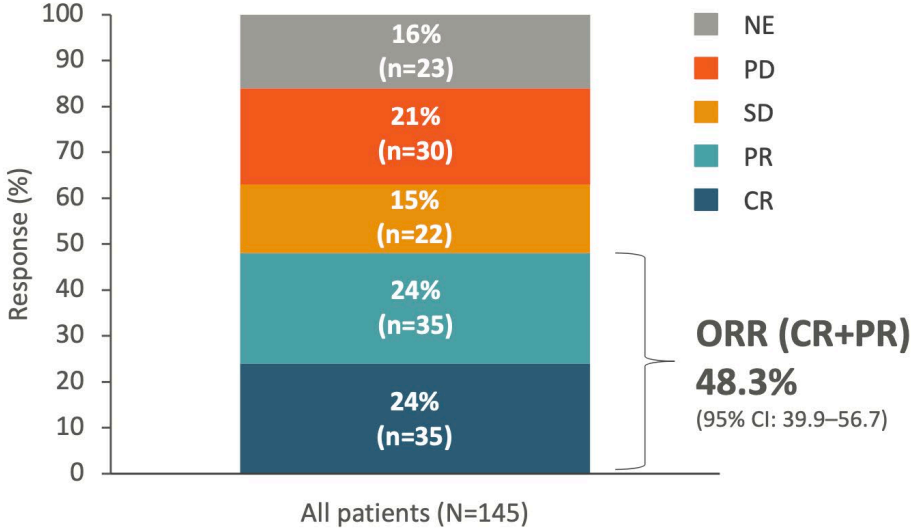
LOTIS-2 trial: patients characteristics

Patient and disease characteristics (N=145)	
Sex, n (%)	
Female	60 (41.4)
Median age, years (range)	66.0 (23–94)
Age, n (%)	
<65 years	65 (44.8)
≥65 to <75 years	59 (40.7)
≥75 years	21 (14.5)
Race, n (%)	
White	130 (89.7)
Black or African American	5 (3.4)
Asian	3 (2.1)
Other	7 (4.8)
ECOG score, n (%)	
0	58 (40.0)
1	78 (53.8)
2	9 (6.2)
Histology†, n (%)	
DLBCL, NOS	128 (88.3)
HGBL‡	10 (6.9)
Primary mediastinal DLBCL	7 (4.8)

Disease characteristics and treatment history (N=145)	
Transformed DLBCL, n (%)	30 (20.7)
Double/triple hit, n (%)	
Double hit	12 (8.3)
Triple hit	3 (2.1)
Stage, n (%)	
I–II	33 (22.8)
III–IV	112 (77.2)
Median number of prior systemic therapies (range)	3.0 (2–7)
Prior systemic therapies, n (%)	
2 prior lines	63 (43.4)
3 prior lines	34 (23.4)
>3 prior lines	48 (33.1)
Refractory, n (%)	
Primary refractory	29 (20.0)
Refractory to last therapy	89 (61.4)
Prior SCT, n (%)	24 (16.6)
Prior CAR T-cell therapy, n (%)	14 (9.7)

Caimi PF *et al*, Haematologica 2024; 109:1184

LOTIS-2 trial: response rates



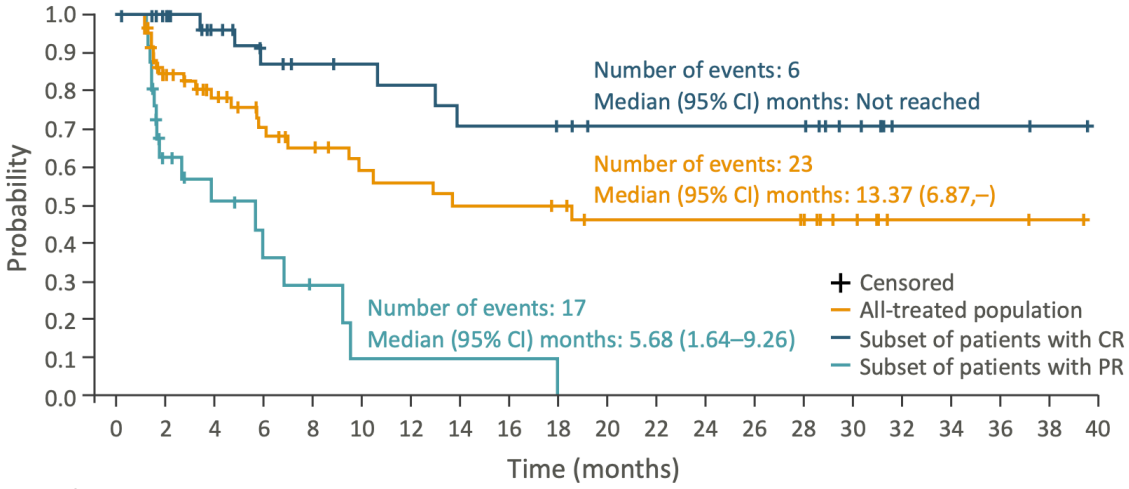
- **ORR** by central review in the as-treated population was 70/145 **48.3%** (95% CI: 39.9–56.7)
- CR rate was 24.1% (95% CI: 17.4–31.9)
- PR rate was 24.1% (95% CI:[2] 17.4–31.9)

Median time to first response (CR or PR) was **41 days**

Median number of Lonca cycles administered: 3 (IQR 2–5; range 1–15)

Caimi PF *et al*, Lancet Oncol 2021; 22:790

LOTIS-2 trial: duration of response



Patients at risk

All-treated population	70	63	42	38	33	29	25	22	21	20	18	17	17	16	15	15	15	15	13	11	11	11	11	11	11	11	11	7	6	5	2	2	2	2	2	1	1	0
Subset of patients with CR	36	35	30	29	25	22	20	18	18	17	17	16	16	15	14	14	14	14	12	11	11	11	11	11	11	11	11	7	6	5	2	2	2	2	2	2	1	0
Subset of patients with PR	34	28	12	9	8	7	5	4	3	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

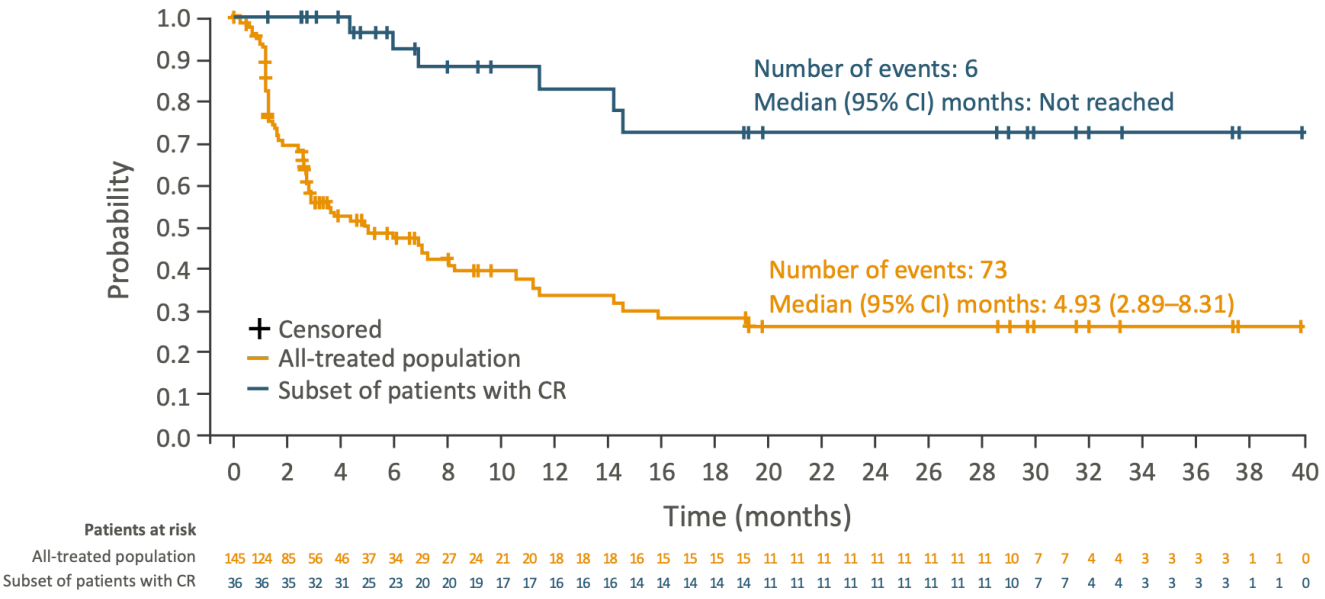
mDOR for the **70 responders**
13.4 months
(95% CI: 6.9–NE)

mDOR for patients with a **CR (n=36)**
Not reached

mDOR for patients with a **PR (n=34)**
5.7 months
(95% CI: 1.6–9.3)

Caimi PF *et al*, Haematologica 2024; 109:1184

LOTIS-2 trial: progression-free survival



mPFS for all-treated population (N=145)

4.9 months

(95% CI: 2.9–8.3)

mPFS for patients with **CR (n=36)**

Not reached

Caimi PF *et al*, Haematologica 2024; 109:1184

LOTIS-2 trial: safety

Haematological TEAE	Patients, n (%) All grades	Patients, n (%) Grades 3 or 4
Neutropenia	57 (40)	37 (26)
Thrombocytopenia	48 (33)	26 (18)
Anaemia	38 (26)	15 (10)
Leukopenia	21 (14)	13 (9%)
Febrile neutropenia	5 (3)	5 (3)

Laboratory TEAE	Patients, n (%) All grades	Patients, n (%) Grades 3 or 4
GGT increase	**59 (40)**	**24 (16)**
ALP increase	29 (20)	1 (1)
AST increase	23 (16)	1 (1)
ALT increase	23 (16)	4 (3)

- Haematological parameters generally decreased with treatment but tended to partially recover between cycles
- Increased GGT was **not associated with synthetic dysfunction** or severe hepatic events

Caimi PF *et al*, Lancet Oncol 2021; 22:790

LOTIS-2 trial: CAR-T cell before lonca

13 (9%) patients from LOTIS-2 had received prior CAR T-cell therapy;
CD19 expression was required per protocol, but no prior CAR-T patients failed screening due to a lack of CD19

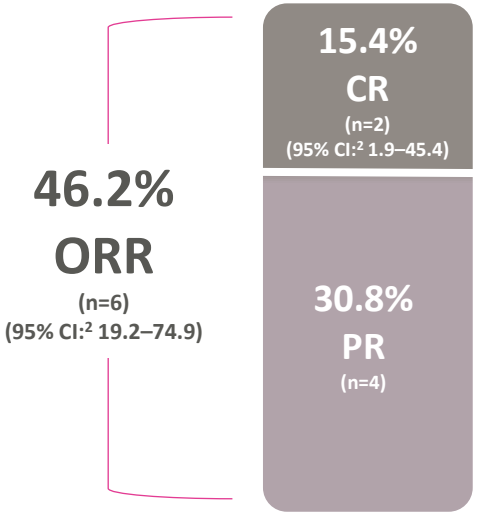
Patient & disease baseline characteristics	N=13
Sex, male, n (%)	9 (69)
Race, n (%)	
White	12 (92)
Pacific Islander	1 (8)
Lymphoma subtype, n (%)	
DLBCL, NOS	5 (38)
Transformed follicular	4 (31)
Richter transformation	1 (8)
HGBL – DH/TH	3 (23)
DH/TH, n (%)	5 (38)
Stage at diagnosis	
Stage I – II	2 (15)
Stage III – IV	11 (85)
Primary refractory, n (%)	10 (77)

CAR T-cell therapy characteristics	N=13
Time between diagnosis and CAR T-cell infusion, median (range), months	10 (2–79)
No of LOT prior to CAR T-cell, median (range)	3 (1–6)
Time from CAR T-cell to Lonca, median (range)	7 mo (45–400 d)*
Type of CAR T-cell therapy, n (%)	
Axi-cel	7 (54)
Liso-cel	2 (15)
Investigational CD19	2 (15)
Investigational CD19/CD20	1 (8)
Investigational CD19/CD22	1 (8)
Best response to CAR T-cell, n (%)	
Complete response	7 (54)
Partial response	2 (15)
No response	4 (31)

Caimi PF *et al*, Clin Lymphoma Myeloma Leuk 2022; 22:e335

Response to Lonca after CAR T-cell therapy

After a median follow-up of 8 months, 13 patients received a median of 2 cycles of Lonca (range 1–9)



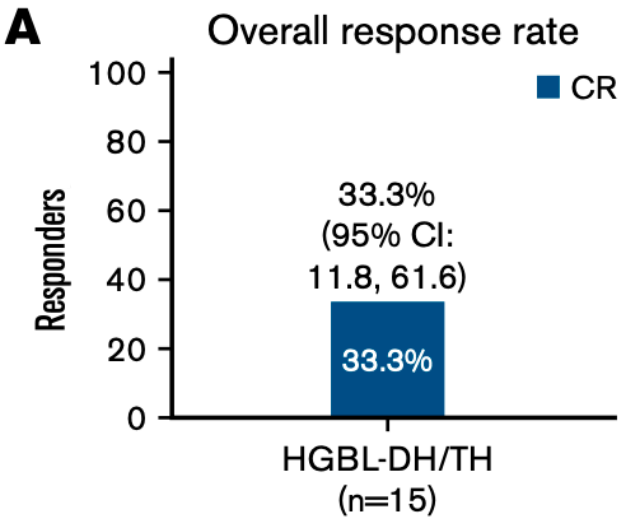
Median DOR: 8 months
(95% CI: 103 days–NR)

Response to Lonca, based on independent review, was seen in 6/13 (46.2%) patients already treated with CAR T-cell therapy

Of these, 5 had previously presented response to CAR T-cell therapy and the sixth patient had prolonged, stable disease for > 1 year after CAR T-cell therapy

While limited by its small sample size, the response rates observed in this high-risk population are comparable to those observed in other patient subsets

LOTIS-2 trial: RR-HGBL subgroup analysis



Median time to CR 43d
Median F-up 5.8m
mPFS 3.7m
mOS 9.2m
In responding pts DOR > 12m
mDOR NR

Table 1. Baseline clinical characteristics in patients with HGBL-DH/TH

	Responders (n = 5)	Nonresponders (n = 10)
Age, median (min, max), y	75 (53, 84)	74 (27, 85)
Age group, n (%)		
<65 y	2 (40.0)	3 (30.0)
≥65 to <75 y	0 (0.00)	4 (40.0)
≥75 y	3 (60.0)	3 (30.0)
Diagnosis to first dose, median mo (min, max)	50.0 (23.6, 86.6)	11.04 (5.4, 73.2)
Prior systemic therapies, n (%)*		
2	1 (20.0)	3 (30.0)
3	1 (20.0)	5 (50.0)
>3	3 (60.0)	2 (20.0)
Prior stem-cell transplant, n (%)	1 (20.0)	2 (20.0)
Prior CAR T-cell therapy	1 (20.0)	3 (30.0)
Response to most recent line of systemic therapy, n (%)		
Relapse	2 (40.0)	2 (20.0)
Refractory†	0 (0.00)	8 (80.0)
Other‡	3 (60.0)	0 (00.0)

Alderuccio JP *et al*, Blood Adv 2022; 6:4736

Real-world analysis of Lonca in R/R DLCBL in the US

Retrospective chart review of R/R DLBCL patients treated with Lonca at 21 academic centres

n (%)*	Real-world cohort (N=187)
Male	119 (64)
Age, years	
<65	72 (39)
65–75	66 (33)
>75	39 (21)
Histology	160
de novo DLBCL	85 (53)
HGBCL	40 (25)
DH/TH	37 (21)
Transformed DLBCL	28 (18)
Advanced stage disease	161 (86)
IPI >3	63 (77)
ECOG PS >2	13 (7)
eGFR <60	34 (19)
Bulky disease (>10 cm)	32 (17)
CNS involvement	12 (7)
Cell of origin	157
GCB	96 (61)
Non-GCB	61 (38)
Double expressor	61 (39)

n (%)*	Real-world cohort (N=187)
CD19 status overall	128
Positive	109 (85)
Negative	19 (15)
CD19 status post CAR-T	90
Positive	70 (78)
Negative	20 (22)
n (%)*	**cohort (N=187)**
Lonca line of therapy	
>3rd	151 (81)
Primary refractory	47 (25)
Prior ASCT	31 (16)
Median time from ASCT (months)	25.9
Prior CAR-T	112 (60)
CAR-T as 2nd line	11 (10)
Median time from CAR-T (months)	7.7
Last response prior to Lonca	
CR	16 (9)
PR	15 (8)
PD	144 (77)

In the real-world cohort, there were 66 documented adverse events (35%)

AEs led to Lonca discontinuation in 14%

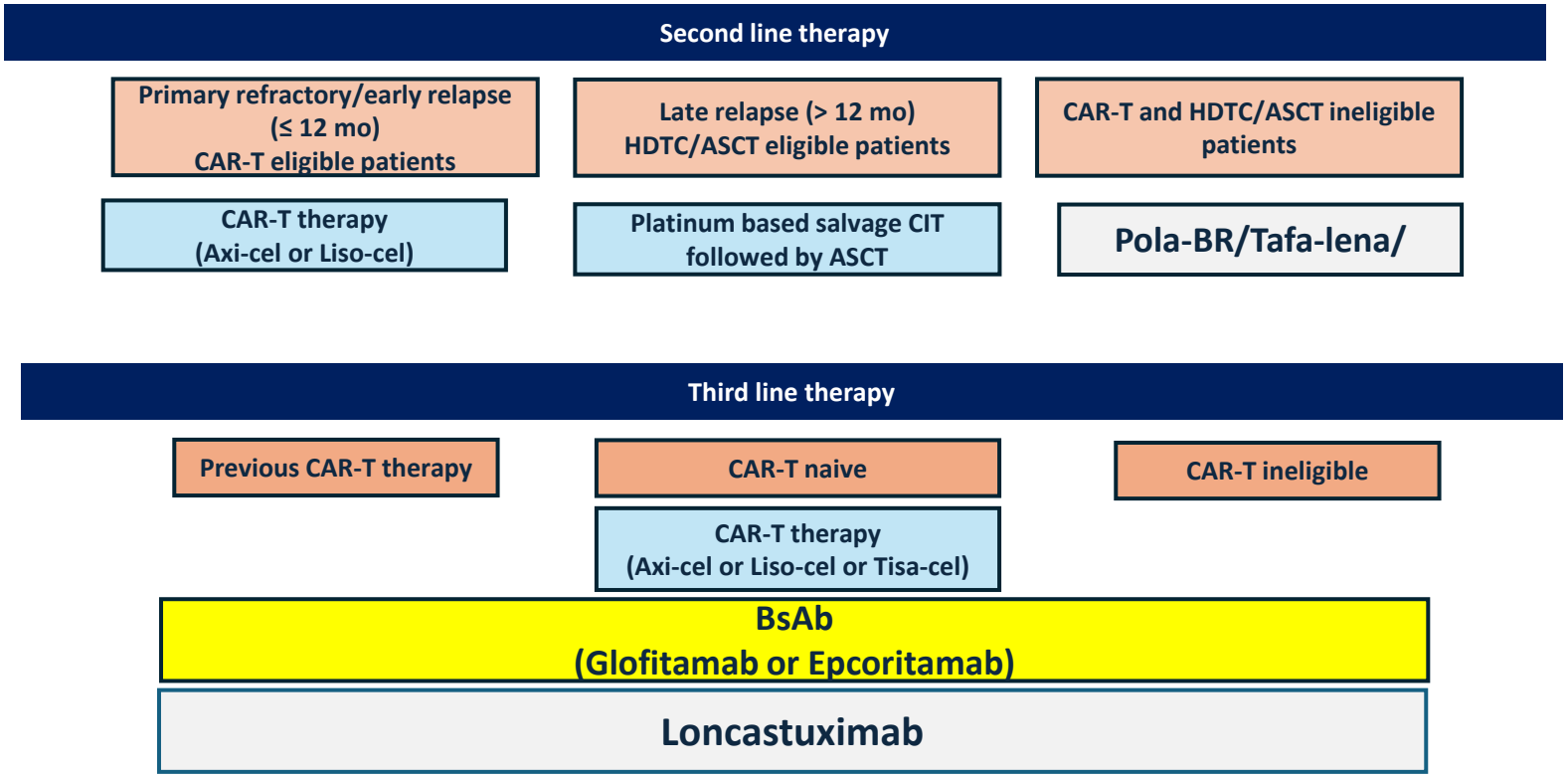
n (%)	Incidence	Main reason for discontinuation
Pleural effusion	6 (3)	1 (<1)
Peripheral oedema	21 (11)	7 (4)
Pericardial effusion	1 (<1)	0 (0)
Rash	18 (10)	7 (4)
Cytopenias	31 (17)	13 (7)

Real-world analysis of Lonca in R/R DLCBL in the US

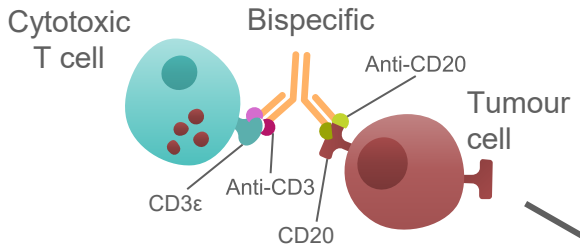
Lonca : take home messages

- Lonca showed efficacy in R/R DLBCL/HGBL patients, including DH/TH and CAR T-cell recipients
- Tolerability profile was manageable, without increase in toxicity in elderly patients
- Lonca treatment allowed for response to subsequent CAR T-cell therapy
- In an exploratory analysis, responses were demonstrated in patients with low levels of CD19 expression
- Lonca as bridge to allogeneic transplant?

RR- DLBCL: patients journey in the era of novel drug



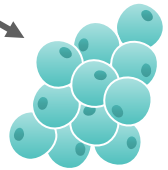
Anti-CD20/CD3 bispecific antibodies



1. Local secretion of chemokines leading to the recruitment of T cells from the periphery

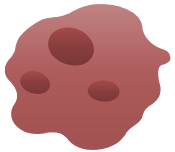
Anti-CD20/CD3 bispecifics redirect endogenous non-specific T cells to engage and eliminate malignant B cells in NHL[1–3]

2. T cells undergo proliferation and expansion at the tumour site



3. T-cell activation occurs via downstream signalling events leading to the secretion of cytotoxic granules

5. Apoptosis

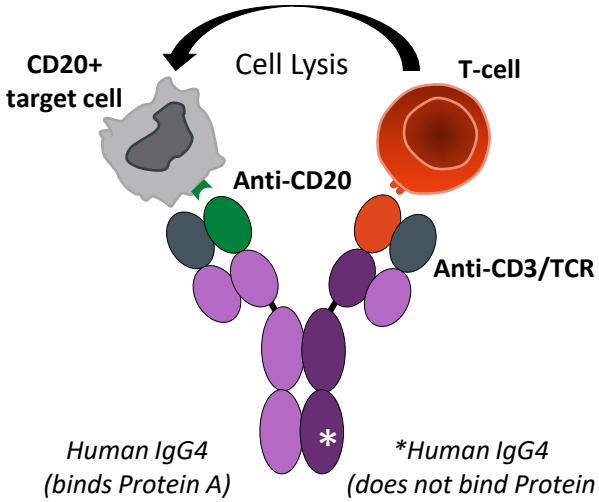


4. Potent lysis of tumour cells

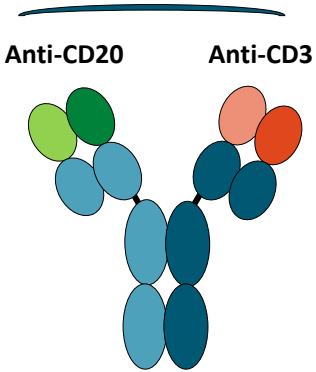
6. T cell–mediated tumour killing

1. Sun LL, et al. Sci Transl Med 2015;7:287ra70; 2. Dieckmann NM, et al. J Cell Science 2016;129:2:2881–6
3. Bacac M, et al. Clin Cancer Res 2018;24:4785–97
Adapted from Aldoss I, et al. Leukemia 2017;31:777–87

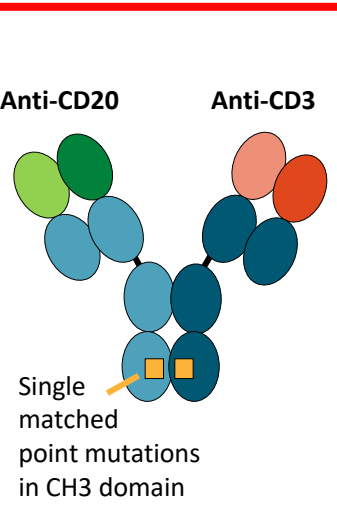
CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas



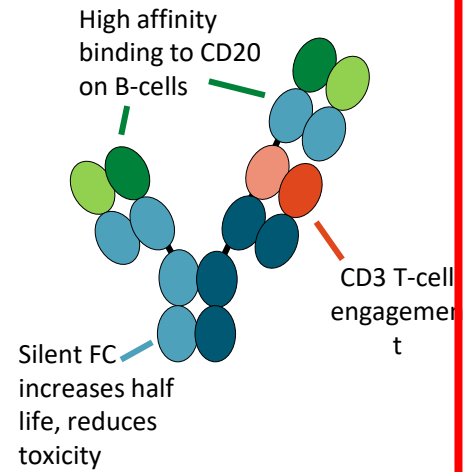
Odronextamab
(IV)



Mosunetuzumab
(IV/SC)



Epcoritamab
(SC)



Glofitamab
(IV)

Humanized mouse IgG1-based mAb

Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399.
Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutching. ASH 2020. Abstr 403.

Glofitamab monotherapy in patients with relapsed/refractory DLBCL: extended follow-up and landmark analyses from a pivotal Phase II study

Study overview

Pivotal Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, trFL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

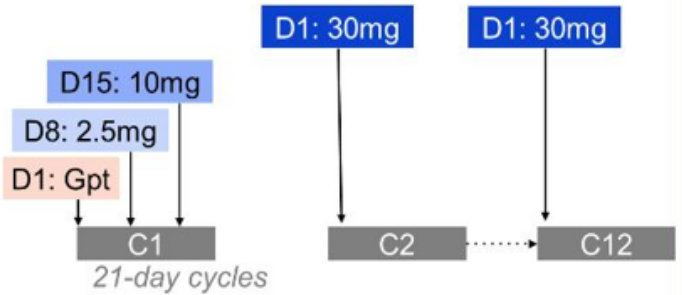
Glofitamab IV administration

Fixed-duration treatment

- Maximum 12 cycles

CRS* mitigation:

- Obinutuzumab pre-treatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

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

Landmark analyses

- PFS and OS post-hoc analysis were performed by response (landmark at C3, or EOT)

Fixed treatment duration max 12 cycles 8.3 months

Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Baseline characteristics

n (%)*		All patients (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/II	35 (22.7)
	III/IV	116 (75.3)
NHL subtype	DLBCL	110 (71.4)
	trFL	28 (18.2)
	HGBCL	10 (6.5)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	19 (12.3)

n (%)*	All patients (N=154)†
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	61 (39.6)
≥3 prior lines	93 (60.4)
Prior CAR-T	51 (33.1)
Refractory to prior CAR-T§	46 (29.9)
Prior ASCT	29 (18.8)
Refractory to any prior therapy	138 (89.6)
Refractory to last prior therapy	131 (85.1)
Refractory to first line of prior therapy	90 (58.4)
Refractory to any prior anti-CD20	128 (83.1)

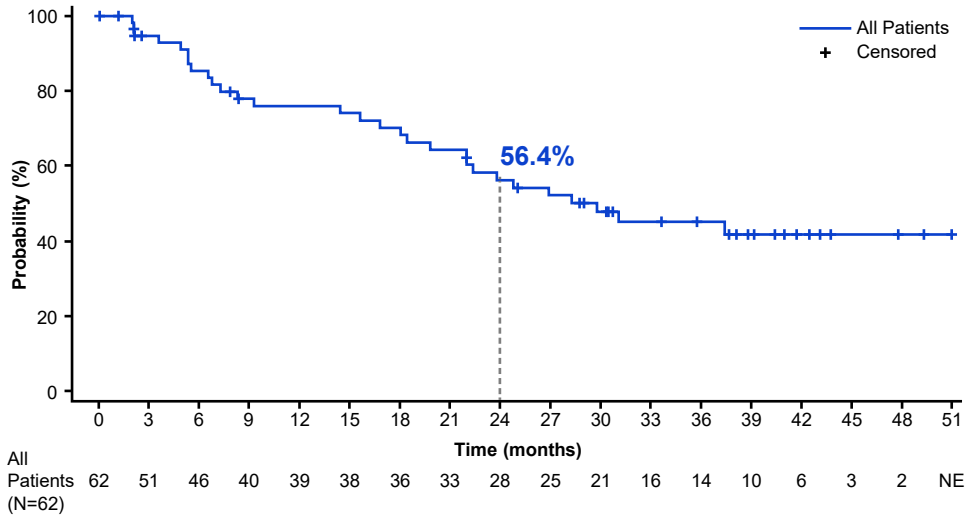
The patient population was heavily pre-treated and highly refractory to prior therapy

Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Complete responses remained durable following fixed-duration glofitamab treatment

	(N=155)*
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median DoCR, months (95% CI)	29.8 (22.0–NE)
24-month DoCR, % (95% CI)	56.4 (42.9–69.8)
Ongoing CRs, n/N (%)	33/62 (53.2)
Median CR follow-up, months (range)	37.7 (0–51)

DoCR by IRC



- Median time on study: 41.0 months (range: 0–52)

An estimated 56.4% of patients with a CR at any time remained in remission at 24 months

Dickinson M et al; Oral Presentation ASH 2024 (abstract #865).

Safety summary

- **CRS* remained the most common AE**
  - CRS occurred in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon
- **The incidence of AEs and SAEs was stable compared with earlier analyses[1,2]**
  - No new AEs were reported, including ICANS, CRS, infections, or Grade 5 AEs

N (%)	N=154
AE Glofitamab-related	152 (99) 140 (91)
Grade ≥3 AE Glofitamab-related	100 (65) 69 (45)
SAE Glofitamab-related	75 (49) 46 (30)
Grade 5 (fatal) AE Glofitamab-related	11 (7) 0
AE leading to treatment discontinuation Glofitamab-related	14 (9) 5 (3)
AE leading to dose modification/interruption of glofitamab Glofitamab-related	29 (19) 16 (10)

Hutchings M, et al. ASH 2023; oral presentation (abstract #433).

Epcoritamab: phase I/II single agent clinical trial

Dose escalation

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

B-NHL:

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

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

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→

Treatment until PD[b,c] or unacceptable toxicity

→

LBCL Cohort N=157
DLBCL, HGBCL, PMBCL, and FL Gr3B

- 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

Treatment duration until progression

Thieblemont et al. J Clin Oncol. 2023; 41:2238-2247

Epcoritamab: phase I/II single agent clinical trial

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 et al. J Clin Oncol. 2023; 41:2238-2247

Responses Rate and Duration of Response

63.1%

Overall Response Rate
95% CI: 55.0–70.6

40.1%

Complete Response Rate
95% CI: 32.4–48.2

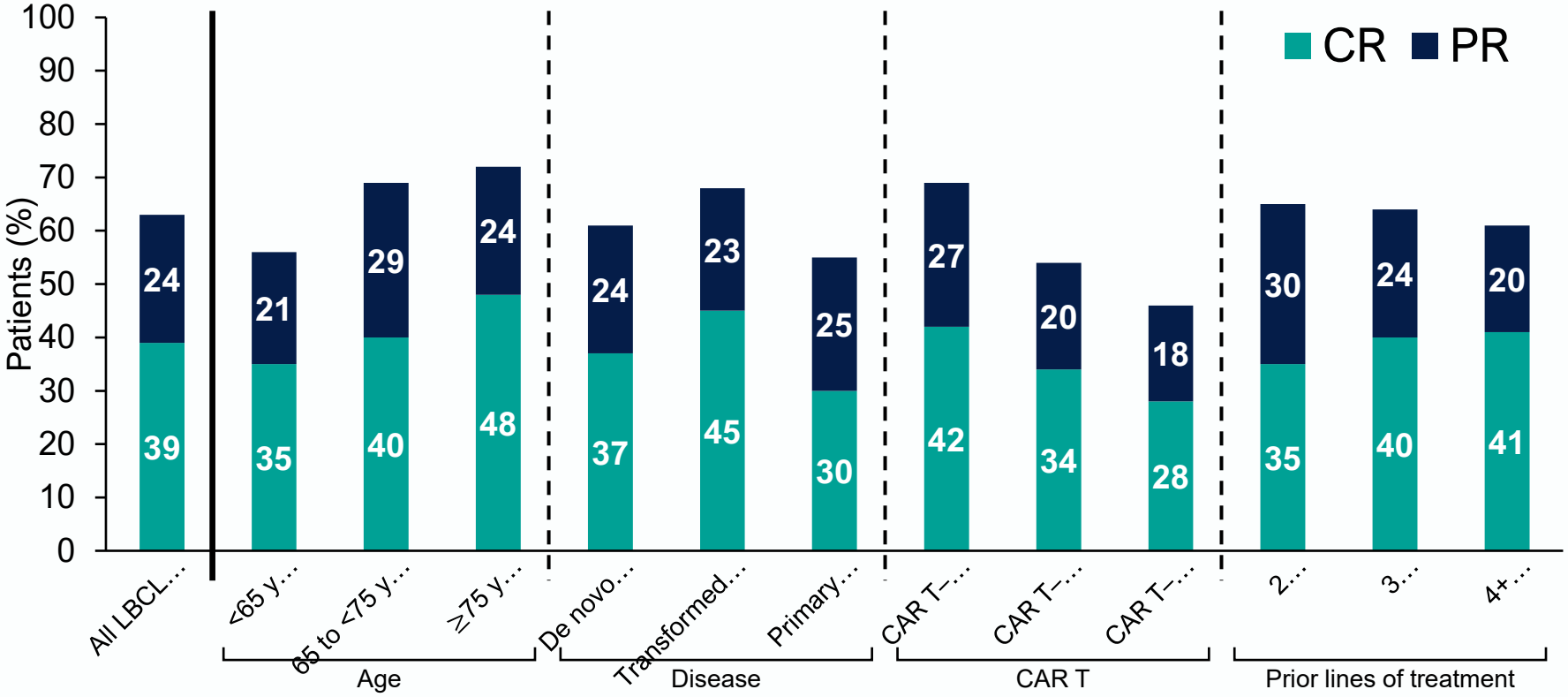
11 patients converted from PR to CR after wk 36 as later as wk 96

Median Duration of Response
95% CI: 9.7–26.5

Median Time to Response
95% CI: 1–8.4

Median follow-up time: 25.1 months (95% CI: 24–26)

Responses by IRC Across Key Subgroups



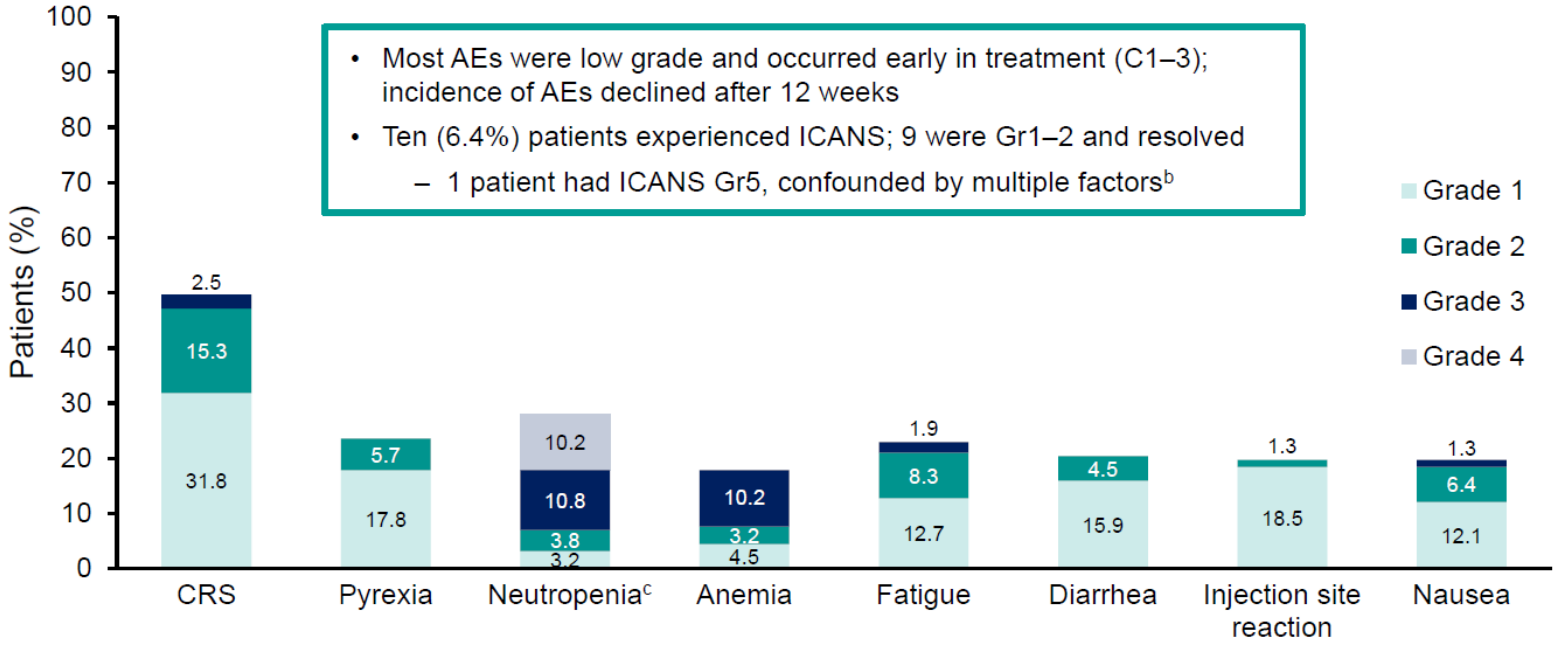
Slide Courtesy of C. Thieblemont

Thieblemont et al. J Clin Oncol. 2023; 41:2238-2247

Epcoritamab: phase I/II single agent clinical trial

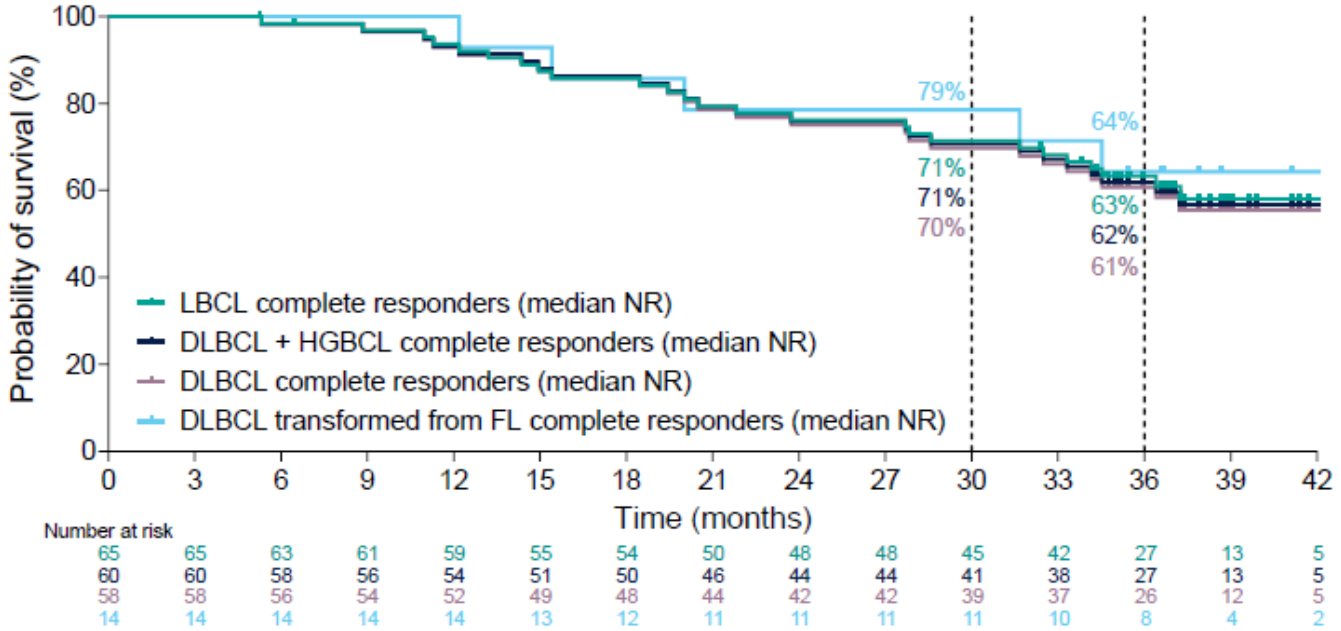
Adverse Events Were Primarily Low Grade

Treatment-Emergent Adverse Events[a] (≥15%) by Grade



Thieblemont et al. J Clin Oncol. 2023; 41:2238-2247

Long term PFS and OS Benefits with CR

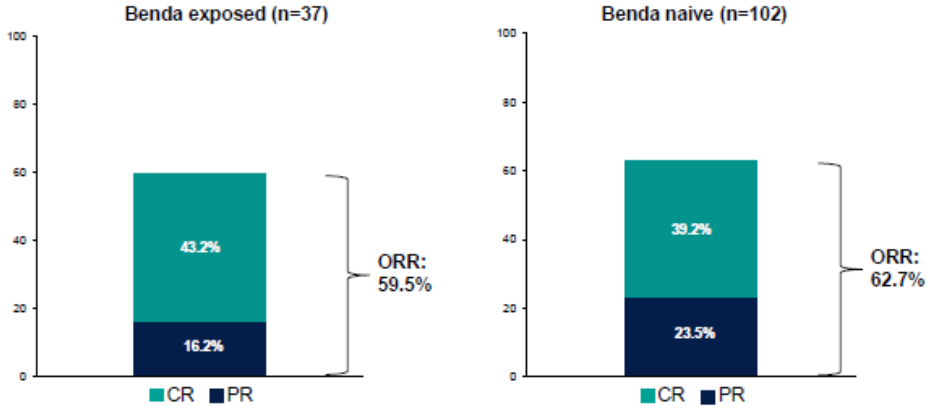


- **Among complete responders** (n=65), **median PFS** was **37.3 mo** (95% CI, 26-NR)
- **Median OS** for the overall population (n=157) was 18.5 mo, among **CR was NR** (**63% at 36 mo** in LBCL)

Vose JM et al. ASH 2024; Dec 2024; P4480, San Diego, Virtual

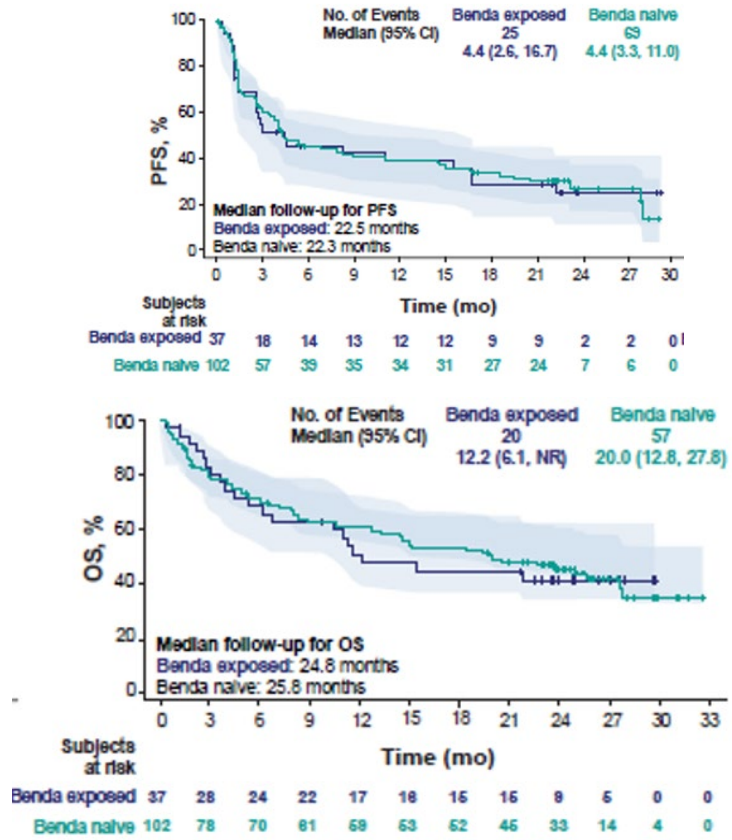
Bendamustine Exposure Did Not Impact Clinical Outcomes

Similar Response Rates With or Without Prior Benda Exposure



	Benda exposed	Benda naive
Duration of epcoritamab exposure, median (range), mo	3.5 (0.3–29.7)	4.32 (0.03–31.7)
Number of cycles, median	4	5
Time from benda exposure to start of epcoritamab, n (%)		
<6 mo	11 (29.7)	–
<12 mo	23 (62.2)	–

Benda, bendamustine; CR, complete response; ORR, overall response rate; PR, partial response.



Phillips T et al. ASH 2024 poster

Glofitamab

DLBCL

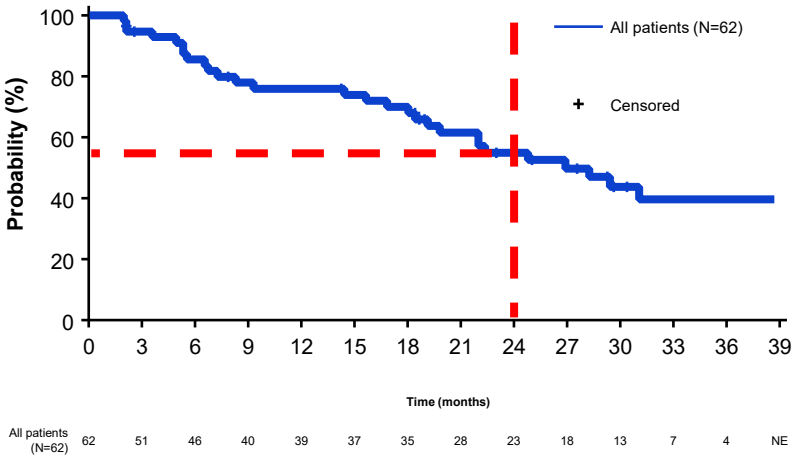
Epcoritamab

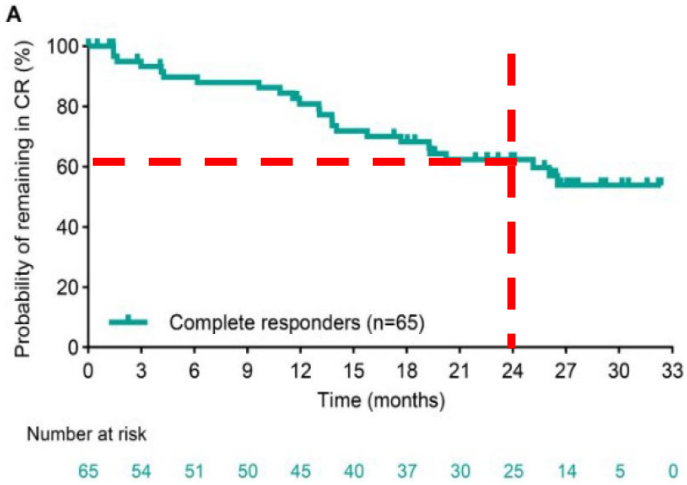
CR RATE

40%

40%

DOCR





- Median follow-up: 32 months

- Median follow-up: 31 months

ROUTE ADMINISTRATION

IV

SC

TREATMENT SCHEDULE

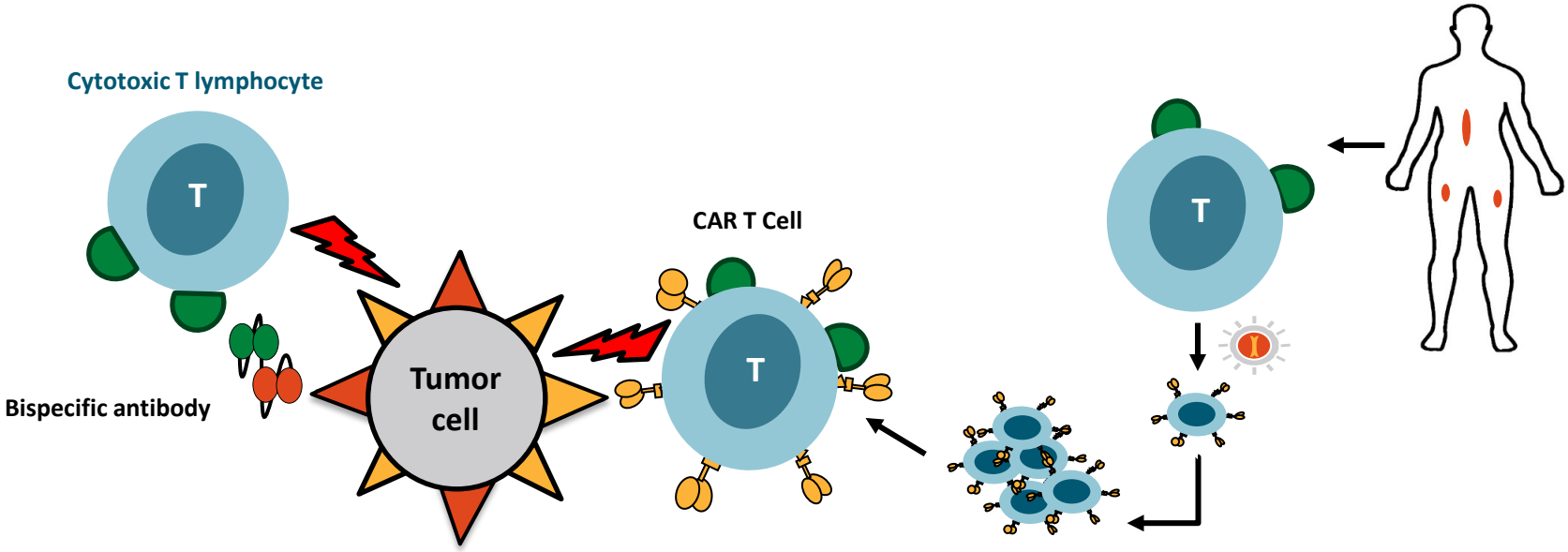
FIXED DURATION

UNTIL PROGRESSION/TOX

BSAB vs CAR-T cell Therapy RR-DLBCL 3L+

STUDIES	PRODUCTs	mFUP (m)	CRS ≥G3	ICANS ALL GRADES	CR RATE	ONGOING CR
ZUMA-1 JULIET TRASCEND	AXICEL TISACEL LISOCEL	63 40 24	13-23%	21-64%	39-58%	26-30%
NP30179 EPCORE NHL-1	GLOFITAMAB EPCORITAMAB	32 31	3-4%	6-8%	40%	22%-25%

Bispecific Antibodies vs CAR T-Cell Therapy in 3L



Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	In vitro manufacturing (3-4 wks)
Dosing	Repetitive	Single (following lymphodepleting CT)
CRS incidence	Less	Greater

Take home messages

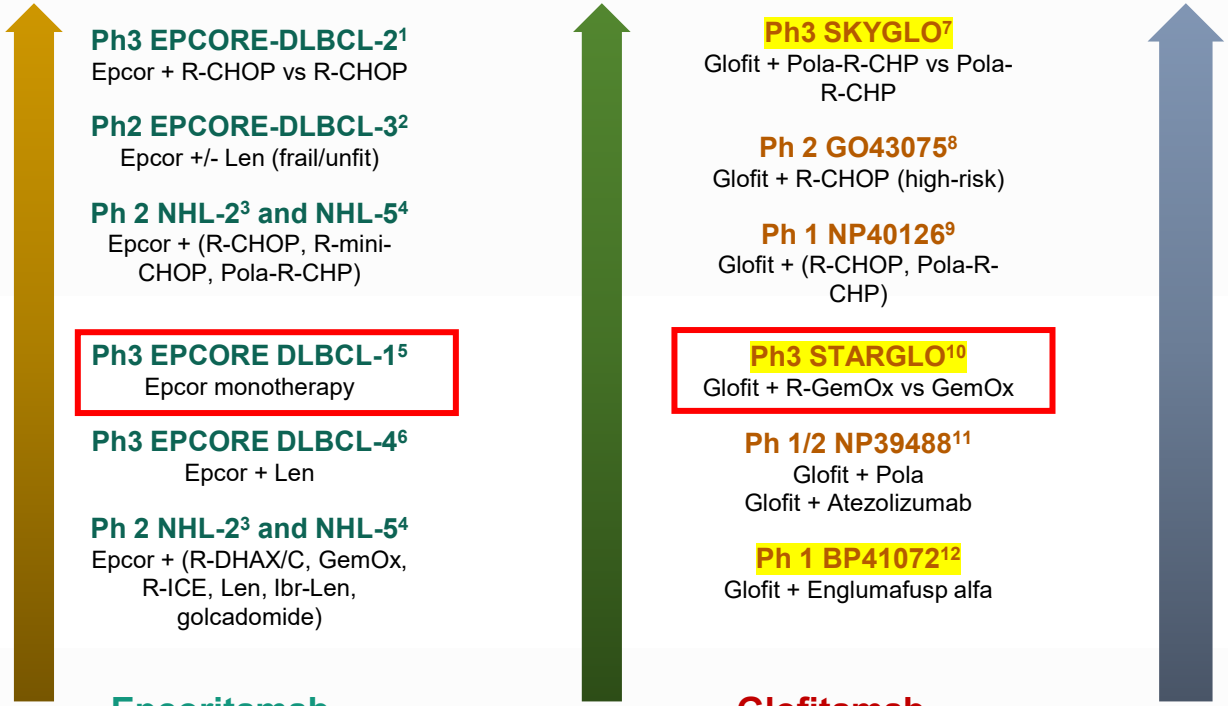
- Treatment paradigms for RR-NHL have shifted dramatically in the last decade following the introduction of **highly active immunotherapies**.

- **Bispecific antibodies (BsAb)** are showing encouraging activity in high-risk pretreated and refractory DLBCL both pre- and **post CAR T-cell therapy**

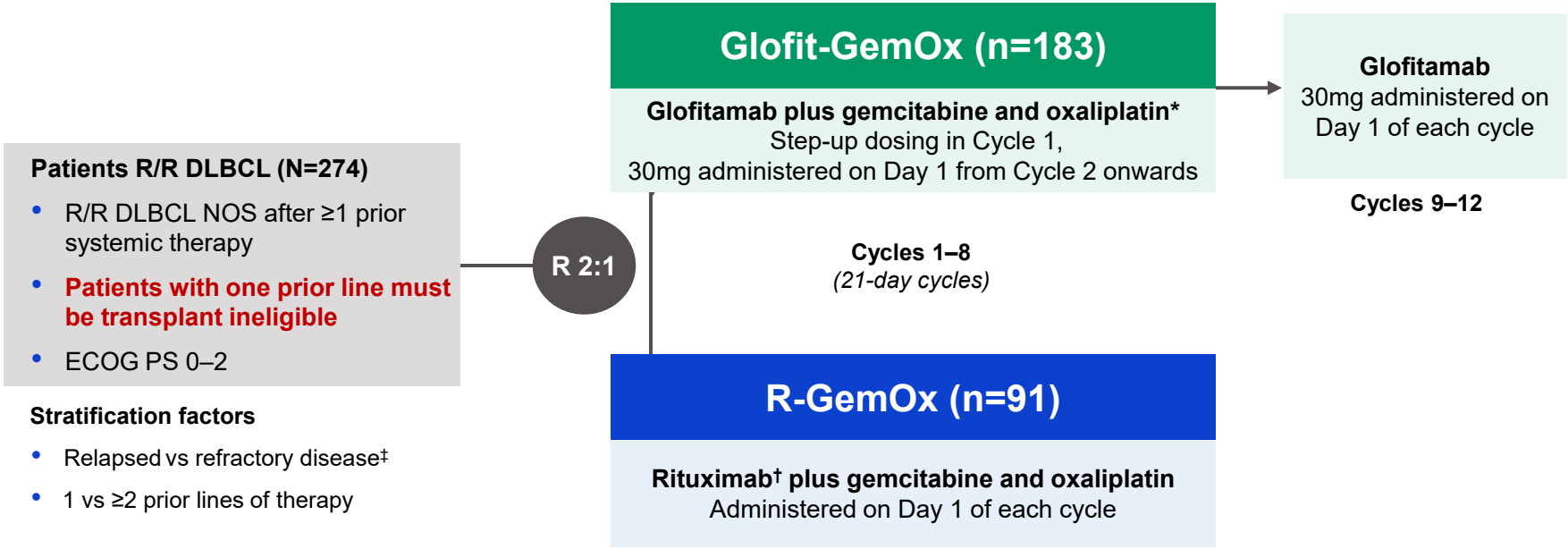
- **BsAb** are being increasingly used **in combination with other agents** to improve the rate and DORs, and numerous such trials underway attest to the appeal of this new therapeutic modality.

- **BsAb** are currently the **standard therapy for 3L + of DLBCL** patients . Novel BsAb based combinations will challenge **2L e 1L treatment algorithms in the next future**

Bispecific future perspective in DLBCL



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



Primary endpoint	**Overall survival**
Key secondary endpoints (hierarchical)	Progression-free survival by IRC assessment
	Complete response rate by IRC assessment
	Duration of complete response by IRC assessment

Abramson.J et al Lancet 2024

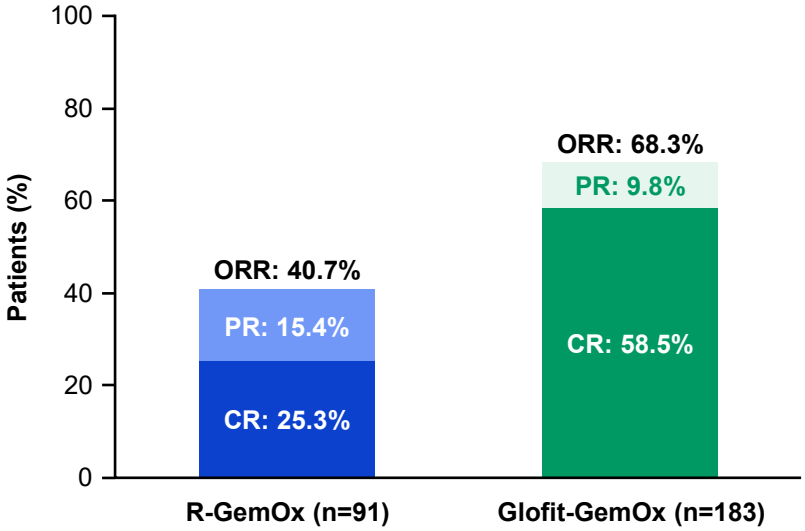
Baseline characteristics

n (%), unless otherwise stated		R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years	Median (range) ≥65 years	68.0 (20–84) 56 (61.5)	68.0 (22–88) 116 (63.4)
Sex	Male	53 (58.2)	105 (57.4)
Race	Asian Black or African American White Unknown	51 (56.0) 1 (1.1) 33 (36.3) 6 (6.6)	86 (47.0) 2 (1.1) 82 (44.8) 13 (7.1)
ECOG PS	0 1 2	44 (50.0) 36 (40.9) 8 (9.1)	72 (40.0) 89 (49.4) 19 (10.6)
Ann Arbor stage	I–II III–IV	20 (22.0) 70 (76.9)	60 (32.8) 123 (67.2)
Number of prior lines of therapy	1 ≥2	57 (62.6) 34 (37.4)	115 (62.8) 68 (37.2)
Primary refractory	Yes	47 (51.6)	106 (57.9)
R/R to last prior therapy	Relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Bulky disease (≥10cm)	Present	14 (15.4)	23 (12.6)
Cell of origin at initial diagnosis	GCB Non-GCB (including ABC) Unknown	29 (31.9) 50 (54.9) 12 (13.2)	60 (32.8) 103 (56.3) 20 (10.9)
Prior CAR T-cell therapy	Received	8 (8.8)	13 (7.1)

Abramson.J et al Lancet 2024

Response rates by IRC assessment

Response rates at the updated analysis

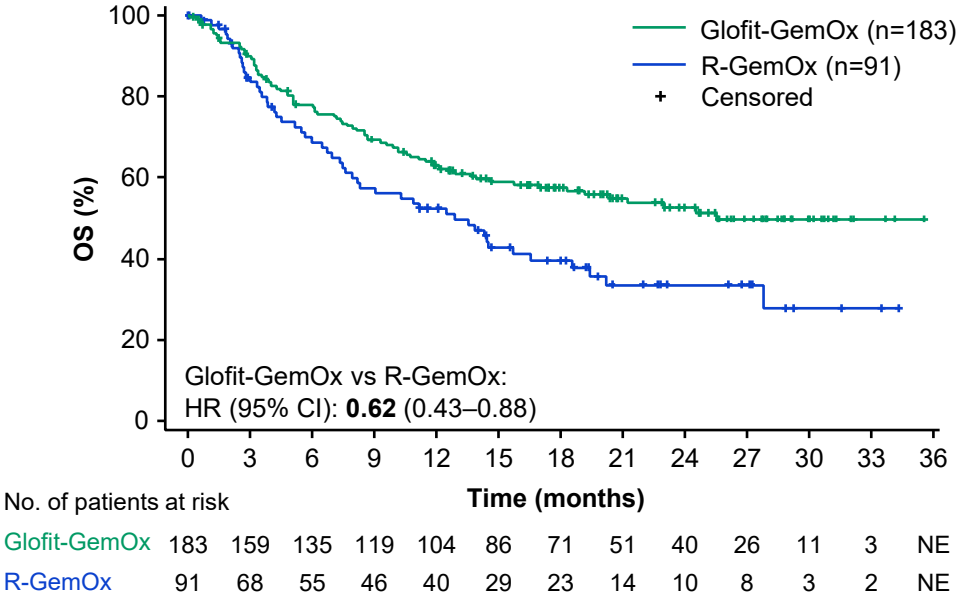


- **33.2%** difference in CR rate between treatment arms (95% CI: 19.7–44.5)
- CR rate significantly better with Glofit-GemOx vs R-GemOx (descriptive p-value **<0.0001***)

CR rate was statistically significant at primary analysis, with increased difference between treatment arms at the updated analysis

Primary endpoint: overall survival

Updated analysis

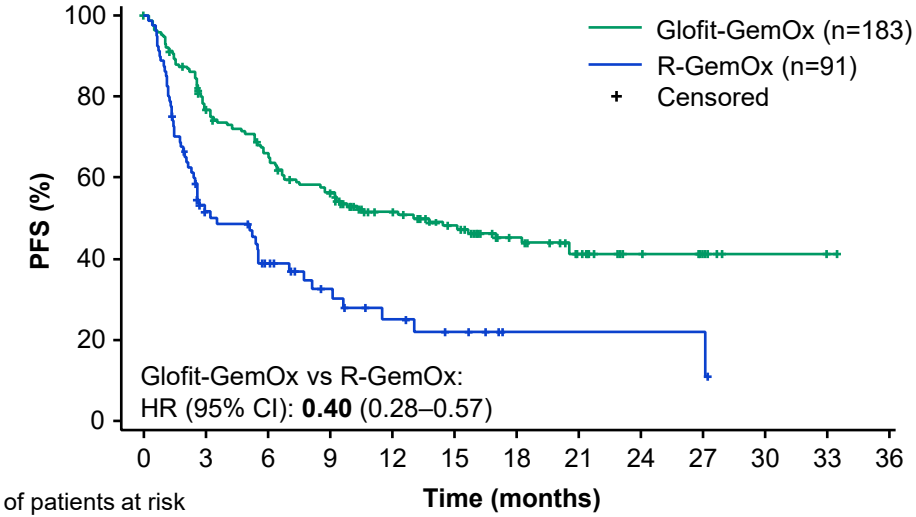


	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)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

Progression-free survival by IRC assessment

Updated analysis



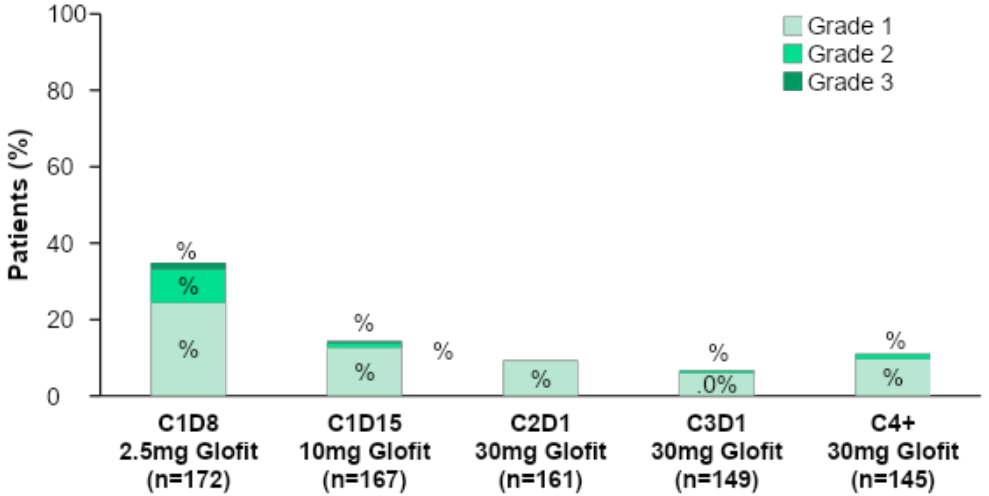
	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 9.6 months)		
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)
HR (95% CI)	**0.37** (0.25–0.55)	
p-value*	<0.000001	
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
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)

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

Cytokine release syndrome

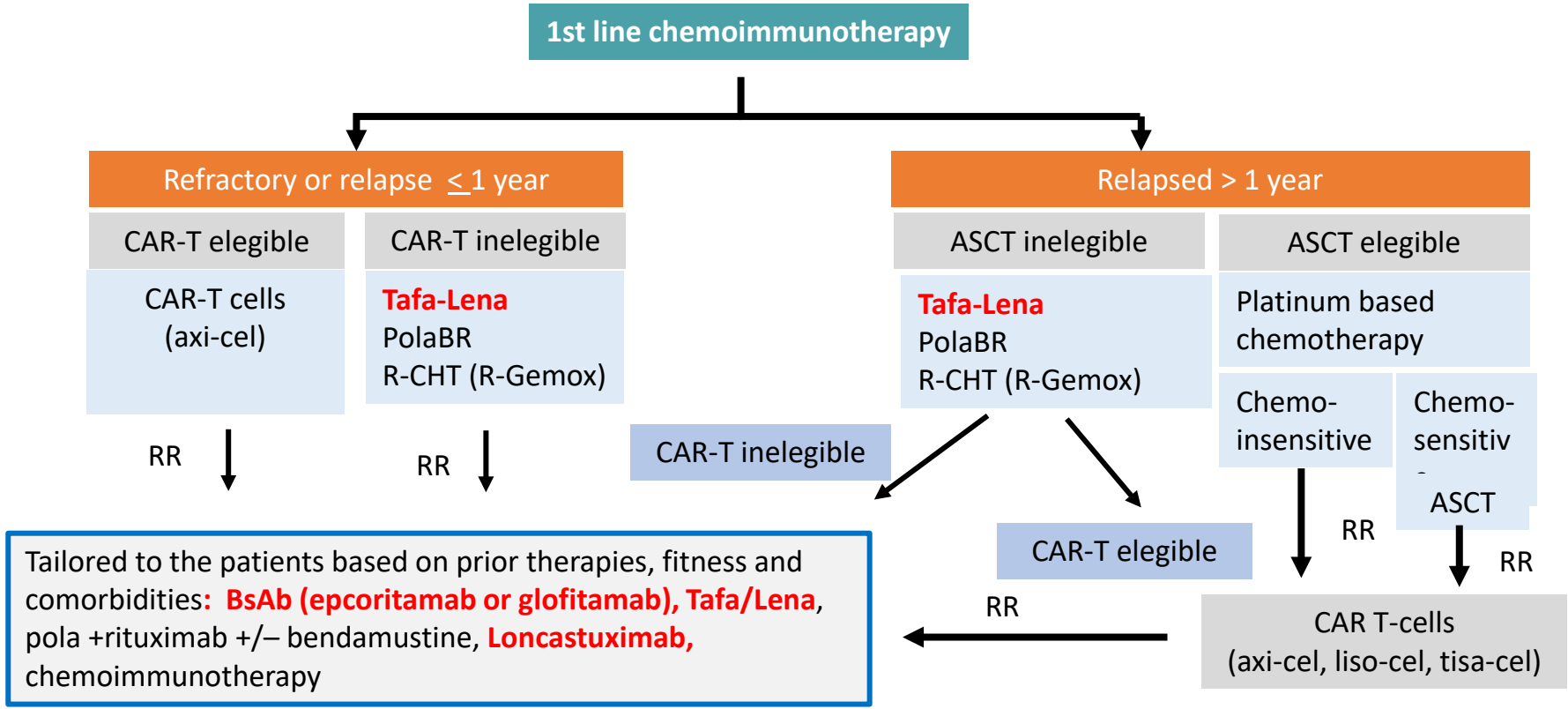
n (%) of patients with ≥1 CRS AE*	Glofit-GemOx (Glofit exposed) n=172
Any grade†	76 (44.2)
Grade 1	54 (31.4)
Grade 2	18 (10.5)
Grade 3	4 (2.3)‡
Median time to CRS onset, hours (range)	
2.5mg glofitamab (C1D8)	13.5 (4.4–134.9)
10mg glofitamab (C1D15)	32.4 (7.4–564.3)
Median CRS duration, hours (range)	
2.5mg glofitamab (C1D8)	22.7 (0.0–168.0)
10mg glofitamab (C1D15)	24.0 (0.0–248.5)
Tocilizumab for CRS management, n / n (%)	28 / 76 (36.8)
Corticosteroids for CRS management, n / n (%)	39 / 76 (51.3)

CRS by cycle and grade in the updated analysis



CRS mainly occurred in C1 and was predominantly low grade

Therapeutic algorithm for relapsed LBCL



Adapted from Haydu JE, Blood Advances 2024

SAPIENZA
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Grazie!

… a voi tutti per l'attenzione

Gruppo per la terapia dei linfomi non Hodgkin
Ematologia Sapienza Roma