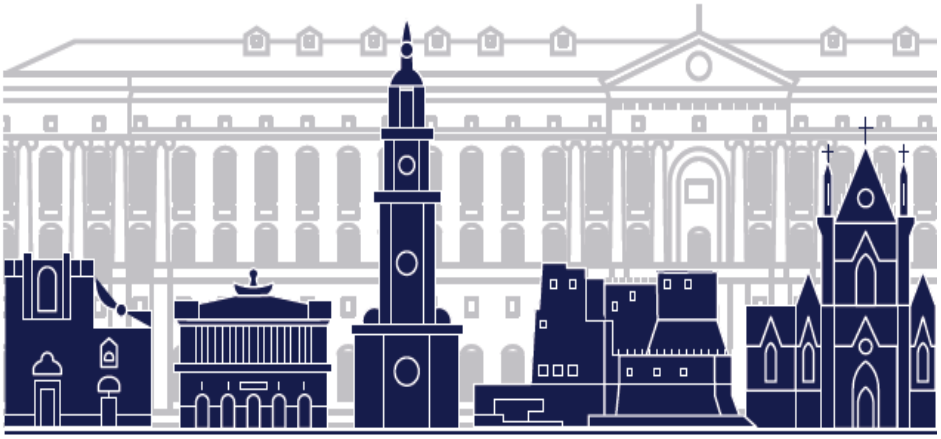
con il patrocinio di

AIL Caserta Valentina Picagio

SIE
Società Italiana
di Ematologia

2024:
È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

Napoli, Hotel Paradiso • 29-30 aprile 2024



SESSIONE I – DLBCL

Moderatori: *A. Di Rocco (Roma), C. Patti (Palermo)*

Quando è possibile l'approccio con anticorpi ingegnerizzati o «Drug-coniugati»?

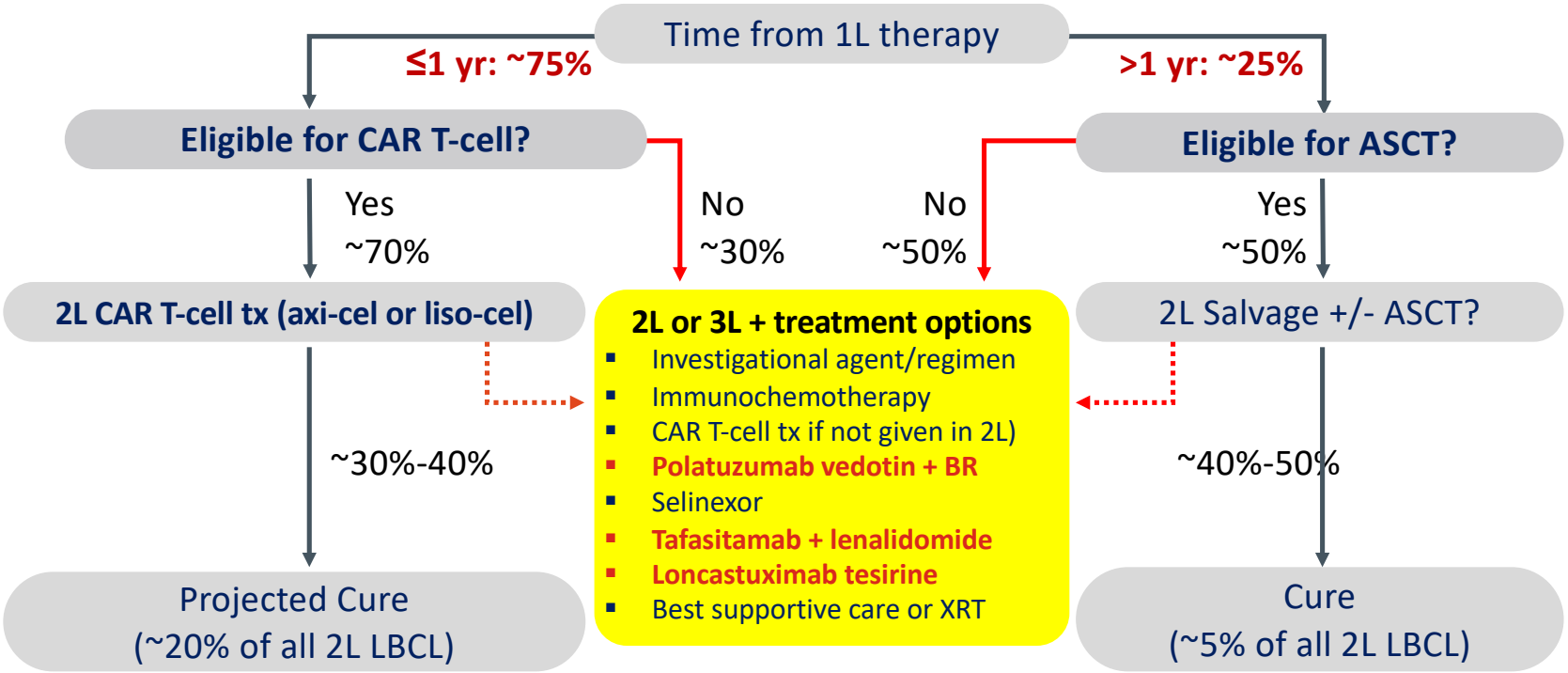
Maurizio Martelli
Dip. Medicina Traslazionale e di Precisione
Università Sapienza Roma

Disclosure

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Gilead					X	X	
Novartis						X	
Takeda						X	
Recordati					X	X	
Incyte					X	X	
Janssen					X	X	
BMS						X	
Beigene					X	X	
Alexion	x						

CD19-Targeted CAR T-Cell Therapy Has Dichotomized the Management of R/R DLBCL

New algorithm for Second-line Therapy of LBCL

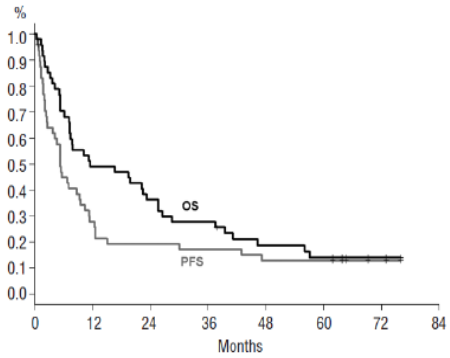


Westin. Blood. 2022;139:2737.

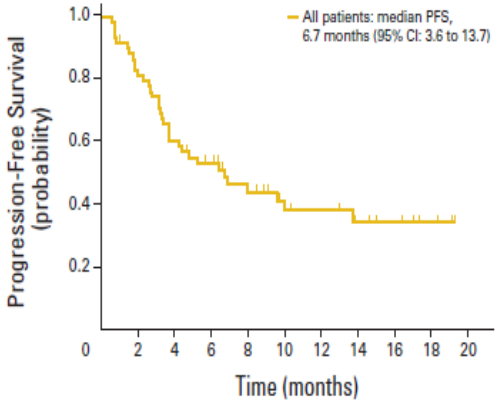
Unsatisfactory outcome among patients non-eligible to ASCT

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	32	65	78	50	Median 9 mo	Corazzelli G, Cancer Oncol 2009
R-Bendamustine	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

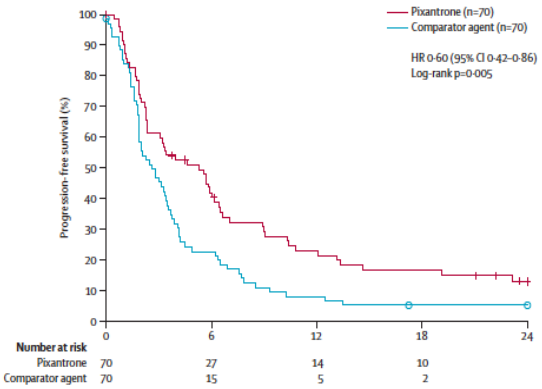
R-GemOx



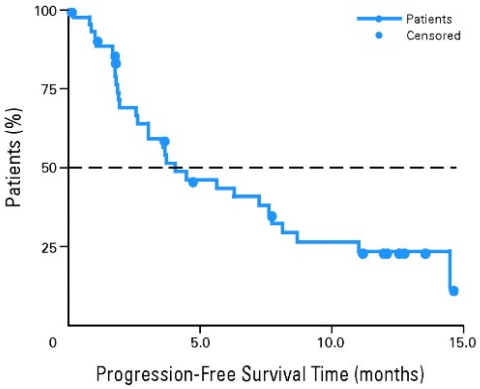
R-bendamustine



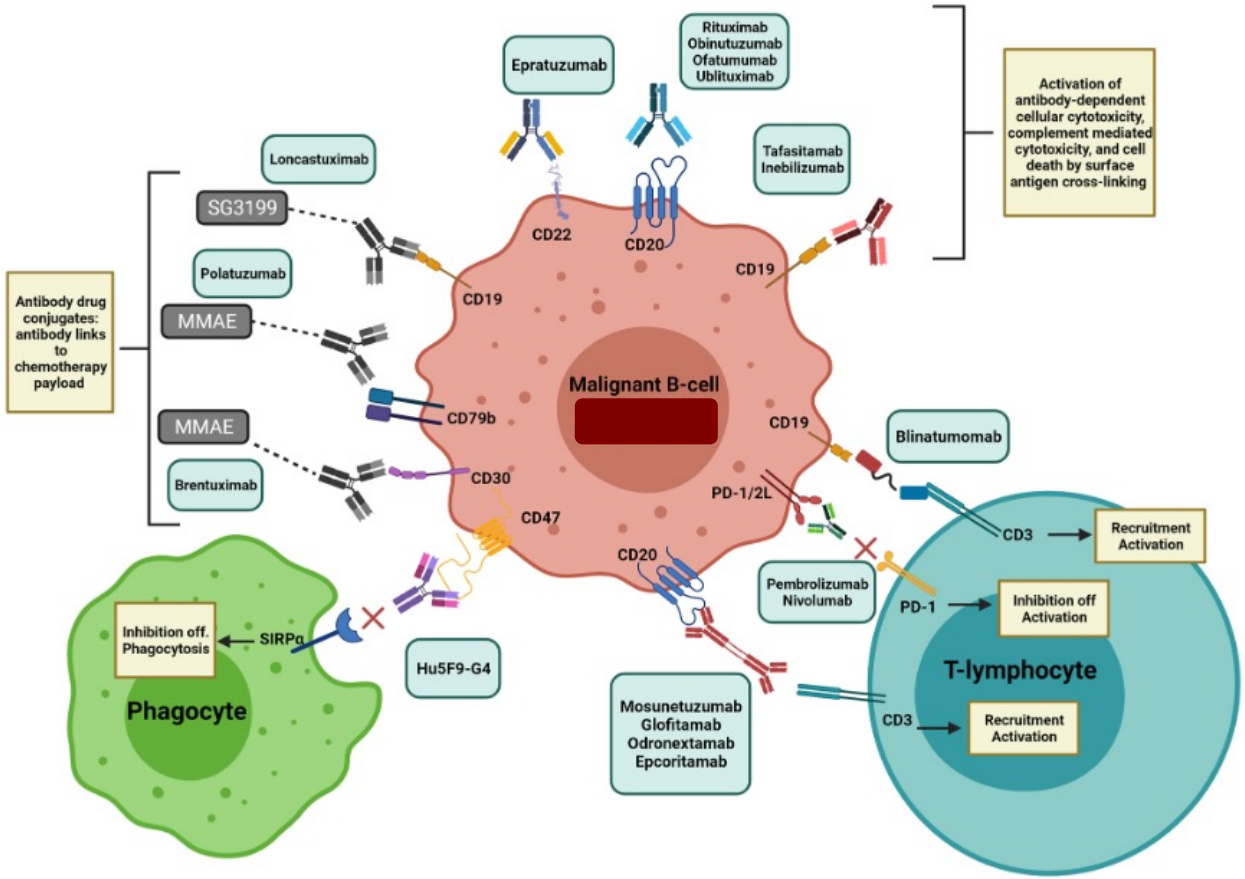
Pixantrone



Lenalidomide



Novel strategies on immune-based therapy in DLBCL



BTKI inhibitor

ADC - Polatuzumab Vedotin/R-Benda*

ADC - Loncastuximab Tesirine*

Engineered Ab - Tafasitamab/Lena*

CAR-T Cells*

Bispecific Antibodies-
Glofitamab* ,Epcoritamab*

* FDA/EMA approved

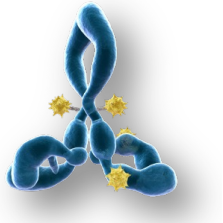
Willard et al. Leukemia Research Reports 16 (2021) 100275

Novel therapies approved in RR-DLBCL

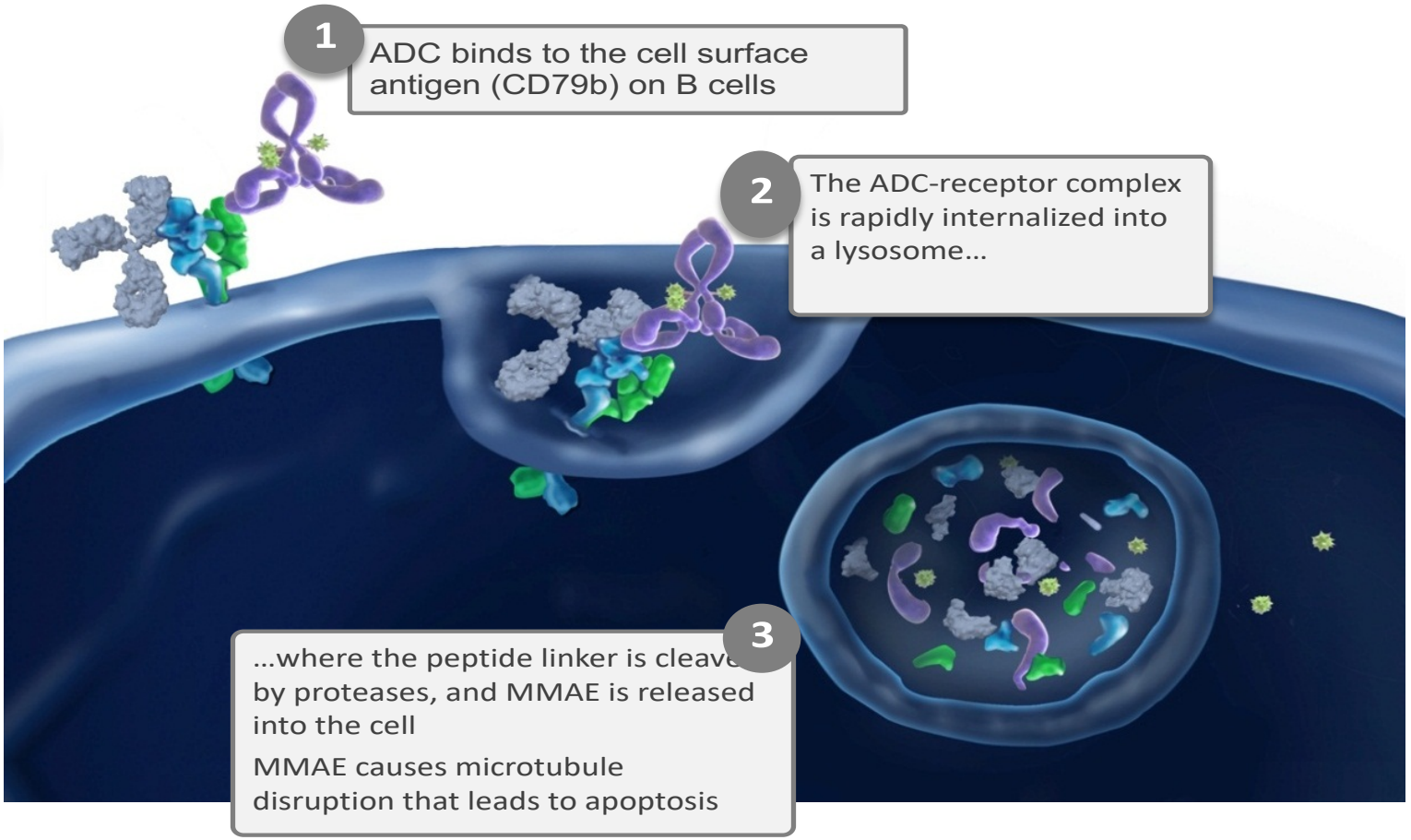
	Pola-BR	Tafasitamab/Lenalidomide	Loncastuximab Tesirine
MOA	Anti-CD79b ADC	Anti-CD19 mAb/Immunomodulator	Anti-CD19 ADC
ORR	45%	58%	48%
CR rate	40%	40%	24%
PFS	9.2 m	11.6 m	4.9 m
DOR	12.6 m	43.9 m	10.3 m
OS	12.4 m	33.5 m	9.9 m

Sehn LH et al Blood Adv.2022; Caimi PF et al Lancet Oncol. 2021 ;Duell J.et al Haematologica 2021;

Polatuzumab vedotin: ADC binds CD79b



Binds CD79b and ADC-receptor complex internalized

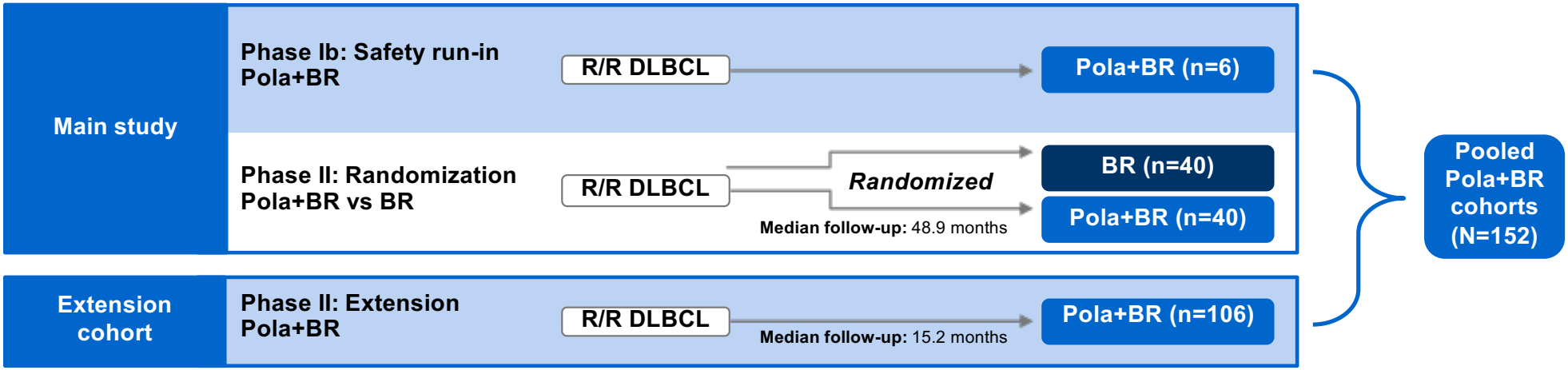


Randomised Phase II study of pola-BR versus BR (GO29365): study design

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



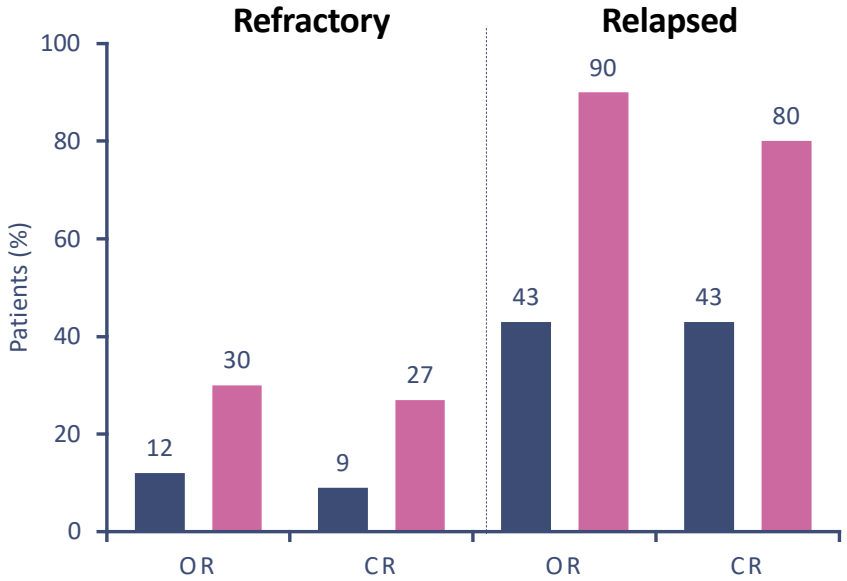
Patient clinical characteristics

	Randomized		Extension cohort	Pooled Pola+BR*
	BR (N=40)	Pola+BR (N=40)	Pola+BR (N=106)	Pola+BR (N=152)
Median age, years (range)	71 (30–84)	67 (33–86)	70 (24–94)	69 (24–94)
Male, n (%)	25 (62.5)	28 (70.0)	52 (49.1)	84 (55.3)
ECOG PS score, n (%)†				
0–1	31 (77.5)	33 (82.5)	92 (86.8)	131 (86.2)
2	8 (20.0)	6 (15.0)	14 (13.2)	20 (13.2)
Ann Arbor Stage III/IV at study entry, n (%)	36 (90.0)	34 (85.0)	84 (79.0)	122 (80.0)
IPI score 3–5 at enrollment, n (%)	29 (72.5)	22 (55)	70 (66.0)	94 (61.8)
Median no. of prior therapies (range)	2 (1–5)	2 (1–7)	2 (1–7)	2 (1–7)
1 line	12 (30.0)	11 (27.5)	37 (34.9)	50 (32.9)
2 lines	9 (22.5)	11 (27.5)	27 (25.5)	42 (27.6)
3 lines	10 (25.0)	12 (30.0)	19 (17.9)	31 (20.4)
≥4 lines	9 (22.5)	6 (15.0)	23 (21.7)	29 (19.1)
Prior stem cell transplant, n (%)	6 (15.0)	10 (25.0)	17 (16.0)	27 (17.8)
Primary refractory, n (%)‡	28 (70.0)	21 (52.5)	73 (68.9)	97 (63.8)
Refractory to last prior therapy, n (%)‡	33 (82.5)	30 (75.0)	81 (76.4)	116 (76.3)

GO29365: Pola-BR improved response rates versus BR independent of patients' prior treatment experience

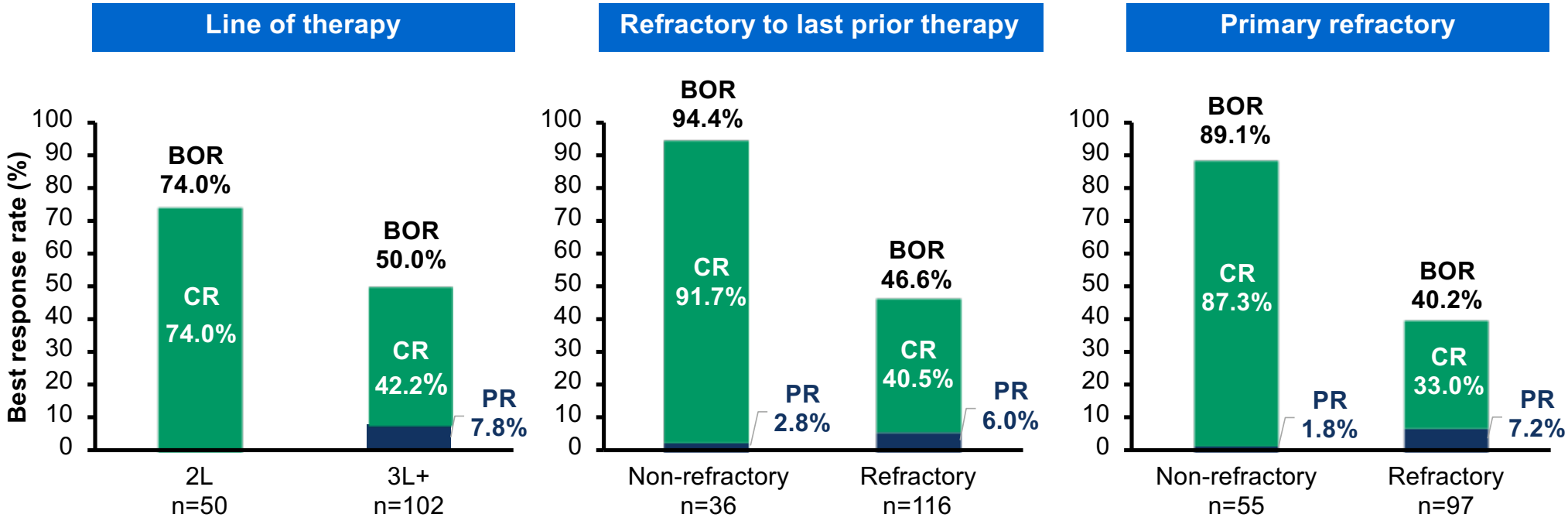
OR and PET-CR rates by prior line of therapy

OR and PET-CR rates by refractory status



Sehn L, et al. J.Clin Oncol 2019

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

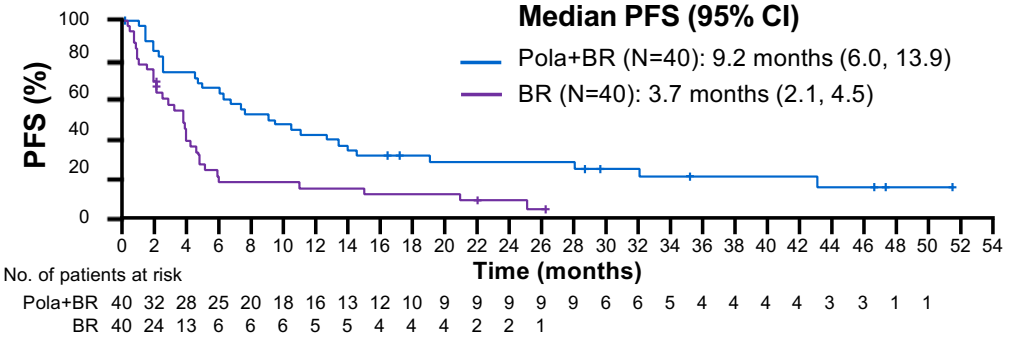


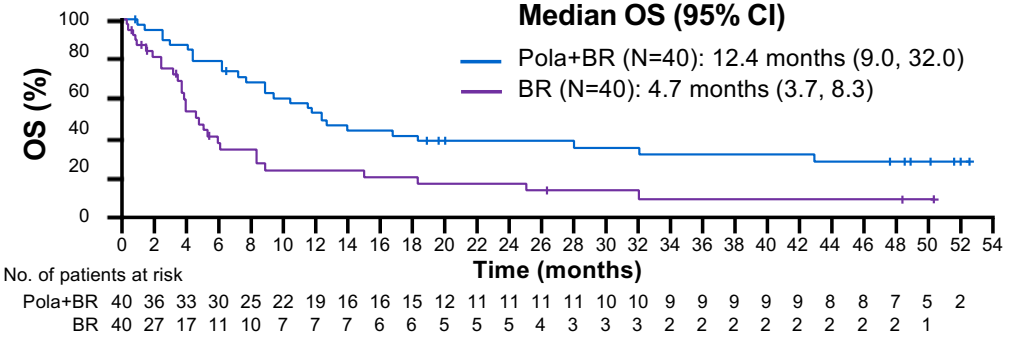
Responses were observed regardless of line of therapy and refractory status.
The vast majority of responding patients achieved a CR

Sehn LH, et al. Blood advances 2021

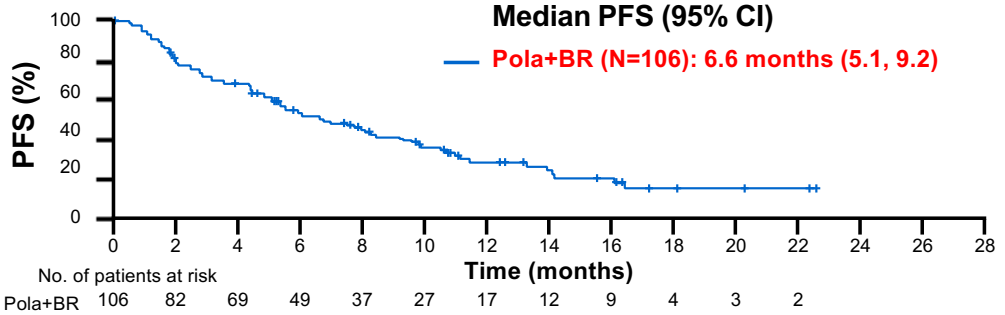
PFS and OS in randomized and extension cohorts

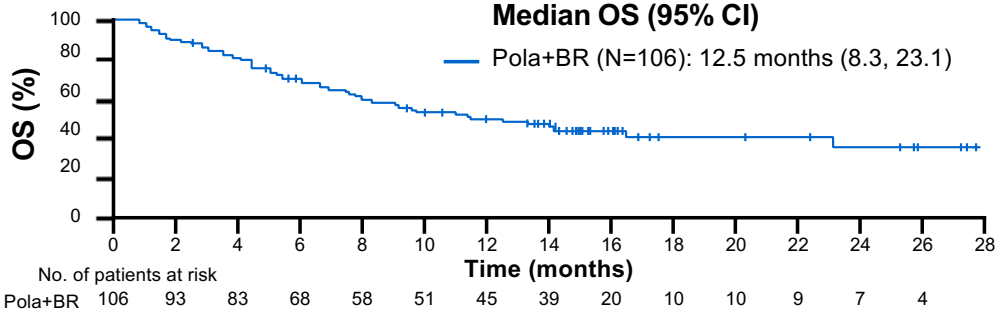
Randomized





Extension cohort





Sehn LH, et al. Blood advances 2021

Pola-BR Real Word Experience comparison

	n	Refractory to last prior therapy	Median n° prior lines tx	mOS months	mPFS months	CR rate	ORR	mFUP months
Sehn et al. Pooled cohort	152	76.3	2 (1-7)	12.5	**6.6**	**40.1**	57.9	
Vodicka et al.	21	76.2		8.7	3.8	23.8	33.3	6.8
Dimou et al.	49*	78.0	2 (1-9)	8.5	4.0	20.0 25.0 (best)	35.0 43.0 (best)	10.8
Segman et al.	47	23.0	3 (2-4)	8.3	5.6	40.0	61.0	6.8
Liebers et al.	54	87	3	5.5	3.25	14.8 (best)	48.1 (best)	7.5
Northend et al.	133	68.4		8.2	4.8	31.6 (best)	57.0(best)	7.7
Argnani et al.	55	81.8		9.0	4.9	18.2 27.3 (best)	32.7 49.1(best)	11

Pola-BR Real Word Experience: conclusions

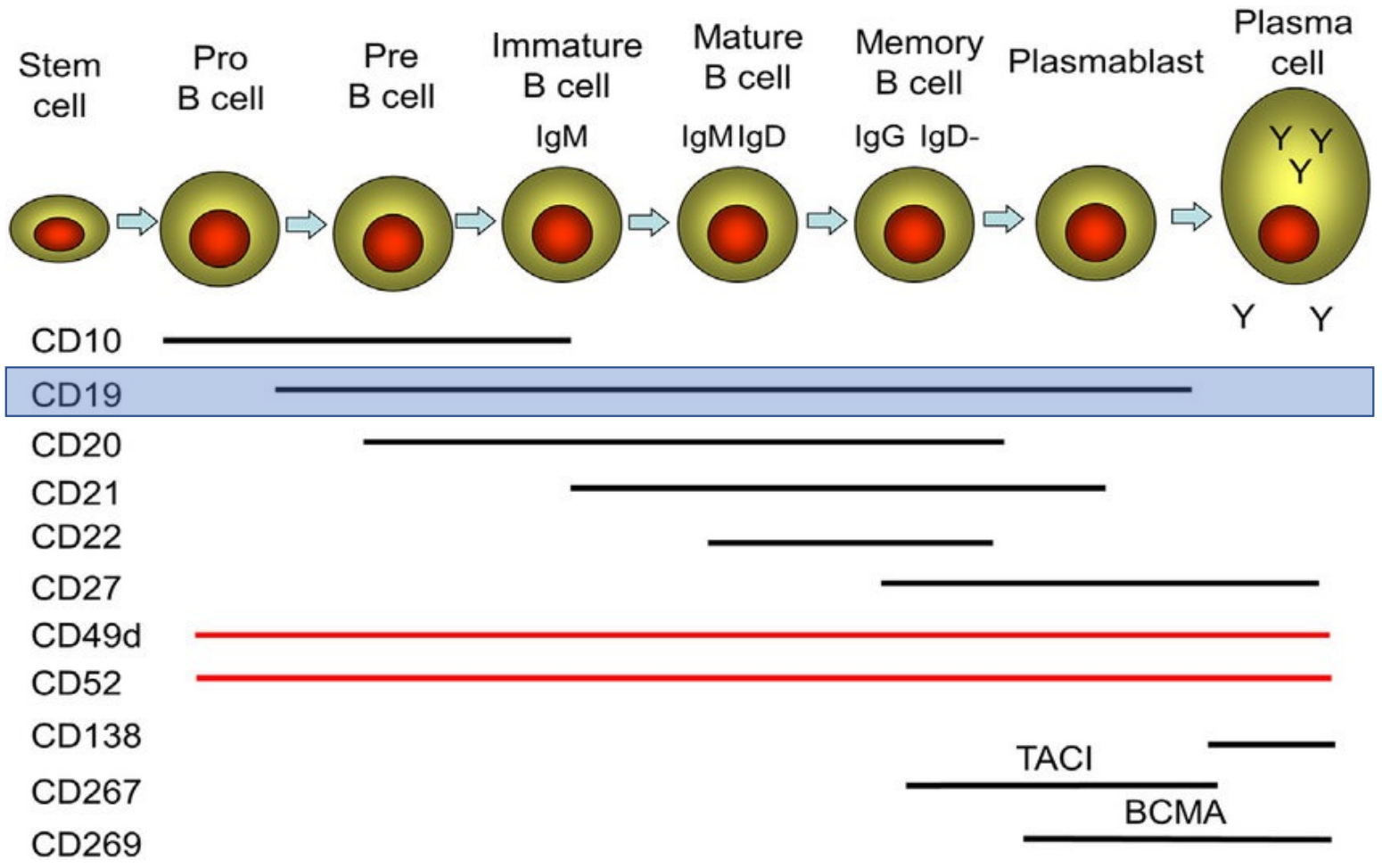
OVERALL INFERIOR OUTCOME RESULTS:

- More heavily pretreated patients
- Prior CART treated patients

USEFUL INFORMATION:

- No New Safety Signal
- **Pola-R Similar Efficacy than Pola-BR** (No Randomized Data!) (Israel And Italian Data)
- 1 Prior Line patients Or No Refractoriness Are Better Candidates (Greek And Uk Data)
- **Pola-R Useful Bridge To Cart** (German Data)
- Signal possible efficacy post CART (few patients)

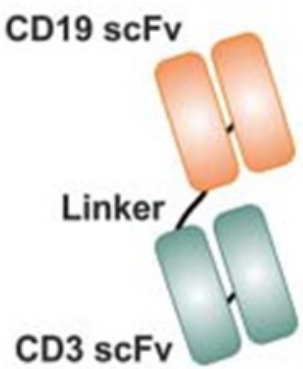
CD19 expression in B cells



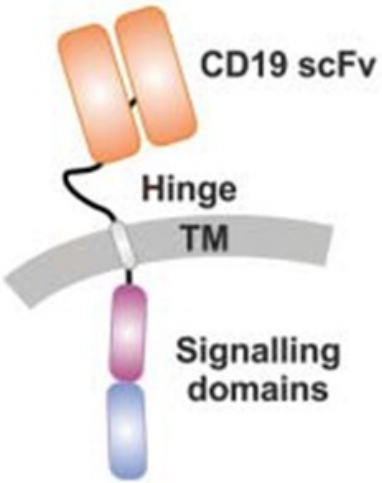
Baker et al, Lancet Disc Sci 2017

Multiple Targeting anti CD19 strategies

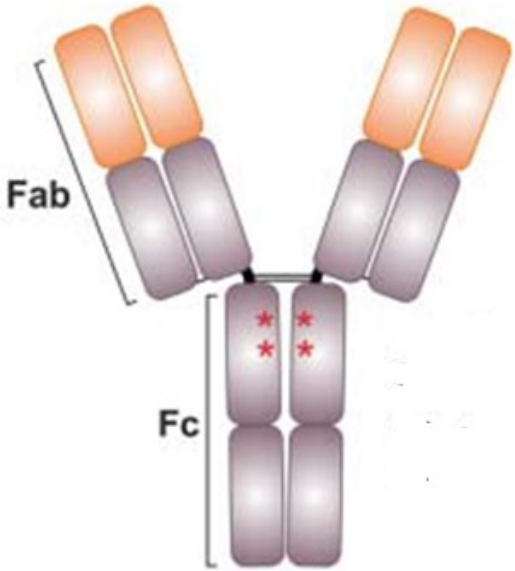
BLINATUMOMAB (BITE)



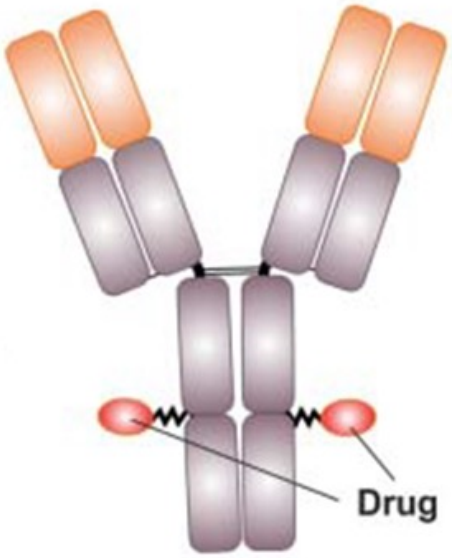
CAR-T cells



TAFASITAMAB (engineered Ab)



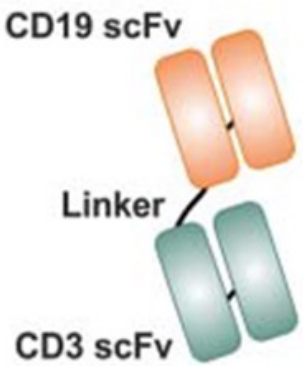
LONCASTUXIMAB TESIRINE (ADC)



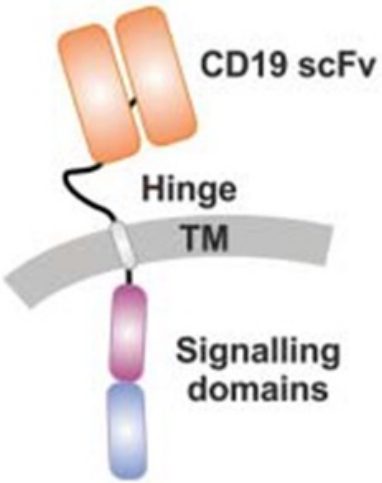
Kellner et al., Oncoimmunol 2018.

Multiple Targeting anti CD19 strategies

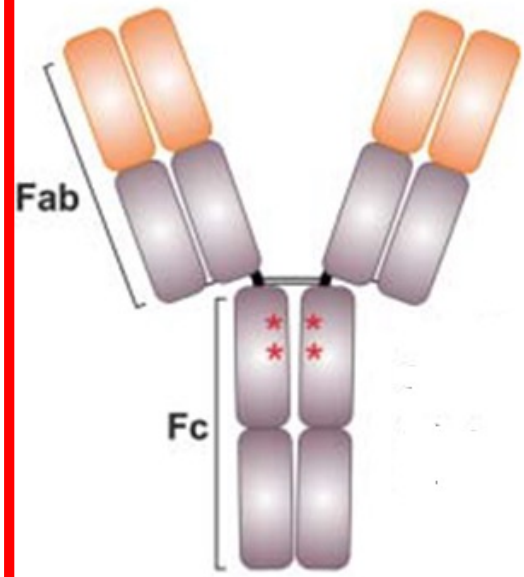
BLINATUMOMAB (BITE)



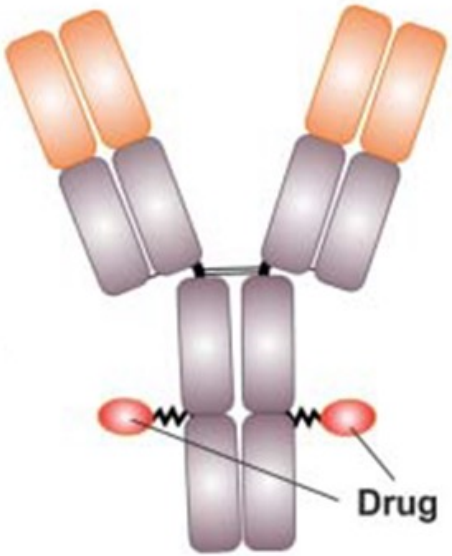
CAR-T cells



TAFASITAMAB (engineered Ab)

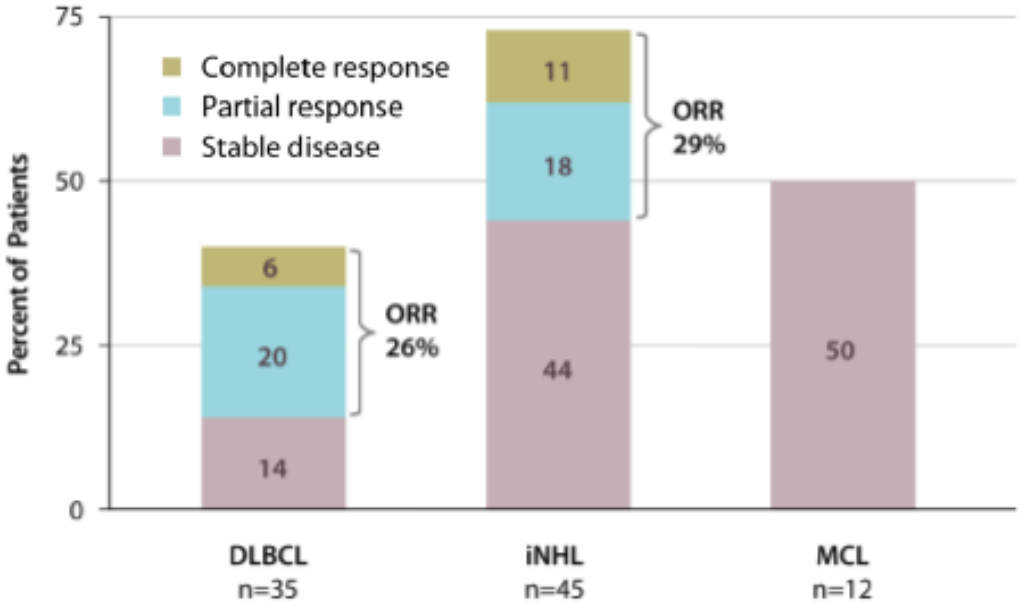


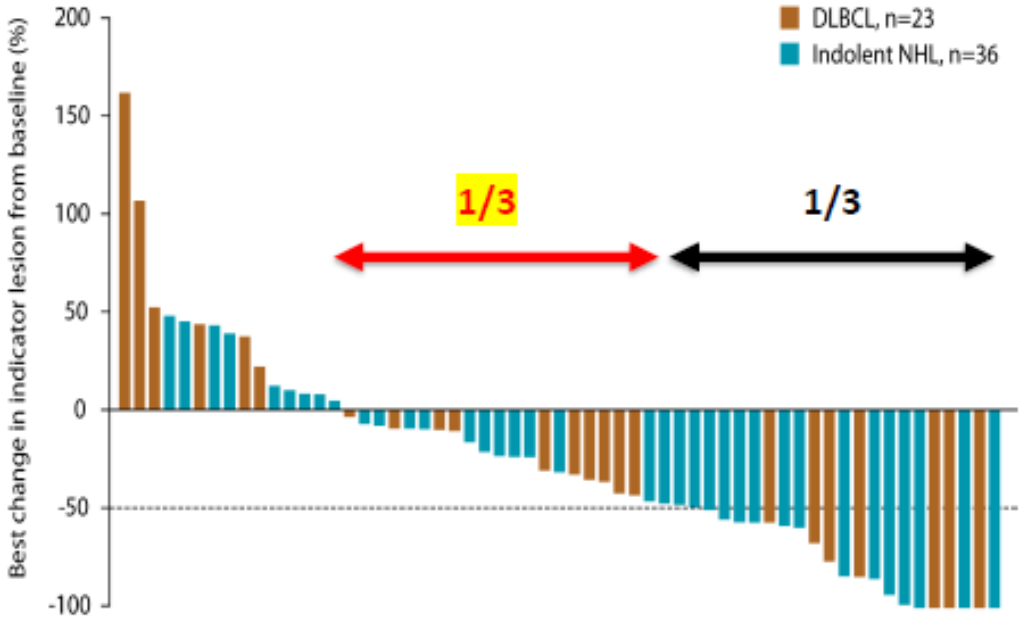
LONCASTUXIMAB TESIRINE (ADC)



Kellner et al., Oncoimmunol 2018.

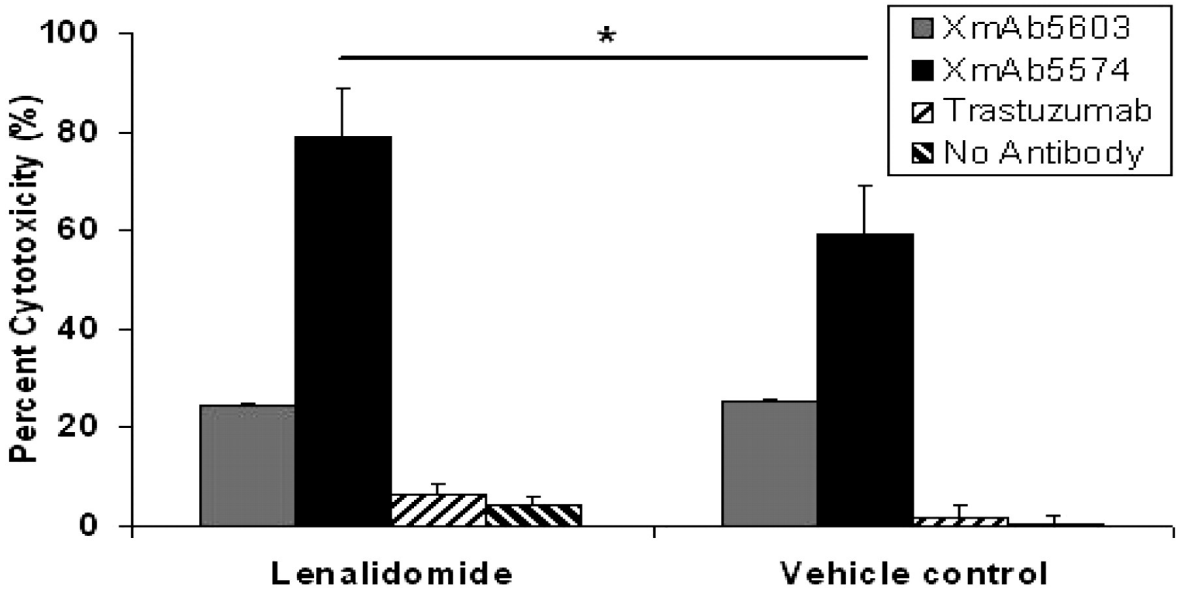
Phase II a: MOR208 in R-R NHL – Best Overall Response Rate





Jurczak W and Zinzani PL, *Ann Oncol* 2018

LENALIDOMIDE INCREASES NK-CELL EXPRESSION OF FCγRIII, ENHANCING XMAB5574 (TAFASITAMAB)-INDUCED NK CELL-MEDIATED ADCC AGAINST CLL



Lapalombella et al., Blood 2010

MODE OF ACTIONS PROVIDE THE RATIONALE FOR TAFASITAMAB + LENALIDOMIDE COMBINATION

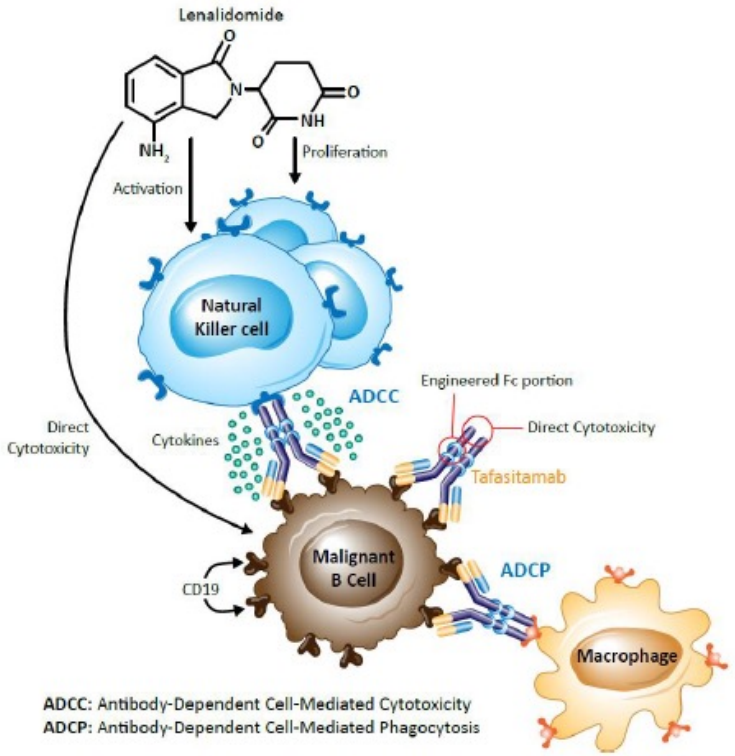
Tafasitamab MoA

- Antibody Dependent Cellular Cytotoxicity via NK cells (ADCC)
- Antibody Dependent Cellular Phagocytosis (ADCP)
- Direct cytotoxicity

Lenalidomide MoA

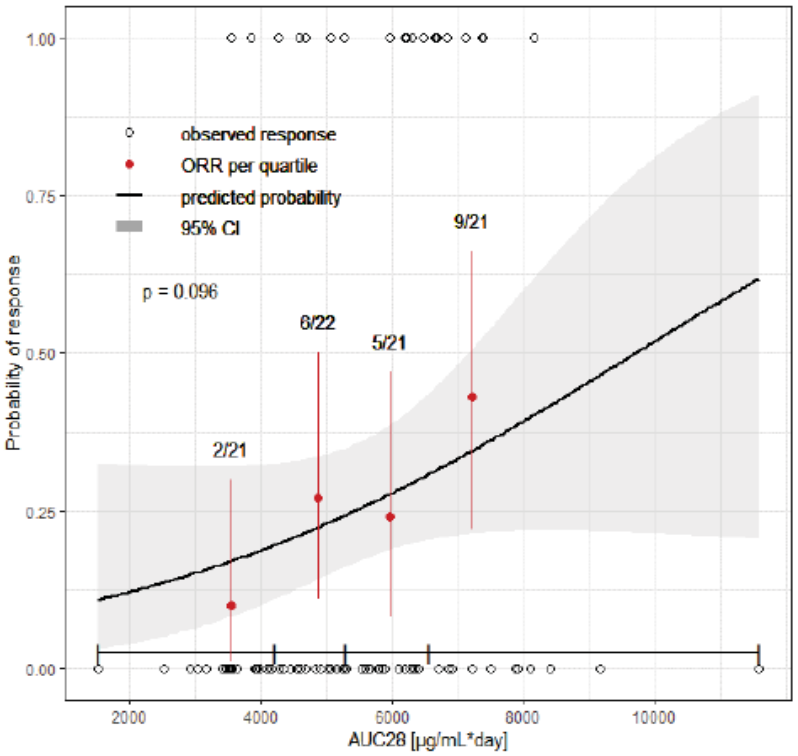
- Direct cytotoxicity
- Increase NK cell numbers (ADCC)
- Activate NK cells

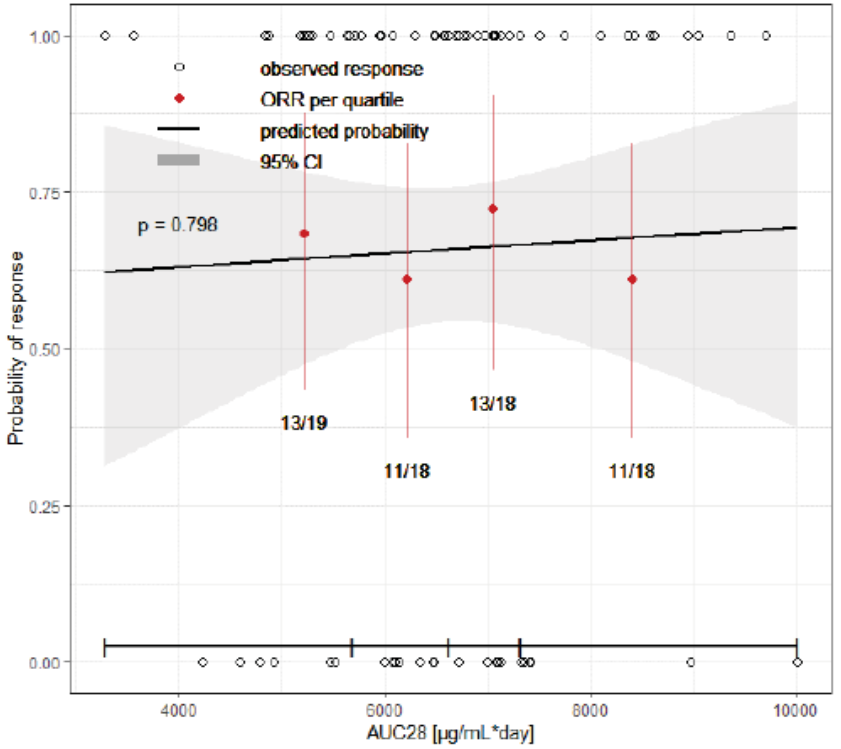
Increased anti-tumor effects



Salles 2020 on file

RESPONSE PROBABILITY VERSUS AUC28 FOR TAFASITAMAB AND TAFASITAMAB-LENALIDOMIDE

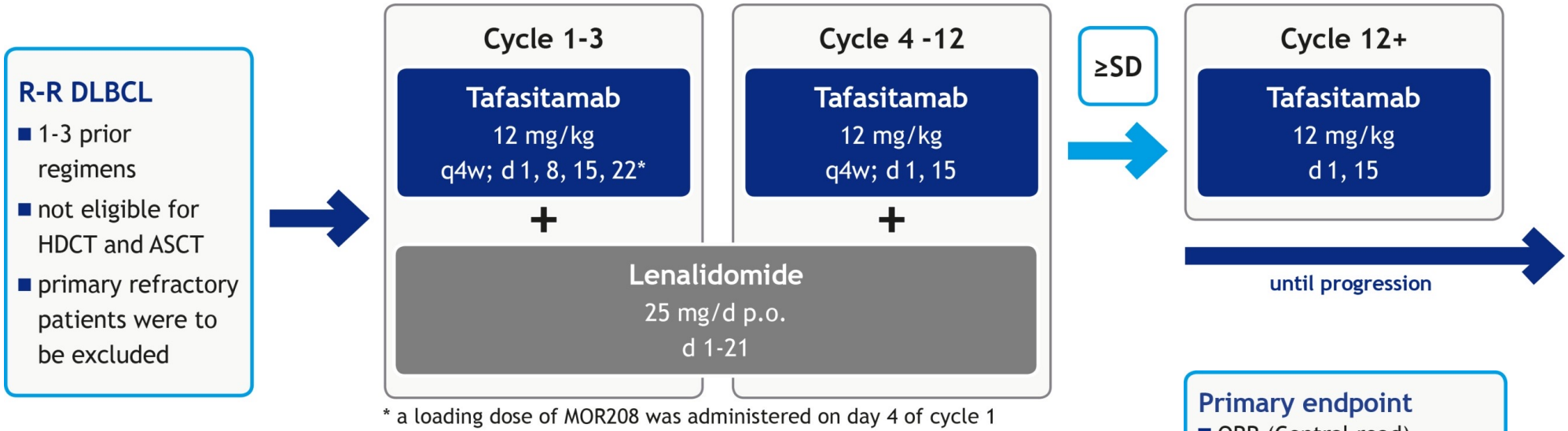




FDA review

L-MIND: study design

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



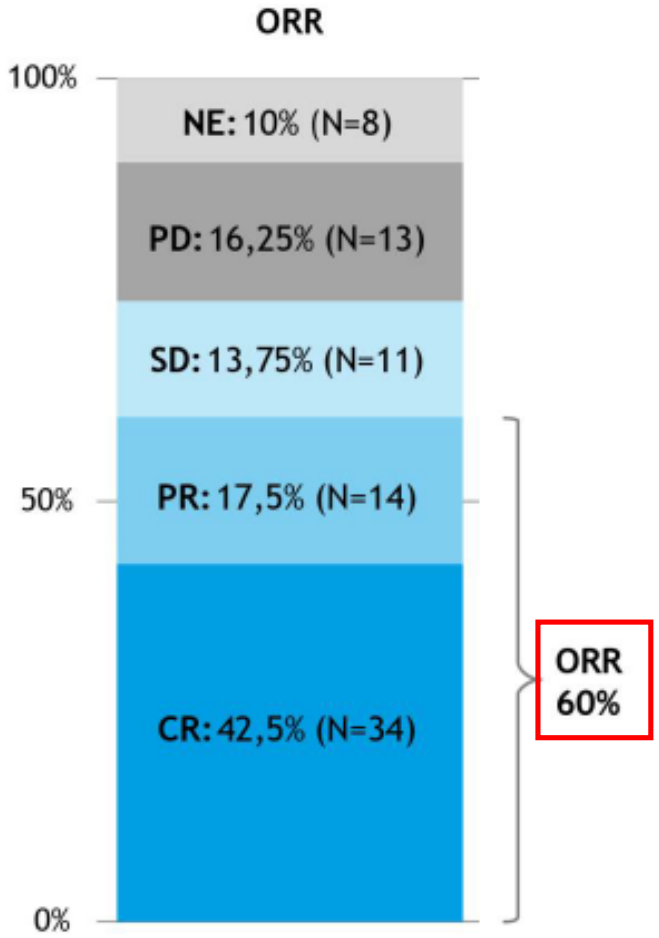
- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

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 (80pts)



- 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

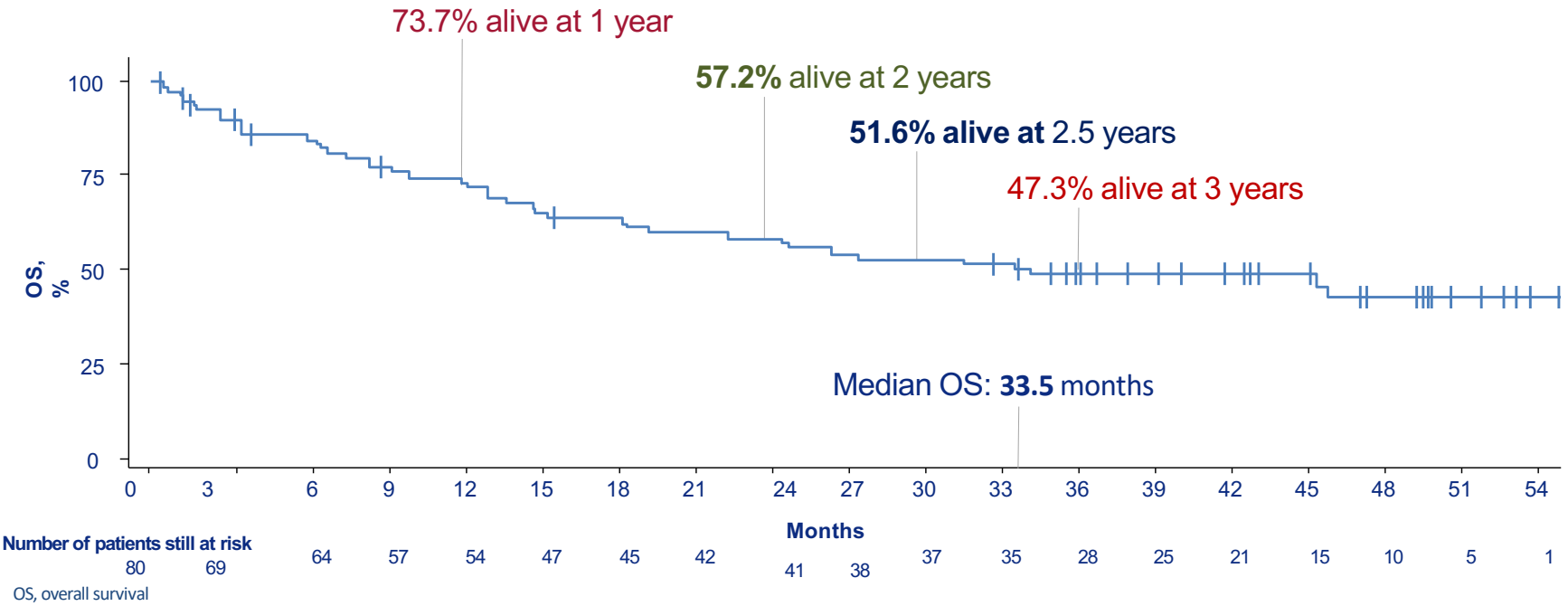
N=80: full analysis set → patients receiving at least one dose of tafasitamab and LEN

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

MOR 208 (Tafasitamab) and Lenalidomide (L-MIND) : patients alive after 3 years of follow-up



- OS, overall survival

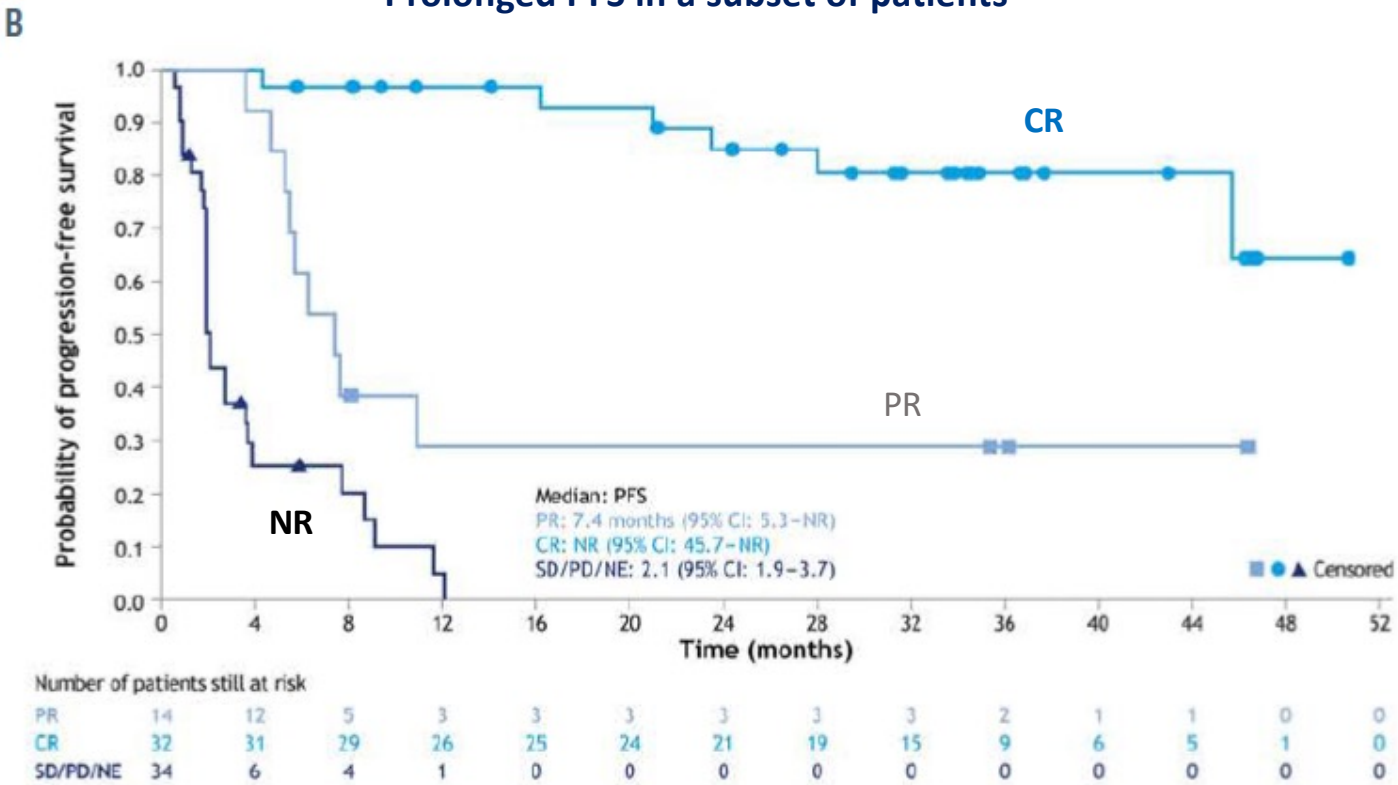
Duell J, ICML 2021

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

Tafa-Lena US Real World: Patients

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%

L-MIND Eligible: 11%

Reasons for L-MIND ineligibility:

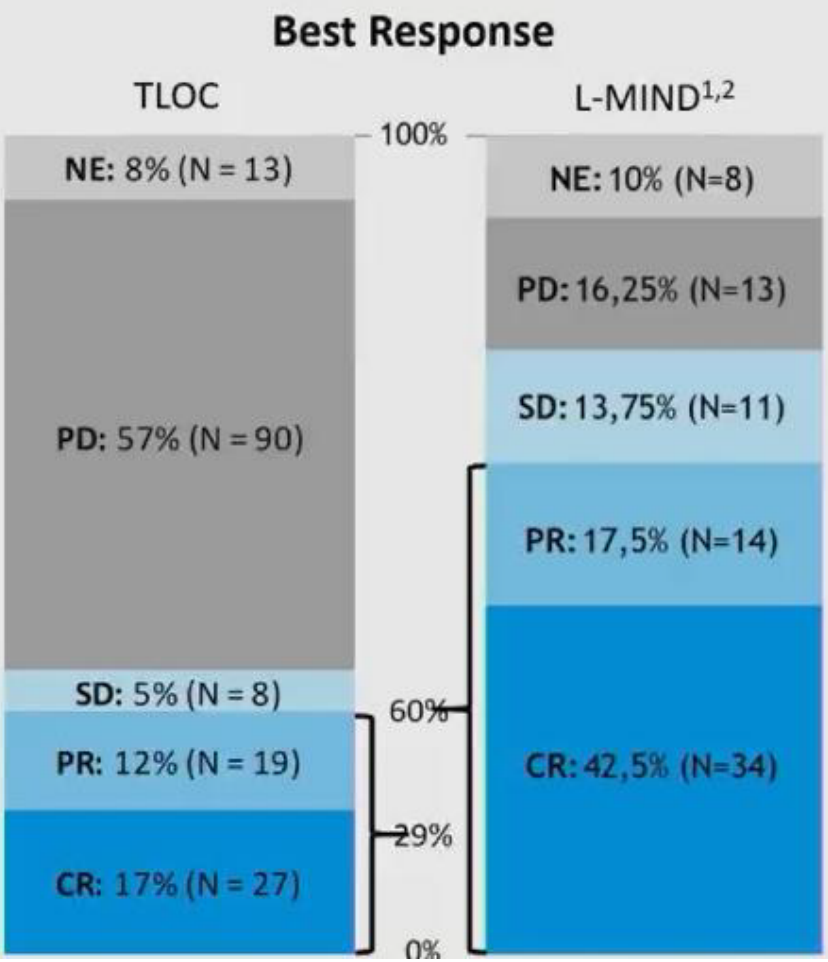
- EGFR < 60 ml/min 33%
- Prior anti-CD19 therapy 28%
- >3 prior lines of therapy 23%
- ECOG PS 3-4 18%
- High-grade B cell lymphoma 15%

Qualls et al. ASH2022

Tafa-Lena L-MIND and US Real World: 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%

[1]Duell J et al., Haematologica 2021
[2]Duell J et al., presented at ASCO 2021



Qualls et al. ASH2022

Tafa-Lena L-MIND and US Real World: advers events

Clinically significant adverse events: resulting in dose reduction, treatment delay, treatment discontinuation, hospitalization, or death

Event	Proportion affected (%)
Hematological (All)	38
Neutropenia	28
Anemia	15
Thrombocytopenia	15
Febrile Neutropenia	8

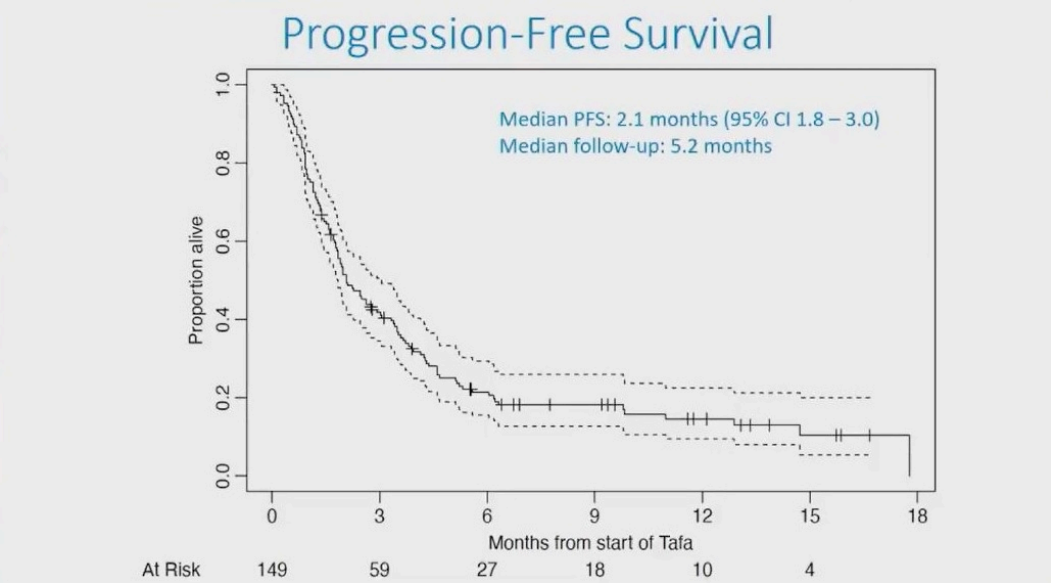
*Other: autoimmune hemolysis (1), neuropathy (1), MDS, bowel obstruction/perf, AKI, pruritis, hypotension (2), pleural effusions, transaminase/bili elevations (2), myalgias, constipation, hematuria, cognitive decline, cough

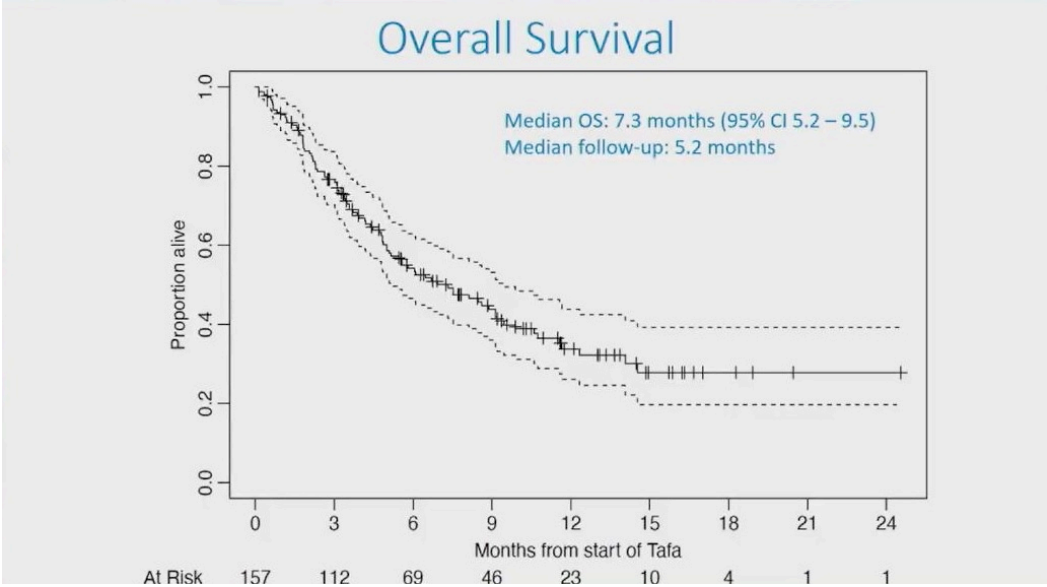
Event	Proportion affected (%)
Infection	16
COVID-19	3
Asthenia	13
Decreased appetite	9
Fevers	7
Diarrhea	4
Rash	3
Peripheral Edema	3
DVT/PE	3
Other*	13

Treatment discontinued: 137 patients (POD 80%, Toxicity 13%, Death 3%, Other 13%)
Deaths: 91 patients (POD 85%, Toxicity 1%, Unrelated 5%, Unknown 9%)

Qualls et al. ASH2022

Tafasitamab Lenalidomide Outcomes Consortium





90% did not meet L-MIND eligibility criteria

Patient related outcome

↓

More lines of therapy, prior CAR-T, ECOG >3, GFR

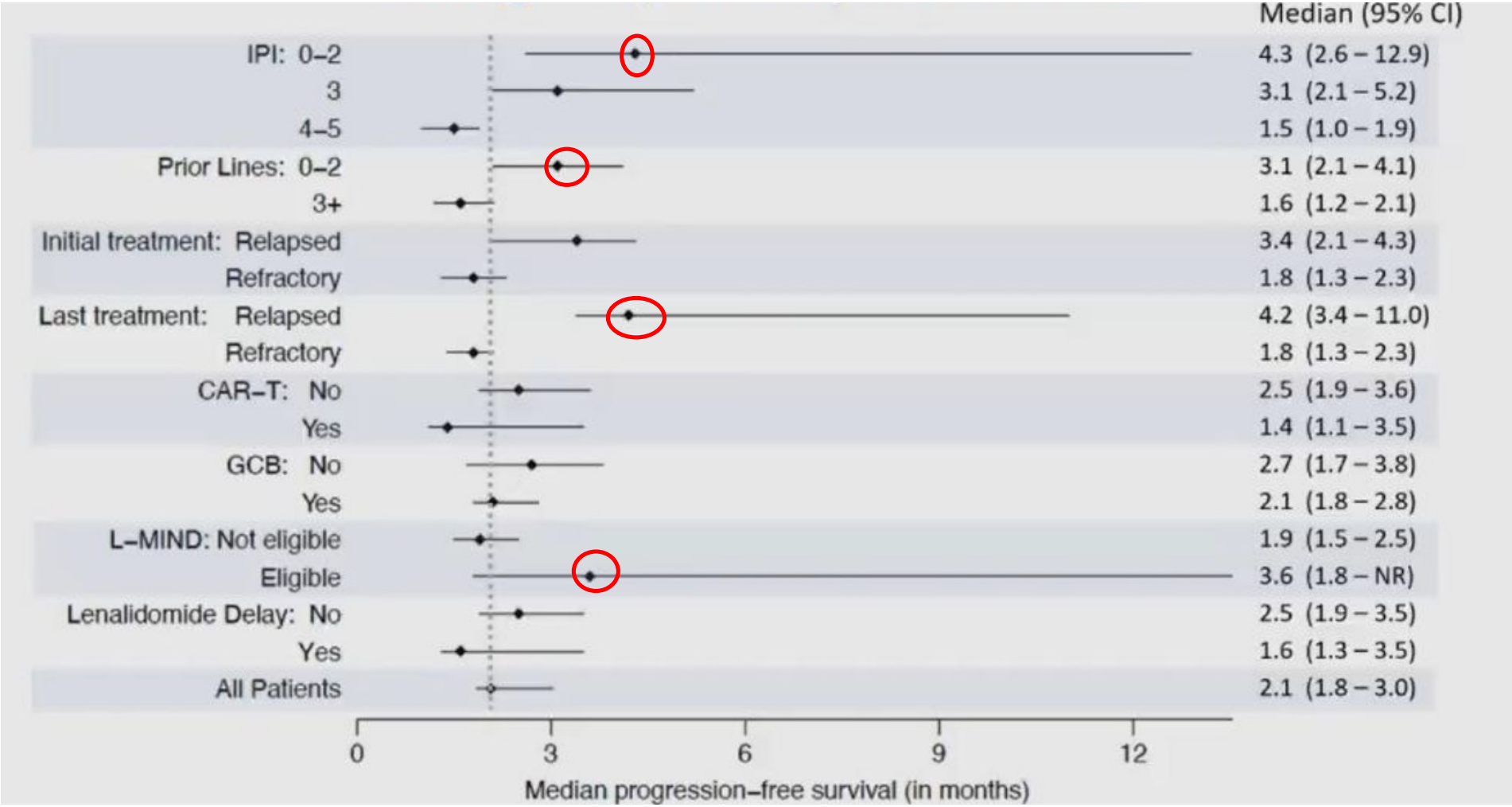
Disease related outcome

↓

Higher IPI, >Stage III/IV, primary refractory, HGBCL

Qualls DA et al Blood 2023

Subgroup analysis of PFS



Tafasitamab for the Treatment of R/R DLBCL in the US Real-World Setting

Characteristics		All patients (N=181)	Tafasitamab 2L (n=130)	Tafasitamab 3L (n=43)
ECOG PS at tafasitamab initiation, n (%)	0-1 ≥2	95 (52.5) 86 (47.5)	69 (53.1) 61 (46.9)	21 (48.8) 22 (51.2)
Ann Arbor stage at tafasitamab initiation, n (%)	Stage I/II Stage III Stage IV Unknown	10 (5.5) 58 (32.0) 111 (61.3) 2 (1.1)	9 (6.9) 50 (38.5) 70 (53.8) 1 (0.8)	1 (2.3) 7 (16.3) 35 (81.4) 0
R-IPI at tafasitamab initiation, n (% patients with data available)*	1-2 (good prognosis) 3-5 (poor prognosis)	33 (19.5) 136 (80.5)	22 (18.3) 98 (81.7)	8 (19.0) 34 (81.0)
Double-hit or triple-hit at tafasitamab initiation, n (%)	Yes, double-/triple-hit Tested, found to be negative Unknown	22 (12.2) 130 (71.8) 29 (16.0)	14 (10.8) 103 (79.2) 13 (10.0)	8 (18.6) 26 (60.5) 9 (20.9)
Cell of origin information, n (%)	GCB Non-GCB/ABC Unknown	81 (44.8) 39 (21.5) 61 (33.7)	60 (46.2) 28 (21.5) 42 (32.3)	17 (39.5) 9 (20.9) 17 (39.5)
Refractory to line prior to tafasitamab†		59 (32.6)	33 (25.4)	19 (44.2)
Lines of treatment, n (%)	2L 3L+	130 (72) 51 (28)		

Saverno K et al ASH 2023

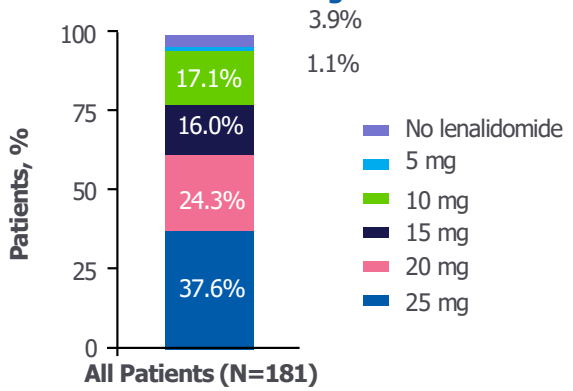
Lenalidomide Treatment With Tafasitamab

(Median follow-up time: 6.5 months)

	All Patients (N=181)
Prior ASCT therapy, n (%)	21 (11.6)
Prior CAR-T therapy, n (%)	6 (3.3)
Subsequent CAR-T therapy, n (%)	5 (2.8)

Tafasitamab discontinuation	Patients, %
Confirmed by scan	50
Progression defined clinically	17
Toxicity	15
Patient/caregiver request	3
Complete response	2
Other reasons	13

Lenalidomide Starting dose



Common reasons for lenalidomide dose reduction

Reasons for dose reduction	Patients, %
Neutropenia	73
Thrombocytopenia	33
Performance status/patient frailty	27
Renal dysfunction	18

Thirty-three patients (19%) had ≥1 lenalidomide dose reduction during the treatment

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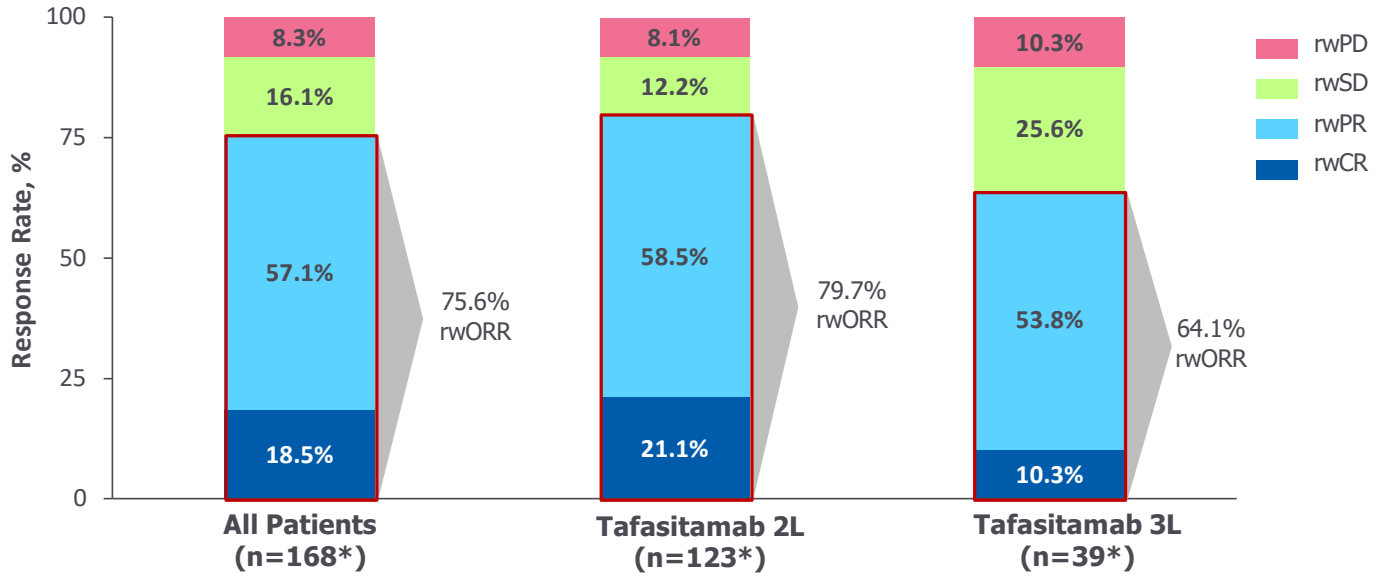
Real-World Best Response



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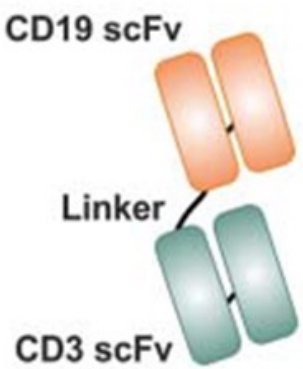
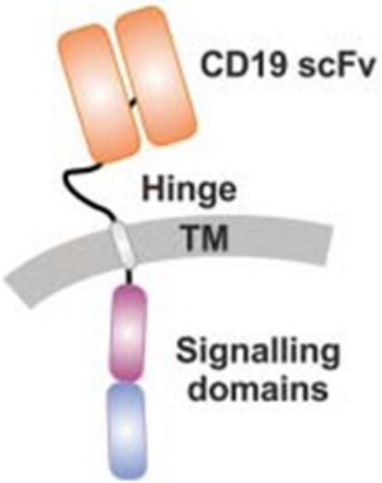
Multiple Targeting anti CD19 strategies

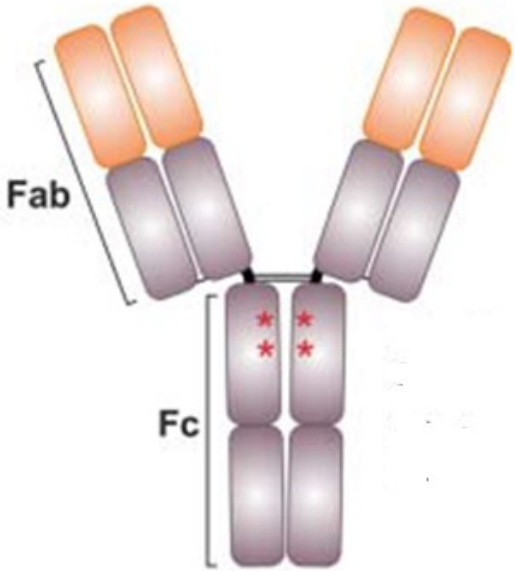
BLINATUMOMAB (BITE)



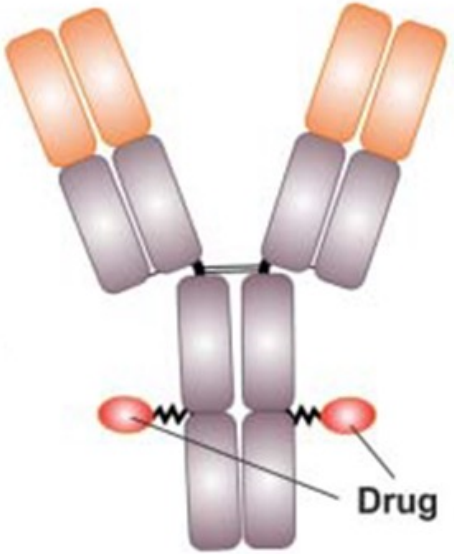
CAR-T cells



TAFASITAMAB (engineered Ab)

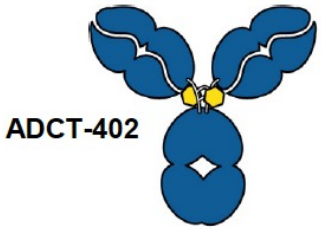


LONCASTUXIMAB TESIRINE (ADC)



Kellner et al., Oncoimmunol 2018.

Loncastuximab Tesirine (ADCT-402)



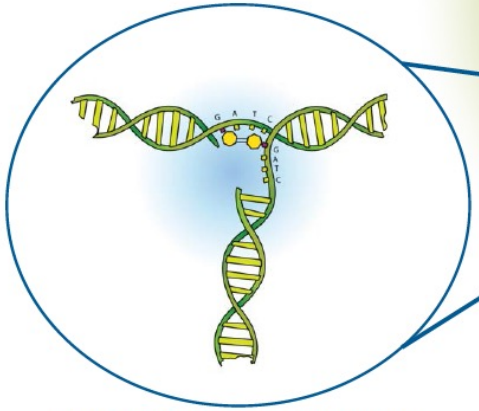
ADCT-402

Anti-CD19 Ab

ADCT-402 binds to the CD19 antigen on the tumor cell surface

CD19

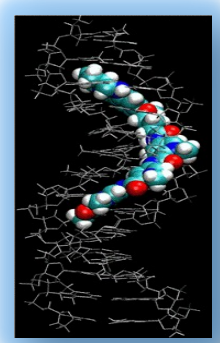
Following internalization of the ADC, the protease-sensitive linker is cleaved and the cytotoxic PBD dimer is released inside the cell



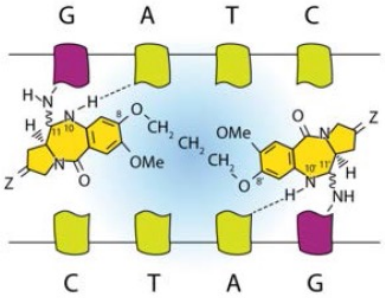
Stalled DNA replication fork

The free PBD dimers bind in the minor groove of the cell DNA and forms potent cytotoxic DNA cross-links in a sequence-selective fashion.

The cross-links result in a stalled DNA replication fork, blocking cell division and causing cancer cell death



Pyrrolobenzodiazepine (PBD)

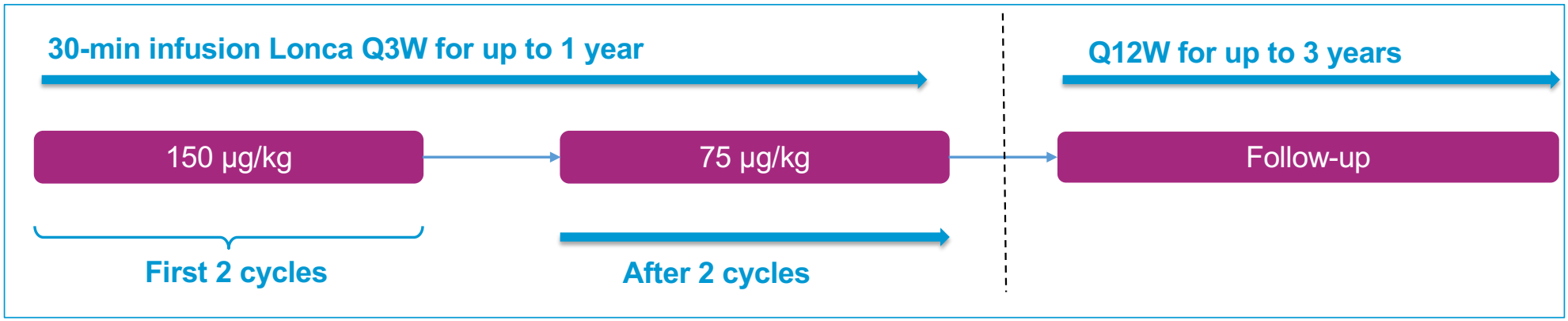


Cytotoxic cross-links

Lotis 2: single-arm, open-label Phase 2 Study

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

Primary objective:
Evaluate efficacy, using ORR (central review), and safety of the full Phase 2 study population



Futility requirements met:
ORR for first 52 patients[1]

Total enrolment:
145 patients

Carlo-Stella C, et al. EHA 2020

Baseline Characteristics

Patient characteristics		Total (N=145)
Sex, n (%)	Female Male	60 (41.4) 85 (58.6)
Age, years, median (min, max)		66.0 (23–94)
Histology, n (%)	DLBCL HGBCL PMBCL	127 (87.6) 11 (7.6) 7 (4.8)
Double/triple hit, n (%)		15 (10.3)
Double/triple expressor, n (%)		20 (13.8)
Transformed disease, n (%)		29 (20.0)
Stage, n (%)	I–II III–IV	33 (22.8) 112 (77.2)

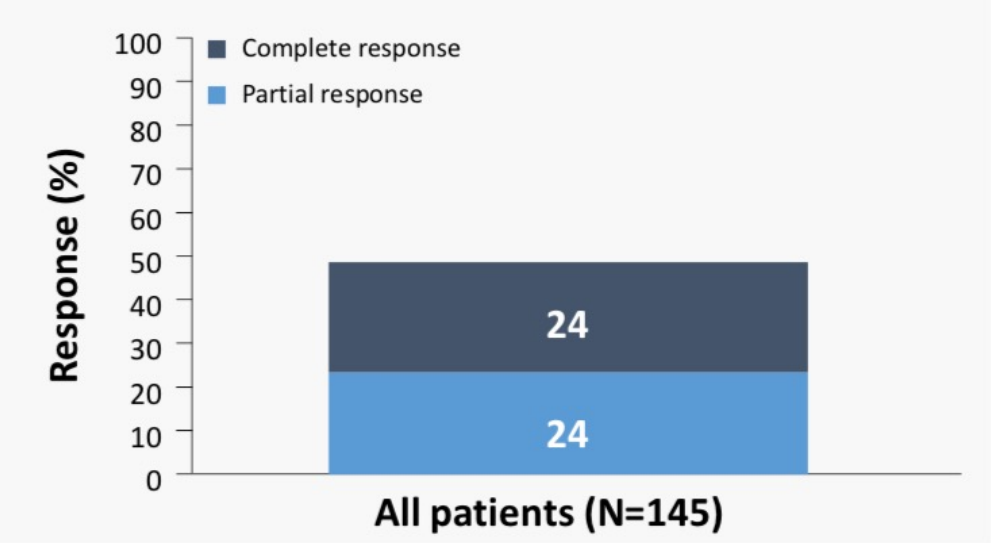
Patient treatment history		Total (N=145)
No. of previous systemic therapies,* median (range)		3 (2–7)
First-line systemic therapy response, n (%)	Relapse Refractory† Other‡	99 (68.3) 29 (20.0) 17 (11.7)
Last-line systemic therapy response,¶ n (%)	Relapse Refractory† Other‡	43 (29.7) 84 (57.9) 18 (12.4)
Refractory to all prior therapies, n (%)	Yes No Other‡	25 (17.2) 115 (79.3) 5 (3.4)
Prior stem cell transplant, n (%)	Allogeneic Autologous Both	2 (1.4) 21 (14.5) 1 (0.7)

145 patients were enrolled and received a mean of 4.3 cycles of Lonca (range: 1–15)

Carlo-Stella C, et al. EHA 2020

Loncastuximab Teserine: LOTIS-2 Phase 2 Trial

1st end-point: ORR



Lonca ORR

48%

(95% CI, 39.9-56.7)

Median time to first response

41.0 days

(IQR, 38-44)

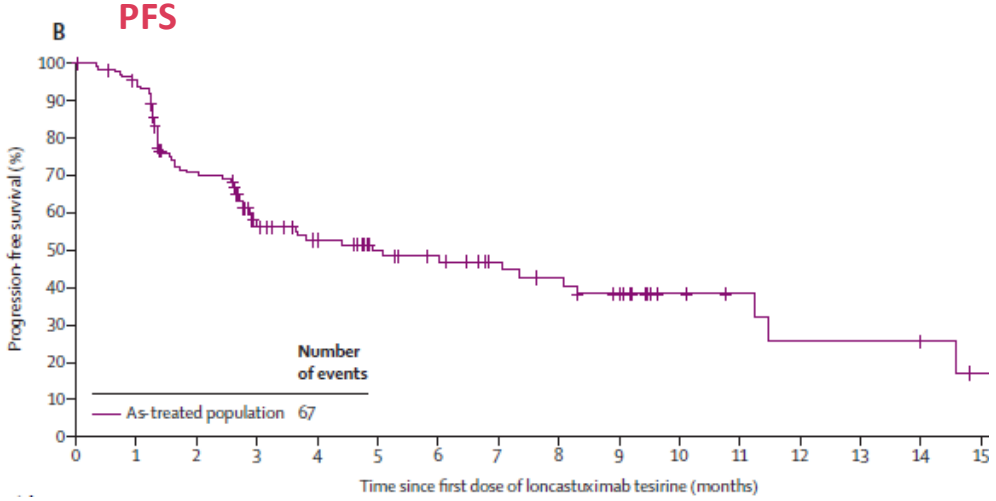
- At data cut-off, 44,4% of pts remained in CR with no further treatment
- 13 patients received previously CART
- **Most responders had a response after 2 cycles**
- Median number of lonca cycles: 3 (1-26)

Carlo-Stella C, et al. EHA 2020

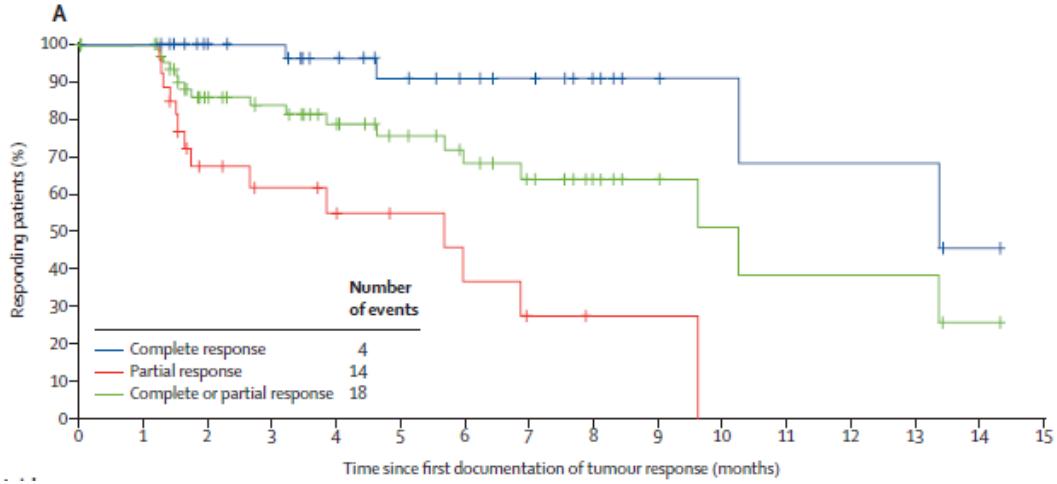
Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial

Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshna, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luigi Zinzani, Karin Havenith, Jay Feingold, Shui He, Yajuan Qin, David Ungar, Xiaoyan Zhang, Carmelo Carlo-Stella

PFS



Duration of response by BOR

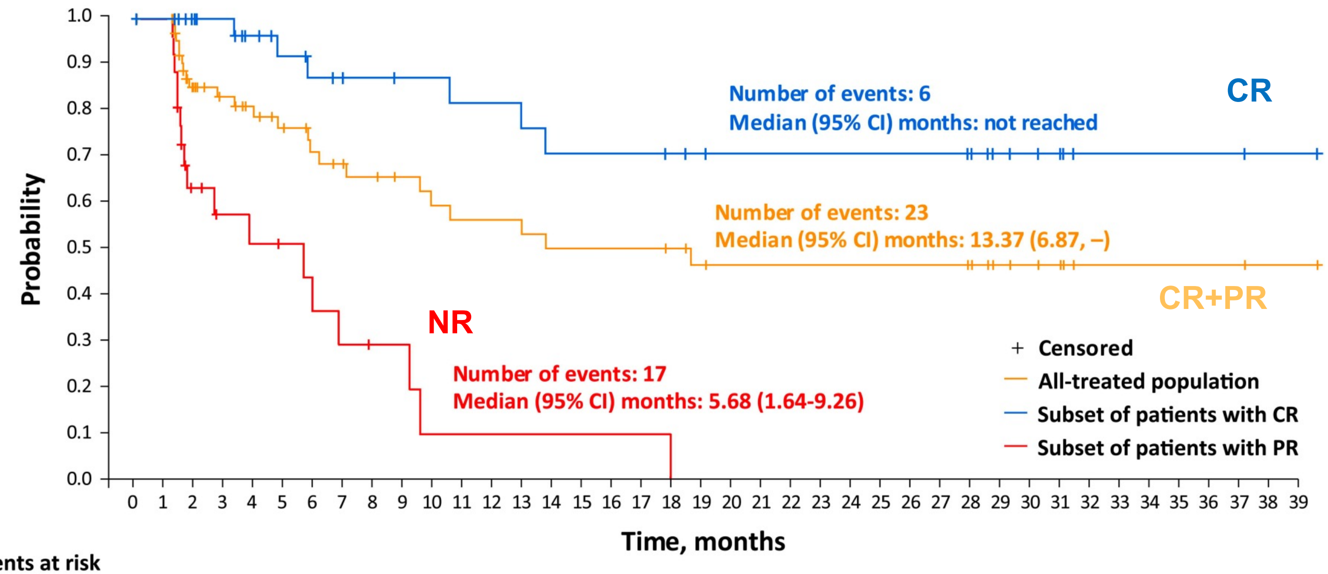


Median duration of response was 10.25 months

Caimi F.L et al Lancet Oncology 2021

Duration of response by best overall response

Final analysis: 2-year update



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	11	7	6	5	2	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	11	7	6	5	2	2	2	2	2	2	1	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	0	0

mDOR for patients with a **CR**
Not reached

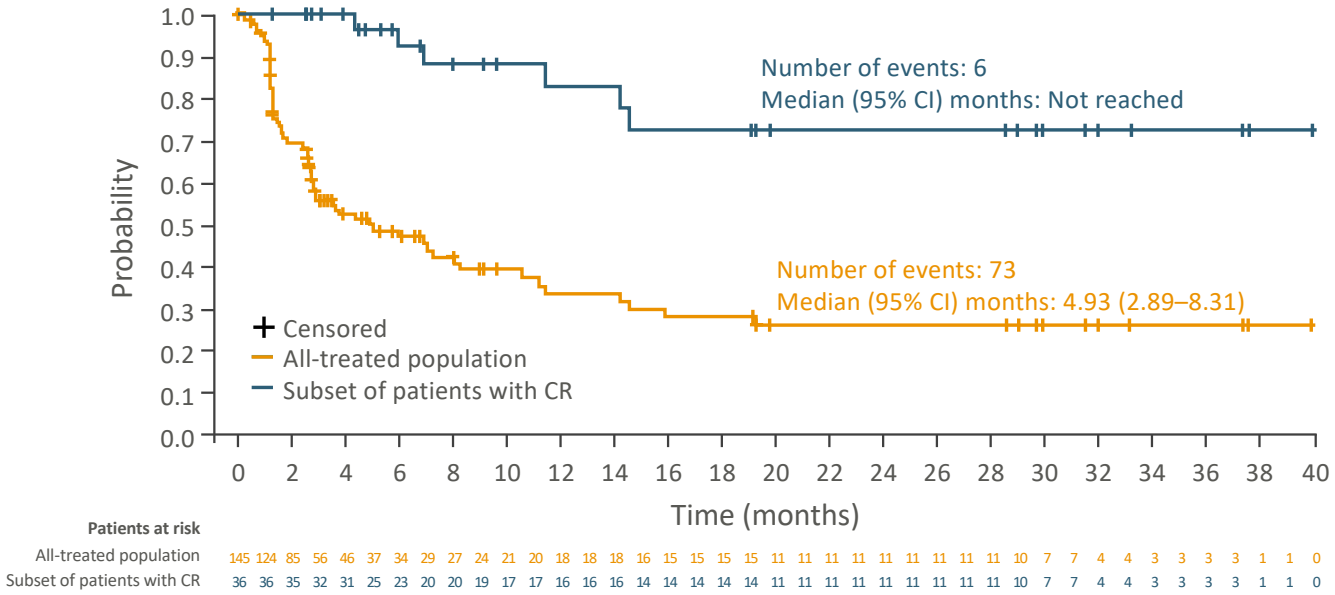
mDOR for the **70 responders**
13.4 months
(95% CI: 6.9–NE)

mDOR for patients with a **PR**
5.7 months

Caimi et al. Haematologica 2023

Progression-free survival

Final analysis: 2-year update



mPFS for all-treated population (N=145)

4.9 months

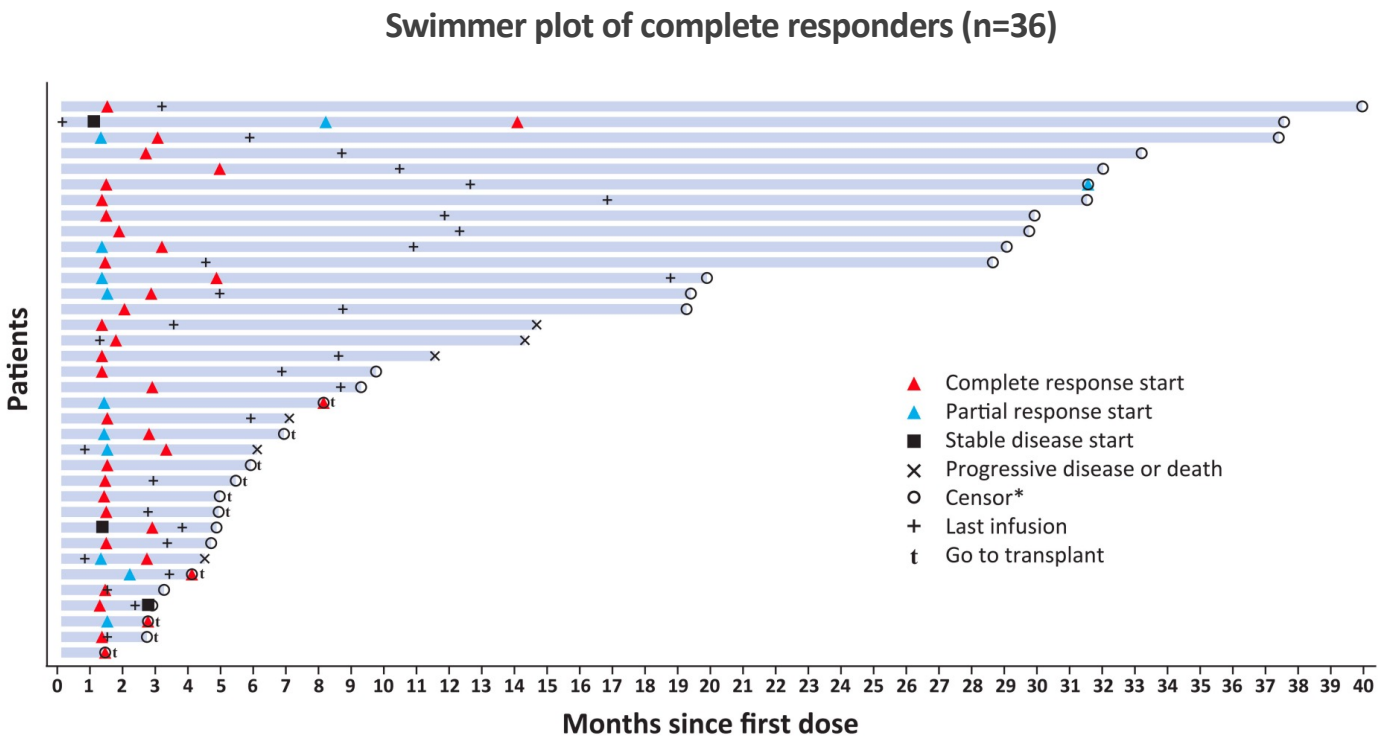
(95% CI: 2.9–8.3)

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

Not reached

Caimi et al. *Haematologica* 2023

Follow-up of complete responders



At data cut-off, 44.4% (16/36) of patients remained in CR with no further treatment

36.1% (13/36) were censored; of them, 10 patients were censored due to transplant while in CR

19.4% (7/36) patients had PD or death

After longer follow-up, durable responses continue to be observed

Caimi et al. *Haematologica* 2023

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 in the US

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 (%)*	Real-world cohort (N=187)
Lonca line of therapy	
2nd or 3rd	36 (19)
>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%)

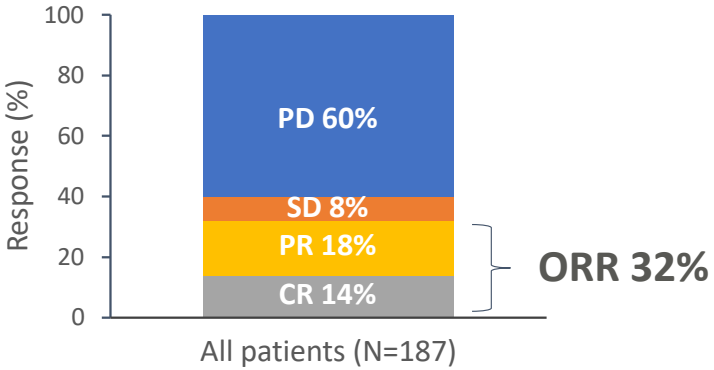
AEs led to Lonca **discontinuation** in **14%**

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)

Ayers et al, ASH 2023, #312

NP-32928

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



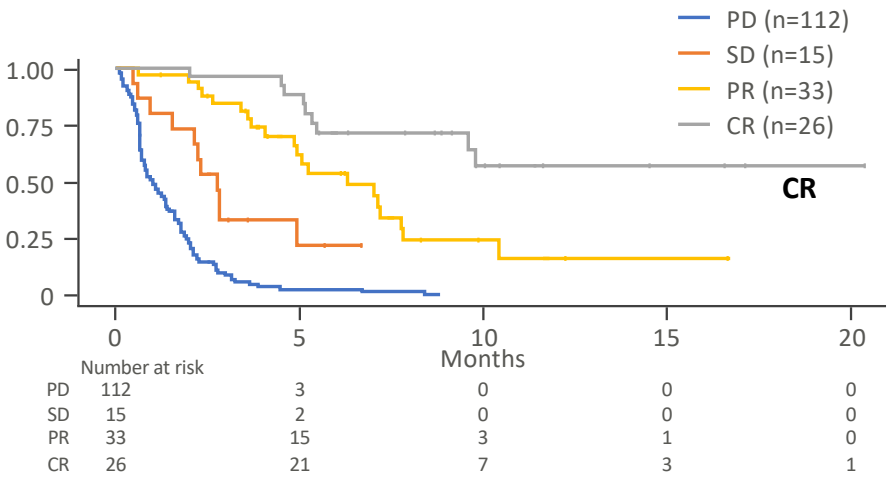
Median duration of treatment was 42 days (LOTIS-2 was 45 days)

Response	mPFS (mo)
ORR	7.8
CR	NR
PR	6.3
SD	2.8
PD	0.9

Progression-free survival

2.1 mos	NR	12%
mPFS	mPFS in patients with CR	12-month PFS

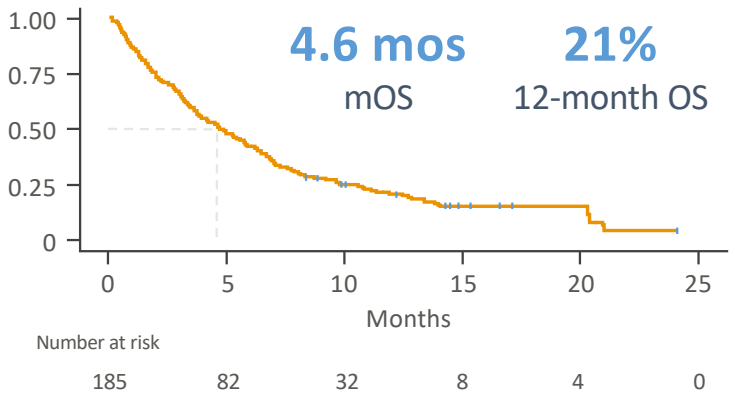
PFS by response to Lonca



Ayers et al, ASH 2023, #312

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

Overall survival



Impact of characteristics on outcomes

Associated with inferior outcomes*

- Elevated LDH
- Bulky disease
- HGBCL histology

Associated with superior outcomes*

- CR prior to Lonca, CR to Lonca
- Non-GCB cell of origin (predicts CR and improved PFS)

Prior CAR-T exposure, CD19 status, and line of therapy did not impact outcomes

Response to subsequent treatments

Treatment (N=53)	N, (%)	ORR, %	CR, %
Immuno-therapy	18 (31)	50	29
CAR-T	6 (10)	33	33
Tafa + Len	10 (17)	10	10
Clinical trial	4 (7)	25	0
Radiation	5 (9)	25	0
Other	15 (26)	46	15

Compared to LOTIS-2 cohort, this cohort was enriched with high-risk features to likely explain the lower response rates. Importantly, **receipt of prior CAR-T did not negatively impact outcomes to Lonca.**

Ayers et al, ASH 2023, #312

Real-world effectiveness of Lonca monotherapy in R/R DLBCL following CAR-T therapy

Non-site based, online, retrospective chart review, in adult patients with R/R DLBCL† who initiated Lonca monotherapy following CAR-T therapy (2L or 3L)

Study design

Index period

April 2021

≥6 months prior to data entry date

Follow-up period

Date of data entry

Eligible for inclusion
therapy in 2L or 3L, subsequently disease progression before initiating on Lonca monotherapy as 3L/4L treatment between April 2021 and the date ≥6 months prior to data entry date.

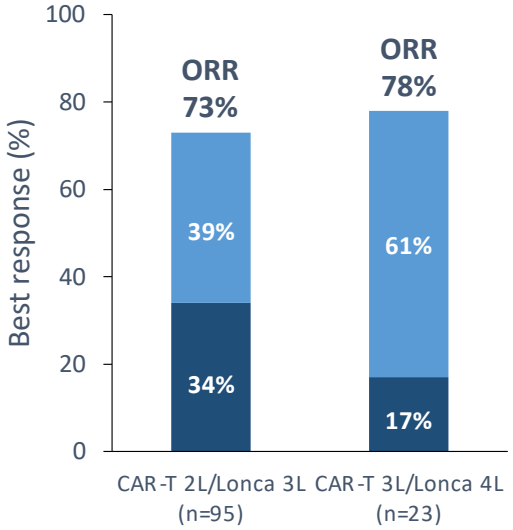
The follow-up period began *≥6 months* prior to data entry date to allow for a minimum follow-up of 6 months for all patients.

Patient characteristics and treatment patterns (%, unless otherwise specified)	**CAR-T 2L / Lonca 3L (N=121)**	**CAR-T 3L / Lonca 4L (N=27)**
Median age (IQR), years	66.0 (60.5, 71.5)	59.0 (50.0, 72.0)
Male sex	59	44
DLBCL NOS, or high-grade	68	93
Transformed from low-grade	31	7
DHL/THL	41	11
Bulky disease (>7.5 cm) at index	23	7
Stage III–IV at index	70	85
High-intermediate risk/high-risk at index*	60	26
Primary refractory†	29	23
SCT received at 1L or 2L	25	59
Axicabtagene ciloleucel received	62	67
Lisocabtagene maraleucel received	38	0
Tisagenlecleucel received	0	33
CR to CAR-T	21	44
PR to CAR-T	49	19
Refractory to CAR-T	29	37
Bridging therapy to CAR-T received	11	48

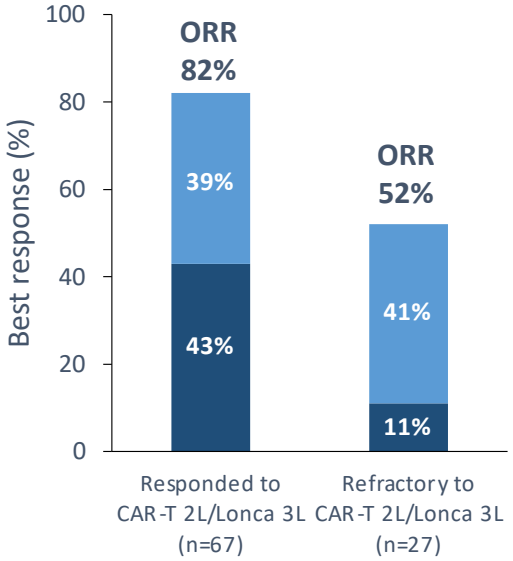
Epperla et al. poster ASH 2023

Real-world effectiveness of Lonca monotherapy in R/R DLBCL following CAR-T therapy

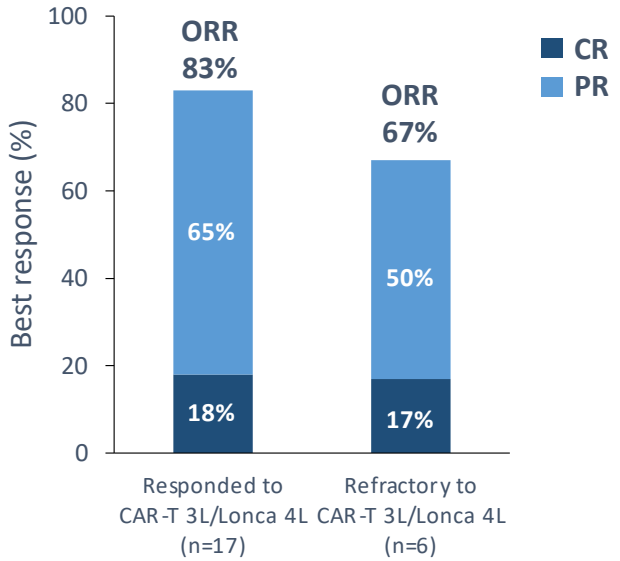
Best response for Lonca received at 3L and 4L post CAR-T therapy



Best response to Lonca in 2L CAR-T/3L Lonca



Best response to Lonca in 3L CAR-T/4L Lonca



NP-34223

Lonca monotherapy, in both 3L and 4L after CAR-T, can be a reasonable and effective treatment option for patients who are resistant/progressed after CAR-T

Conclusions

- ***Relapsed/refractory DLBCL (RR-DLBCL)*** treated with standard CHT-ASCT have a poor survival
- ***Pola + R-Bendamustina , Tafasitamab + Lenalidomide (L-MIND)*** *are* the first positive phase 2 studies in RR-DLBCL patients who are unfit for transplant
- Novel therapies as ***conjugated (Loncastuzimab) or other monoclonal antibodies*** as single agent may improve outcome in RR-DLBCL.
- **Loncastuzimab** showed efficacy in LOTIS-2 population including patients with DH/TH, refractory to previous therapies and who previously received CAR T-cell therapy.
- **Loncastuzimab r**esponses were confirmed in the 2-year follow-up analysis and in the Real Word analysis also in patients previously treated with CAR-T

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Grazie!

… a voi tutti per l'attenzione