Nuove prospettive future nei linfomi: Aspetti terapeutici

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Disclosure: Luigi Rigacci

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead				X	X	
Novartis				X	X	
Sandoz				X	X	
Abbvie				X	X	
Sobi					X	
Celgene				X		
Janssen				X	X	
Incyte				X	X	
Menarini		X				
Takeda					X	

DLBCL prima linea

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

N.Engl.J .Med December 14, 2021

Polarix: study design overview

- **Double-blind, randomized controlled**
- Collaboration with LYSA
- NCT03274492

Patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

N=879

Stratification factors
- IPI score (2 vs 3–5)
- Bulky disease (≥7.5cm vs absence)
- Geographic region*

R 1:1

ARM A

Polatuzumab vedotin 1.8mg/kg
R-CHP + vincristine placebo
Q21D x 6 cycles

→ **Rituximab** 375mg/m² Cycles 7 & 8

1 Cycle=21 days

ARM B

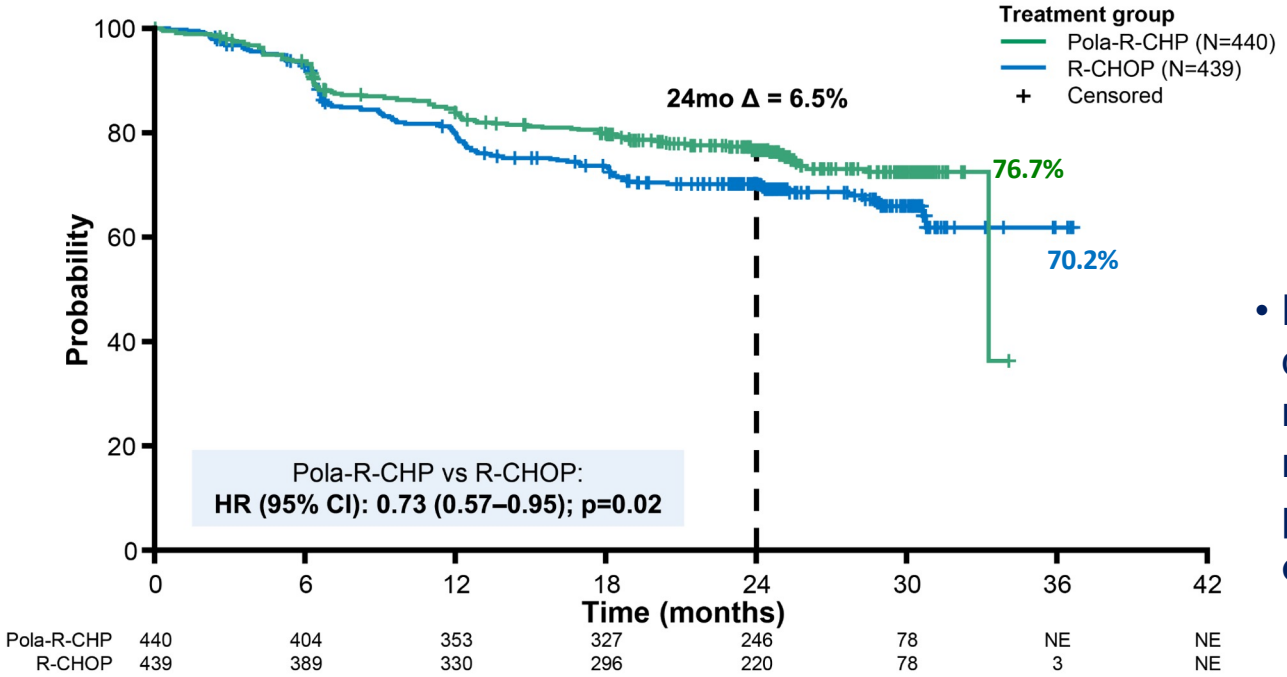
R-CHOP + polatuzumab vedotin placebo
Q21D x 6 cycles

→ **Rituximab** 375mg/m² Cycles 7 & 8

Primary endpoint	**PFS by INV**
Key secondary endpoints	$EFS_{efficacy}$ by INV, PET CR at EOT by BICR, OS, and safety

Tilly H, et al. New Engl J Med 2021

Primary end-point
Investigator-assessed PFS (ITT population)

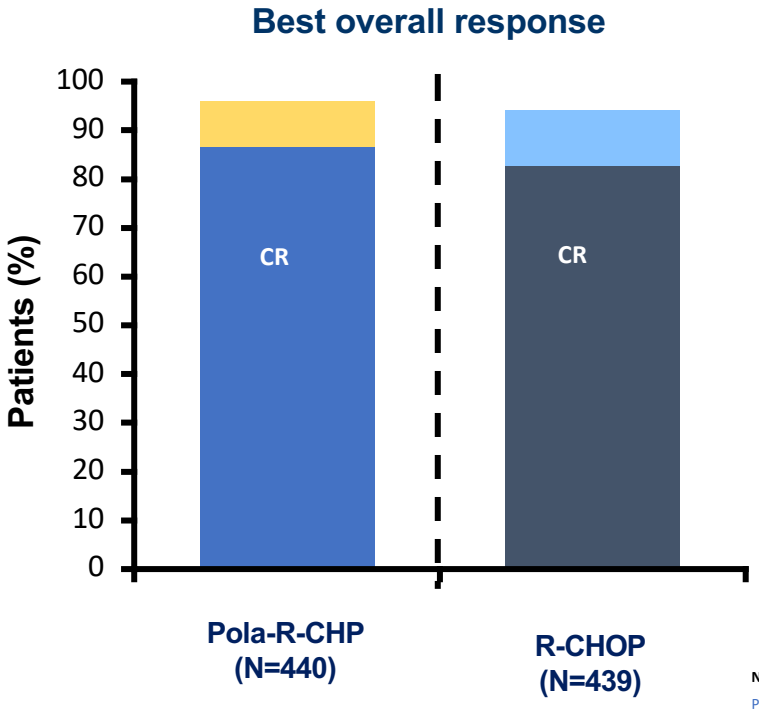


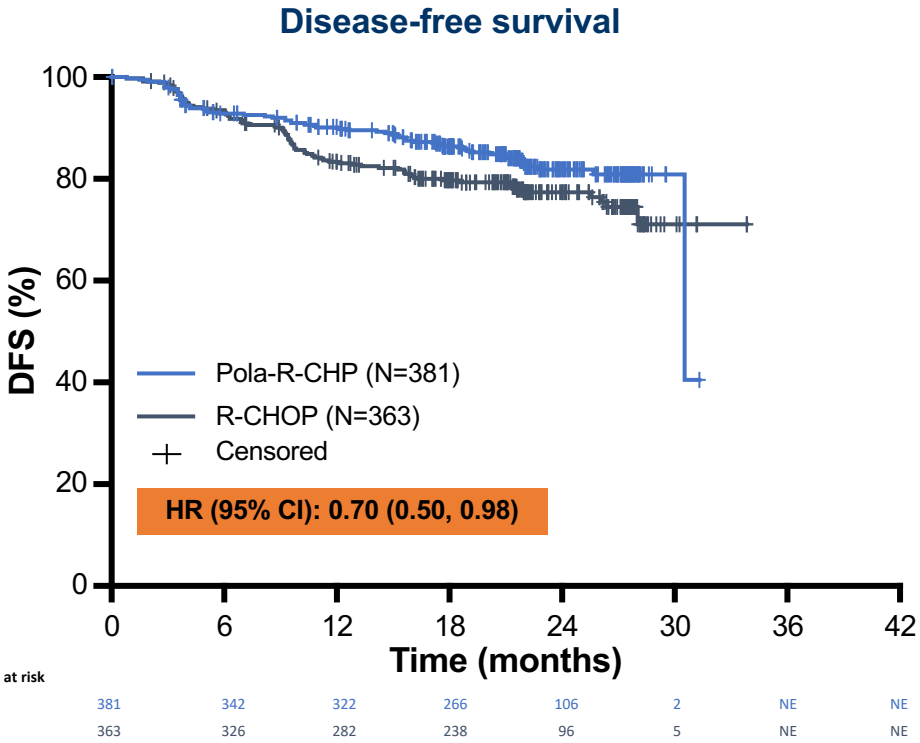
HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP

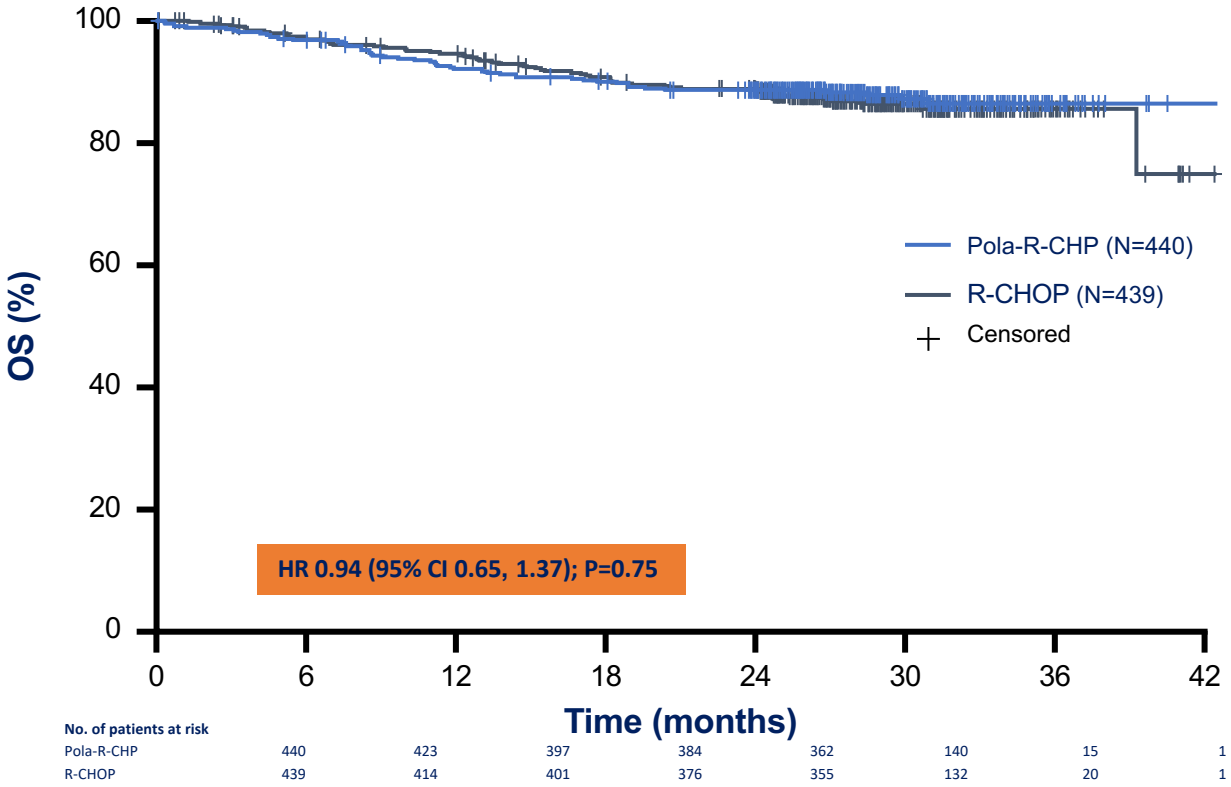
Tilly H, et al. New Engl J Med 2021

Response rates and disease-free survival





Overall survival



Mosunetuzumab and Polatuzumab Vedotin Demonstrates Preliminary Efficacy in Elderly Unfit or Frail Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

Adam J. Olszewski,[1] Herbert Eradat,[2] Abraham Avigdor,[3,4] Netanel A. Horowitz,[5] Sunil Babu,[6] Itai Levi,[7] Matthew McKinney,[8] Seung Tae Lee,[9] Juan Miguel Bergua Burgues,[10] Antonia Rodriguez,[11] Mariana Bastos-Oreiro,[12] Chezi Ganzel,[13,14] Tae Min Kim,[15] Youngwoo Jeon,[16] Michal Taszner,[17] Mayur Narkhede,[18] Won Seog Kim,[19] Ho-Jin Shin,[20] David Lavie,[21] Dariusz Woszczyk,[22] Diana Dunshee,[23] Amy V. Kapp,[23] Mingzhu Zhou,[24] Connie Lee Batlevi,[23] Wahib Ead,[23] Gila Sellam,[25] Wojciech Jurczak[26]

[1]Brown University, Providence, RI, USA; [2]University of California, Los Angeles, CA, USA; [3]Sheba Medical Center, Ramat Gan, Israel; [4]Tel Aviv University, Tel Aviv, Israel; [5]Rambam Health Care Campus, Technion, Haifa, Israel; [6]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [7]Soroka University Medical Center, Be'er-Sheva, Israel; [8]Duke Cancer Institute, Durham, NC, USA; [9]University of Maryland School of Medicine, Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; [10]San Pedro de Alcántara Hospital, Cáceres, Spain; [11]University Hospital October 12, Madrid, Spain; [12]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [13]Shaare Zedek Medical Center, Jerusalem, Israel; [14]Hebrew University of Jerusalem, Jerusalem, Israel; [15]Seoul National University Hospital, Seoul, Republic of Korea; [16]Lymphoma and Cell Therapy-Research Center, Yeouido St. Mary's Hospital, Seoul, Republic of Korea; [17]University Clinical Center, Medical University of Gdańsk, Gdańsk, Poland; [18]University of Alabama at Birmingham, Birmingham, AL, USA; [19]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [20]Biochemical Research Institution, Pusan National University Hospital School of Medicine, Busan, Republic of Korea; [21]Hadassah Medical Center, Jerusalem, Israel; [22]University of Opole, Provincial Hospital, Opole, Poland; [23]Genentech, Inc., South San Francisco, CA, USA; [24]F. Hoffmann-La Roche Ltd, Shanghai, China; [25]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [26]Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland

Study overview

Key inclusion criteria

- Previously untreated DLBCL
- Age ≥80 years OR age 65–79 years and considered ineligible* for CIT
- ECOG PS 0–2

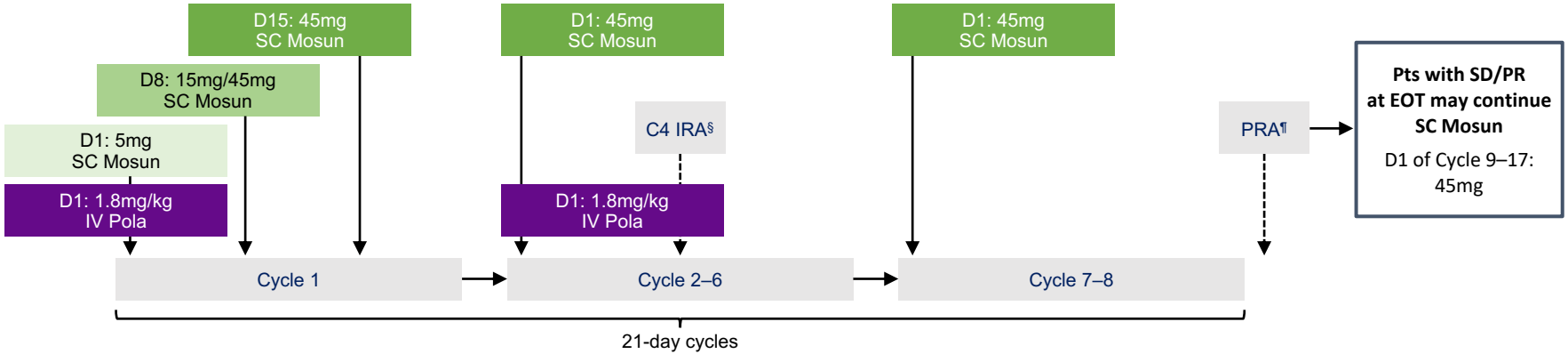
CRS mitigation strategies

- Step-up SC Mosun dosing in Cycle 1
- Pre-medication with dexamethasone in Cycle 1†
- Pre-medication with acetaminophen and diphenhydramine may also be given‡

Primary efficacy endpoint

- ORR by PET-CT at the PRA as assessed by IRC according to Lugano 2014 criteria[1]
- **Additional objectives:** Evaluation of safety, immunogenicity, pharmacokinetics, and pharmacodynamics

SC Mosun-Pola administration: Cohort C1 (N=7): 5/15/45mg; Cohort C2 + C Expansion (N=101): 5/45/45mg (target dose cohort)

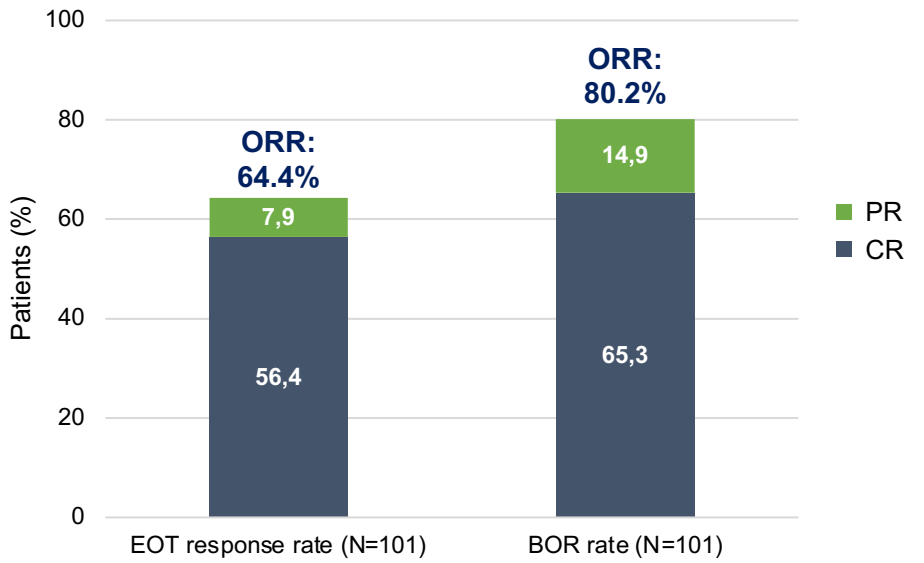


simplified geriatric assessments

Olszewski et al., Oral presentation ASH 2023

Investigator-assessed EOT and BOR response rates

EOT response and BOR rates in Mosun-Pola target dose cohort



Response rate, n (%)	EOT N=101	BOR N=101
ORR	65 (64.4)	81 (80.2)
CR	57 (56.4)	66 (65.3)
PR	8 (7.9)	15 (14.9)
SD	4 (4.0)	4 (4.0)
PD	10 (9.9)	4 (4.0)
ND	22 (21.8)*	12 (11.9)†

- 6/8 pts with PR at EOT continued treatment beyond Cycle 8, and 3/6 pts converted from PR to CR during continuation
- The difference between BOR and EOT is attributed to 22 patients who did not reach the EOT visit due to AEs, death, and subject withdrawal, which reflects the frailty and high co-morbidity burden of the study population

Mosun-Pola induces encouraging response rates in elderly unfit or frail pts with previously untreated DLBCL

Olszewski et al., Oral presentation ASH 2023

Fatal AE summary

n (%)	All N=108 Any	Treatment-related
Gr 5 AEs	18 (16.7)	5 (4.6)
Infections	13 (12.0)	4 (3.7)
COVID-19 pneumonia	9 (8.3)	1 (0.9)
COVID-19	1 (0.9)	1 (0.9)
Staph bacteremia	1 (0.9)	1 (0.9)
Sepsis	1 (0.9)	0
Pneumonia	1 (0.9)	1 (0.9)
Other Gr 5 AEs	5 (4.6)	1 (0.9)
Unexplained death	2 (1.9)	1 (0.9)
Pulmonary embolism	1 (0.9)	0
Suicide	1 (0.9)	0
Cardiac arrest	1 (0.9)	0

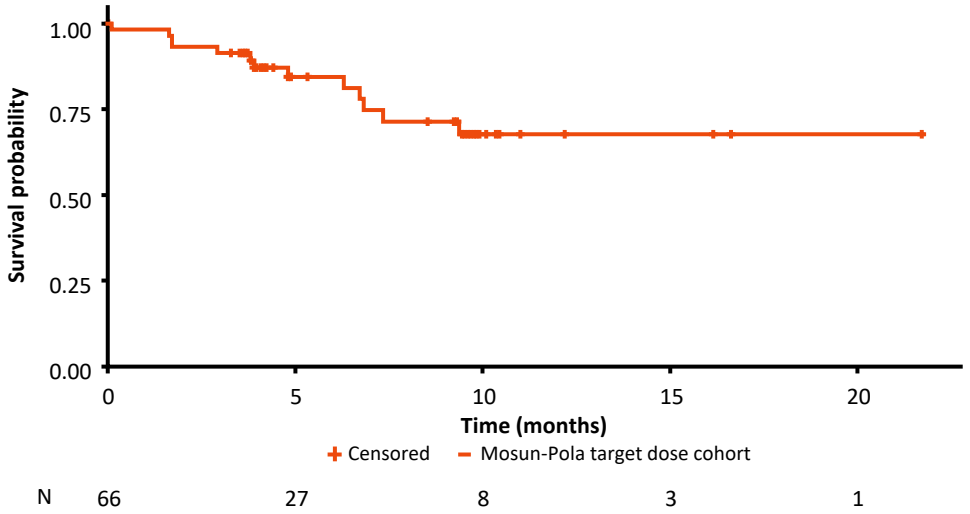
- 13/18 fatal AEs were infections
  - 77% (10/13) of fatal AEs of infection were COVID-19
  - 80% (8/10) of fatal COVID-19 events occurred during the Omicron waves in 2022, with no trend related to geographic location
  - 80% (8/10) of pts with fatal COVID-19 events were frail per simplified geriatric assessment
  - All pts had received at least one dose of COVID-19 vaccine
  - 70% (7/10) of pts with fatal COVID-19 events received COVID-specific antiviral treatments

The COVID-19 pandemic impacted the safety profile observed in the current study; other fatal AEs were comparable with those observed in similar patient populations

Olszewski et al., Oral presentation ASH 2023

DOCR in Mosun-Pola target dose cohort

KM curve of DOCR in the Mosun-Pola target dose cohort



	Mosun-Pola target dose cohort N=101
Complete responders, n (%)	66 (65.3)
Median follow up time, months (range)	12.6 (1–25)

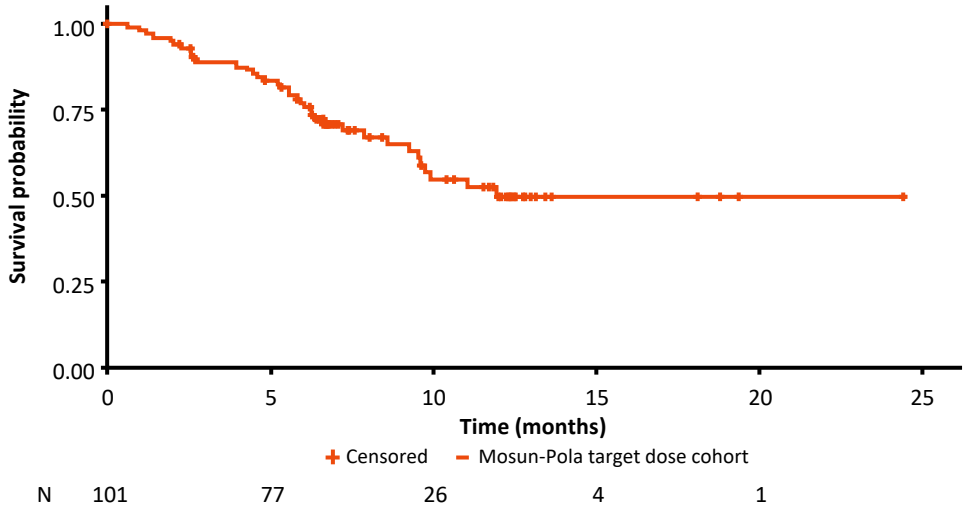
	Mosun-Pola target dose cohort N=66
Median DOCR, months (range)	NE
9-month DOCR event-free rate, % (95% CI)	71.4 (56.8, 85.9)
Patient disposition	
Censored/no event at CCOD	53 (80.3)
Event	13 (19.7)
Disease progression	2 (3)
Death after CR	11 (17)

Mosun-Pola induces durable CRs in elderly unfit or frail pts with previously untreated DLBCL

Olszewski et al., Oral presentation ASH 2023

PFS in Mosun-Pola target dose cohort

KM curve of PFS in Mosun-Pola target dose cohort



	Mosun-Pola target dose cohort N=101
Median PFS, months (95% CI)	11.9 (9.5, NE)
9-month PFS event-free rate, % (95% CI)	64.8 (54.2, 75.5)
12-month PFS event-free rate, % (95% CI)	49.7 (36.8, 62.5)
Patient disposition	
Censored/no event at CCOD	64 (63.4)
Event	37 (36.6)
Disease progression	12 (12)
Death	25 (25)

Early data show encouraging PFS with Mosun-Pola in elderly unfit or frail pts with previously untreated DLBCL

Olszewski et al., Oral presentation ASH 2023

DLBCL R/R

Novel therapies approved in RR-DLBCL

Other than CAR-T

	Pola-BR	Loncast. Tesirine	Tafasitamab/Lena	Selinexor
MOA	Anti-CD79b ADC	Anti-CD19 ADC	Anti-CD19 mAb/Immunomod	XPO-1 inhibitor
ORR	**45%**	48%	**58%**	28%
CR rate	**40%**	24%	**40%**	10%
PFS	**9.2 m**	4.9 m	**11.6 m**	2.6 m
DOR	**12.6 m**	10.3 m	**43.9 m**	9.3 m
OS	**12.4 m**	9.9 m	**33.5 m**	NR

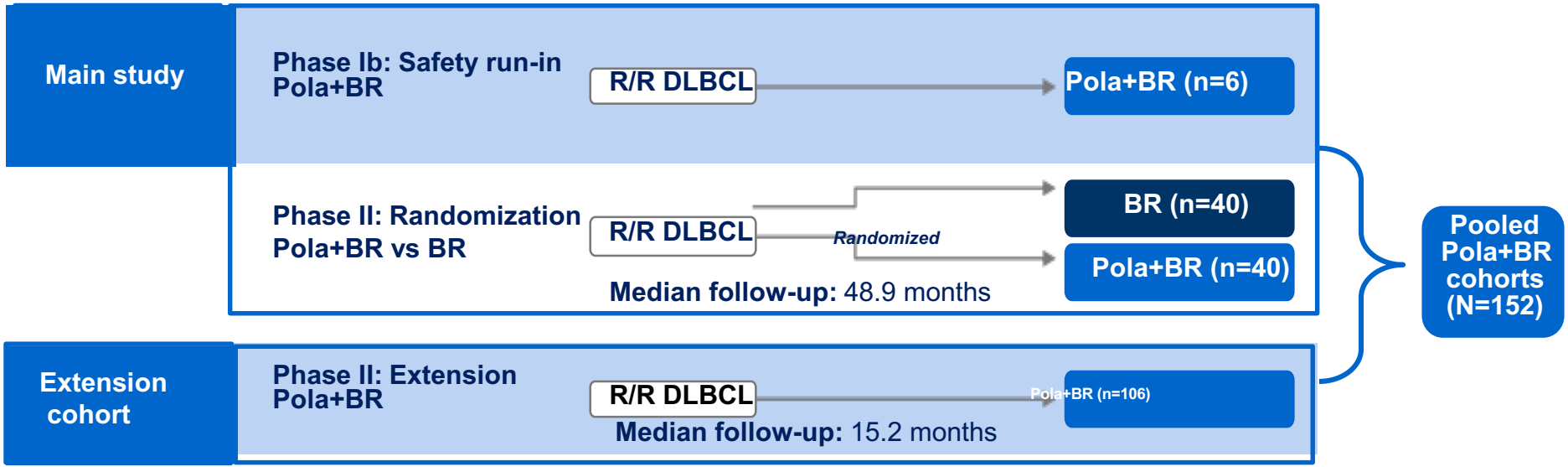
Sehn LH et al Blood Adv.2022; Caimi PF et al Lancet Oncol. 2021 ;Duell J.et al Haematologica 2021; Kalakonda Lancet Haematol 2020

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

Key eligibility criteria

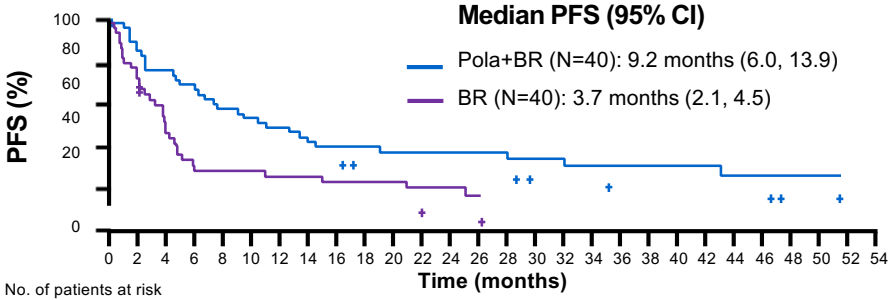
Inclusion: transplant-ineligible DLBCL, after at least 1 line of therapy

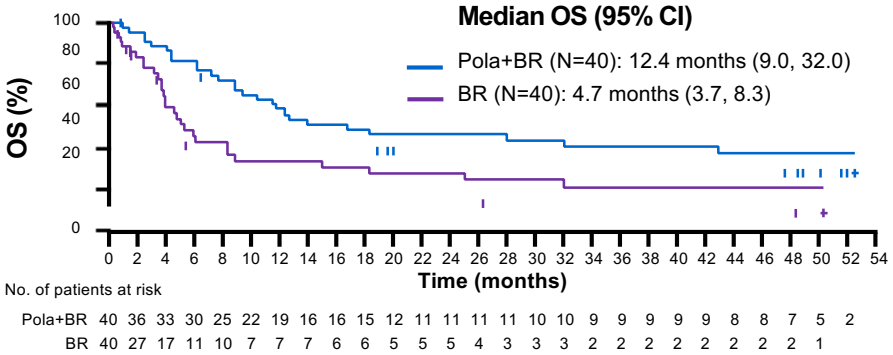
Exclusion: prior allogeneic SCT; history of transformation from indolent disease; current Grade >1 PN



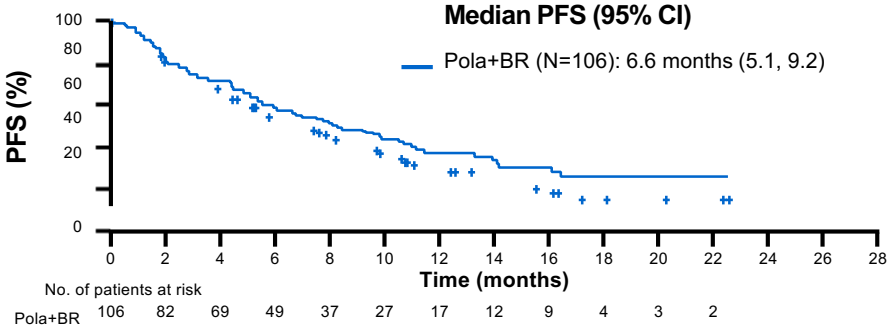
PFS and OS in randomized and extension cohorts

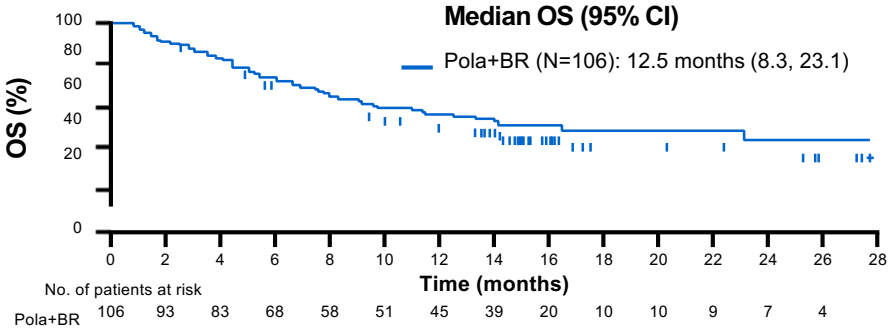
Randomized





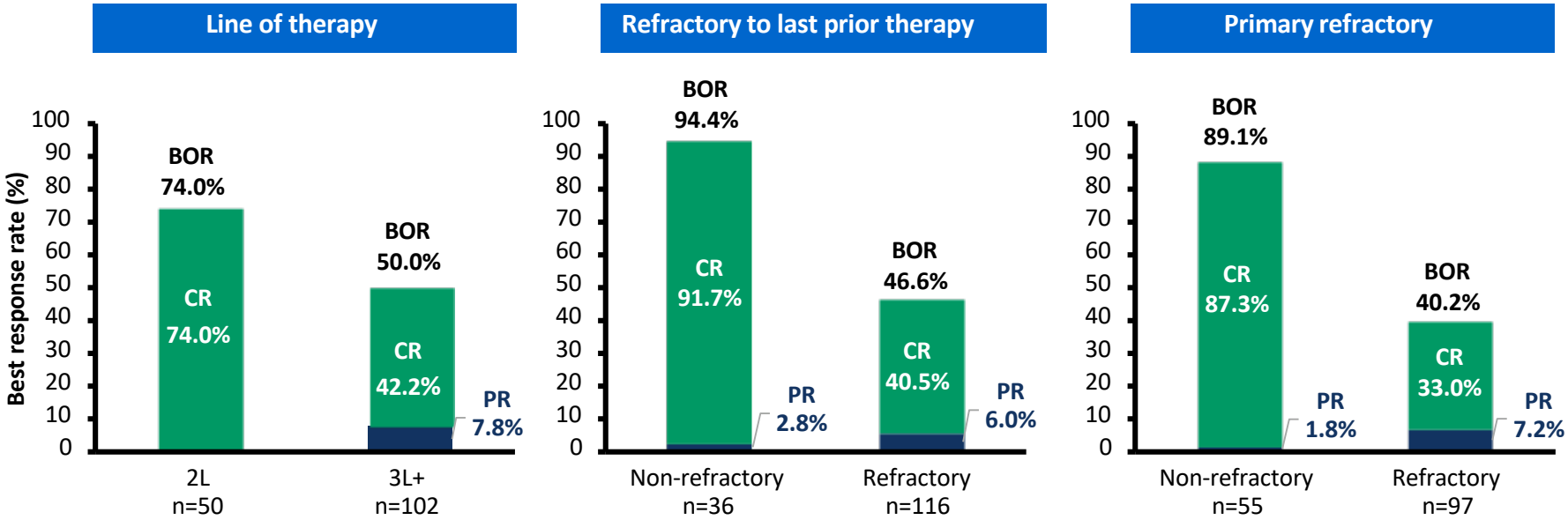
Extension cohort





Sehn LH, et al. Blood advances 2021

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

MODE OF ACTIONS PROVIDE THE RATIONALE FOR TAFASITAMAB + LENALIDOMIDE COMBINATION

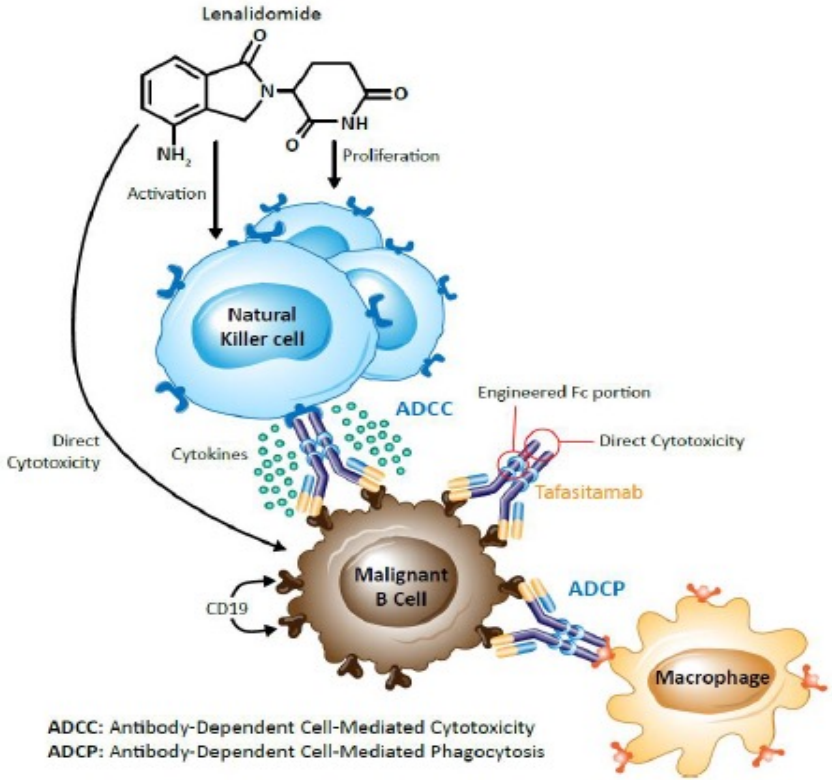
Tafasitamab MoA

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

Lenalidomide MoA

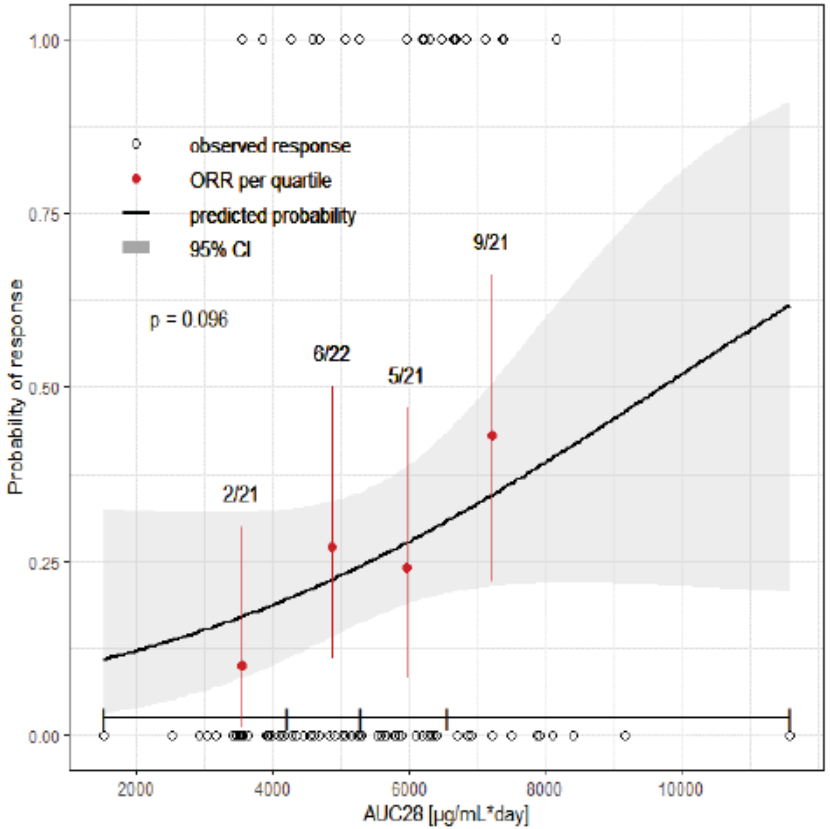
- Direct cytotoxicity
- Increase NK cell numbers (ADCC)
- Activate NK cells

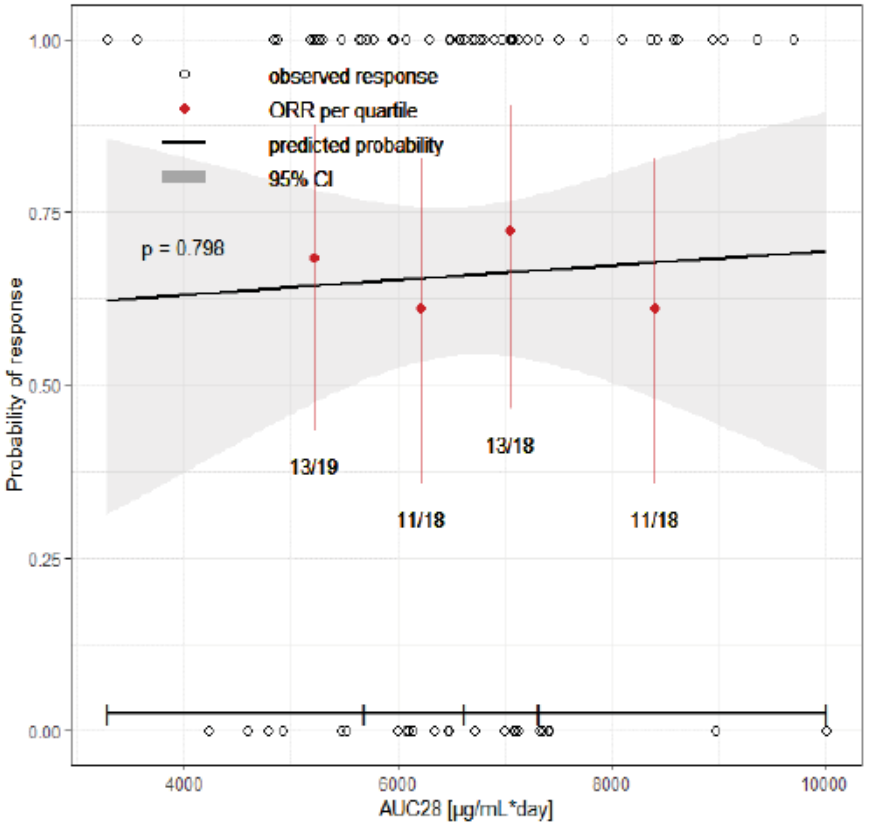
Increased anti-tumor effects



Salles 2020 on file

RESPONSE PROBABILITY VERSUS AUC28 FOR TAFASITAMAB AND TAFASITAMAB-LENALIDOMIDE

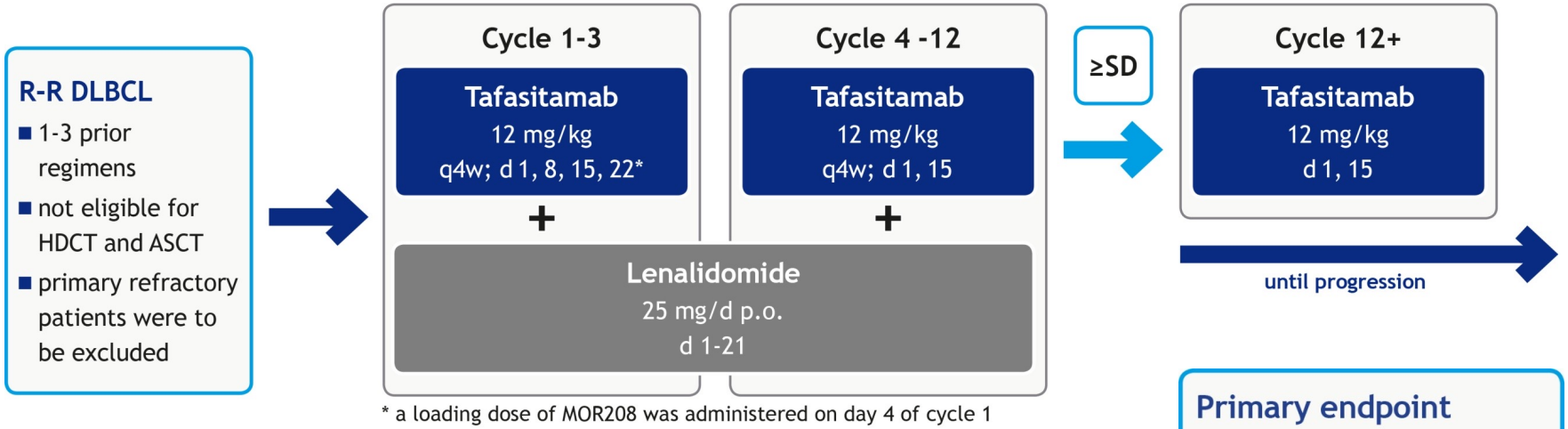




FDA review

L-MIND: study design

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



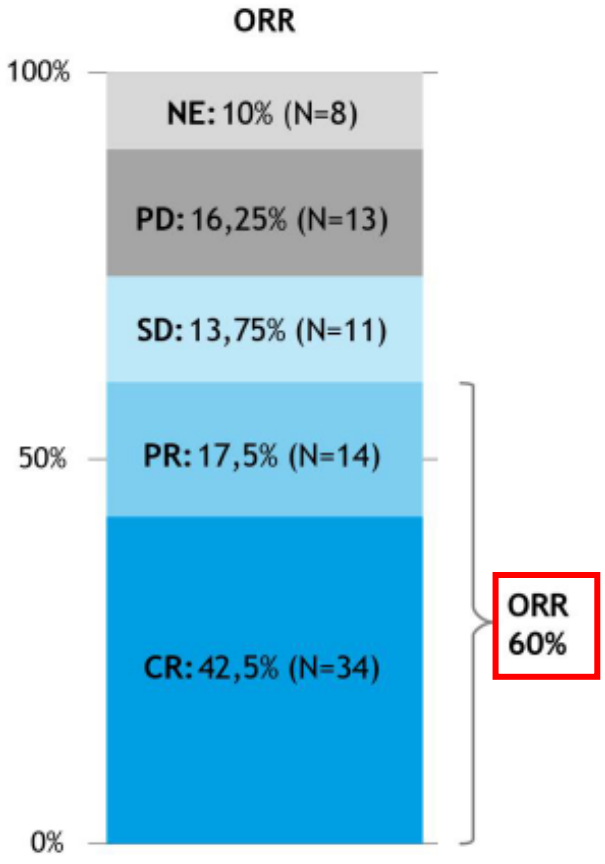
- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

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

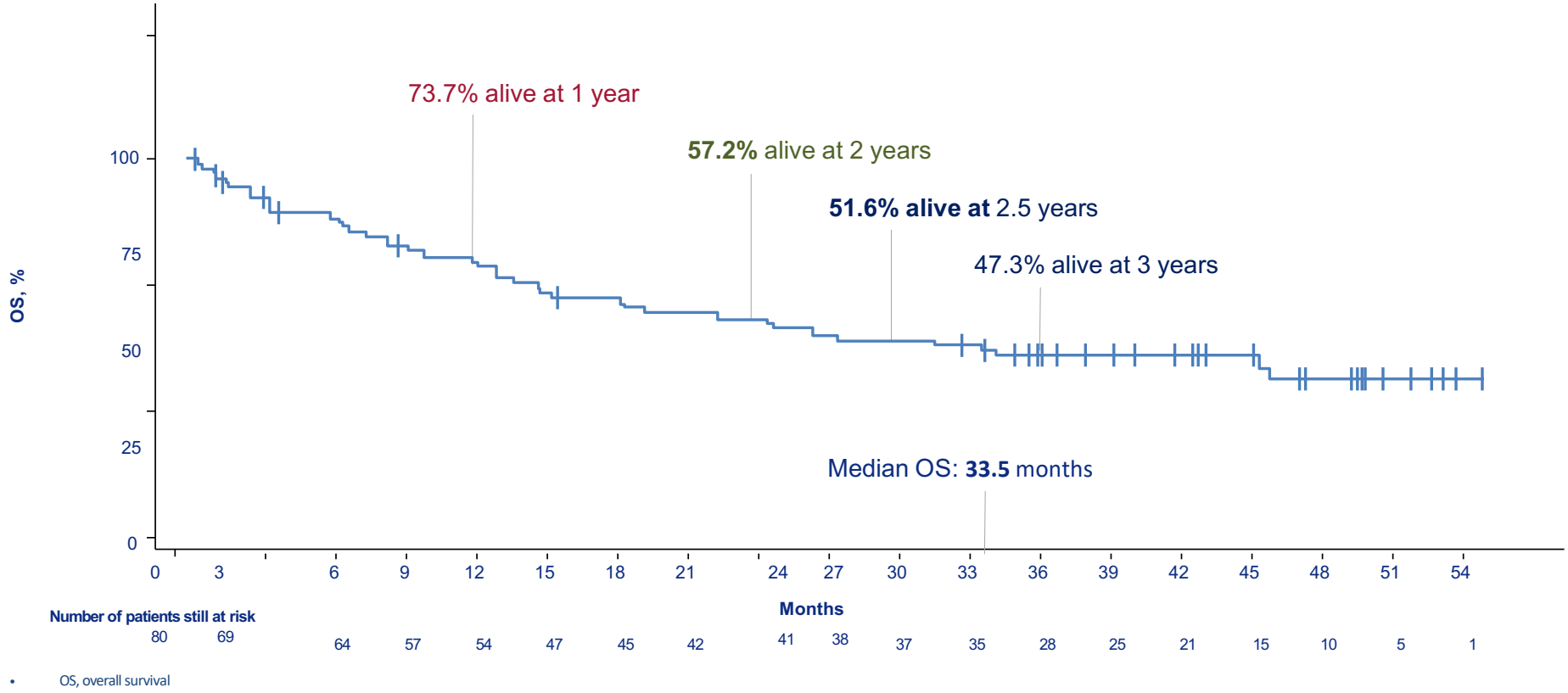
N=80: full analysis set → patients receiving at least one dose of tafasitamab and LEN

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

Tafa-Lena US Real World: Patients

Patient and Disease

Characteristic	TLOC	L-MIND
Number of patients	81	80
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)
Refractory to last therapy	66%	44%
Prior SCT	13%	11%
Prior CAR T	28%	0%

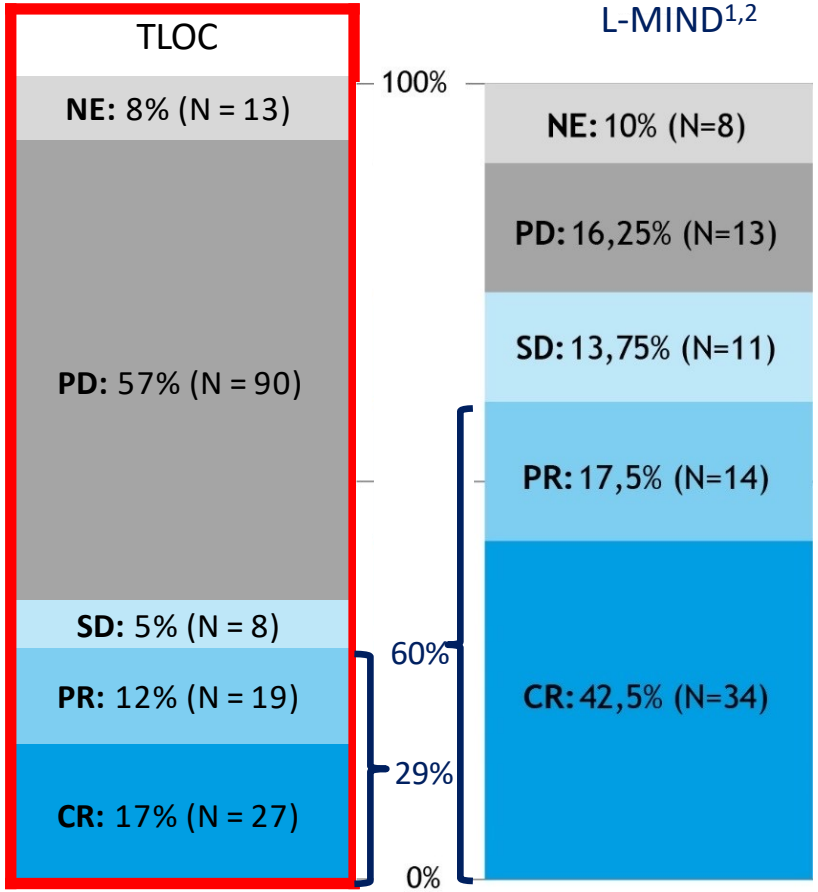
68%

50%

Qualls et al. ASH2022

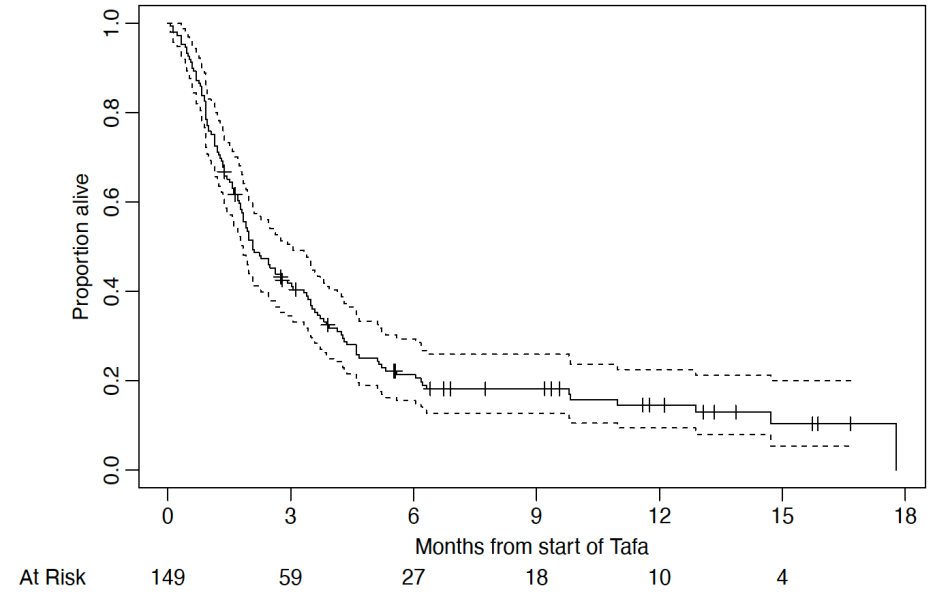
Treatment exposure and responses

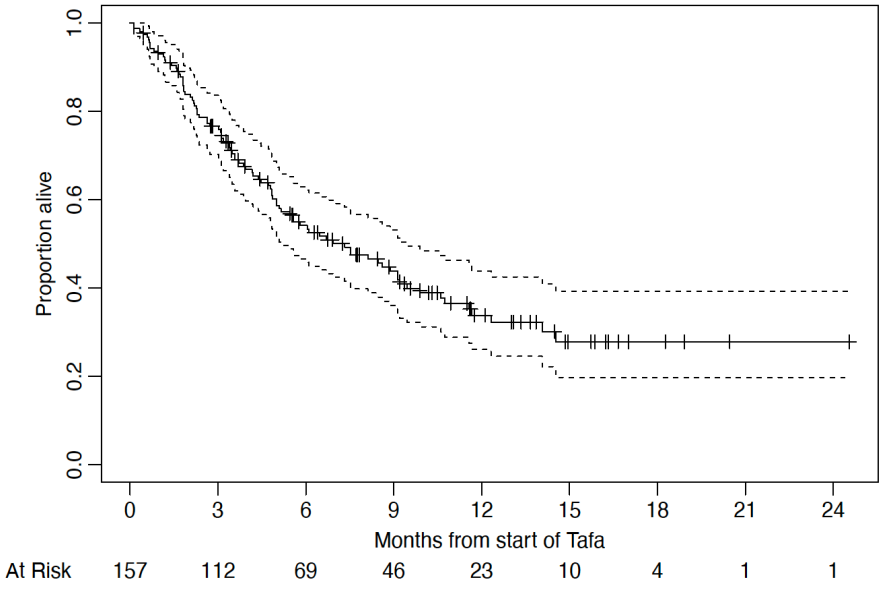
Treatment	
Time on treatment	
Median (IQR), days	59 (28 - 118)
Lenalidomide treatment timing	
Patients with delay in initiation	46%
Median delay time, days (IQR)	7 (4-20)
Starting daily lenalidomide dose (L-MIND: 25 mg)	
Patients with dose reduction at initiation	66%
Median starting dose, mg (IQR)	20 (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 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

Qualls et al. ASH2022

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:

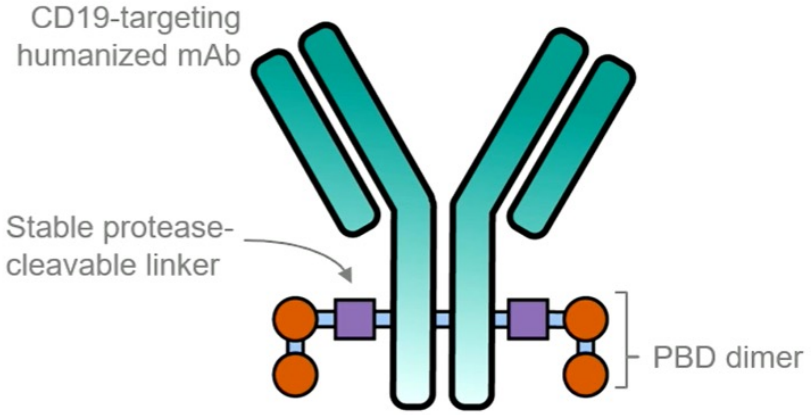
- EGFR < 60 ml/min
- Prior anti-CD19 therapy
- >3 prior lines of therapy
- ECOG PS 3-4
- High-grade B cell lymphoma

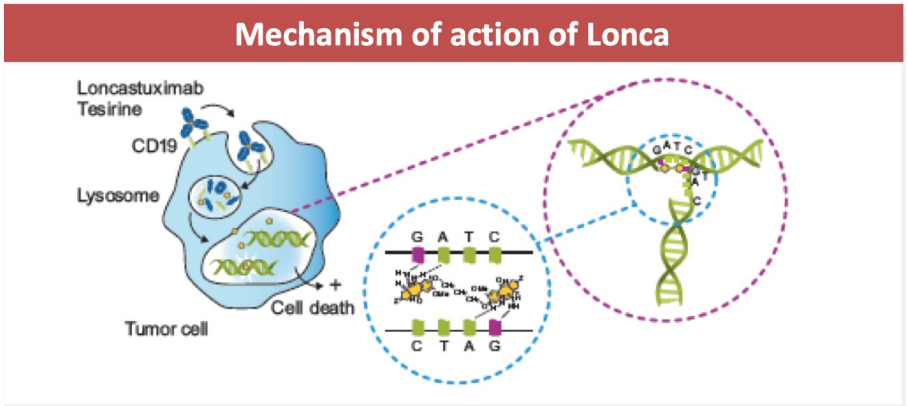
Qualls et al. ASH2022

Loncastuximab tesirine: an ADC targeted to CD19

- Humanized anti-CD19 antibody, stochastically conjugated through a cathepsin-cleavable valine-alanine linker to a pyrrolobenzodiazepine (PBD) dimer toxin causing DNA crosslinking

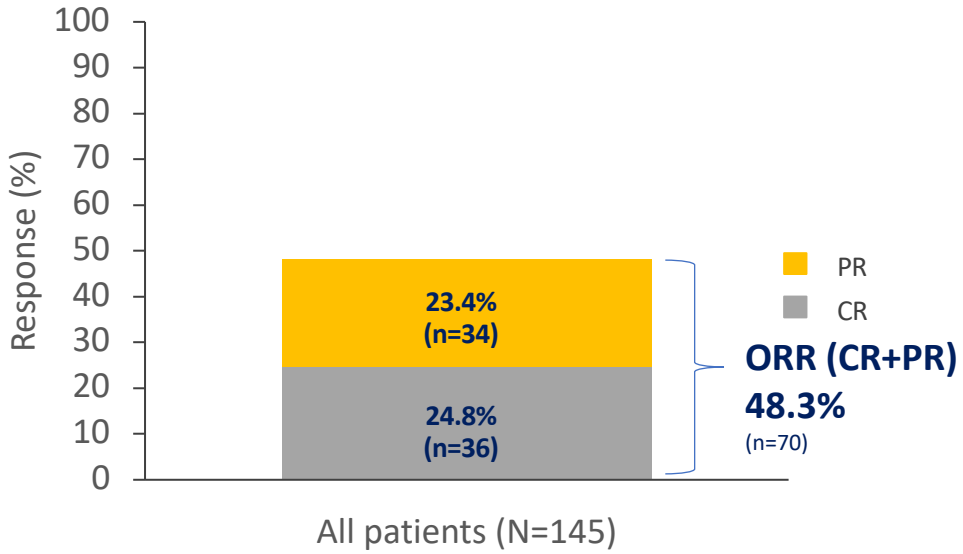
- April 2021: FDA grants accelerated approval for DLBCL patients r/r NTE, after two or more lines of sistemic therapy (LOTIS-2 trial)





Caimi P et al. Lancet Oncol 2021

Efficacy: ORR data and Follow-up analysis



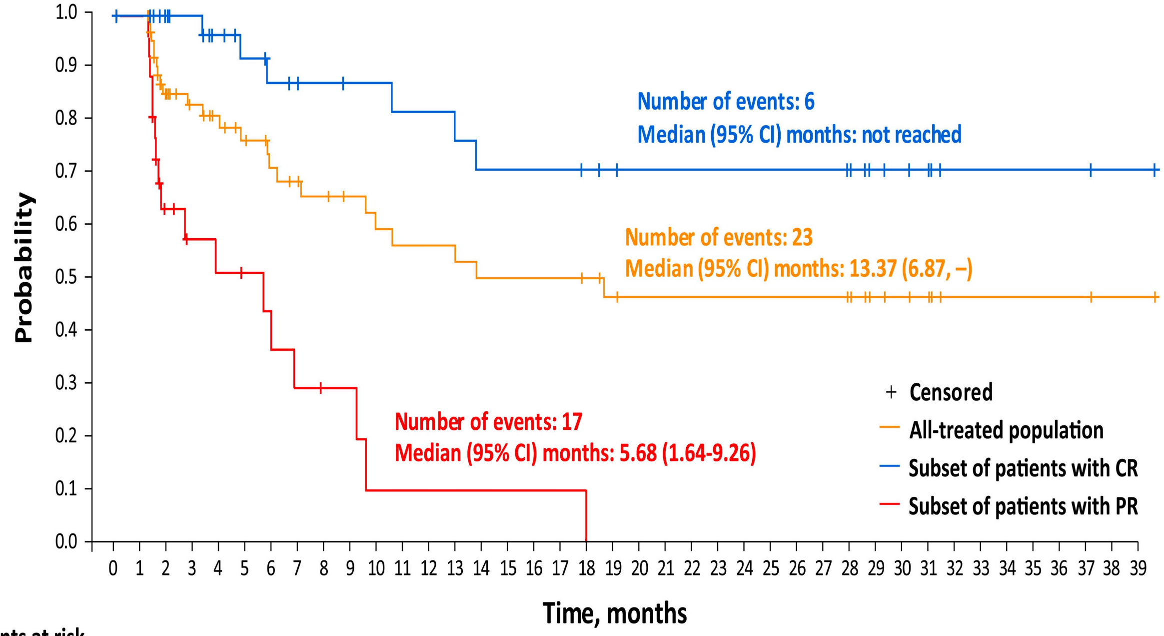
- **ORR** by central review was 70/145 **48.3%** (95% CI:[2] 39.9–56.7)

- CR rate 24.8% (95% CI:[2] 18.0–32.7)
- PR rate 23.4% (95% CI:[2] 16.8–31.2)

Median follow-up: 7.8 months (range 0.3–31.0)

Mean number of Lonca cycles administered: 4.6 (range 1–26)
Median number of Lonca cycles administered: 3 (range 1–26)
Mean number of Lonca cycles in responders (n=70): 6.8 (range 1–26)

Duration of response by best overall 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	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

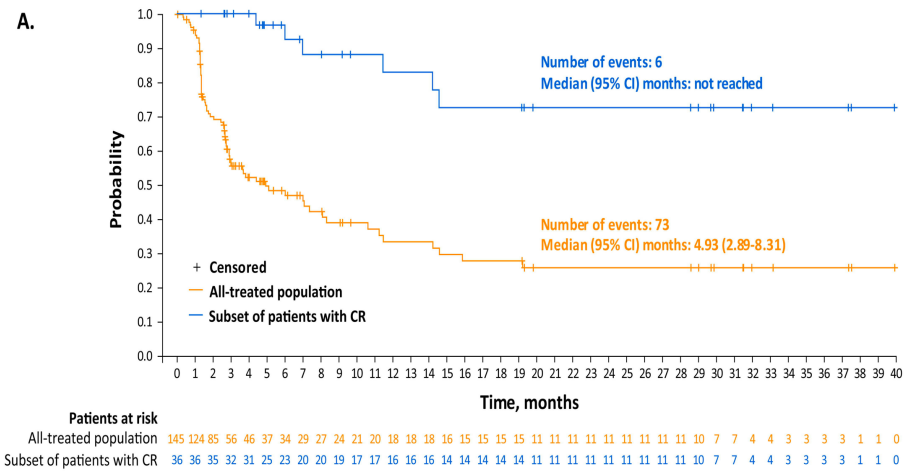
mDOR for patients with a **CR**
Not reached

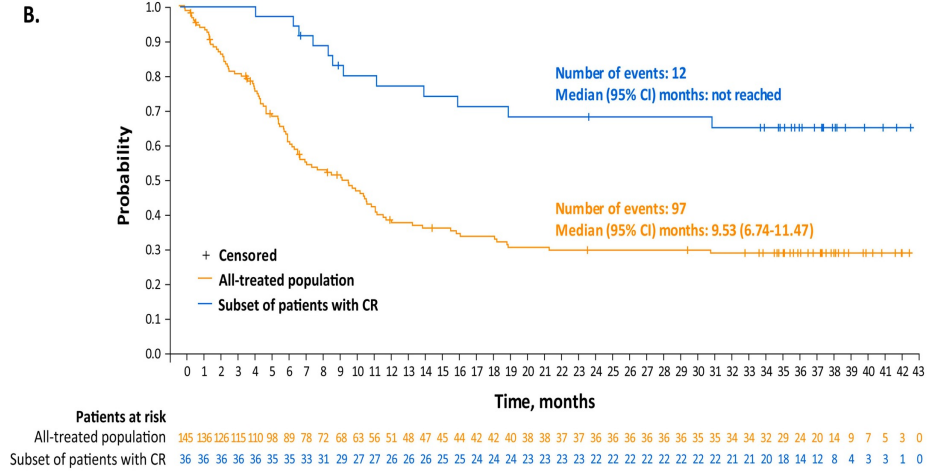
mDOR for the **70 responders**
13.4 months
(95% CI: 6.9–NE)

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

Caimi et al. Haematologica 2023

PFS and OS





mPFS was 4.9 months

mOS was 9.5 months

Caimi et al. Haematologica 2023

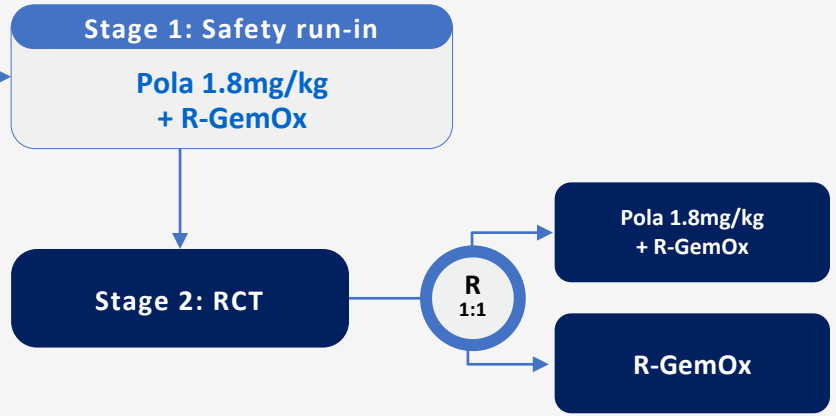
POLARGO Phase III study : Pola in combination with R-GemOx in R/R DLBCL

Rationale

- Pola + BR had an acceptable safety profile and demonstrated benefit vs BR in the GO29365 study
- R-GemOx is another widely used combination in DLBCL

Patients

- Ages ≥18 years
- Histologically confirmed R/R DLBCL
- ≥1 bi-dimensionally measurable lesion
- ECOG PS 0–2
- Adequate haematological function



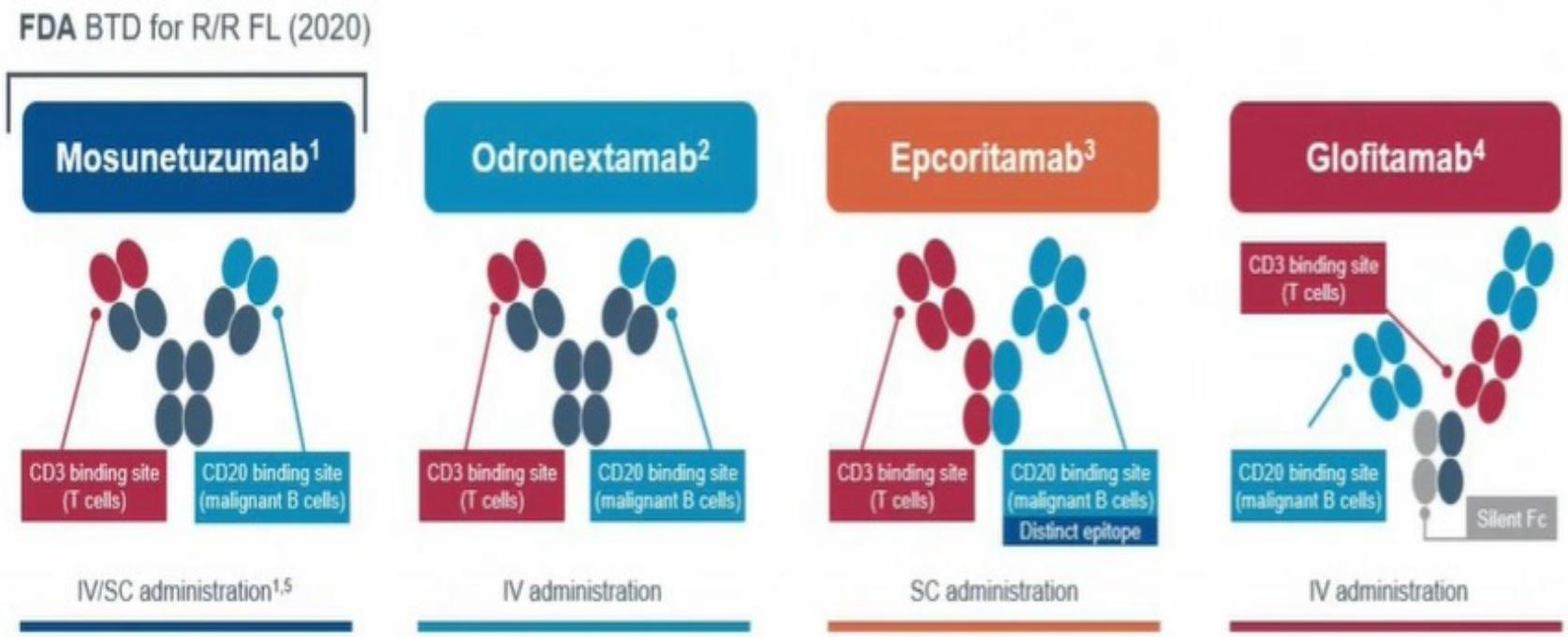
Endpoints

Primary: OS

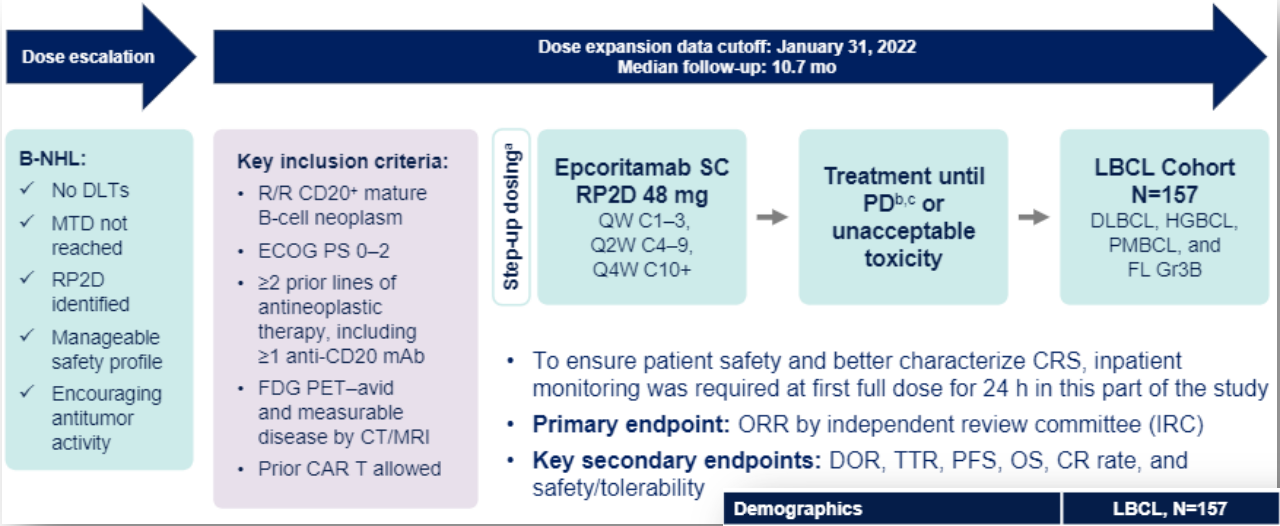
Secondary: Other efficacy and safety

EUDRACT NUMBER: 2018-003727-10

Anti-CD20 / anti-CD3 Bispecific Antibodies



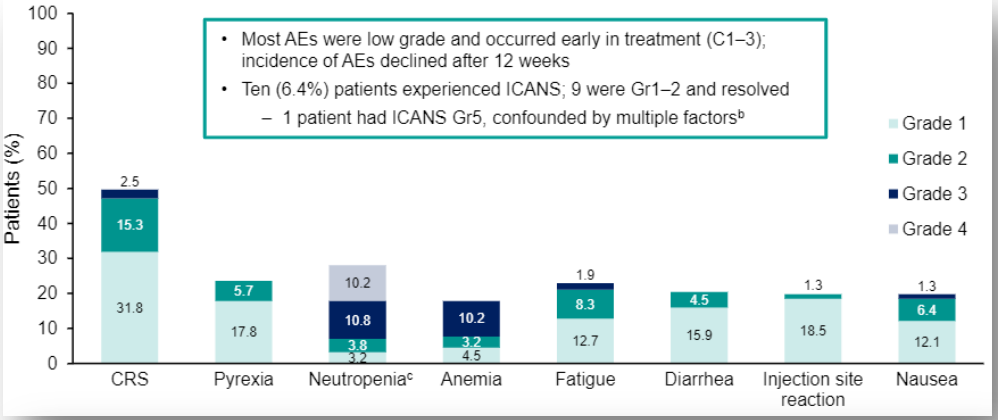
Epcoritamab in RR-DLBCL – EHA 2022



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)

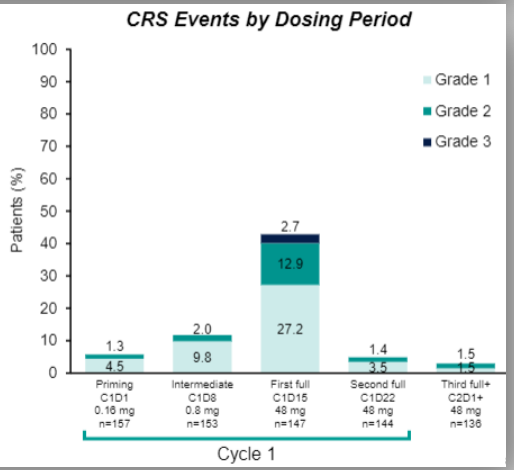
Epcoritamab: Adverse Events and Efficacy



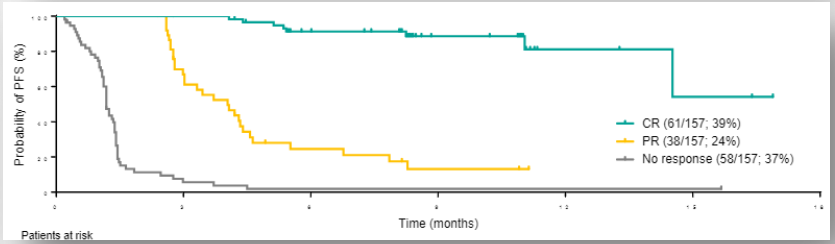
	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**

[a]Graded by Lee et al. 2019 criteria.

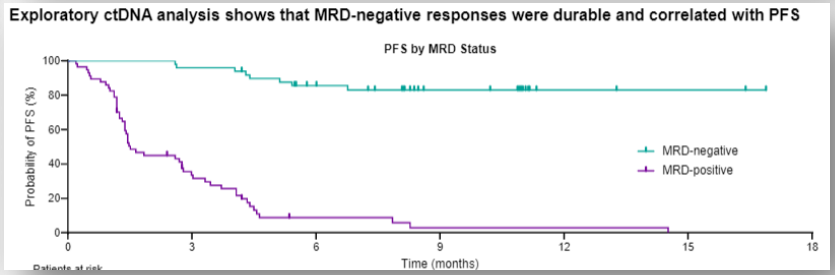
CRS was primarily low grade and predictable: most events occurred following the first full dose



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



Exploratory ctDNA analysis shows that MRD-negative responses were durable and correlated with PFS



Abstract 443

Subcutaneous Epcoritamab + R-DHAX/C in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Eligible for Autologous Stem Cell Transplant: Updated Phase 1/2 Results

Pau Abrisqueta, MD, PhD,[1] Raul Cordoba, MD, PhD,[2] Lorenzo Falchi, MD,[3] Sven de Vos, MD, PhD,[4] Marcel Nijland, MD, PhD,[5] Fritz Offner, MD, PhD,[6] Jun Wu, MD, MS,[7] Irina Bykhovski, PharmD,[8] Liwei Wang, PhD,[8] Ali Rana, MD, PhD,[8] Tycel Phillips, MD[9]

Study Design: EPCORE NHL-2 Arm 4

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R-DHAX/C in adults with R/R DLBCL who are eligible for transplant

Key inclusion criteria

- R/R CD20+ DLBCL
  - DLBCL, NOS
  - "Double-hit" or "triple-hit" DLBCL[a]
  - FL grade 3B
  - T-cell/histiocyte-rich DLBCL
- Eligible for R-DHAX/C and HDT-ASCT
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: September 16, 2022
Median follow-up: 12.6 mo
ClinicalTrials.gov: NCT04663347

Dose escalation, n=8 → **Expansion, n=21**

Step-up dosing

Epcoritamab (SC)
24 mg (n=3) or
48 mg (n=5)
QW C1–4,
Q2W C5–9,
Q4W C10+*

+ R-DHAX/C
C1–3

Primary objectives: DLT/Safety and tolerability
Key secondary objective: Antitumor activity[b]

Step-up dosing

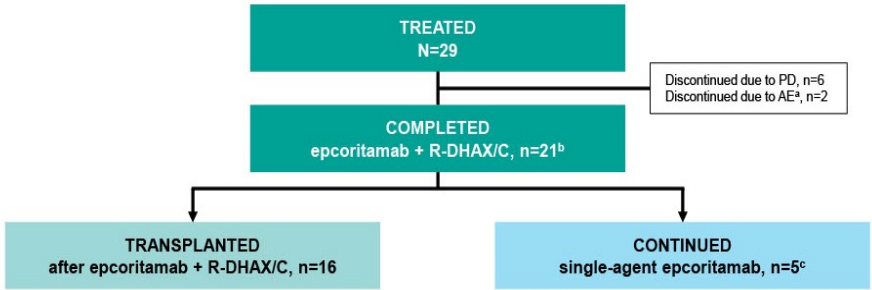
Epcoritamab (SC)
48 mg
QW C1–4,
Q2W C5–9,
Q4W C10+*

+ R-DHAX/C
C1–3

Primary objective: Antitumor activity[b]
Primary endpoint: ORR per Lugano criteria
***Epcoritamab treatment until HDT-ASCT or PD (whichever is earlier)**

R-DHAX/C regimen in C1–3, 21 d each: rituximab 375 mg/m² IV Q3W; dexamethasone 40 mg/d IV or orally on days 1–4; cytarabine 2 g/m² IV repeated after 12 h Q3W; carboplatin AUC = 5 mg/mL x min (Calvert formula) or oxaliplatin 100 mg/m² IV Q3W. Cycle 4 was 21 d; cycles 5+ were 28 d each. [a]Classified as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations. [b]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression.

Patient Disposition



The primary reason for patients not proceeding to transplant was patient and/or investigator choice

Median[d] (range) follow-up was 12.6 (2.0+ to 17.1) mo

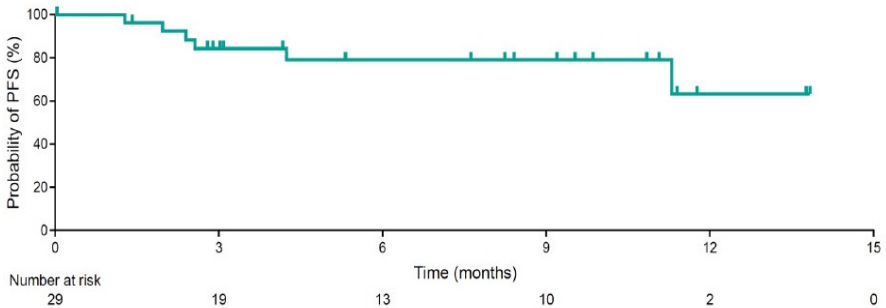
Overall and Complete Response Rates Were High

Response, n (%)[a]	Received ASCT n=16	Did not receive ASCT n=11[b]	Total efficacy evaluable n=27
Overall response	**16 (100)**	**7 (64)**	**23 (85)**
CMR	13 (81)	5 (45)	18 (67)
PMR	3 (19)	2 (18)	5 (19)
Stable disease	0	2 (18)	2 (7)
Progressive disease	0	1 (9)	1 (4)

Data cutoff: September 16, 2022. [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose. One patient died within 60 d of first dose without assessment. [b]Includes 5 patients who continued epcoritamab monotherapy and 6 patients who discontinued prior to reaching transplant.

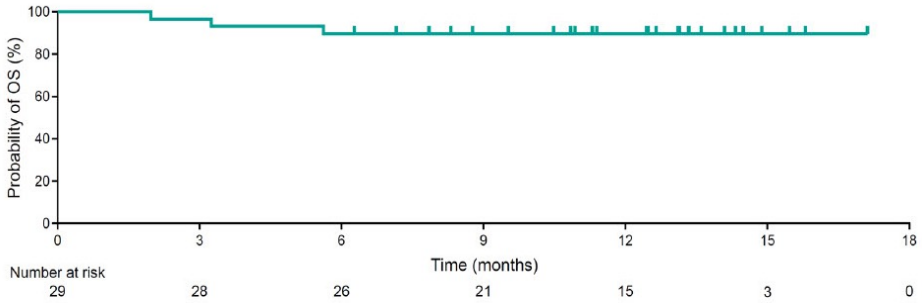
- Median* follow-up was 12.6 mo (range, 2.0+ to 17.1)
- Median duration of response and median duration of CMR were not reached
- Median time to response and complete response was 1.4 mo (range, 1.2–2.2 and 1.2–5.6, respectively)
- Efficacy was consistent in primary refractory patients: ORR 82%; CMR 59%

Progression-Free Survival



mPFS not reached at a median follow-up of 12.6 mo

Overall Survival



An estimated 90% (95% CI, 71%–97%) of patients remained alive at 12 mo;
mOS not reached at a median follow-up of 12.6 mo

Subcutaneous Epcoritamab Plus Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma From EPCORE NHL-5

Irit Avivi, MD,[1] Won Seog Kim, MD,[2*] Po-Shen Ko, MD,[3] Carlos Grande Garcia, MD, PhD,[4] David Lavie, MD,[5] David Chism, MD, MS,[6] Mostafa Seliem, PharmD,[7] Edwin E. Jeng, PhD,[7] Neha Joshi, PhD,[7] Satya Siddani, PhD,[7] Wissam Assaily, PhD,[7] Mariana Sacchi, MD,[8] Minh Dinh, MD,[7] Abraham Avigdor, MD[9]

[1]Hematology Division, Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [2]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; [3]Division of Hematology, Taipei Veterans General Hospital Division of Hematology, Taipei, Taiwan; [4]Clínica Universidad de Navarra, Madrid, Spain; [5]Department of Hematology, Hadassah Medical Center, Jerusalem, Israel; [6]Thompson Cancer Survival Center, Knoxville, TN, USA; [7]AbbVie, North Chicago, IL, USA; [8]Genmab, Plainsboro, NJ, USA; [9]Sheba Medical Center, Ramat Gan and Tel Aviv University, Tel Aviv, Israel

*Presenting author

Presented at the American Society of Hematology; December 9–12, 2023; San Diego, CA, USA

Study Design: EPCORE NHL-5 (NCT05283720)

Key inclusion criteria: arm 1

- Adults ≥18 y
- Histologically confirmed CD20+ DLBCL[a]
  - DLBCL, NOS
  - High-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* translocations
  - FL grade 3B
- R/R disease[b] with ≥1 prior anti-CD20 mAb–containing systemic therapy
- ASCT ineligible or failed prior ASCT
- Prior CAR T allowed, but prior CD3/CD20 bispecific antibodies not allowed
- ECOG PS 0–2
- Measurable disease

Data cutoff: Oct 6, 2023
Median follow-up: 8.2 mo

Dose escalation and dose expansion

Arm 1	Arm 2	Arm 3	Arms 4–5	Arms 6–7
Epcoritamab + lenalidomide (12 x 28-day cycles) R/R DLBCL	Epcoritamab + ibrutinib + lenalidomide R/R DLBCL	Epcoritamab + polatuzumab + R-CHP 1L DLBCL	Epcoritamab + CC-99282 (CELMoD) R/R DLBCL, R/R FL	Epcoritamab + ibrutinib ± venetoclax R/R MCL, 1L MCL

Epcoritamab dosing schedule

Step-up dosing (SUD)

- Cycle 1, day 1: SUD1 (0.16 mg)
- Cycle 1, day 8: SUD2 (0.8 mg)
- Cycle 1, days 15, 22: full dose (48 mg)
- Cycles 2–3, days 1, 8, 15, 22: full dose (48 mg)
- Cycles 4–12, day 1: full dose (48 mg)

Lenalidomide dosing schedule

Cycles 1–12: 25 mg once daily on days 1–21

Premedication and CRS prophylaxis

Diphenhydramine, acetaminophen, and corticosteroids were mandatory for CRS prophylaxis with the first 4 epcoritamab doses

- Prednisone 100 mg for 4 d was initially recommended
- Current recommendation is dexamethasone 15 mg for 4 d[c]

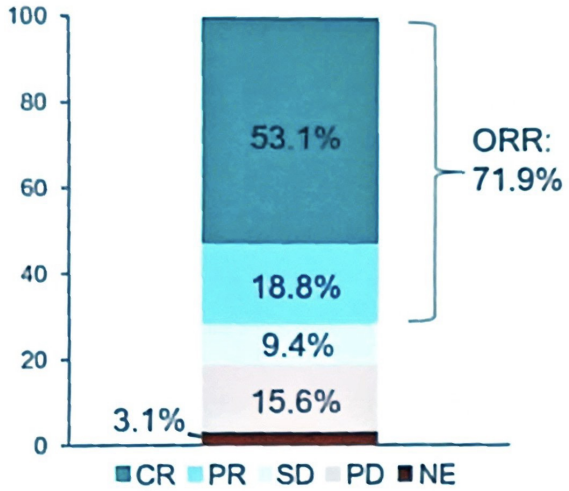
Objectives

Dose escalation: safety, tolerability, and identify expansion dose (RP2D)
Dose expansion: safety, tolerability, and antitumor activity

[a]Per WHO 2016 classification
[b]Relapsed disease is defined as disease that previously responded to therapy but progressed ≥6 mo after completion of therapy. Refractory disease is defined as disease that either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed within 6 mo after completion of therapy (including maintenance therapy)
[c]Additional information can be found in the following presentation: Vose J, et al. ASH 2023, abstract 1729

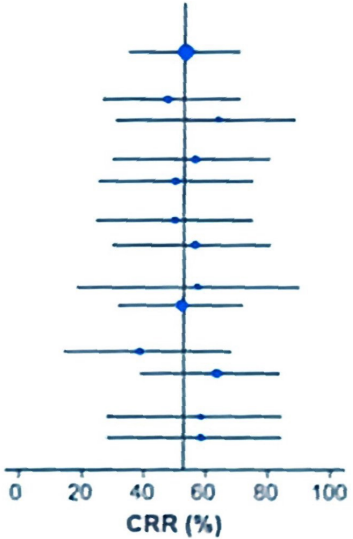
Frequent and Deep Responses Observed

Best overall response[a] (N=32)



Complete response in subgroups (N=32)

Subgroup	N	CRR, % (95% CI)
All patients	32	53.1 (34.7, 70.9)
Age		
<75 y	21	47.6 (25.7, 70.2)
≥75 y	11	63.6 (30.8, 89.1)
Prior lines of therapy		
1	16	56.3 (29.9, 80.2)
≥2	16	50.0 (24.7, 75.3)
Time from end of last therapy to first dose		
<6 mo	16	50.0 (24.7, 75.3)
≥6 mo	16	56.3 (29.9, 80.2)
Prior CAR T therapy		
Yes	7	57.1 (18.4, 90.1)
No	25	52.0 (31.3, 72.2)
Primary refractory status		
Yes	13	38.5 (13.9, 68.4)
No	19	63.2 (38.4, 83.7)
Molecular classification		
GCB	12	58.3 (27.7, 84.8)
ABC/non-GCB	12	58.3 (27.7, 84.8)

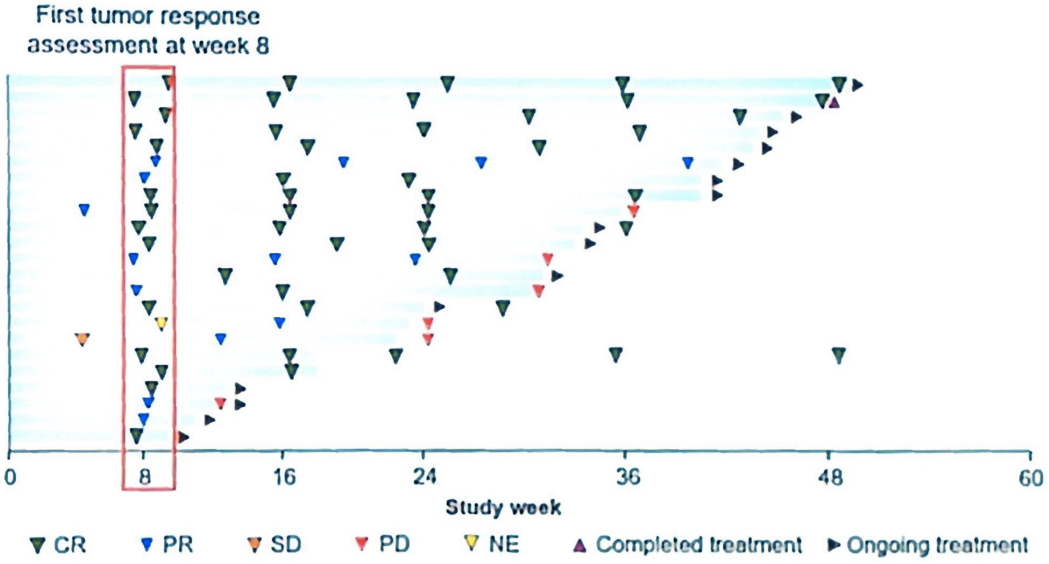


Data cutoff: Oct 6, 2023

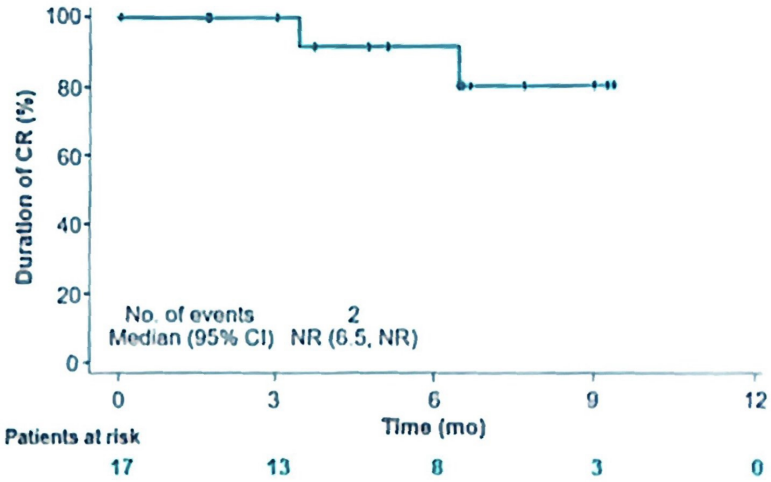
[a]Based on response-evaluable population, defined as patients with measurable disease at baseline and ≥1 postbaseline disease evaluation, or who had died within 60 d of the first dose of study drug without a postbaseline assessment.

Early and Durable Responses Observed[a]

Patients with responses (N=23)[b]



Duration of complete response



- Median time to response was 1.8 mo (range: 1.0–3.6)
- Median time to CR was 1.9 mo (range: 1.6–3.6)
- Median duration of CR was not reached

[a]Based on investigator assessment per Lugano criteria
[b]Radiographic response assessments occurred Q8W for 24 weeks, Q12W through week 48, then Q24W, and as clinically indicated, until disease progression

Glofitamab Monotherapy in Relapsed or Refractory Large B-Cell Lymphoma: Extended Follow-Up from a Pivotal Phase II Study and Subgroup Analyses in Patients with Prior Chimeric Antigen Receptor T-Cell Therapy and by Baseline Total Metabolic Tumor Volume

Martin Hutchings,[1] Carmelo Carlo-Stella,[2] Franck Morschhauser,[3] Lorenzo Falchi,[4] Emmanuel Bachy,[5] Guillaume Cartron,[6] Cyrus Khan,[7] Monica Tani,[8] Joaquin Martinez-Lopez,[9] Nancy L. Bartlett,[10] Antonio Salar,[11] Joshua Brody,[12] Sirpa Leppä,[13] Pauline Baumlin,[14] Estefania Mulvihill,[14] James Relf,[15] Saibah Chohan,[16] Derrick Kaufman,[17] Linda Lundberg,[14] Michael Dickinson[18]

Presented at the 65th ASH Annual Meeting | December 9–12, 2023

Study design

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

Key inclusion criteria

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

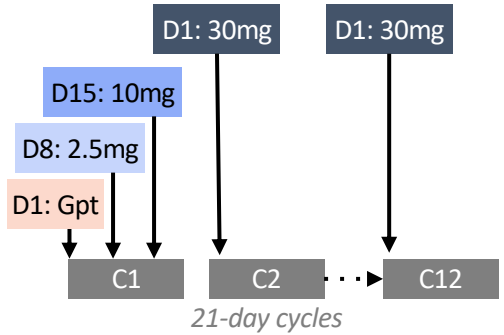
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

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



Endpoints

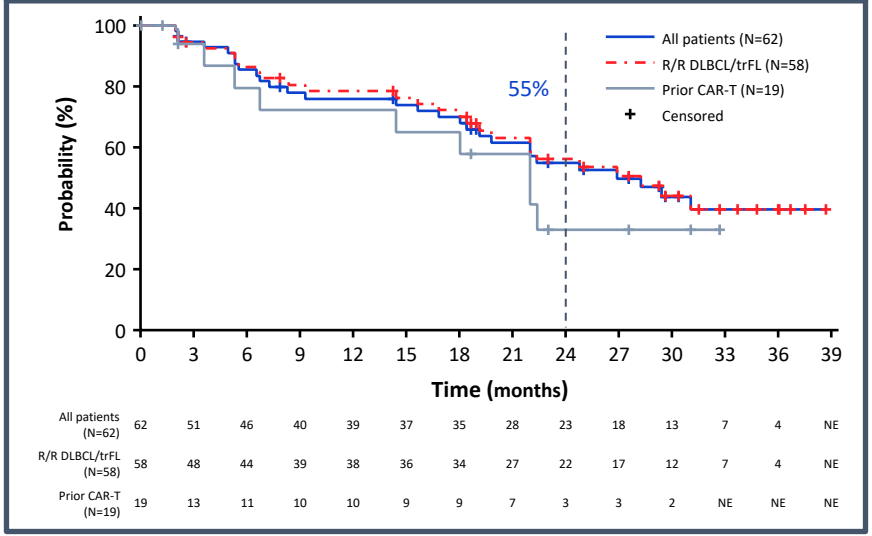
- **Primary:** CR (best response) rate by IRC*
- **Key secondary:** ORR,† DoR,† DoCR,† PFS, and OS

Hutchings et al., oral presentation ASH 2023

Response rates and DoCR

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

DoCR by IRC



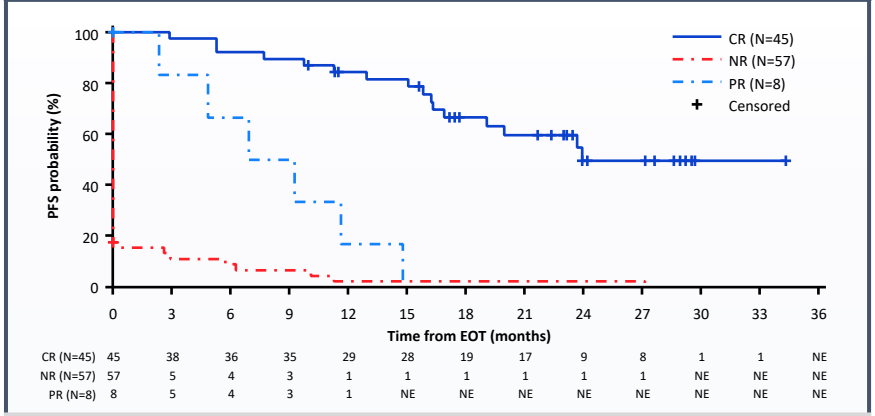
- Median time on study: 32.1 months (range: 0–43)

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

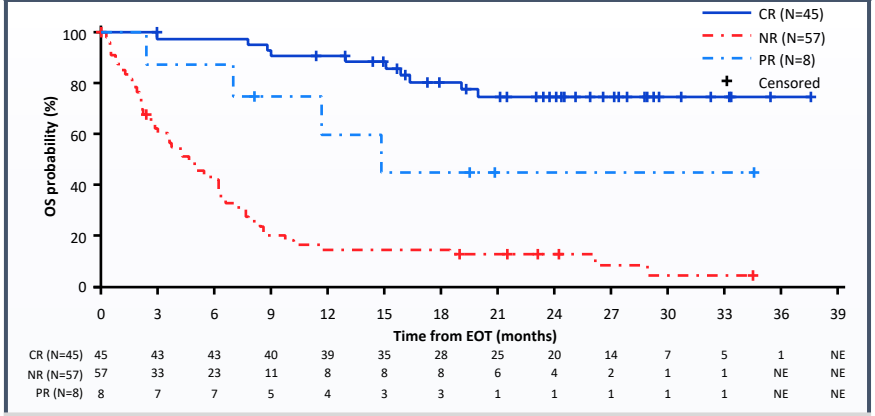
Hutchings et al., oral presentation ASH 2023

Landmark analysis by response at EOT

PFS



OS



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

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

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

Hutchings et al., oral presentation ASH 2023

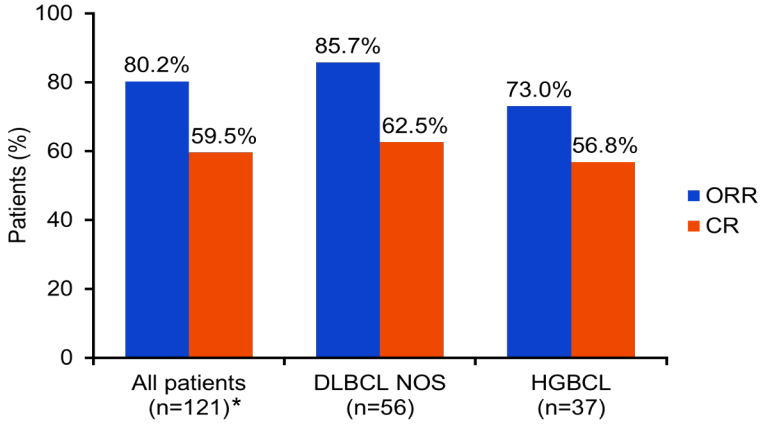
Glofitamab plus Polatuzumab Vedotin Continues to Demonstrate Frequent and Durable Responses and Has a Manageable Safety Profile in Patients with ≥2L Relapsed/Refractory DLBCL, Including HGBCL, and in Patients with Prior CAR T-Cell Therapy: Updated Results from a Phase Ib/II Study

Martin Hutchings et al

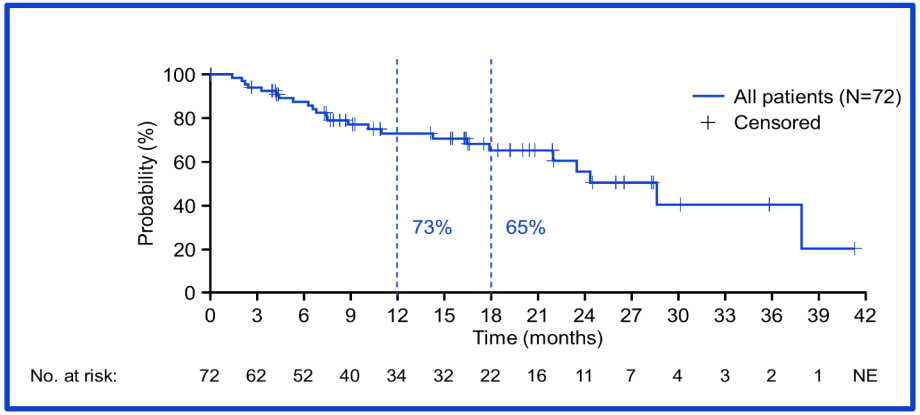
n (%) unless stated	N=125
Median age (range), years	67 (23–84)
Male	79 (63.2)
ECOG PS	
0–1	118 (94.4)
2	7 (5.6)
Histology	
de novo DLBCL	56 (44.8)
trFL	26 (20.8)
HGBCL	41 (32.8)
PMBCL	2 (1.6)
IPI score	
0/1	23 (18.4)
2/3	68 (54.4)
4/5	34 (27.2)

n (%) unless stated	N=125
Ann Arbor stage	
I/II	29 (23.2)
III/IV	96 (76.8)
Bulky disease	
>6cm	52 (41.6)
>10cm	19 (15.2)
Median prior lines of therapy (range)	2 (1–7)
Number of prior lines of therapy	
1	50 (40.0)
≥2	75 (60.0)
Prior CAR T-cell therapy	28 (22.4)
Refractory to any prior therapy	100 (80.0)
Refractory to last prior therapy	90 (72.0)

Best overall response by histology

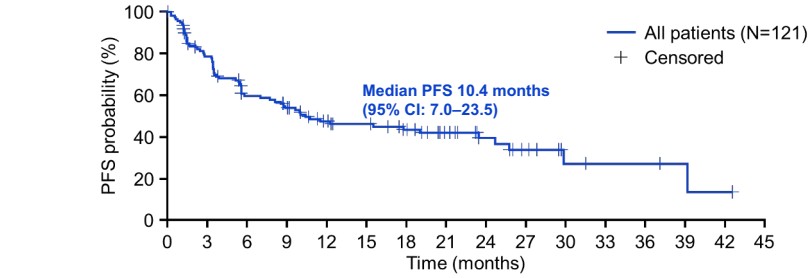


Glofit-Pola DOCR

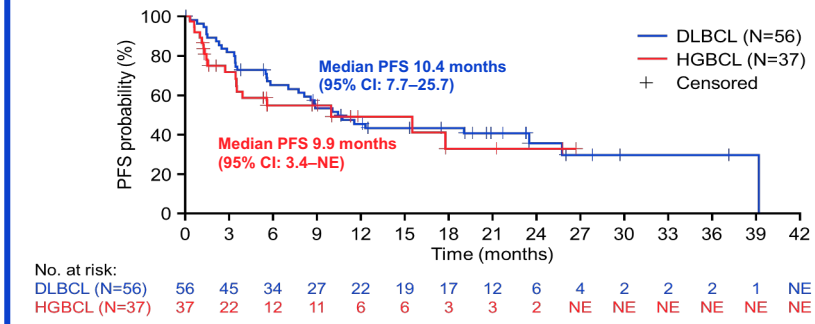


- **Median DOCR for DLBCL was 21.9 months (95% CI: 10.1–NE) and NE for HGBCL‡**

PFS in all patients (N=121)*



PFS by histology



Mosunetuzumab Plus Polatuzumab Vedotin Demonstrates a Favorable Safety Profile and Efficacy in Patients With Relapsed/Refractory LBCL: Primary Analysis of a Phase Ib/II Study

L. Elizabeth Budde,[1] Adam J. Olszewski,[2] Sarit Assouline,[3] Izidore S. Lossos,[4] Catherine Diefenbach,[5] Manali Kamdar,[6] Nilanjan Ghosh,[7] Dipenkumar Modi,[8] Waleed Sabry,[9] Seema Naik,[10] Amitkumar Mehta,[11] Shazia K. Nakhoda,[12] Stephen D. Smith,[13] Kathleen Dorritie,[14] Ting Jia,[15] Song Pham,[16] Ling-Yuh Huw,[17] Hao Wu,[17] Iris To,[17] Michael C. Wei,[17] Julio C. Chavez[18]

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Presented at the 65th ASH Annual Meeting | December 9–12, 2023

Study overview (NCT03671018)

Key inclusion criteria

- LBCL (*de novo* DLBCL, HGBCL, trFL, or Grade 3b FL)
- ≥1 prior line of therapy, including an anti-CD20-directed therapy
- Patients who were ineligible for ASCT

Objectives

- Efficacy and safety of mosun-pola
- Primary endpoint: Best ORR[1] by independent review committee (IRC)

Mosun-pola fixed duration administration*

Mosun†

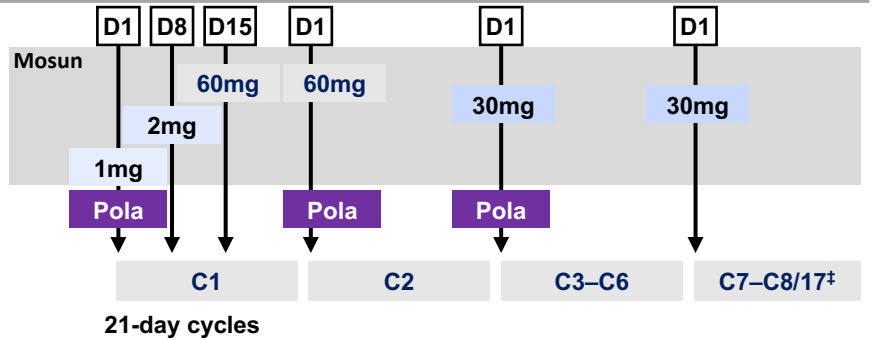
- Cycle (C) 1 step-up dosing for CRS mitigation
- Q3W intravenous infusions at RP2D (C1–8/17)‡

Pola

- Q3W intravenous infusions (1.8mg/kg) (Day [D]1, C1–6)

No mandatory hospitalization

Retreatment with mosun-pola was permitted

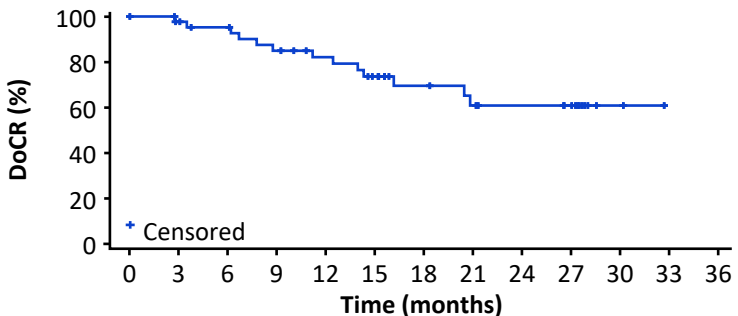


Budde et al., oral presentation ASH 2023

n, unless stated	N=98
Median age, years (range)	68 (20–88)
Gender, male	70 (71.4%)
ECOG PS score	
0	36 (36.7%)
1	55 (56.1%)
2	7 (7.1%)
NHL histology	
DLBCL	68 (69.4%)
HGBCL	18 (18.4%)
trFL	8 (8.2%)
FL Grade 3b	4 (4.1%)
Cell-of-origin (n=94)*	
GCB	53 (56.4%)
Non-GCB	33 (33.7%)
Unknown	8 (8.5%)

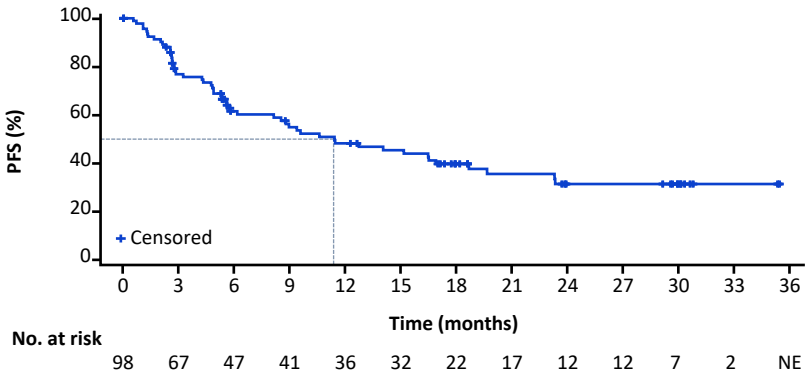
n, unless stated	N=98
Ann Arbor stage III–IV	85 (86.7%)
Bulky disease, ≥6cm	33 (33.7%)
Extranodal involvement	65 (66.3%)
Number of prior lines of therapy	
1	35 (35.7%)
≥2	63 (64.3%)
Median lines of prior therapy, n (range)	2 (1–8)
Prior ASCT	11 (11.2%)
Prior CAR T-cell therapy	35 (35.7%)
Refractory to CAR T-cell therapy	26/35 (74.3%)
Primary refractory	56 (57.1%)
Refractory to†	
Last prior therapy	76 (77.6%)
Any prior CD20 therapy	80 (81.6%)

Efficacy endpoint*	N=98	
	INV	IRC
Best ORR, n [95% CI]	62 (63.3%) [52.9–72.8]	58 (59.2%) [48.8–69.0]
CR rate, n [95% CI]	50 (51.0%) [40.7–61.3]	45 (45.9%) [35.8–56.3]

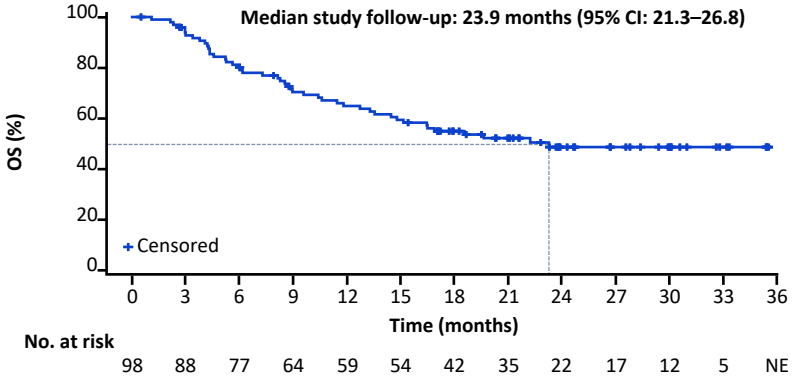


PFS and OS

PFS



OS



	N=98
Median PFS*, months (95% CI)	11.4 (6.2–18.7)
12-month event-free rate, % (95% CI)	48.2 (37.3–59.0)
24-month event-free rate, % (95% CI)	31.3 (20.1–42.6)

	N=98
Median OS, months (95% CI)	23.3 (14.8–NE)
12-month event-free rate, % (95% CI)	64.9 (55.2–74.5)
24-month event-free rate, % (95% CI)	48.6 (37.9–59.3)

Encouraging PFS and OS benefit observed at 2 years

Budde et al., oral presentation ASH 2023

Final analysis of the Phase 2 ELM-2 study: Odronextamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

Sabarish Ayyappan[1], Won Seog Kim[2], Tae Min Kim[3], Jan Walewski[4], Seok-Goo Cho[5], Isidro Jarque[6], Elżbieta Iskierka-Jażdżewska[7], Michelle Poon[8], Sung Yong Oh[9], Francesca Lim[10], Cecilia Carpio[11], Tran-Der Tan[12], Antonio Gutierrez[13], Huilai Zhang[14], Junning Cao[15], Mingzhi Zhang[16], Benoit Tessoulin[17], Jingjin Li[18], Melanie Ufkin[18], Saleem Shariff[19], Jurriaan Brouwer-Visser[18], Lei Chi[18], Aafia Chaudhry[18], Hesham Mohamed[18], Srikanth Ambati[18], H. Miles Prince[20], on behalf of ELM-2 Investigators

[1]City of Hope Cancer Treatment Center, Atlanta, GA, USA; [2]Samsung Medical Center, Center for Hematologic Malignancy, Seoul, South Korea; [3]Seoul National University Hospital, Seoul, South Korea; [4]Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy, Warszawa, Poland; [5]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [6]Hospital Universitario La Fe, Valencia, Spain; [7]Copernicus Memorial Hospital, Medical University of Łódź, Łódź, Poland; [8]National University Hospital, Singapore, Singapore; [9]Dong-A University Hospital, Busan, South Korea; [10]Singapore General Hospital, Singapore, Singapore; [11]University Hospital Vall d'Hebron, Autonomous University of Barcelona (UAB), Barcelona, Spain; [12]Koo Foundation Sun Yat Sen Cancer Center, Taipei City, Taiwan; [13]Hospital Universitari Son Espases, IdISBa Palma, Palma de Mallorca, Spain; [14]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [15]Fudan University Shanghai Cancer Center, Shanghai, China; [16]The First Affiliated Hospital of Zhengzhou University and Lymphoma Diagnosis and Treatment Center of Henan Province, Zhengzhou, Henan, China; [17]Nantes University Hospital, Nantes, France; [18]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [19]Regeneron UK Ltd., Uxbridge, UK; [20]Epworth Healthcare and University of Melbourne, Melbourne, VIC, Australia

ClinicalTrials.gov ID: NCT03888105

This study was funded by Regeneron Pharmaceuticals, Inc. Medical writing support was provided by Georgina Bartle of Oberon, a division of OPEN Health Communications, and funded by Regeneron Pharmaceuticals, Inc.

Presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition, December 9–12, 2023, San Diego, CA, USA

ELM-2 study design: DLBCL cohort

- Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in R/R B-NHL (NCT03888105)
  - The final analysis was performed when all patients with DLBCL had the opportunity for ≥36 weeks of follow-up

Key eligibility criteria

- DLBCL per WHO 2016 classification[1]
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of therapy, including an anti-CD20 antibody and an alkylator

Primary endpoint: ORR* by ICR

Secondary endpoints:

- ORR* by *local* investigator
- CR*, DOR*, PFS*, and OS
- Safety and tolerability
- Patient-reported outcomes

Key exploratory endpoint: MRD

Odronextamab administration (IV, 21-day cycles)

Measures taken to facilitate diverse, inclusive enrollment:

- Diverse trial sites
- Translated consents for under-represented populations
- Extended screening windows for patients with access restraints
- Broad eligibility criteria to include patients with controlled HIV, hepatitis B and C
- Lower thresholds for those with compromised organ function

*According to Lugano criteria.[2] †The study initiated with a Cycle 1 step up regimen of 1/20 mg. This was modified to 0.7/4/20 mg to further mitigate the risk of CRS. Premedication administered during Cycle 1 step up included dexamethasone, diphenhydramine, and acetaminophen.

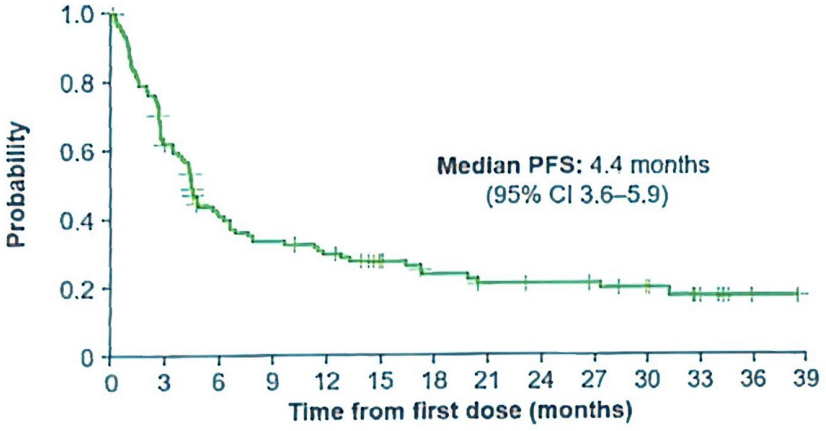
B-NHL, B-cell non-Hodgkin's lymphoma; CD, cluster of differentiation; CR, complete response; CRS, cytokine release syndrome; D, day; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; ICR, independent central review; IV, intravenous; mos, months; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q4W, every 4 weeks; R/R, relapsed/refractory; WHO, World Health Organization

1. Cheson BD, et al. *J Clin Oncol*. 2014;[illegible]59-68. 2. Beham-Schmid C, [illegible]mo. 2017;10(4):248–54.

ELM-2: Progression-free survival

- Median PFS was 20.4 months in complete responders versus 5.8 months in partial responders

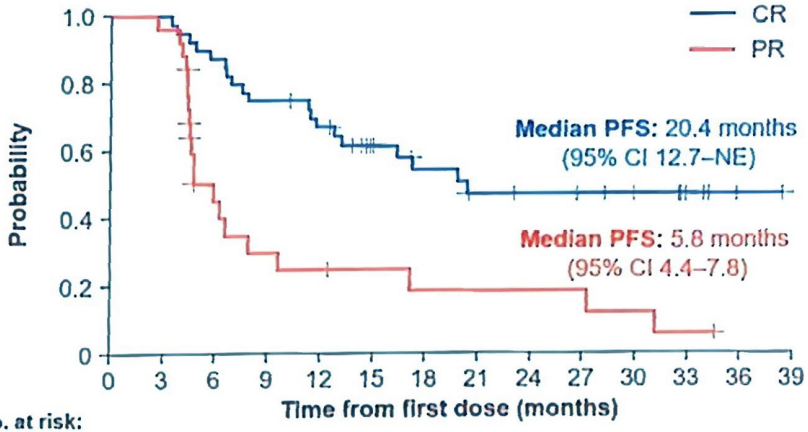
PFS



No. at risk: 127 72 44 36 31 22 18 15 14 13 10 5 1 0

	N=127
12-month PFS rate, % (95% CI)	29.6 (21.5–38.2)
24-month PFS rate, % (95% CI)	21.1 (13.7–29.7)

PFS by best overall response



No. at risk:

CR 40 40 35 30 26 18 15 12 11 10 8 4 1 0

PR 26 25 9 6 5 4 3 3 3 3 2 1 0 0

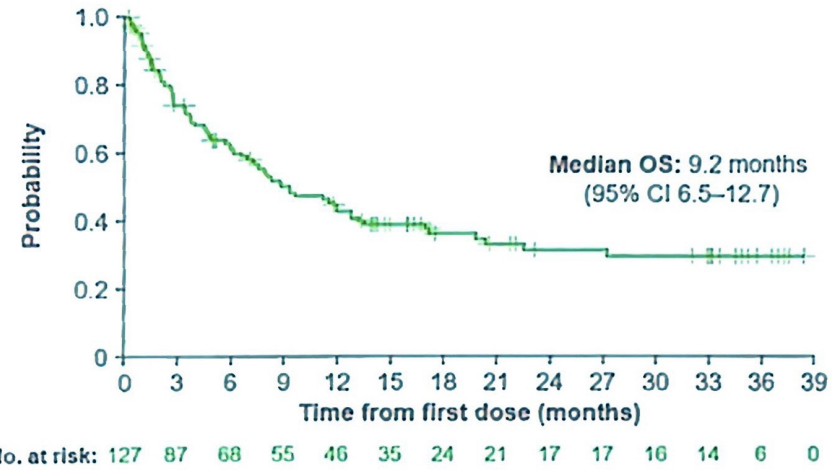
	CR (n=40)	PR (n=26)
12-month PFS rate, % (95% CI)	67.2 (50.3–79.5)	25.2 (9.5–44.7)
24-month PFS rate, % (95% CI)	47.5 (29.9–63.1)	18.9 (5.4–38.6)

Data cut-off date: August 10, 2023. Efficacy per independent central review
CR, complete response; NE, not estimable; OS, overall survival; PFS, progression-free survival; PR, partial response

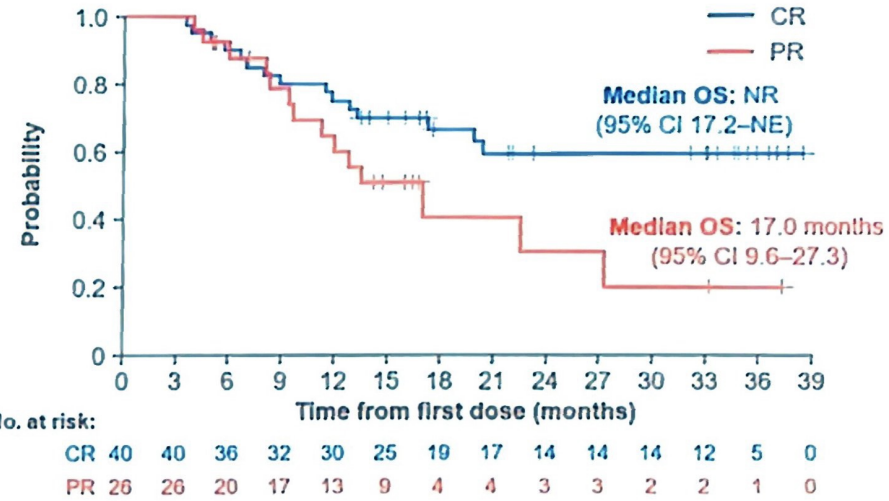
ELM-2: Overall survival

- Median OS was not reached in complete responders versus 17.0 months in partial responders

OS



OS by best overall response



	N=127
12-month OS rate, % (95% CI)	42.9 (33.7–51.8)
24-month OS rate, % (95% CI)	31.6 (22.4–41.1)

	CR (n=40)	PR (n=26)
12-month OS rate, % (95% CI)	75.0 (58.5–85.7)	60.2 (37.2–77.0)
24-month OS rate, % (95% CI)	59.6 (41.7–73.7)	30.5 (9.3–55.3)

Data cut-off date: August 18, 2023
CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response

CONCLUSIONI

- ✓ In less than 5 years the treatment landscape of r/r DLBCL has dramatically changed with a significant improving in OS
- ✓ New antibodies (conjugated and nude) seem to improve R-CHOP results
- ✓ Bispecific antibodies are really improving results in R/R setting
- ✓ We are progressively going towards a chemo–free approach in r/r DLBCL
- ✓ Despite a rapidly growing knowledge on the results of the new approaches, little is still known about the best association and sequencing

GRAZIE