Diffuse Large B-Cell Lymphoma (DLBCL)

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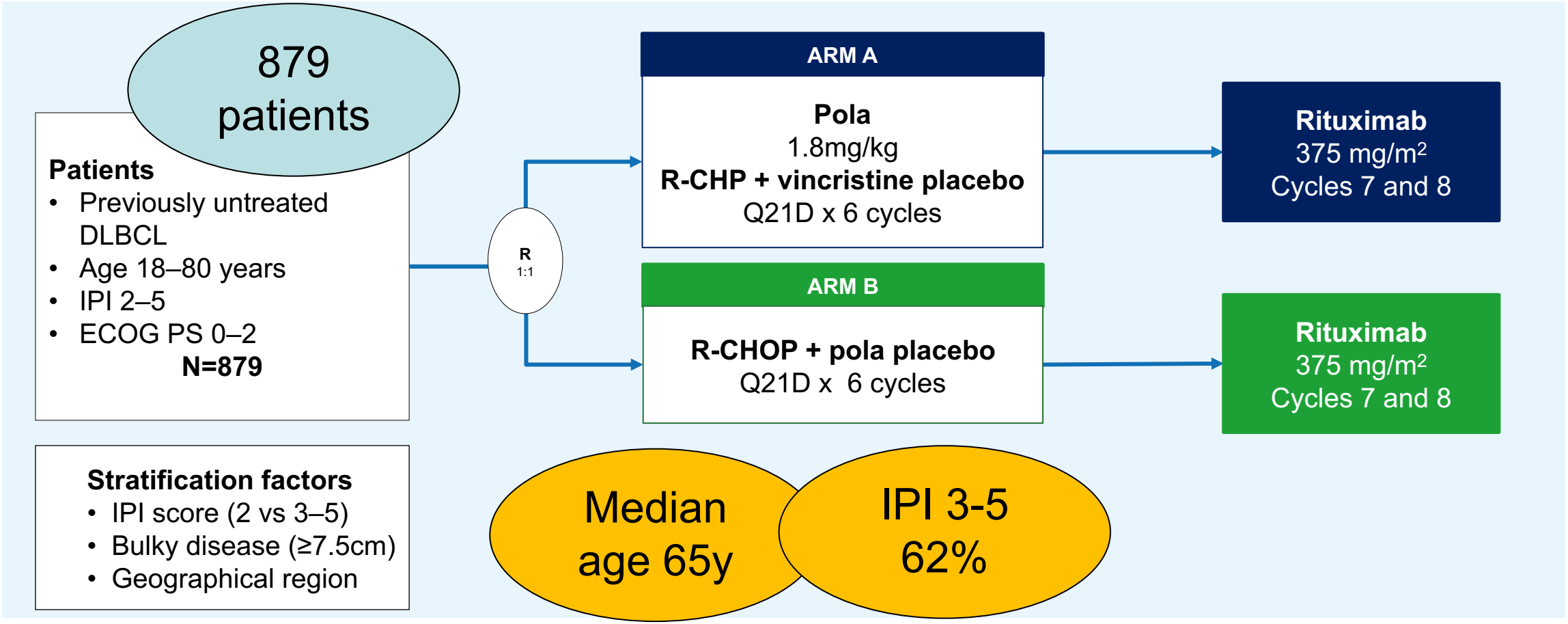
POLARIX: Study design

A double-blinded, phase 3, placebo-controlled trial



LYSA, the lymphoma study association; IPI, international prognostic index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q21D, every 21 days; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Collaboration with LYSA and LYSARC

POLARIX: Outcome data

(median f-up=28m)

Primary endpoint = Progression Free survival met
Hazard ratio 0.73 ; p<0.02

	Pola-R-CHP	R-CHOP	
PFS	76.5 (2y)	70.5 (2y)	HR = 0.73
CR rate	78%	74%	NS
EFS	-	-	HR = 0.75
DFS	-	-	HR = 0.70
OS	-	-	NS
Subsequent therapy - ASCT or CAR T	23% - 5.9%	30% - 10.7%	

ASH Tilly H et al., LBA1 Abstract

POLARIX: Safety

(median f-up=28m)

Adverse events	Pola-R-CHP	R-CHOP
Grade 3-4	57.5%	57.5%
Grade 5	3%	2.3%
AE leading to dose reduction	9.2%	13%
Peripheral neuropathy - gr 3-4	52.9% - 1.6%	53.9% - 1.1%

Double blind study

POLARIX results implication

Improvement of PFS with Pola-R-CHOP demonstrated in patients with newly diagnosed DLBCL with IPI 2-5 (27% of reduction of risk of progression, relapse or death)
without significant increase of toxicity

- **New standard of care?**

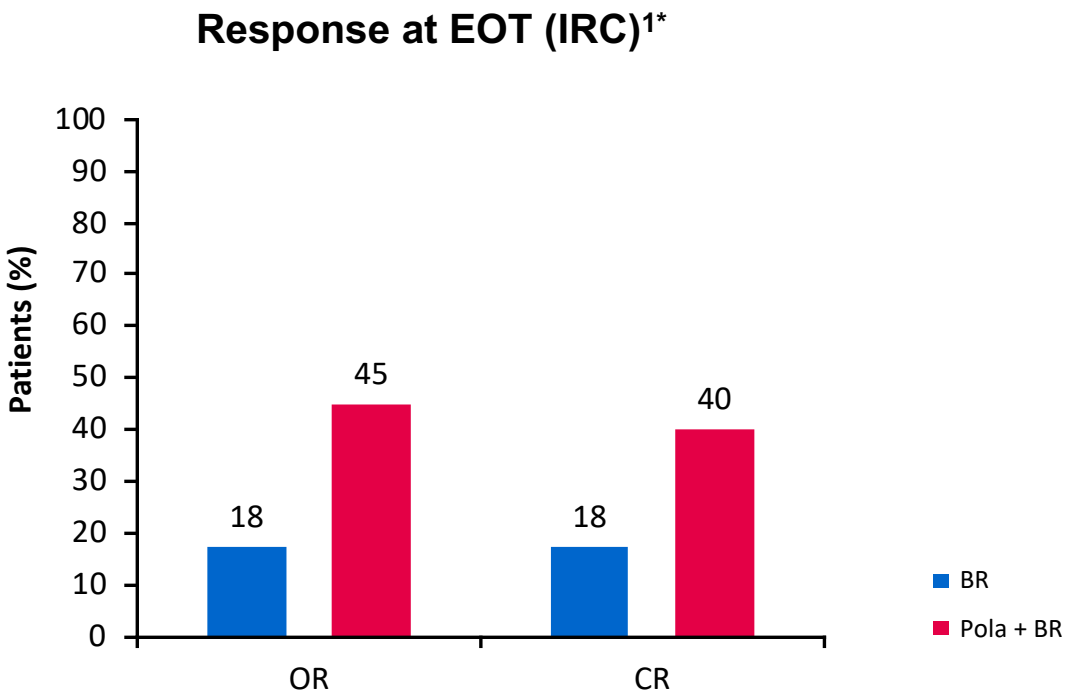
For DLBCL, improved PFS usually results in OS benefits and highest chance of cure:

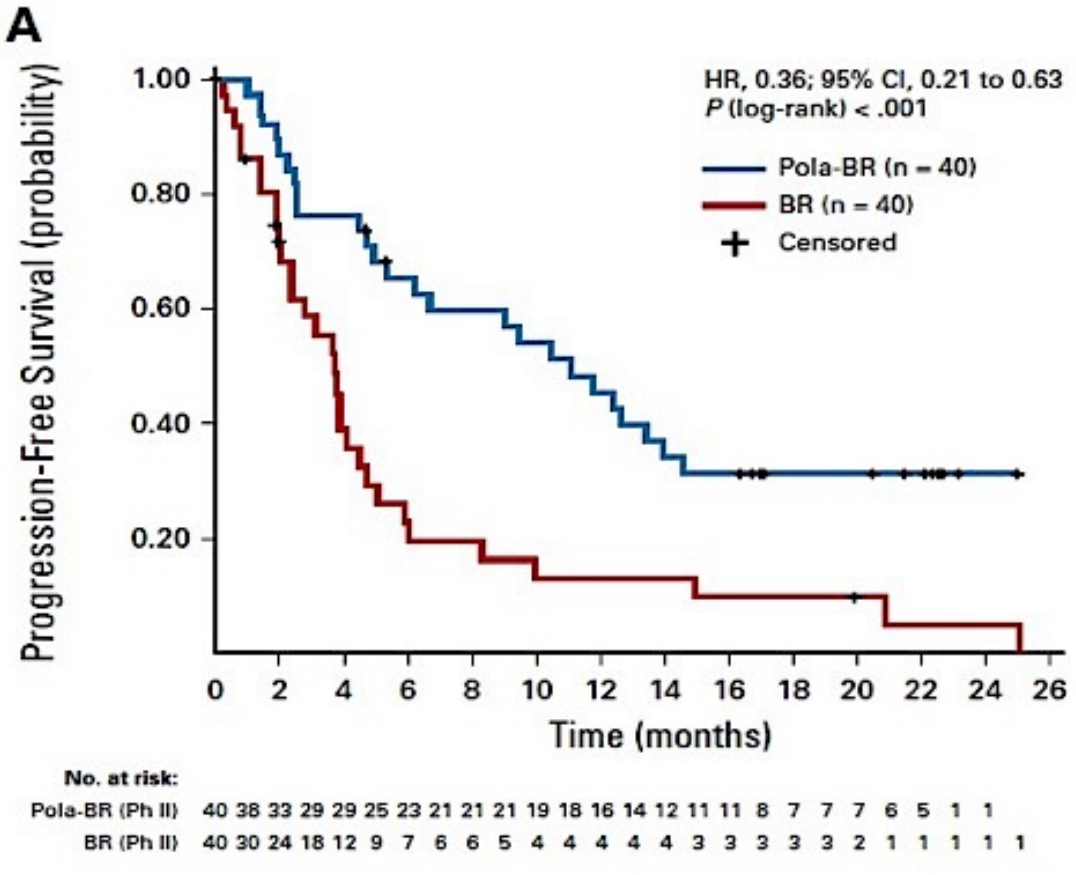
- new drugs effective in R/R DLBCL may explain lack of OS difference at this time
- DFS results encouraging to indicate prolonged response

Look for complete data +++

- Safety ?
- Efficacy in more difficult to treat patients ?

Polatuzumab vedotin added to bendamustine/ rituximab in R/R DLBCL



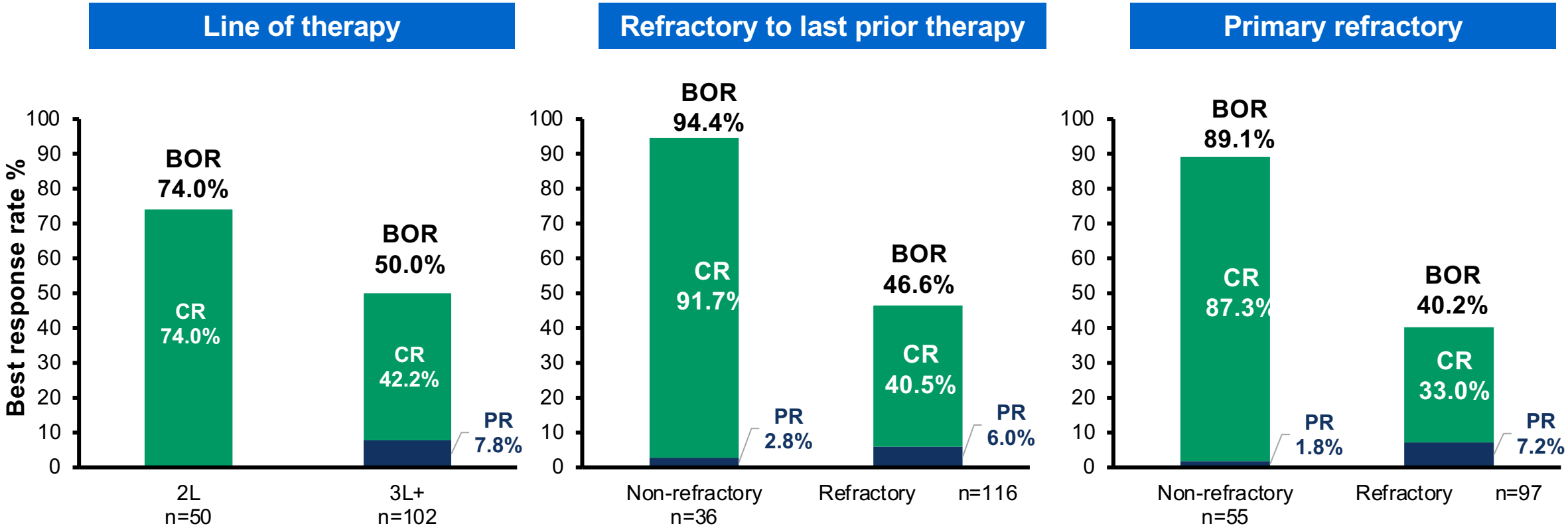


Seven patients have ongoing response durations of ≥20 months at data cut-off

- Toxicities: hematological, infectious, neurological

Sehn LH, et al. J Clin Oncol. 2020 Jan 10;38(2):155-165.

Best response rates in the pooled Pola+BR cohort according to line of therapy and refractory status



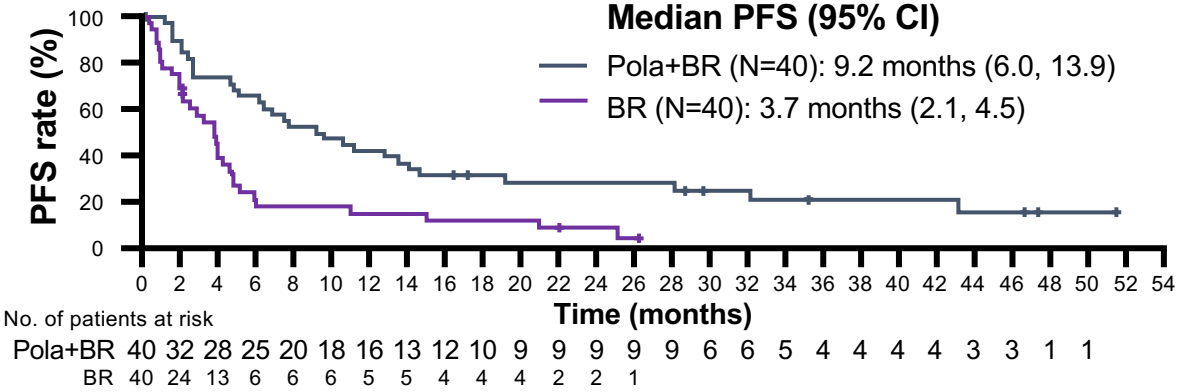
- Subgroup analyses demonstrate strong efficacy benefit in 2L and non-refractory patients; importantly, responses were also observed in 3L+ and refractory patients
- The vast majority of responding patients achieved a CR

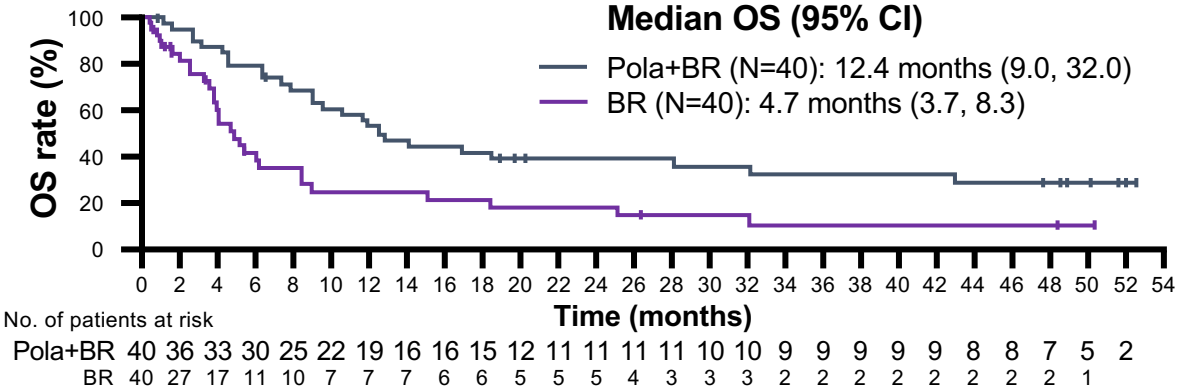
Clinical cut-off date: 07July2020; shown are results in the pooled Pola+BR population (N=152); BOR is best CR (green bars) + best PR (blue bars); 2L, patients had received one prior line of therapy before treatment with Pola+BR; 3L+ patients had received two or more prior lines of therapy before treatment with Pola+BR; refractory defined as no response or progression or relapse within 6 months of first anti-lymphoma therapy end date (primary refractory), or within 6 months of last anti-lymphoma therapy end date

Sehn LH et al, Blood Advances 2021

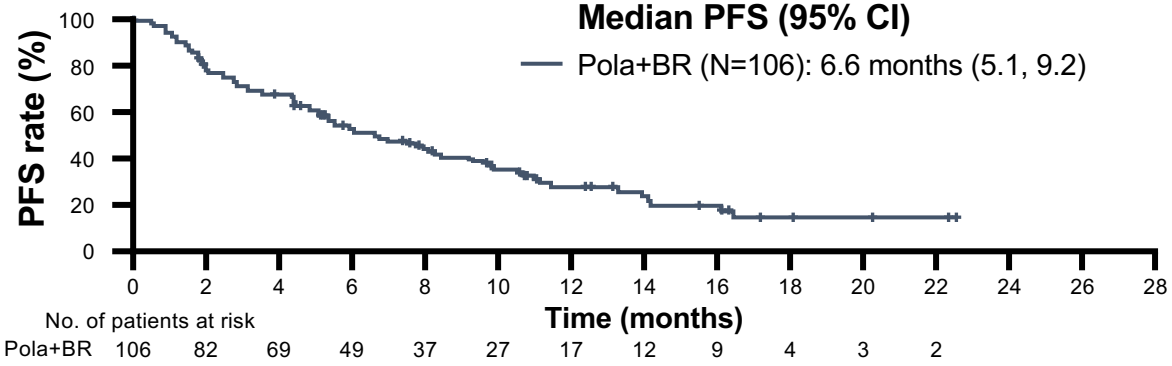
Pola-BR: PFS and OS in randomized and extension cohorts

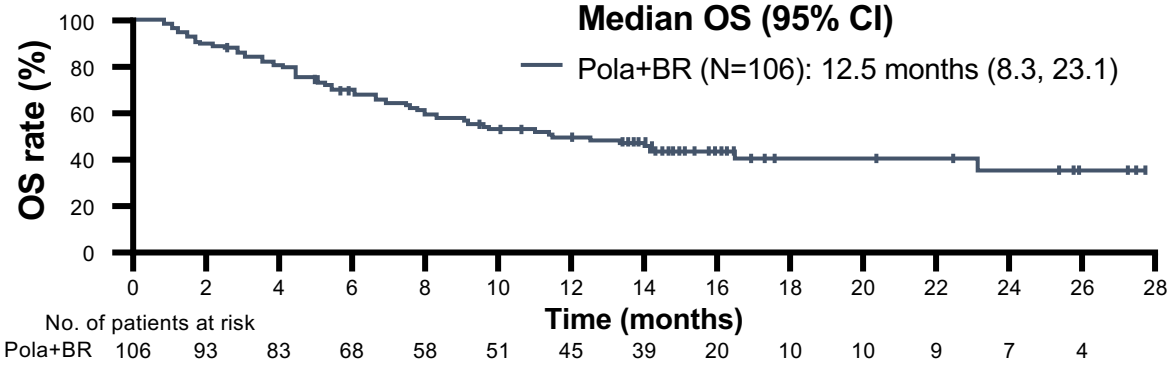
Randomized





Extension cohort

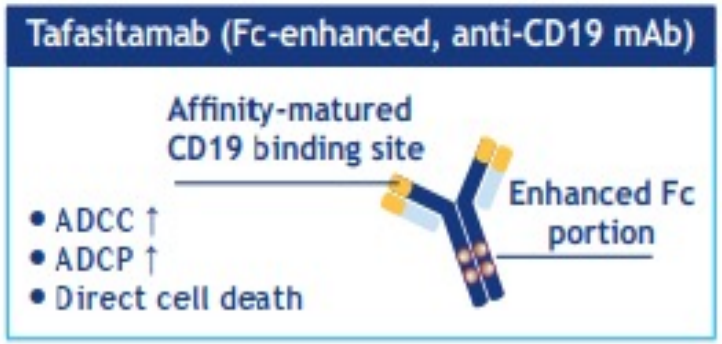


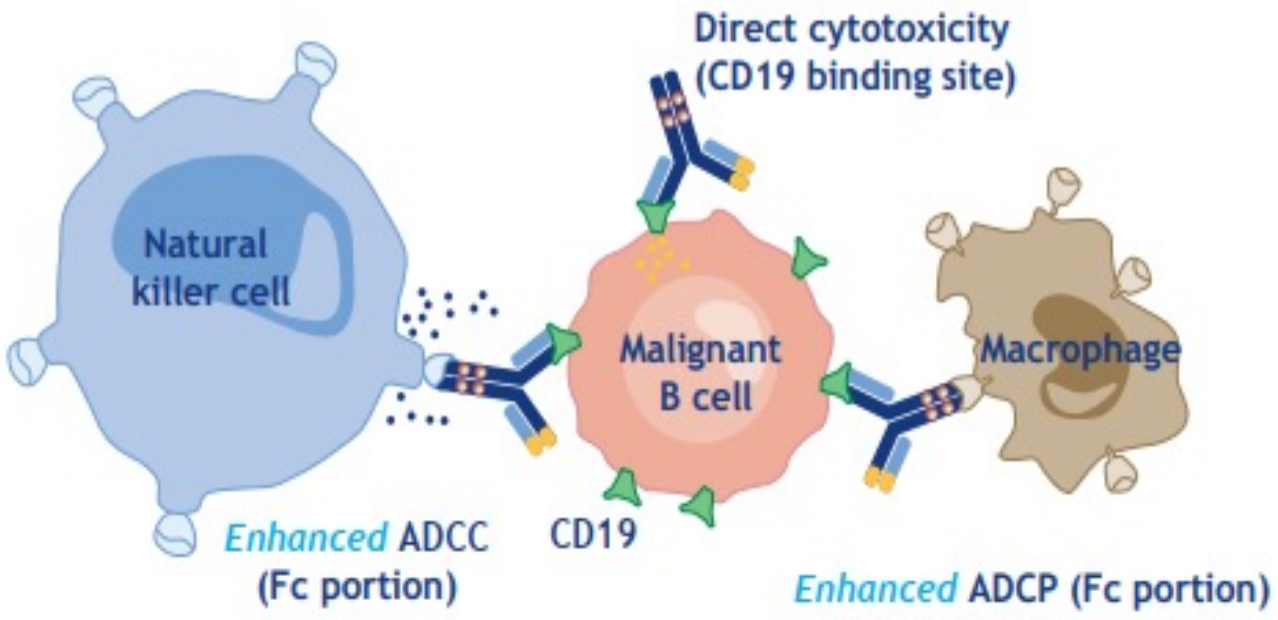


Sehn LH et al, Blood Advances 2021

Tafasitamab a humanized and engineered anti-CD19 Ab

Previously known as XmAb5574, then MOR208

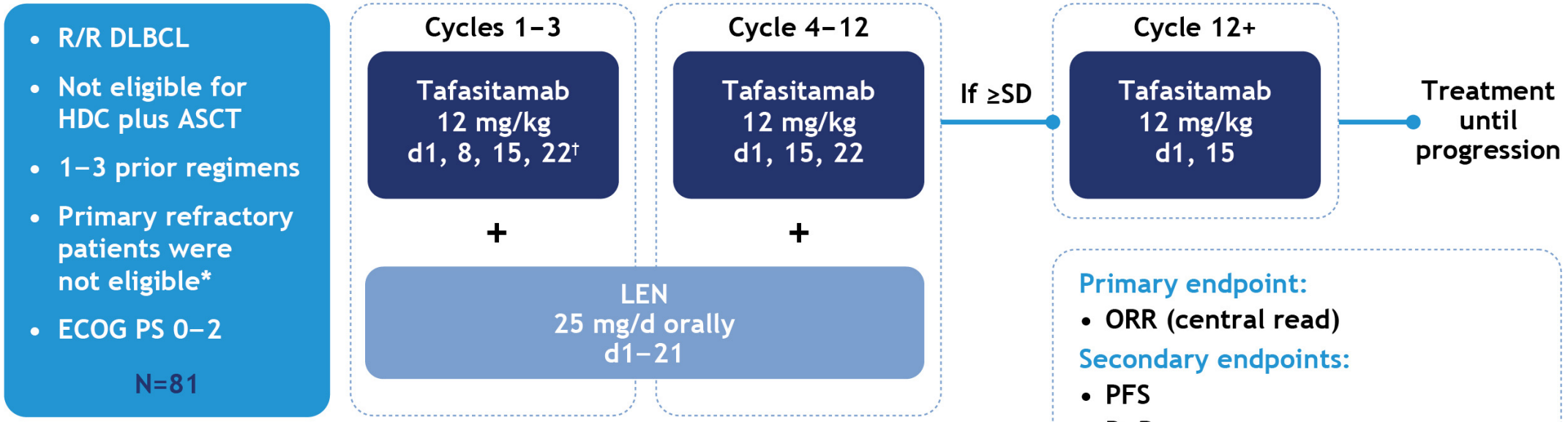




Dusll et al, 2021

L-MIND trial design

- **NCT02399085**

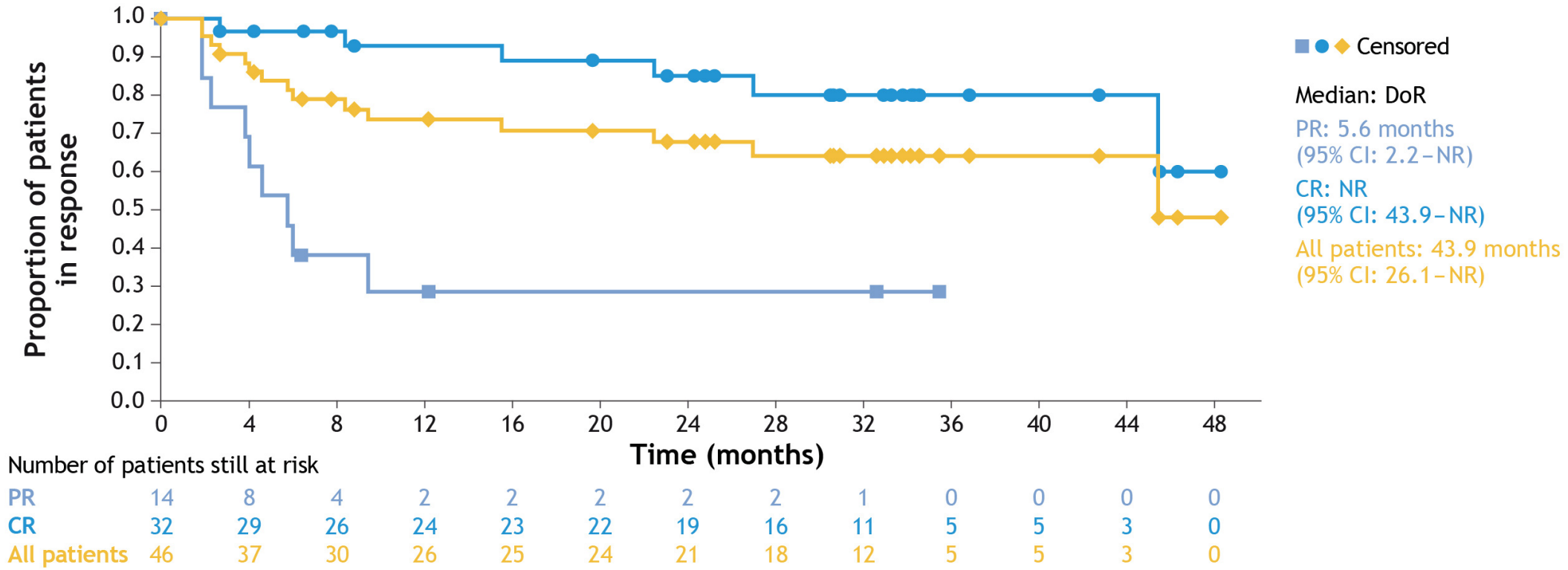


- Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab plus LEN vs LEN monotherapy at 85% power, two-sided alpha of 5%
- Safety data from the first six patients were evaluated in a safety run-in to determine the starting dose of LEN for the remainder of the study

- *Primary refractory is defined as no response to, or progression/relapse during or within 6 months of frontline therapy.
- †A loading dose of tafasitamab was administered on Day 4 of Cycle 1. ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HDC, high-dose chemotherapy; IRC, independent review committee; LEN, lenalidomide; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; SD, stable disease.

L-MIND DoR by best response (3 years f-up)

- Median DoR for the full efficacy population was 43.9 months (95% CI: 26.1-not reached [NR])
- For patients who reached a best response of CR, the median DoR was NR (95% CI: 43.9-NR)



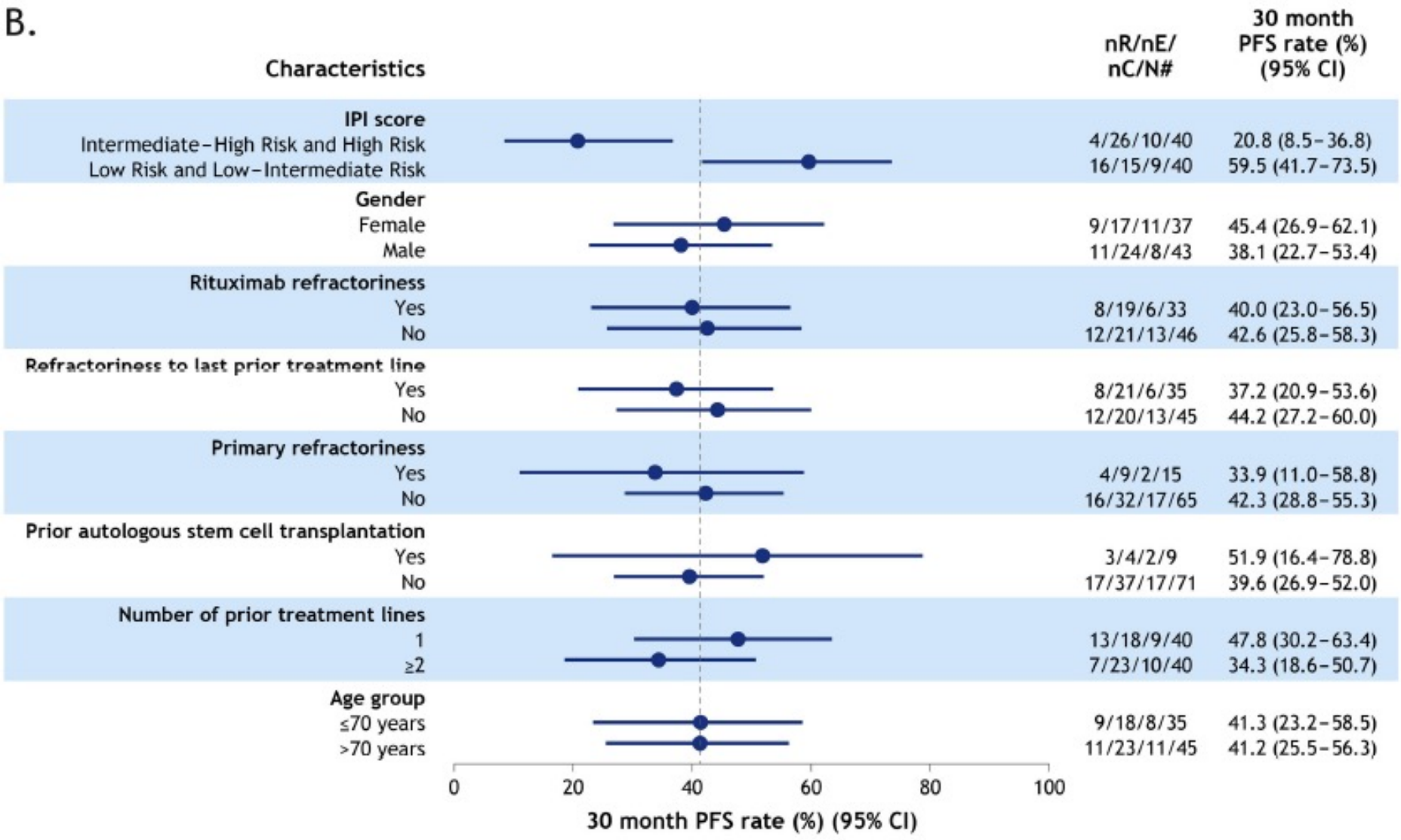
Number of patients still at risk

PR	14	8	4	2	2	2	2	2	1	0	0	0	0
CR	32	29	26	24	23	22	19	16	11	5	5	3	0
All patients	46	37	30	26	25	24	21	18	12	5	5	3	0

- CI, confidence interval; DoR, duration of response; NR, not reached;

Duell et al, Haematologica 2021

L-MIND: 30-months PFS according to clinical characteristics



Duell et al, Haematologica 2021

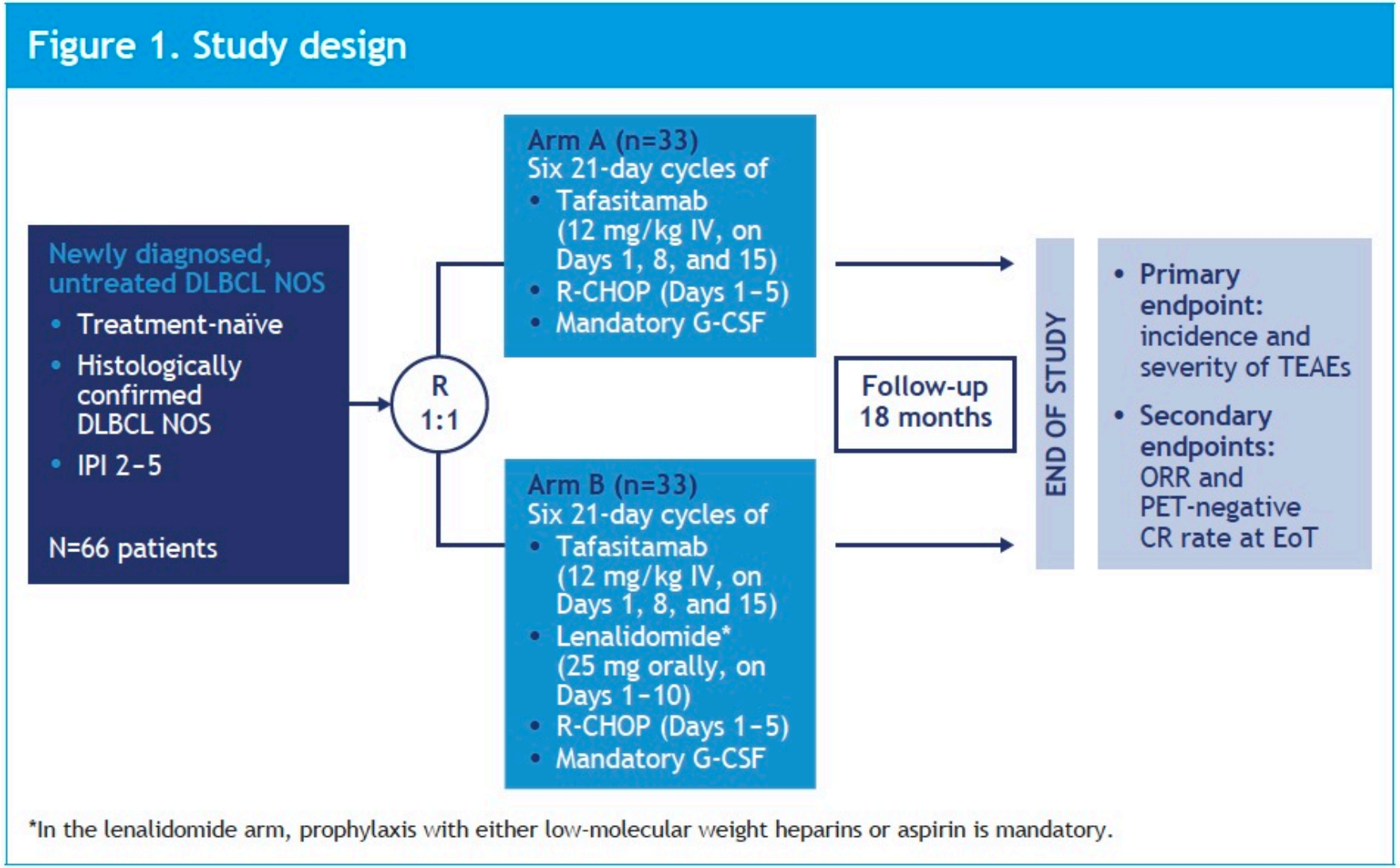
L-MIND: updated safety

Frequent hematologic TEAEs: occurring in ≥10% of patients,
or Grade ≥3 TEAEs in >1 patient

Event	All Grades (≥10%) n (%)	Grade ≥3 (>1 patient) n (%)
Neutropenia	41 (50.6)	40 (49.4)
Anemia	30 (37.0)	6 (7.4)
Thrombocytopenia	25 (30.9)	14 (17.3)
Leukopenia	12 (14.8)	9 (11.1)
Febrile neutropenia	10 (12.3)	10 (12.3)
Lymphopenia	6 (7.4)	3 (3.7)

Duell et al, Haematologica 2021

First-MIND study:
combining tafasitamab with R-CHOP or R2-CHOP in 1st line DLBCL



Bellada et al, EHA 2021

First-MIND study:
combining tafasitamab with R-CHOP or R2-CHOP in 1st line DLBCL

Table 2. Most frequently occurring hematologic TEAEs (≥10% of patients)

	Arm A R-CHOP + tafasitamab (n=33)		Arm B R CHOP + tafasitamab + lenalidomide (n=33)		Total (n=66)	
Hematologic TEAEs, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	20 (60.6)	19 (57.6)	28 (84.8)	28 (84.8)	48 (72.7)	47 (71.2)
Anemia	18 (54.5)	7 (21.2)	20 (60.6)	9 (27.3)	38 (57.6)	16 (24.2)
Thrombocytopenia	6 (18.2)	3 (9.1)	13 (39.4)	11 (33.3)	19 (28.8)	14 (21.2)
Leukopenia	9 (27.3)	6 (18.2)	9 (27.3)	9 (27.3)	18 (27.3)	15 (22.7)
Febrile neutropenia	6 (18.2)	6 (18.2)	6 (18.2)	6 (18.2)	12 (18.2)	12 (18.2)
Lymphopenia	4 (12.1)	4 (12.1)	7 (21.2)	7 (21.2)	11 (16.7)	11 (16.7)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine; TEAEs, treatment-emergent adverse events.

Bellada et al, EHA 2021

First-MIND study:
combining tafasitamab with R-CHOP or R2-CHOP in 1st line DLBCL

Preliminary efficacy (response assessment at EoT)

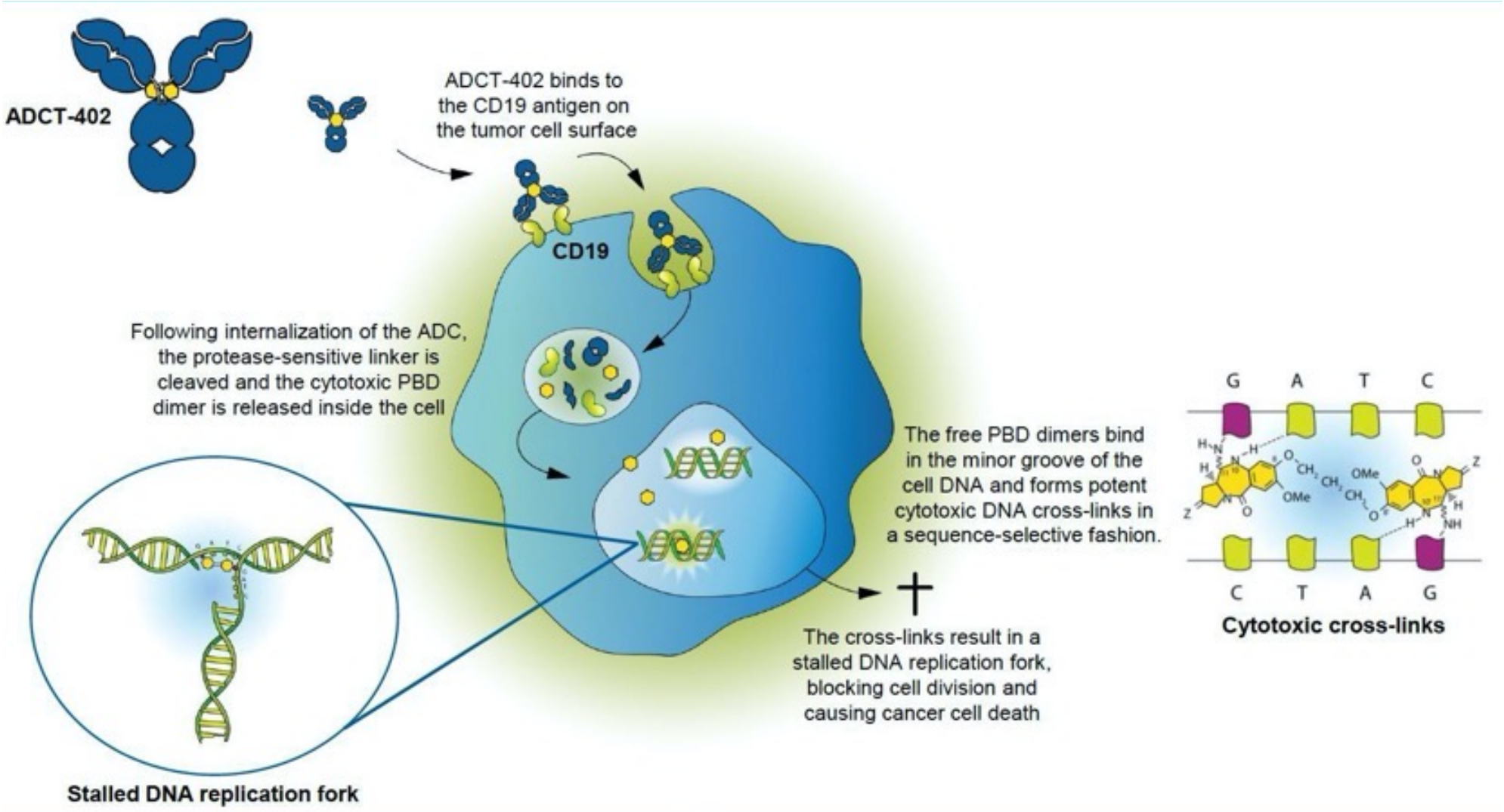
- The average relative dose intensity of R-CHOP in each cycle was maintained in both arms.

  - ORR at EOT was observed in:
  - 25/33 pts (75.8%; 95%CI: 57.7-88.9) in R-CHOP-Tafa
  - 27/33 pts (81.8%; 95%CI: 64.5-93.0) in R2-CHOP-Tafa.

Bellada et al, ASH 2021 – abstract 3556

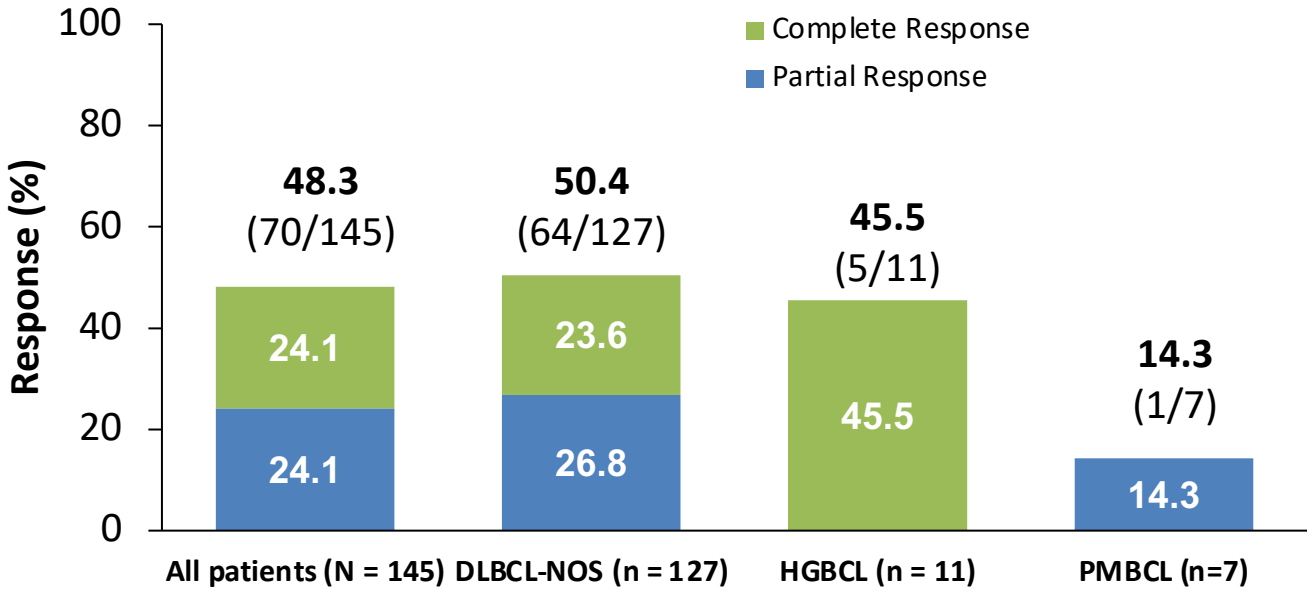
ASH

Another ADC: Loncastuximab tesirine

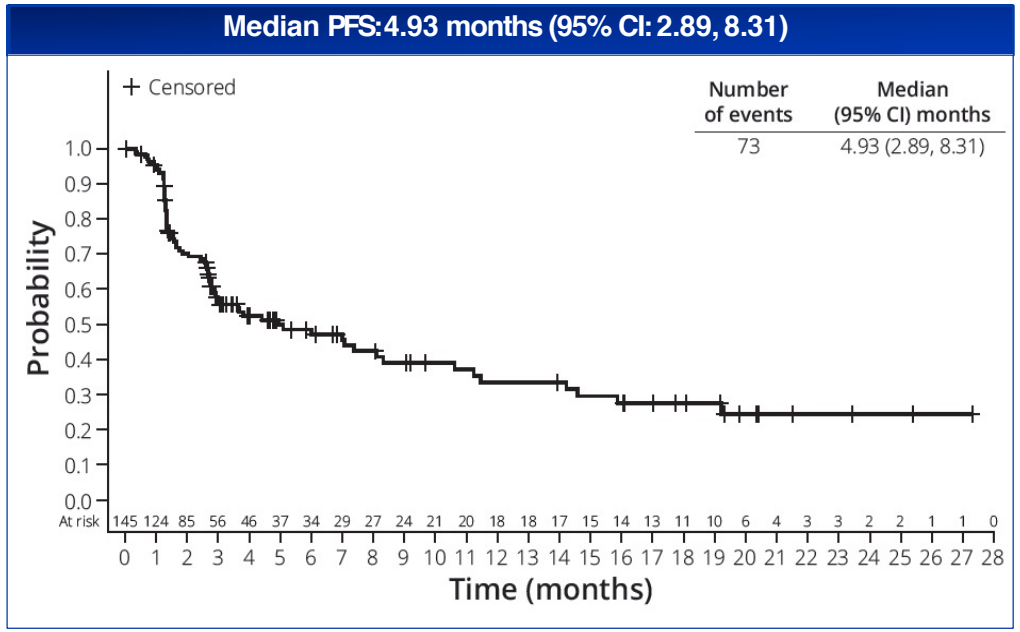


1. Hartley JA. The development of pyrrolobenzodiazepines as antitumour agents. *Expert Opin Investig Drugs* 2011;20(6):733-744.

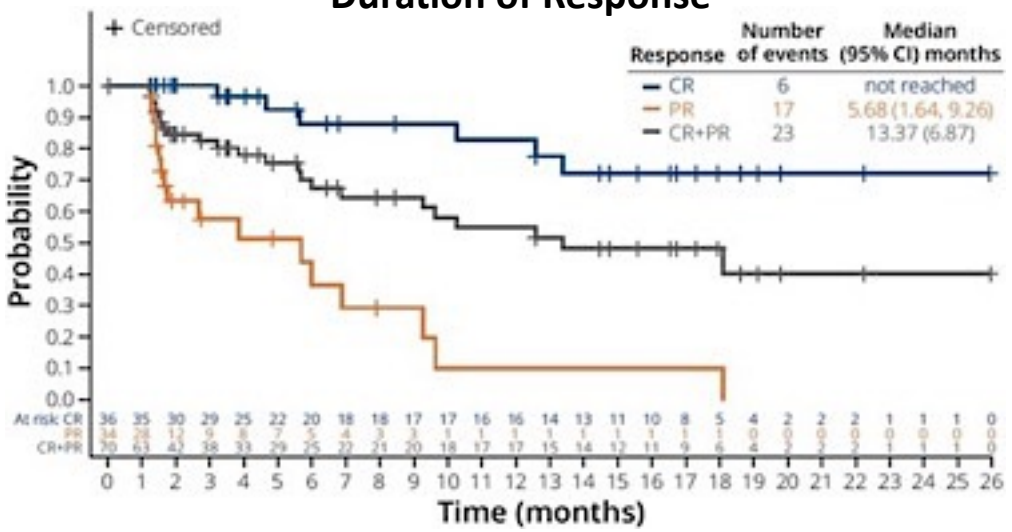
Loncastuximab Tesirine in R/R DLBCL Response by Histology – Lotis-2



Median DOR: 10.25 months (95% CI: 5.98, NR)



Duration of Response



- Caimi et al., Lancet Oncology 2021

Loncastuximab Tesirine in R/R DLBCL

Safety Data

Preferred term, n (%)	Patients (N = 145)
Patients with any TEAE	**143 (98.6)**
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anaemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral edema	29 (20.0)

- The most common grade ≥ 3 TEAEs (≥ 10% of patients) were:
  - Neutropenia (37 patients; 25.5%)
    - Incidence of febrile neutropenia was low (5 patients; 3.4%)
  - Thrombocytopenia (26 patients; 17.9%)
  - GGT increased (24 patients; 16.6%)
  - Anemia (15 patients; 10.3%)

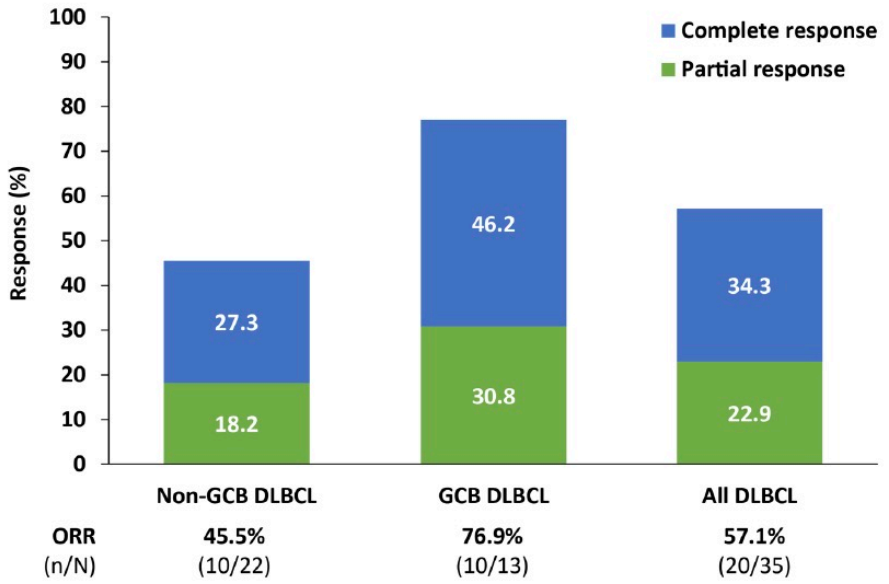
- Caimi et al., Lancet Oncology 2021

Lonca-T - 2021 ASH

Abstract 54: Planned Interim Analysis of a Phase 2 Study of Loncastuximab Tesirine Plus Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma (LOTIS-3)

- 2 cycles of Lonca-T – 60 µg/kg every 3w (up to 6 cycles/consolidation)
- Ibrutinib 560 mg / day 1 year

Figure 1. ORR in the overall DLBCL cohort and by cell of origin (planned interim analysis set)



Abstract 3575; Clinical Characteristics and Responses of Patients with Relapsed or Refractory High-Grade B-Cell Lymphoma Treated with Loncastuximab Tesirine in the Lotis-2 Clinical Trial

- 11 patients ; 45% ORR and CR ; Median DOR not reached

Abstract 2489: The Anti-CD19 Antibody-Drug Conjugate Loncastuximab Tesirine Achieved Responses in Patients with Diffuse Large B-Cell Lymphoma Who Relapsed after Anti-CD19 CAR T-Cell Therapy

- 13 patients after CAR T ; ORR 46.4% (15.4% CR) ; Median PFS = 3.2 months

Carlo Stella C et al, ASH 2021, abstract 54 ; Caimi PF et al, abstract 2489 ; Alderuccio JP et al, abstract 3575

FDA Grants Accelerated Approval to Loncastuximab Tesirine-lpyl for Large B-Cell Lymphoma

Press Release – April 23, 2021

"The Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl, a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Approval was based on LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens. Patients received loncastuximab tesirine-lpyl 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment until progressive disease or unacceptable toxicity."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-loncastuximab-tesirine-lpyl-large-b-cell-lymphoma

Bi-Specifics CD3 x CD20 in patients with R/R DLBCL (updated from ASCO / EHA / ICML 2021)

	Mosunetuzumab[1] (RG7828)	Odronextamab[2] (REGN1979)	Glofitamab[3] (RG6026)	Epcoritamab[4] (GEN3013)
Patients	98	35	28	33
ORR	38%	40%	64%	76%
CR	20%	31%	37%	48%

1. Schuster SJ et al, ASH 2019, Abstract 6 (doses >=2.5 mg); 2. Bannerji R, et al. ASH 2020, Abstract 400 (doses 80-320); 3. Carolo Stella C et al>, ASCO 2021 . 4. Hutchings M, et al. IML 2021 “aggressive lymphoma”

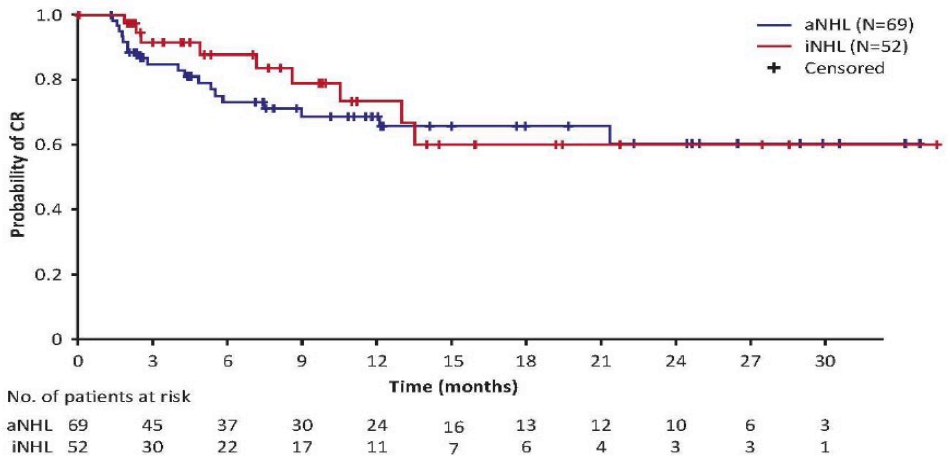
ASH 2021: in progress; 3569 Phase 3 Trial (EPCORE DLBCL-1) of Epcoritamab Versus Standard of Care in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (Fox CP et al., abstract 3569)

Bispecifics (DLBCL) ASH 2021: single agent data

2478 **Glofitamab** Monotherapy Provides Durable Responses after Fixed-Length Dosing in Relapsed/Refractory (R/R) Non-Hodgkin Lymphoma (NHL) Patients (pts)

	aNHL, all doses (n=175)	aNHL, RP2D 2.5/10/30mg (n=14)
Overall response rate, n (%) [95% CI]	94 (53.7) [46.0, 61.3]	11 (78.6) [49.2, 95.3]
Complete response rate, n (%) [95% CI]	69 (39.4) [32.1, 47.1]	10 (71.4) [41.9, 91.6]
Partial response rate, n (%) [95% CI]	25 (14.3) [9.5, 20.4]	1 (7.1) [0.2, 33.9]

Figure. Duration of complete response (efficacy-evaluable population*)



Other agents

3573 Subcutaneous (SC) Administration of **Mosunetuzumab** with Cycle 1 Step-up Dosing Is Tolerable and Active in Patients with Relapsed/Refractory B-Cell Non-Hodgkin Lymphomas (R/R B-NHL): Initial Results from a Phase I/II Study

2494 Safety and Anti-Tumor Activity of **Plamotamab** (XmAb13676), an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Subjects with Relapsed/Refractory Non-Hodgkin's Lymphoma

132 A Phase 1 Dose Escalation Study of **Igm-2323**, a Novel Anti-CD20 x Anti-CD3 IgM T Cell Engager (TCE) in Patients with Advanced B-Cell Malignancies

Dinckinson M et al, abstract 2478 ; Bartlett N et al, abstract 3573 ; Patel K et al, abstract 2494 ; Budde LE et al, abstract 132

Bispecifics (DLBCL) ASH 2021: Combination data

533 **Mosunetuzumab Plus Polatuzumab Vedotin** Has Promising Efficacy and a Favorable Safety Profile in Patients with Relapsed/Refractory Aggressive B-Cell Non-Hodgkin Lymphoma: Updated Results from a Phase Ib/II Study

Table. Response rates in patients with R/R B-NHL

	Dose-escalation and dose-expansion cohorts: patients with R/R B-NHL only		Dose-expansion cohort*	
Response, n (%)	**All (n=60)**	**Post-CAR-T (n=24)**	**All (n=41)**	**Post-CAR-T (n=17)**
ORR	39 (65.0)	15 (62.5)	27 (65.9)	11 (64.7)
CR	29 (48.3)	10 (41.7)	20 (48.8)	8 (47.1)

Response was assessed by investigators using Lugano 2014 criteria.

*Only pts with R/R aggressive B-NHL were enrolled.

525 **Glofitamab** (Glofit) in Combination with **Polatuzumab Vedotin**: Phase Ib/II Preliminary Data Support Manageable Safety and Encouraging Efficacy in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

1413 Subcutaneous **Epcoritamab** in Combination with **R-CHOP** in Patients with Previously Untreated High-Risk Diffuse Large B-Cell Lymphoma: Preliminary Results from a Phase 1/2 Trial

2479 **Glofitamab** Plus **R-CHOP** Induces High Response Rates with Minimal Cytokine Release Syndrome in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma and Previously Untreated (1L) Diffuse Large B-Cell Lymphoma: Preliminary Results from a Dose-Escalation and Safety Run-in Phase Ib Study

3571 Trial in Progress: A Multicentre, Parallel Arm, Open-Label Trial of Frontline **R-CHOP/Polatuzumab Vedotin-RCHP** and **Glofitamab** in Younger Patients with Higher Risk Diffuse Large B Cell Lymphoma (COALITION)

Budde LE et al, abstract 533 ; Hutchings M et al., abstract 525 ; Belada D et al., abstract 1413 ; Ghosh N et al, abstract 2479 ; Minson A et al, abstract 3571