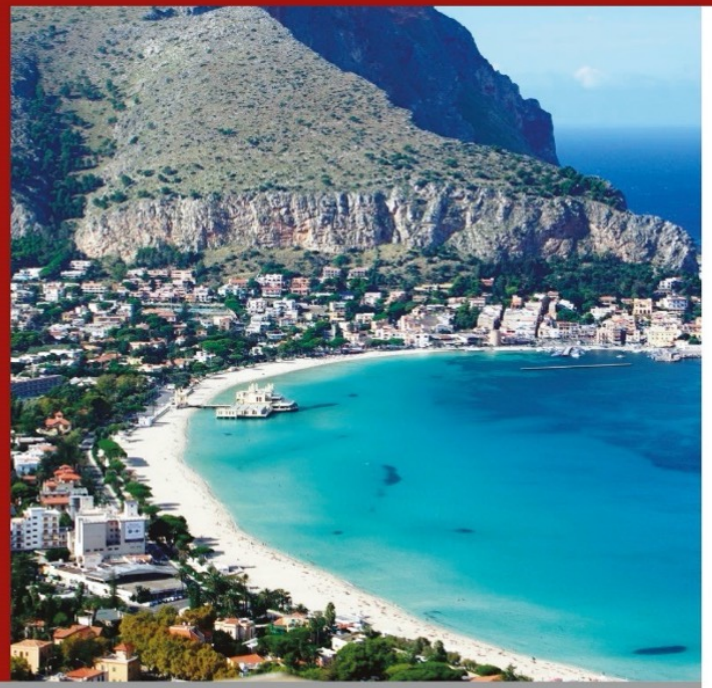
International Palermo Workshop on: Innovative Therapies for Lymphoid Malignancies



Palermo March 18, 2023
Hotel Federico II Central Palace

Advances in the Treatment for R/R DLBCL

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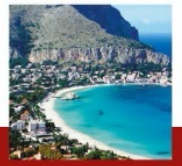
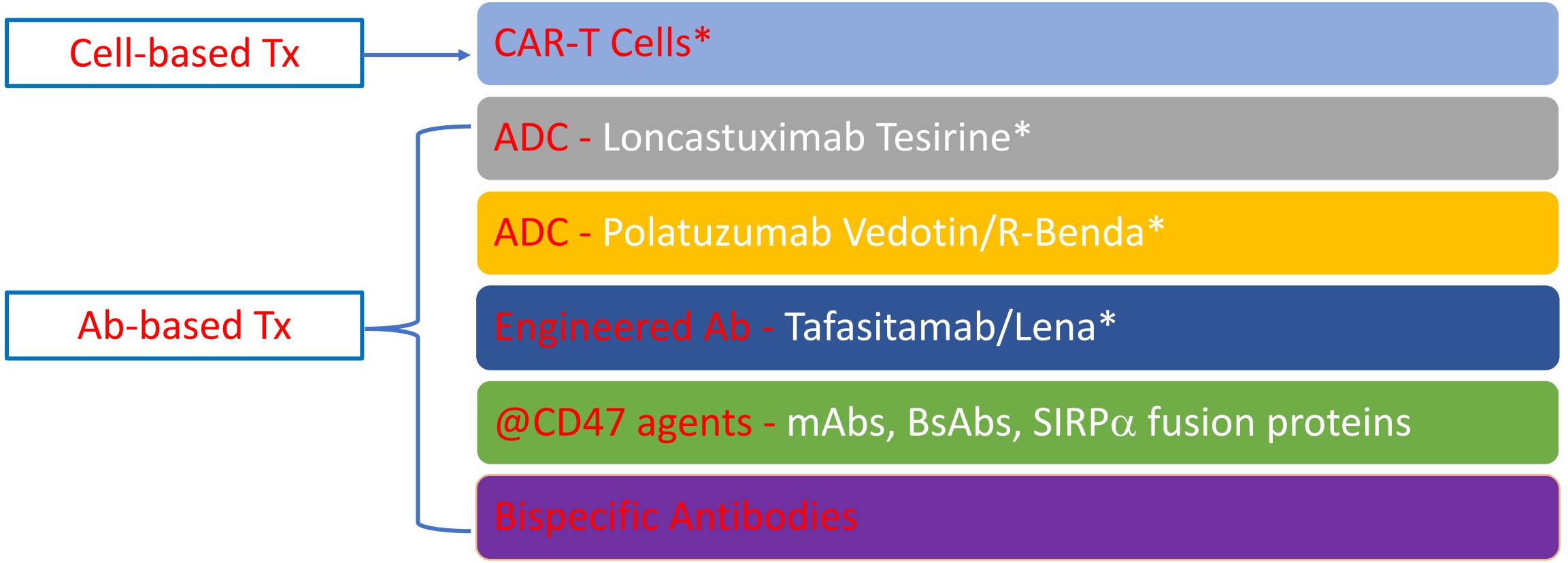
Disclosures of Name Surname

Company name	Research support	Consultant	Advisory board	Other
Sanofi	X	X	X	
ADC Therapeutics	X	X	X	
Karyopharm Therapeutics			X	
Celgene/Bristol-Myers Squibb			X	
Incyte				Honoraria
F. Hoffmann-La Roche Ltd	X		X	Travel grants
Janssen Oncology				Travel grants, Honoraria
Takeda				Travel grants, Honoraria
Merck Sharp & Dohme				Honoraria
AstraZeneca				Honoraria
Gilead				Honoraria



Immunotherapy-based Treatments for DLBCL

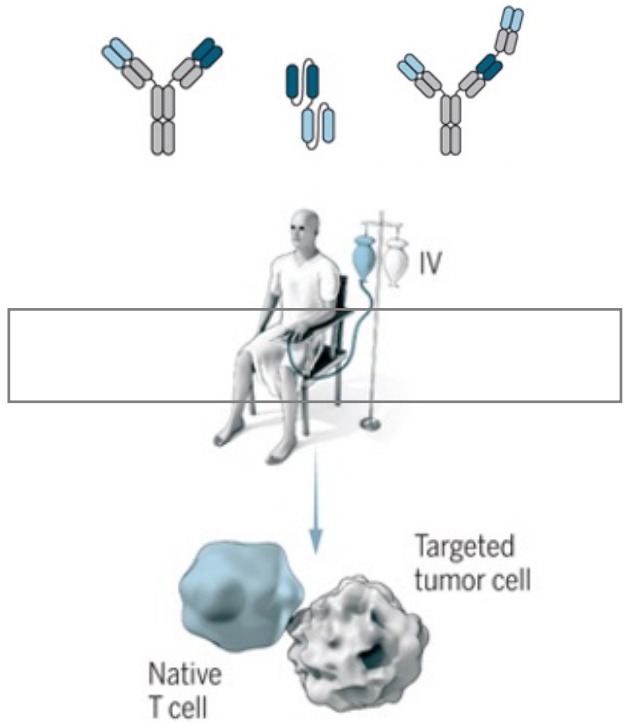


* FDA/EMA approved

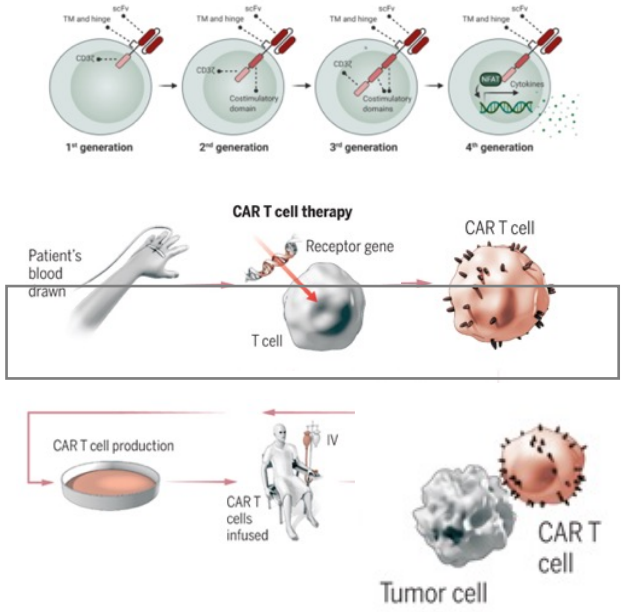
Forced into Battle

Bispecific antibodies unleash T cells against Cancer by physically tethering them to tumor cells.

Bispecific Antibodies



CAR T Cells

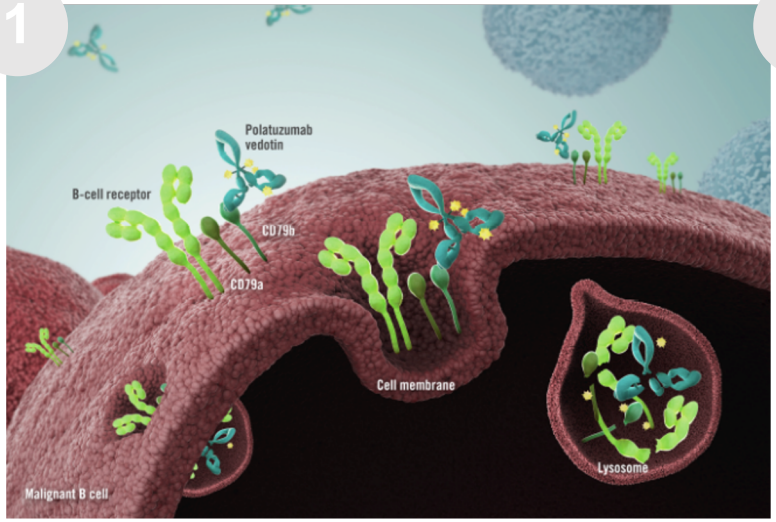


Synthetic Immunity

Kaiser et al, Science 2020

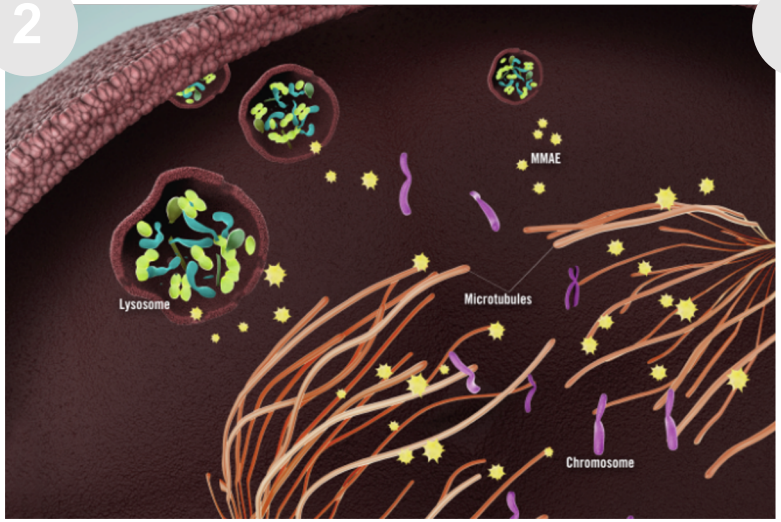
Polatuzumab Vedotin Mechanism of Action

1



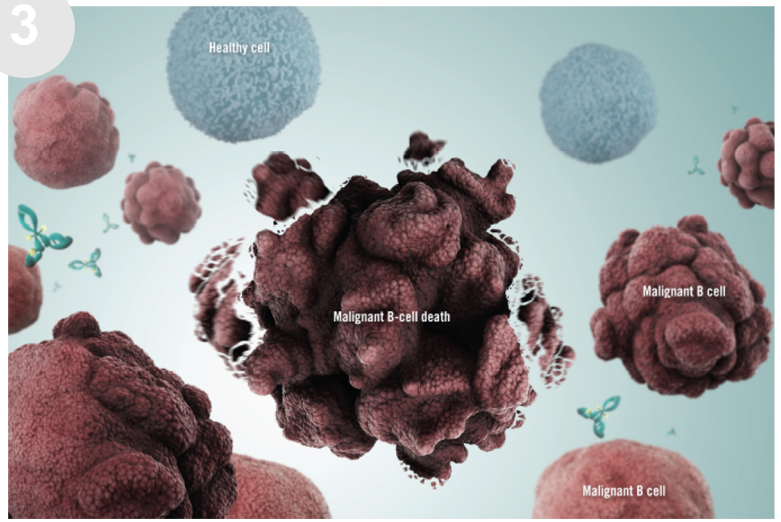
Pola binds to cell surface antigen CD79b, a component of the B-cell receptor, which is expressed only on B-cells and in most NHLs[1-3]

2



Binding to CD79b triggers internalization. The stable VC linker within polatuzumab vedotin is cleaved, releasing MMAE. MMAE binds to microtubules[1-4]

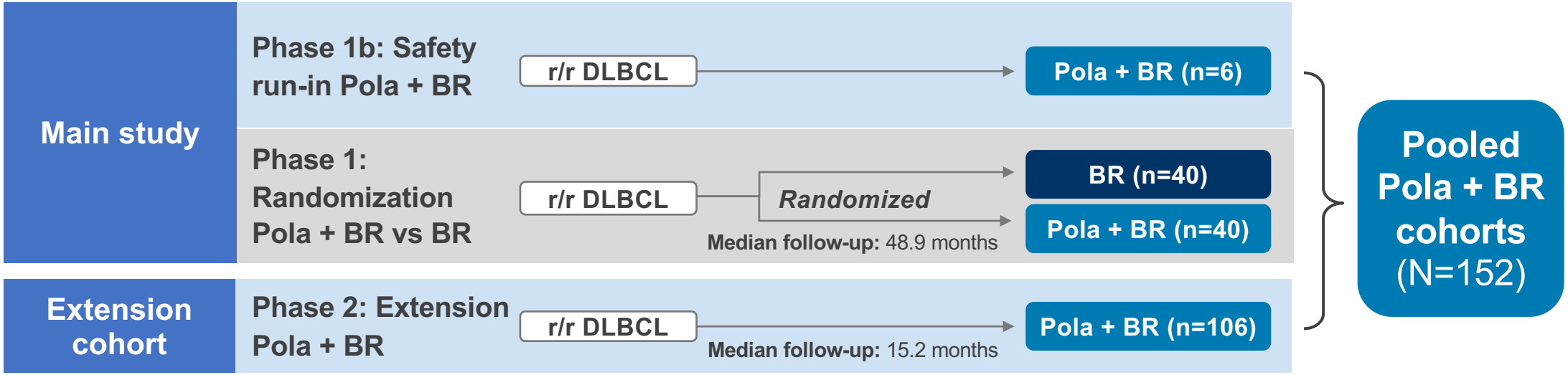
3



MMAE inhibits microtubule polymerization, disrupts cell division, and triggers apoptosis[4,5]

Pola + BR: Phase 1b/2 dose escalation study

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



Primary end-point: Complete response rate according to modified Lugano criteria by PET-CT (Phase 2)

Based on randomized comparison, Pola + BR had regulatory approvals for transplant-ineligible patients with r/r DLBCL

Treatment administered every 21 D x 6 C: Polatuzumab vedotin: 1.8 mg/kg, C1D2, then D1 for C2+; Bendamustine: 90 mg/m2, C1D2/3, then D1/2 for C2+; Obinutuzumab: 1000 mg, C1D1/8/15, then D1 for C2+; Rituximab: 375 mg/m2, D1 for C1+.

BR, bendamustine and rituximab; DLBCL, diffuse large B-cell lymphoma; PET-CT, positron emission tomography-computed-tomography; pola, polatuzumab vedotin-piiq; PN, peripheral sensory neuropathy; r/r, relpased or refractory; SCT, stem cell transplantaton.

Sehn LH, et al. Blood Adv 2022;6(2):533–543.

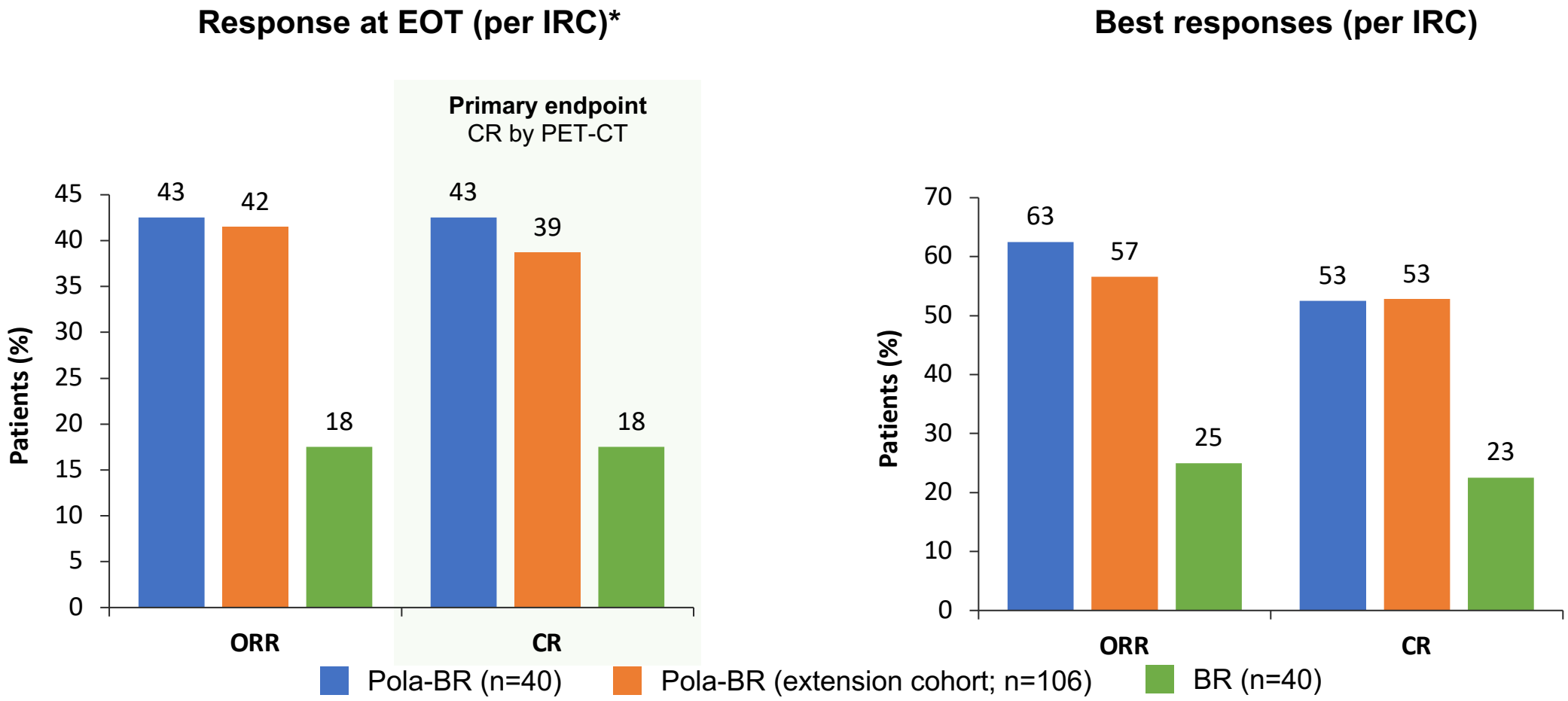
Pola + BR: Baseline characteristics[1,2]

	Randomized Phase 2		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)
IPI ≥3 at enrollment, n (%)	29 (73)	22 (55)	70 (66)	94 (62)
Stratification factor, n (%)				
DOR to last treatment ≤12 months	33 (83)	32 (80)	NA	NA
Lines of prior treatment, median (range)	2 (1–5)	2 (1–7)	2 (1-7)	2 (1-7)
1	12 (30)	11 (28)	37 (35)	50 (33)
≥2	28 (70)	29 (73)	69 (66)	102 (67)
Prior bone marrow transplant, n (%)	6 (15)	10 (25)	17 (16)	27 (18)
Refractory at last prior therapy, n (%)	33 (83)	30 (75)	81 (76)	116 (76)
Primary refractory, n (%)	28 (70)	21 (52)	73 (69)	97 (64)

BR, bendamustine and rituximab; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; IPI, International Prognostic Index; pola, polatuzumab vedotin-piiq; r/r, relpased or refractory.

1. Sehn LH, et al. J Clin Oncol 2020;38(2):155–165; 2. Sehn LH, et al. Blood Adv 2022;6(2):533–543.

Pola + BR: Efficacy

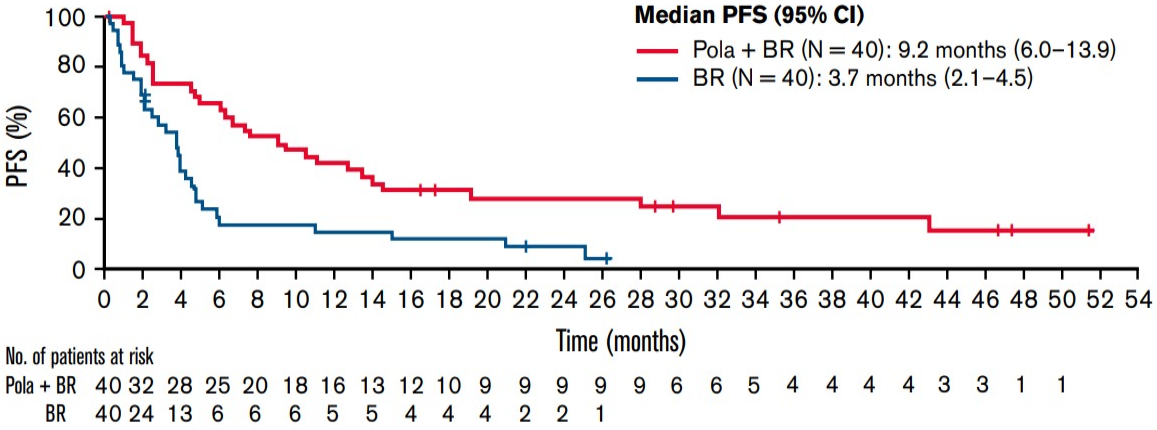


Clinical data cut off: 7 July 2020.
*Measured by PET-CT using modified Lugano Response Criteria.
BR, bendamustine and rituximab; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IRC, independent central review; ORR, objective response rate; PET-CT, positron emission tomography-computed-tomography; pola, polatuzumab vedotin-piiq; r/r, relpased or refractory.
Sehn LH, et al. Blood Adv 2022;6(2):533–543.

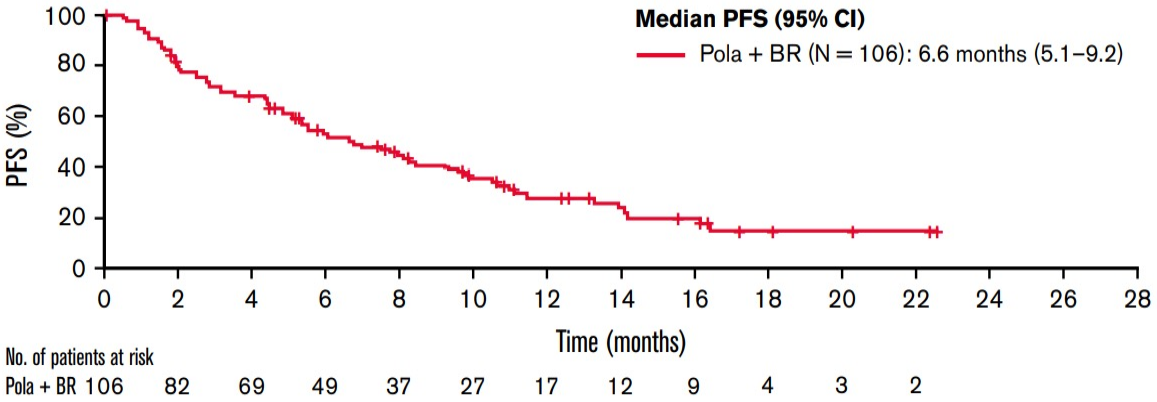
GO29365: Efficacy

Progression-free Survival

Randomised groups

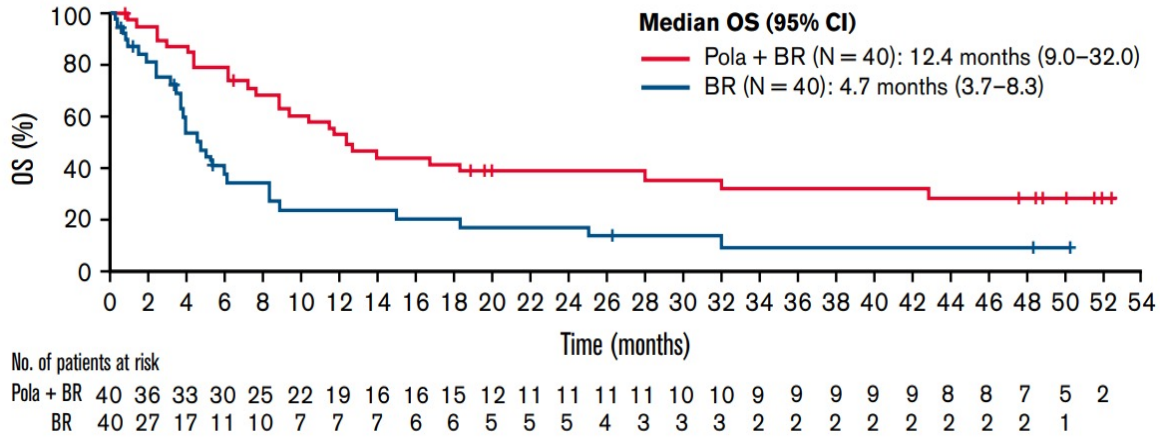


Extension cohort

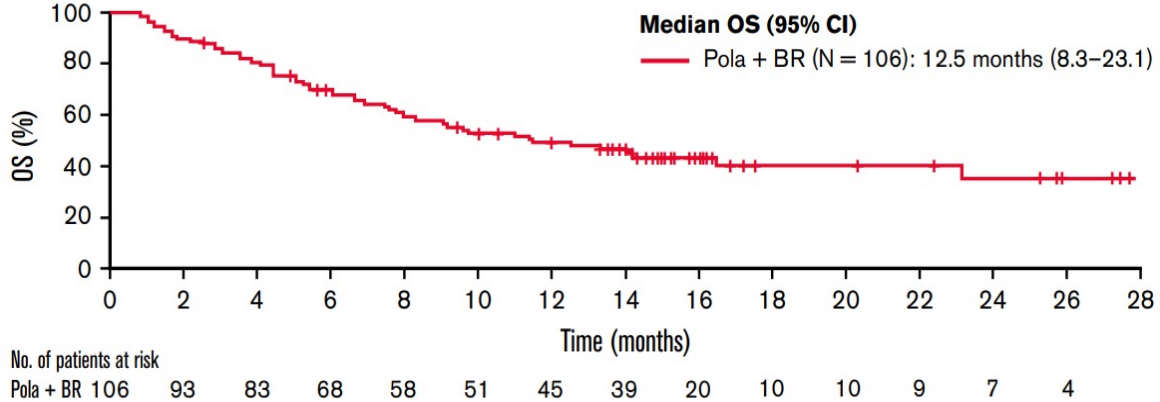


Overall Survival

Randomised groups



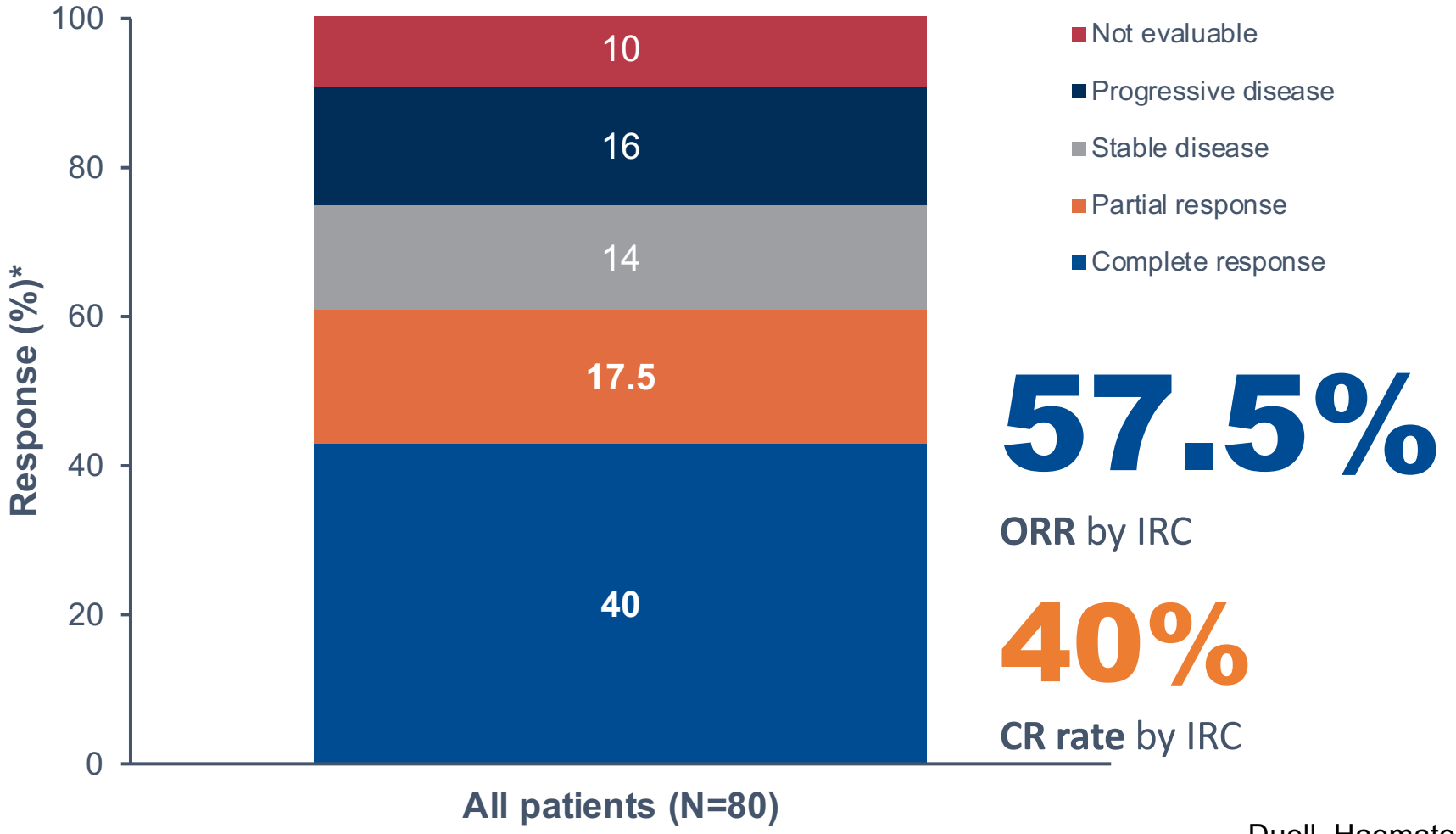
Extension cohort



BR, bendamustine and rituximab; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival; pola, polatuzumab vedotin-piiq; r/r, relpased or refractory.

Sehn LH, et al. Blood Adv 2022;6(2):533–543.

Tafa/Lena ORR



57.5%

ORR by IRC

40%

CR rate by IRC

Duell, Haematologica, 106:2417, 2021

Real-world Tafa-len treatment
N= 157 (retrospective study)

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

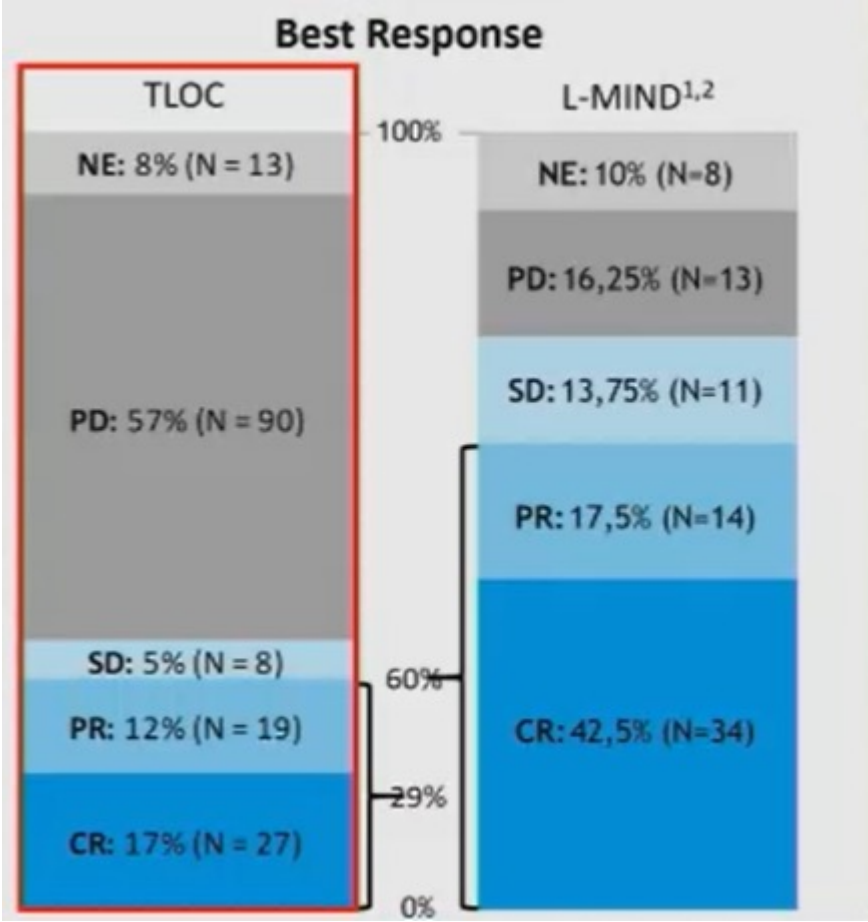
Characteristic	TLOC	L-MIND
Prior lines of therapy for DLBCL		
Median (range)	2 (0-11)	2 (1-4)
0	4%*	0%
1	29%	49%
2	30%	43%
3	16%	6%
4	6%	1%
≥5	16%	0 (0)
Primary Refractory	51%	18%
Refractory to last therapy	66%	44%
Prior SCT	13%	11%
Prior CAR T	28%	0%

68%

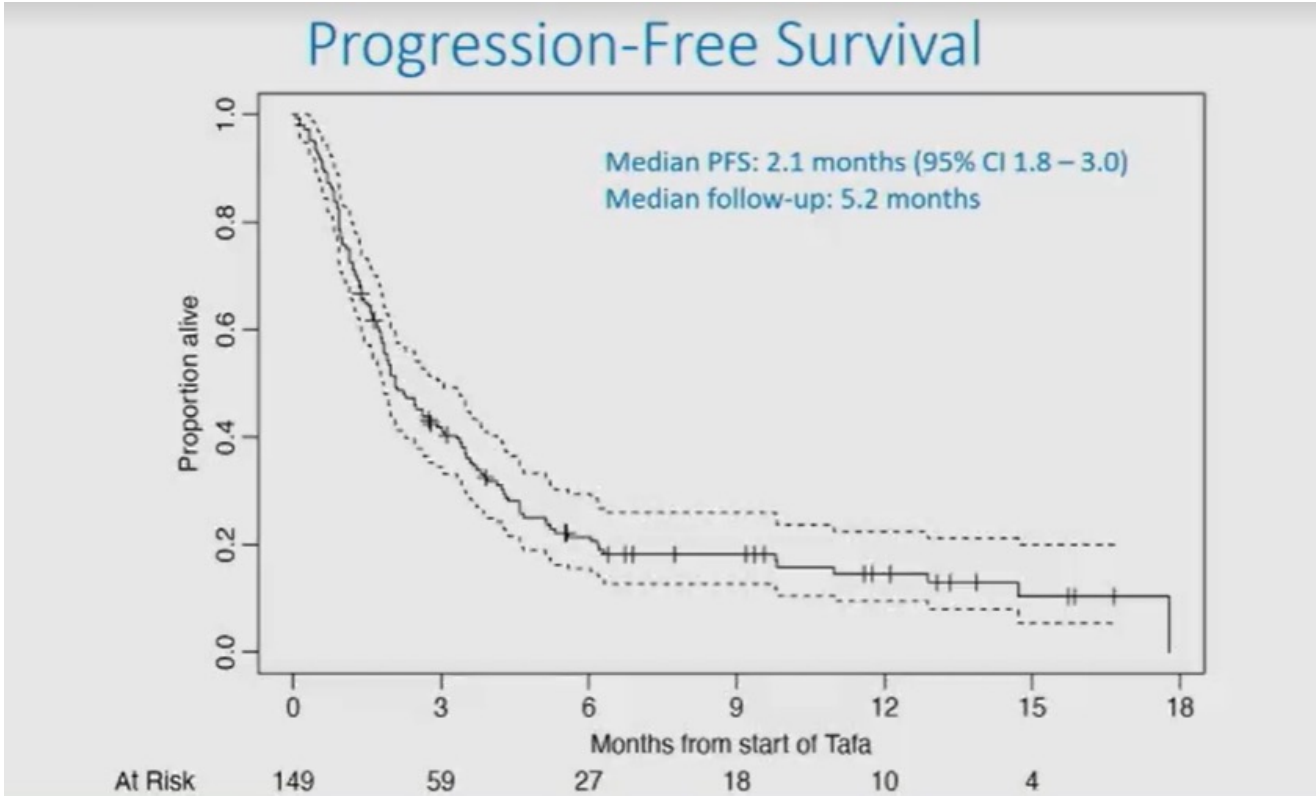
*5 patients with transformed lymphoma; all had received prior treatment for indolent lymphoma.

Quall D. et al. ASH 2022. Abstr 0323

Responses and Progression-Free Survival



42 patients (28%) had CAR-T before TL
- 4/19 CD19 not reported

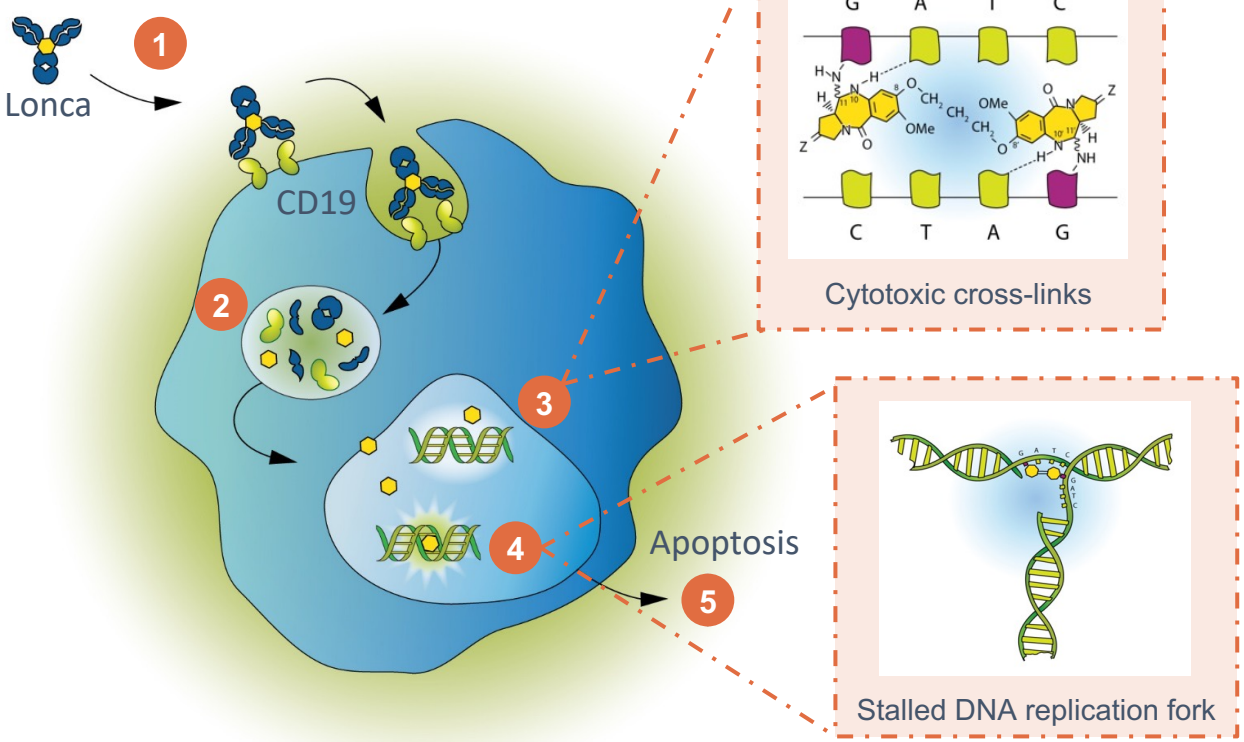


Worse PFS was seen in patients with refractory disease, ≥ 3 lines of therapy, higher IPI

Quall D. et al. ASH 2022. Abstr 0323

Lonca: A PBD dimer-containing ADC

Lonca (ADCT-402) is an ADC comprising a humanized **anti-CD19 antibody** conjugated to a **PBD dimer cytotoxin**, SG3199[2]

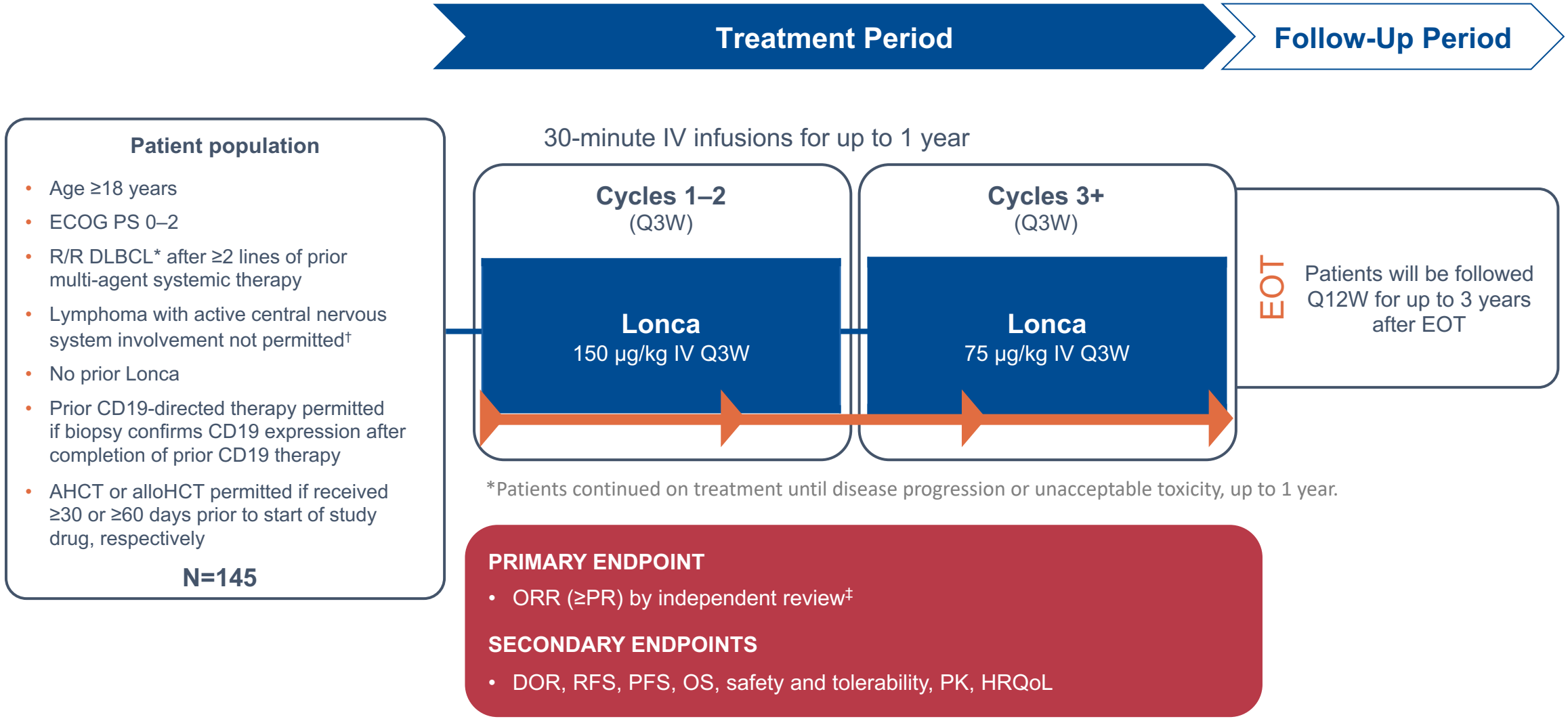


1. Lonca binds to CD19 on the tumor cell surface
2. Following internalization of Lonca, the protease-sensitive linker is cleaved and cytotoxic PBD dimers are released inside the cell
3. The free PBD dimers bind in the minor groove of the cell DNA and form potent cytotoxic DNA cross-links in a sequence-selective fashion
4. The cross-links result in a stalled DNA replication fork, blocking cell division
5. The cancer cell undergoes apoptosis

ADC, antibody−drug conjugate; CD, cluster of differentiation; Lonca, loncastuximab tesirine-lpyl; PBD, pyrrolobenzodiazepine.

1. Kahl BS, et al. Poster presented at the ASCO Annual Meeting, June 03−07, 2016. Abstract 420; 2. Zammarchi F, et al. *Blood* 2018;131:1094−105.

LOTIS-2: Open-Label, Single-Arm, Phase 2 Study in R/R DLBCL

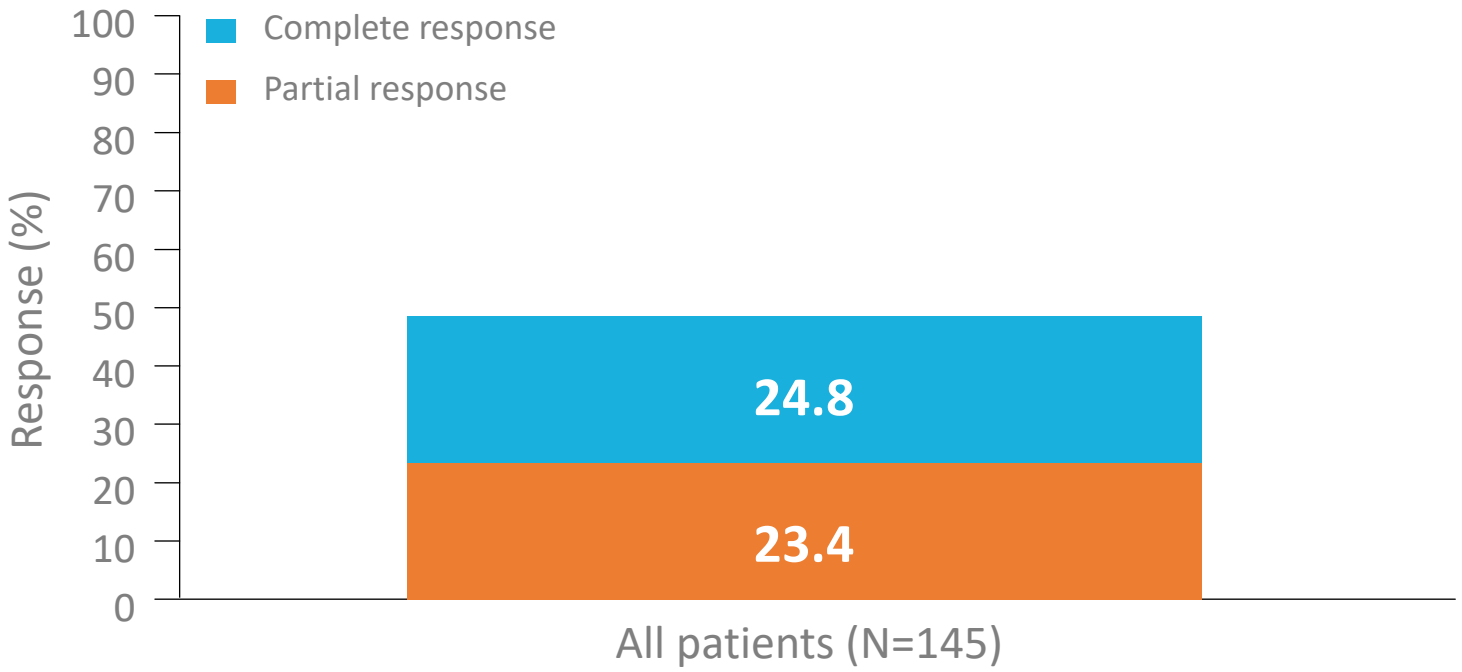


Baseline Characteristics

Characteristic n (%), unless otherwise stated	Total (N=145)
Sex	
Male	85 (59)
Female	60 (41)
Age, years: median (IQR)	66 (56–71)
Histology	
DLBCL	127 (88)
HGBCL	11 (8)
PMBCL	7 (5)
Double/triple hit	15 (10)
***MYC-BCL2* and/or *BCL6* overexpression**	20 (14)
Transformed disease	29 (20)
Stage	
I–II	33 (23)
III–IV	112 (77)
Prior lines of systemic therapy*	
Median (IQR)	3 (2–4)

Characteristic n (%), unless otherwise stated	Total (N=145)
First-line systemic therapy response	
Relapse	99 (68)
Refractory†	29 (20)
Other‡	17 (12)
Last-line systemic therapy response¶	
Relapse	43 (30)
Refractory†	84 (58)
Other‡	18 (12)
Refractory to all prior therapies	
Yes	25 (17)
No	115 (79)
Other‡	5 (3)
Prior hematopoietic cell transplant	
alloHCT	2 (1)
AHCT	21 (14)
Both	1 (1)
Prior CAR-T therapy	
Yes	13 (9)
No	132 (91)

Efficacy Results – ORR



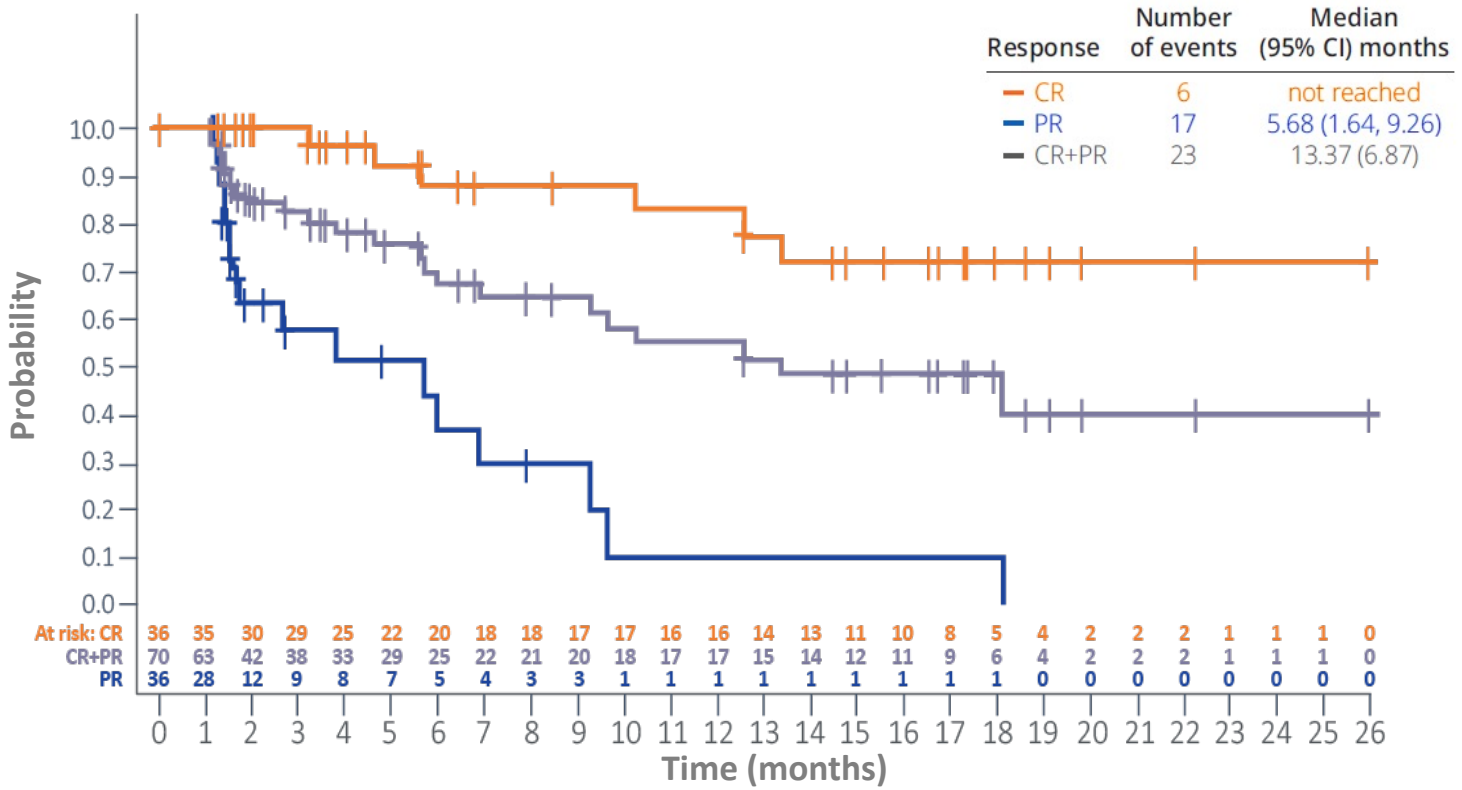
Median (range) follow-up:
7.8 months
(0.3-31.0)

37 patients remain in follow-up

Mean Lonca cycles: 4.6 (SD: ± 4.3) (min, max: 1, 26)
Mean Lonca cycles in responders (n=70): 6.8 (SD: ± 5.0) (min, max: 1, 26)

ORR was assessed by independent reviewer. Data cutoff: March 1, 2021.

Efficacy Results – DOR



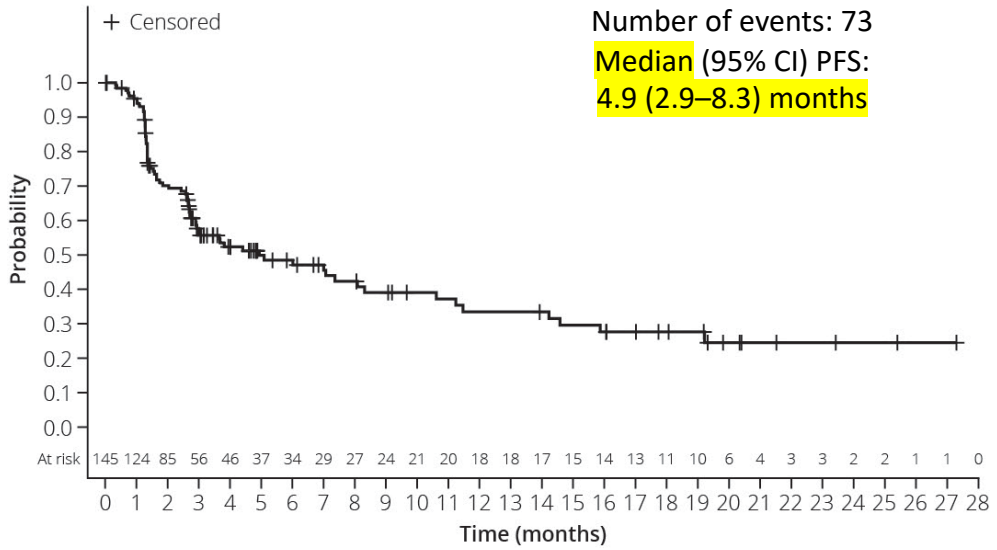
Median DoR

- 70 responders (CR + PR): 13.4 months
- Patients with a CR: not reached
- Patients with a PR: 5.7 months

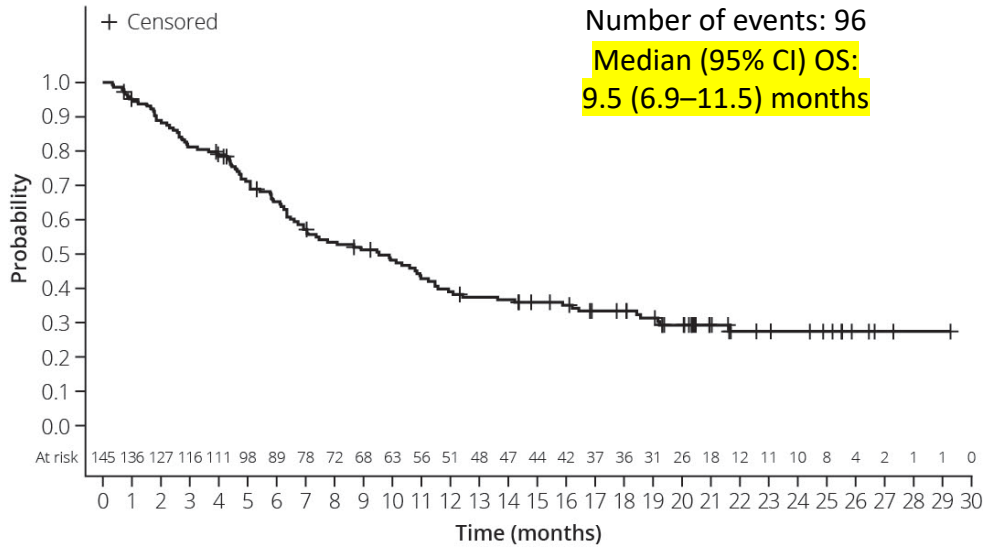
[a]Median follow-up time: 7.8 months (range: 0.3-31.0). Follow-up analysis cutoff date: March 1, 2021.
[b]DOR was defined as the time from earliest date of first response until the first date of either disease progression or death due to any cause.
[c]Patients with events after start of subsequent anticancer therapy or procedure, or progression free and alive at data cutoff, or who had unknown status were censored at last valid tumor assessment on or before start of subsequent anticancer therapy or procedure or data cutoff.

Efficacy Results – PFS and OS

PFS



OS



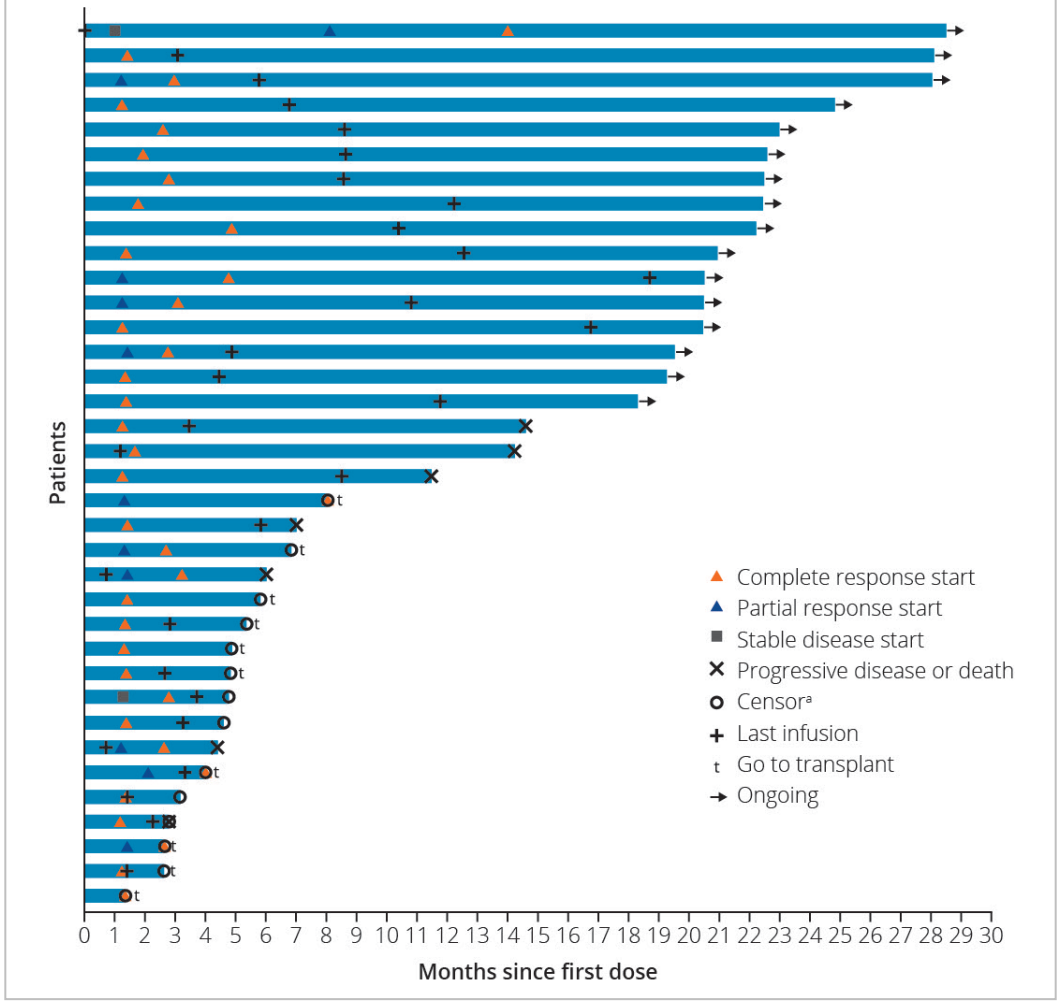
Following Lonca treatment

- **16 patients received CD19-directed CAR-T therapy**, with an investigator-assessed ORR of 43.8% (CR: 37.5%)
- **11 patients proceeded to SCT** as consolidation after responding to Lonca

Data cut-off: March 01, 2021. All-treated population.
CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; SCT, stem cell transplant.

Efficacy Results – Complete Responders

Swimmer plot of complete responders



	Remained in CR with no further treatment % (n/N)	PD or death % (n/N)
Complete remission	44.4 (16/36)	36.1 (13/36)
Complete remission excluding 10 patients censored due to SCT	61.5 (16/26)	34.6 (9/26)

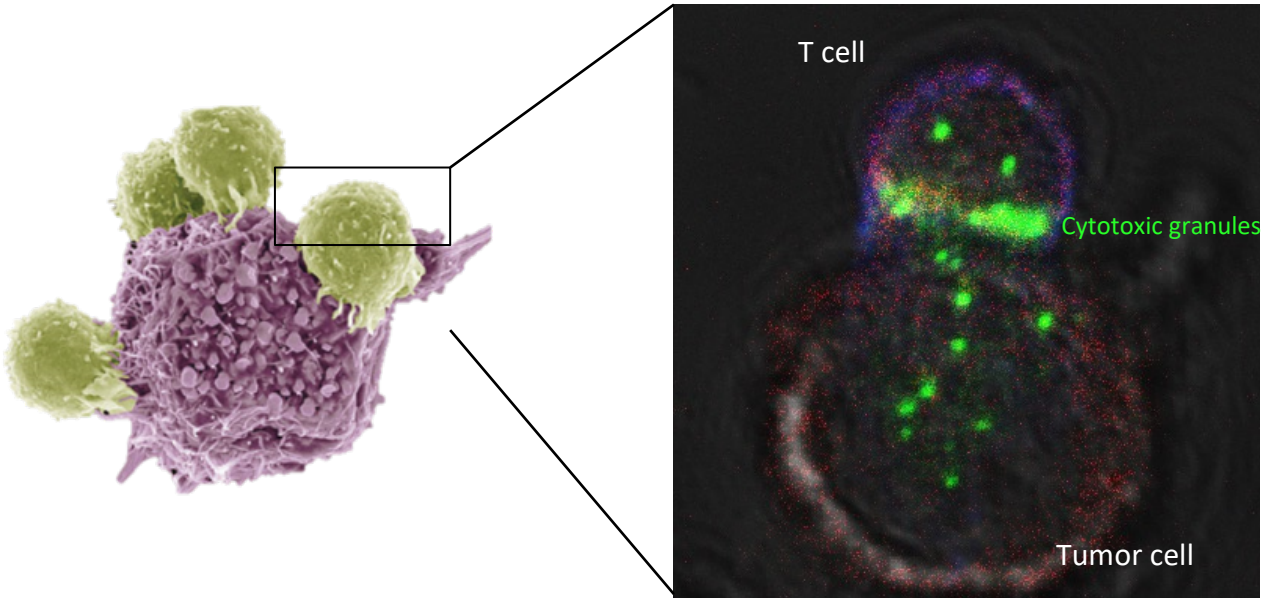
Data cut-off: March 01, 2021. All-treated population.
Each bar represents one patient. [a]Only for censored patients who discontinued the trial due to reasons other than progression or who went onto a different anticancer treatment other than SCT.
CR, complete response; PD, progressive disease; SCT, stem cell transplant.

Features of T-cell Bispecific Antibodies

Simultaneous binding to

tumor antigen and CD3ε chain of TCR independent of peptide-MHC complex;

Recruitment of endogenous T cells: 4 x 10^{11} in the circulation



- **T cell engagement, activation and killing** of tumor cells by cytotoxic granules
- **T cell proliferation** (expansion) at site of activation (blood? Lymph nodes)
- **Cytokine, chemokine release leading to recruitment of additional T-cells**
- Very high potency with EC_{50} values in the fM to pM range
- **Serial killing of tumor cells, activity at low effector-to-target (E:T) ratio**
- T cell killing independent of specificity, activation and differentiation status

EPCORE NHL-1: LBCL Expansion Cohort

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

[a]Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG PET scan that demonstrates positive lesion(s) compatible with CT-defined (or MRI-defined) anatomical tumor sites for FDG-avid lymphomas. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

Thieblemont C, et al. EHA 2022 oral presentation

Patients Were Challenging to Treat and Highly Refractory

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)

[a]Double/triple-hit patients included, many with responses. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within <6 months of completion of therapy.

Thieblemont C, et al. EHA 2022 oral presentation

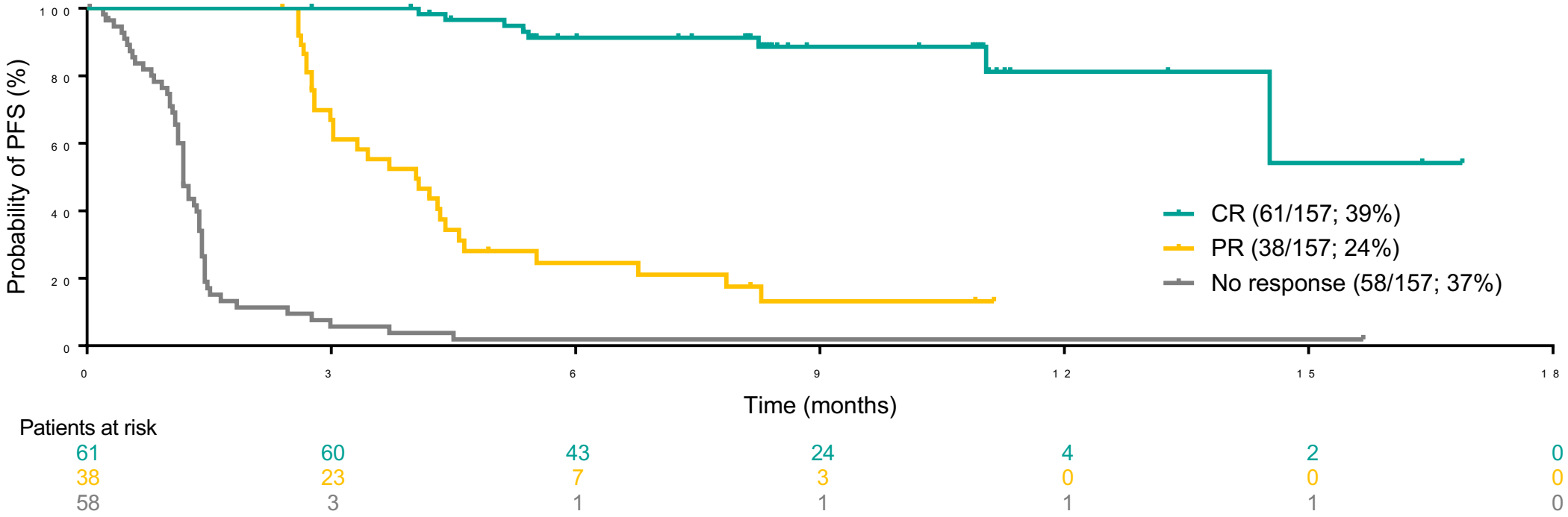
High Response Rates Observed

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

[a]Based on Lugano criteria.

Thieblemont C, et al. EHA 2022 oral presentation

PFS by Best Response per IRC



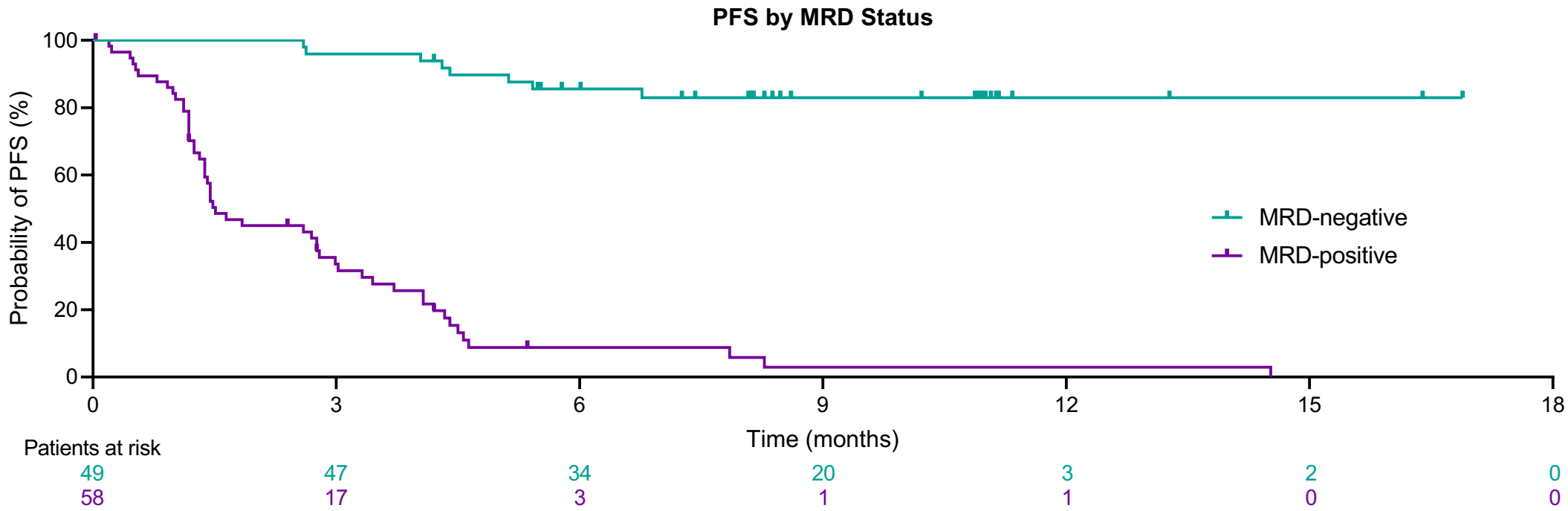
Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

A correlation between depth of response and PFS was observed

Thieblemont C, et al. EHA 2022 oral presentation

MRD Negativity Correlated With Improved PFS

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



MRD Results per ctDNA Assay	All LBCL n=107
MRD-negative rate, n (%)	49 (45.8) [95% CI: 36.1–55.7]

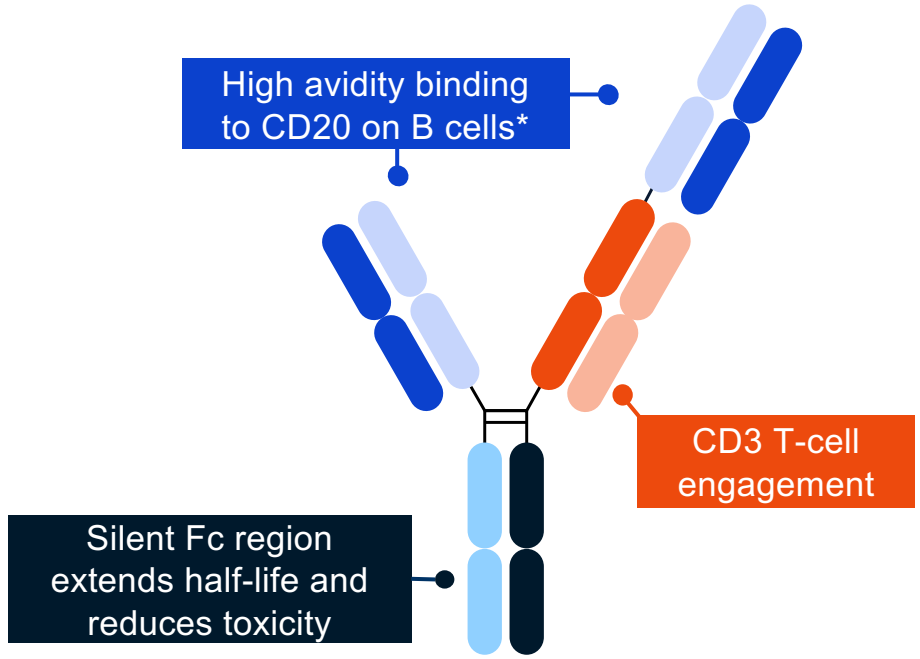
Based on MRD-negative evaluable set, which included patients with ≥1 postbaseline MRD sample/evaluation who had detectable disease (n=104) or were not evaluated (n=3) at baseline. MRD negativity was defined as the absence of detectable clone sequences in plasma at any on-treatment time point (clonoSEQ).

Thieblemont C, et al. EHA 2022 oral presentation

Background

- **Patients with R/R DLBCL (≥2 prior therapies) have a poor prognosis[1,2]**
  - poor outcomes are reported in patients with treatment failure after R-CHOP, particularly in those with refractory disease[3]
  - CAR T-cell therapy is an option for patients with R/R DLBCL but its use may be limited by logistical challenges[4,5]
- **Glofitamab**
  - off-the-shelf and fixed duration treatment[6,7]
- **Phase I experience (NCT03075696)[7]**
  - encouraging efficacy and manageable safety with glofitamab monotherapy in patients with R/R B-cell NHL[6,7]
  - established a step-up dosing schedule and target dose (30mg) in patients with B-cell NHL in multiple cohorts[8]

Glofitamab: *CD20xCD3 bispecific monoclonal antibody with 2:1 format for increased potency vs 1:1 format[6]*



Aim: share pivotal Phase II expansion results – glofitamab in R/R DLBCL and ≥2 prior therapies

*obinutuzumab binds to the same CD20 epitope as glofitamab.
CAR-T, chimeric antigen receptor T-cell therapy; NHL, non-Hodgkin lymphoma.

1. Chien, et al. Future Oncol 2020; 2. Crump, et al. Blood 2017; 3. Sehn and Salles. NEJM 2021; 4. Fujiwara, et al. Pharmaceuticals 2022; 5. Roschewski, et al. NEJM 2022; 6. Bacac, et al. Clin Cancer Res 2018; 7. NCT03075696. Available at: https://clinicaltrials.gov; 8. Hutchings, et al. J Clin Oncol 2021.

Baseline characteristics

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

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

Heavily pre-treated, highly refractory population

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

Response rates – primary endpoint met

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

– At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater ($p<0.0001$) than 20% historical control CR rate‡

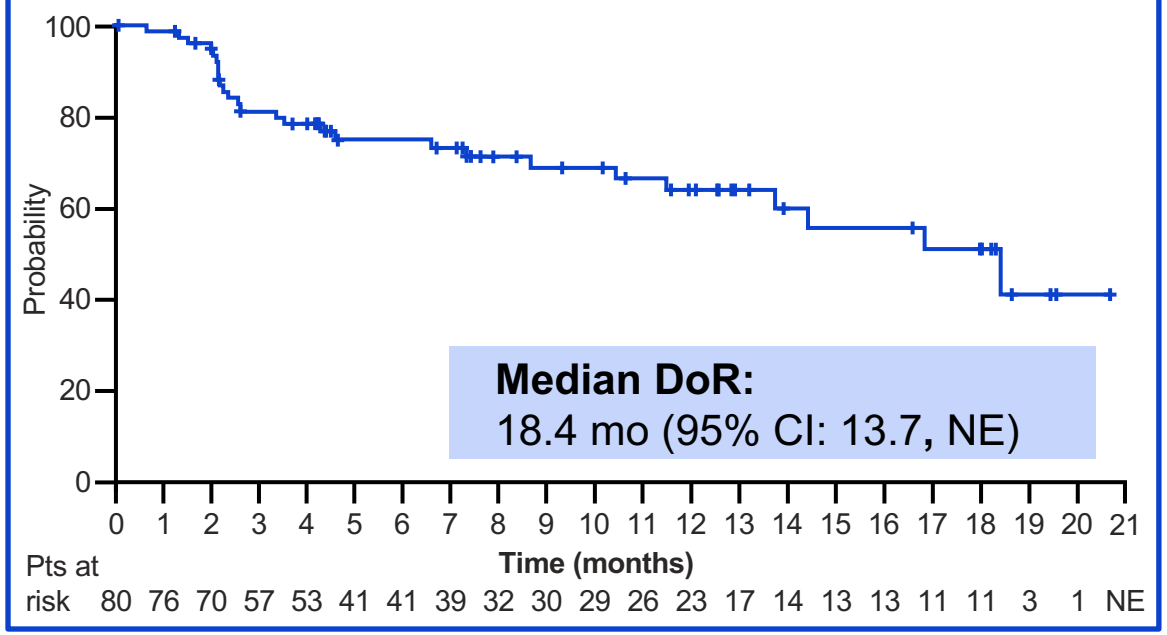
High CR/ORR rate at RP2D

*best response by intent-to-treat population; †the pivotal expansion cohort population; ‡the historical control CR rate was pre-specified based on a meta-analysis in patients with R/R DLBCL (where most [≥50%] had received ≥2 prior therapies) and compared with the CR rate in the primary efficacy-evaluable population using an exact binomial test (2-sided alpha level: 5%).

1. Cheson, et al. J Clin Oncol 2014.

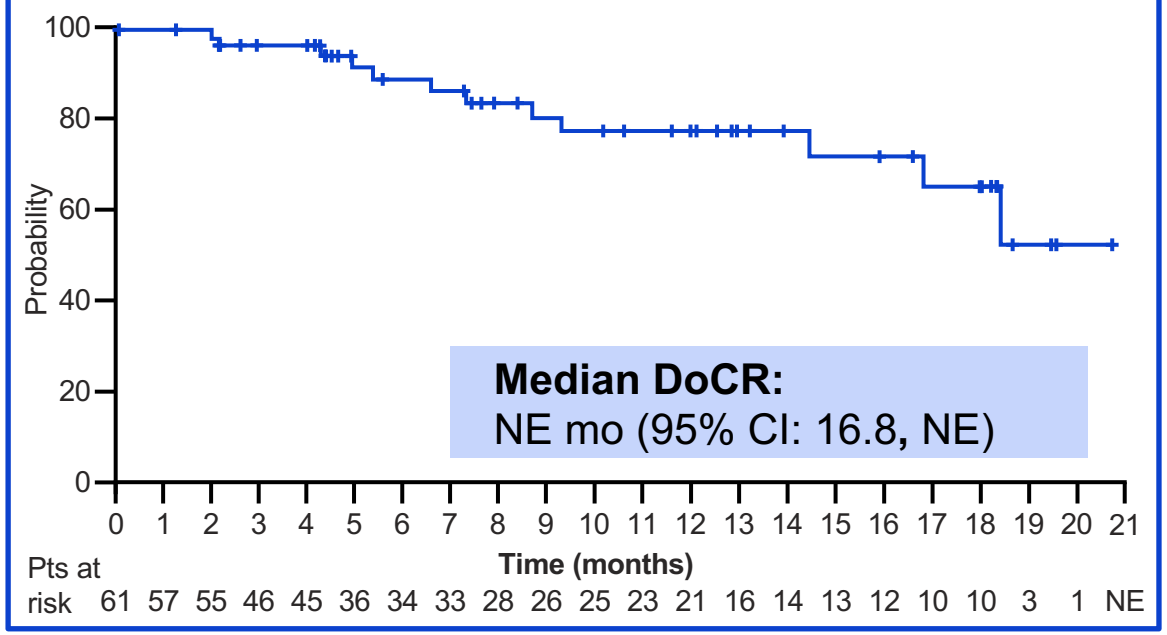
Durable responses maintained after cessation of therapy

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

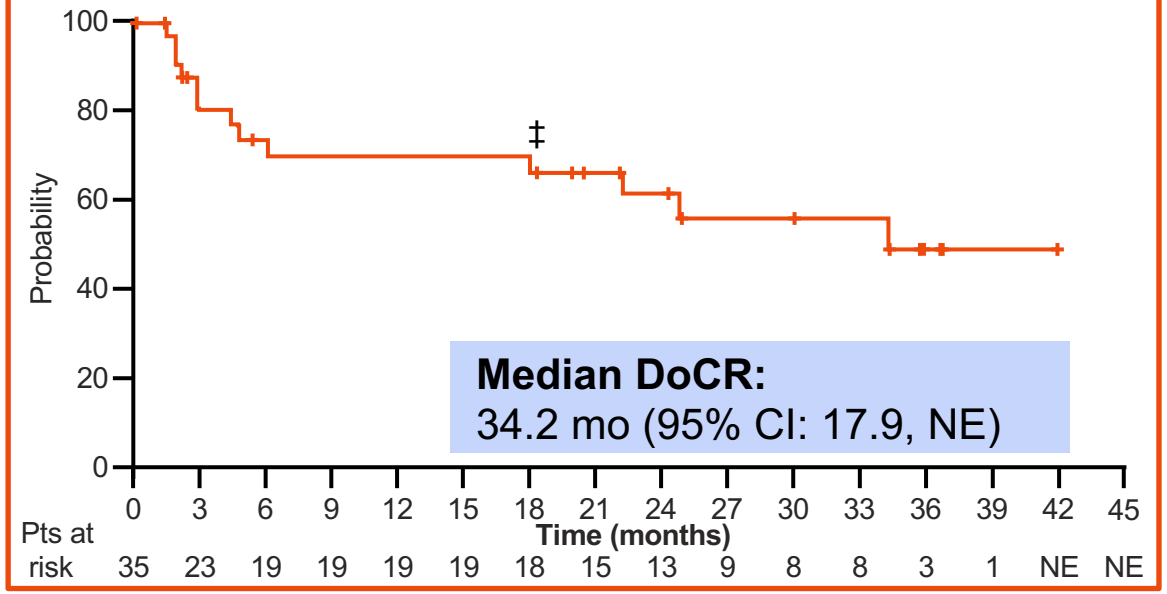
CCOD, clinical cut-off date; mo, months; NE, not estimable.

DoCR in earlier cohorts show durable responses beyond 24 months

Supporting cohort

- **Patients in earlier cohorts have extended follow up for duration of response**
  - R/R DLBCL, HGBCL, trFL and PMBCL ≥2 prior lines (n=101)
  - Doses ≥10mg* (RP2D not included) for a fixed treatment duration of 8–12 cycles (6–9 months)
  - CR rate: 35/101 (35%)†

Duration of complete response by IRC



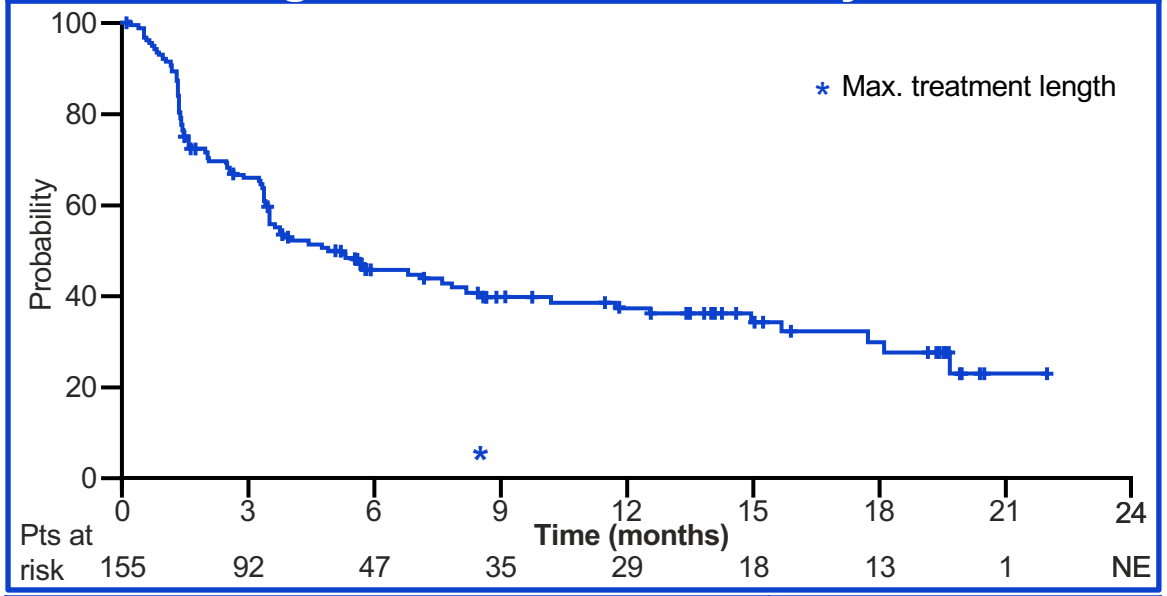
	N=35
Median DoCR follow-up, mo (range)	**24.8 (0, 42)**
24-months DoCR, % (95% CI)	61.4 (43.1, 79.7)
CRs ongoing at CCOD, n (%)	22 (62.9)

Durable responses beyond 24 months achieved after fixed-duration treatment; median: 34.2 months

*10mg, 16mg, 25mg, 10/16mg, 2.5/10/16mg; †intent-to-treat population; RP2D, recommended Phase II dose;
‡DOCR: 17.9 months PD, 22.1 months PD re-treatment (remission), 24.7 months death (unknown reason), 34.2 months death (AML).

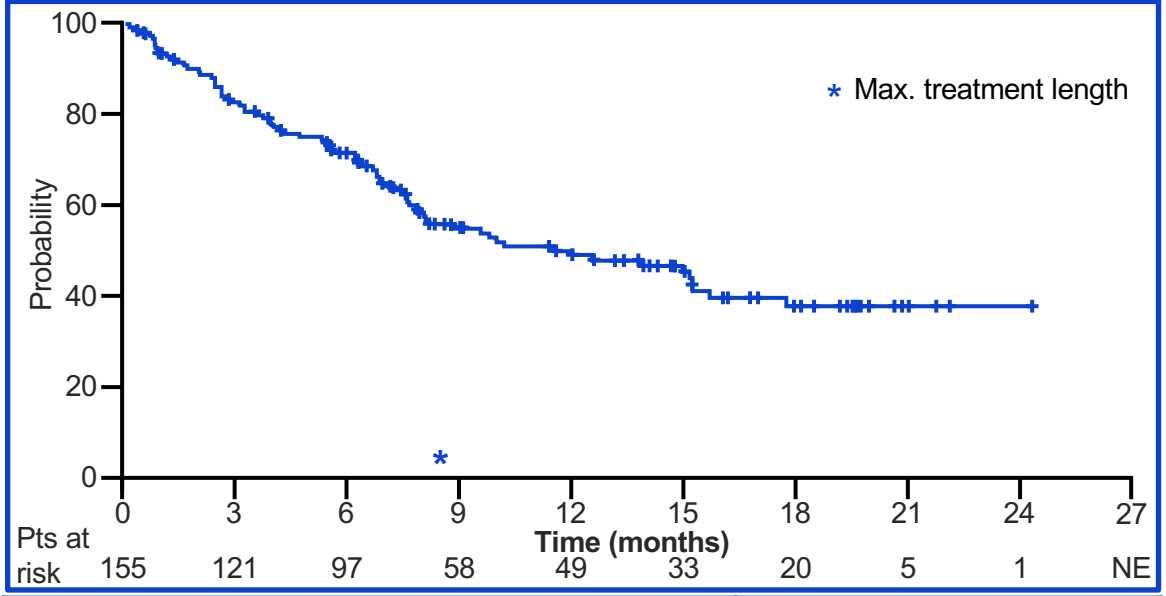
Time-to-event endpoints

Progression-free survival by IRC



	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)‡	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

Overall survival†



	N=155
Median OS, months (95% CI)‡	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

Clinically significant freedom from progression at 12 months and long-term overall survival

†including five deaths due to COVID-19; ‡KM estimates.