New Therapies for Relapse/Refractory DLBCL

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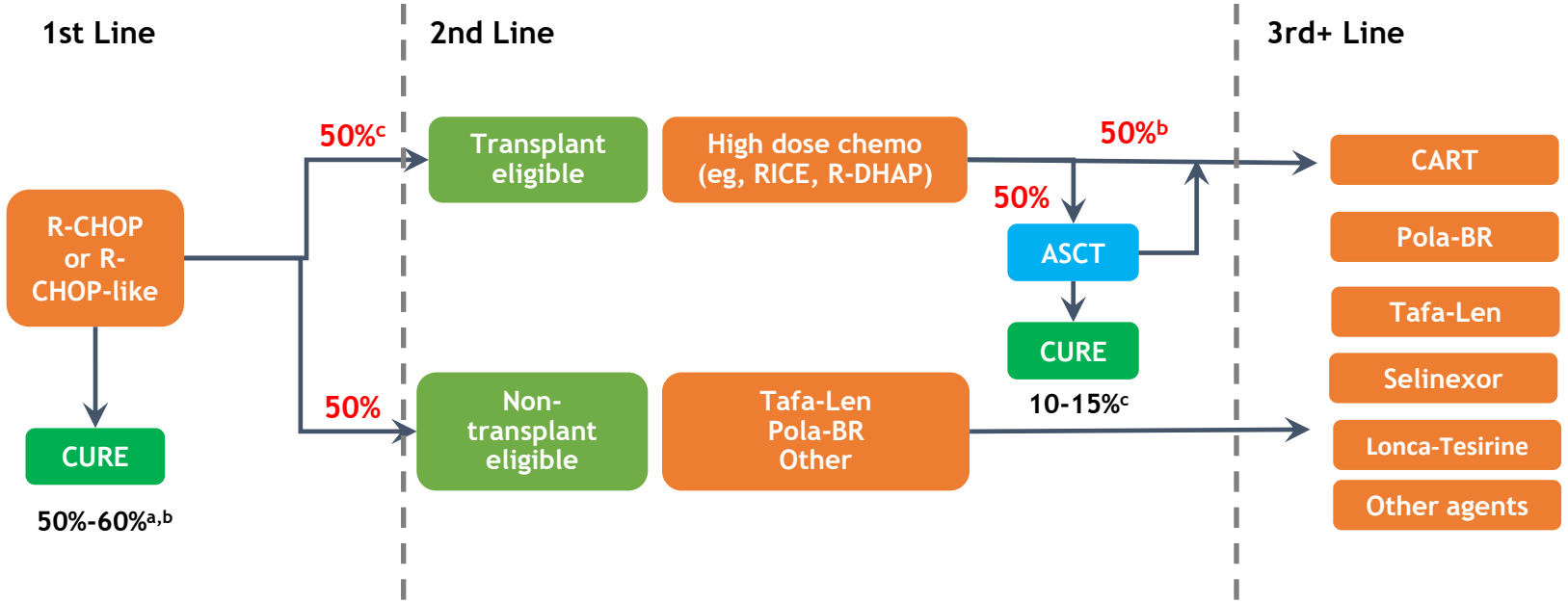
Disclosures for
Stephen Ansell, MD, PhD

In compliance with ACCME policy, Mayo Clinic requires the following disclosures to the activity audience:

Research Support/P.I.	PI – Seattle Genetics, BMS, Affimed, Regeneron, Takeda, AI Therapeutics, Trillium, ADC Therapeutics (clinical trials)
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

N/A = Not Applicable (no conflicts listed)

Pattern of Care in DLBCL



SCT=stem-cell transplantation.

[a] Decisions Resource Group. DLBCL Epidemiology data; [b] Sehn LH, Gascoyne RD. *Blood*. 2015;125:22-32;

[c] Friedberg JW, et al. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505;

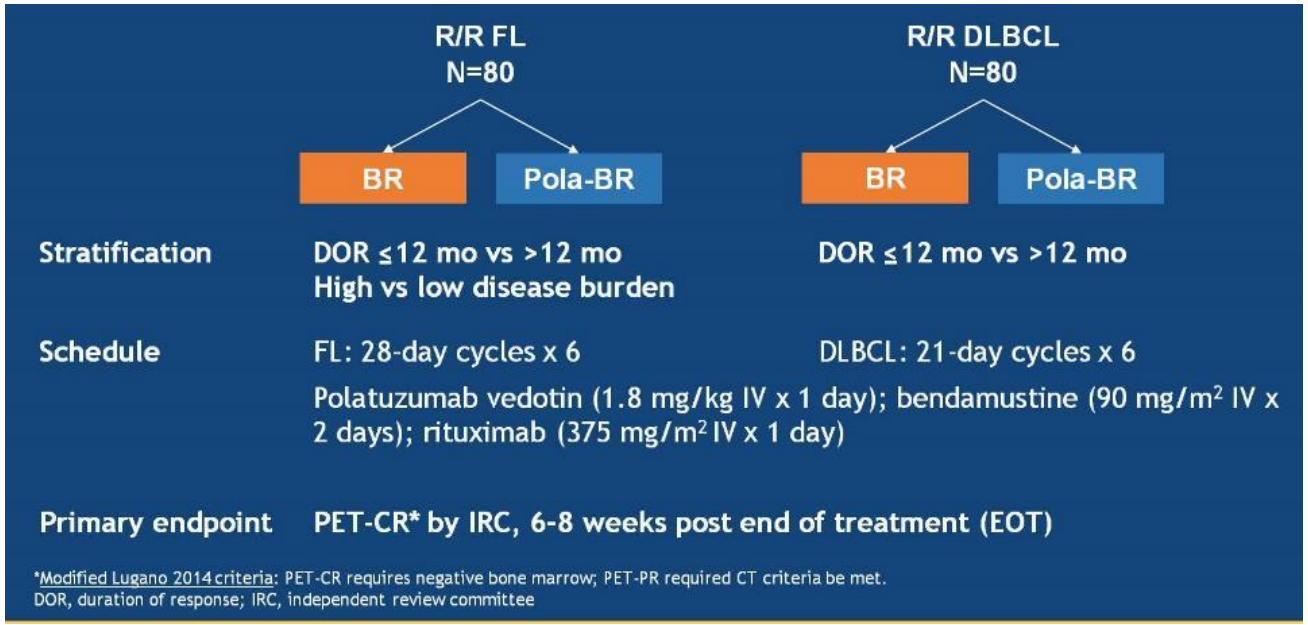
Phase 2 Study of Polatuzumab Vedotin + BR

Inclusion

- Age ≥ 18
- Biopsy-confirmed R/R DLBCL[a]
- ≥ 1 prior line of therapy
- ECOG PS 0-2
- Grade ≤ 1 peripheral neuropathy
- Transplant ineligible or treatment failure with prior ASCT

Exclusion

- Prior allogeneic stem cell transplant
- Autologous stem cell transplant within 100 days prior to Cycle 1 Day 1
- History of transformation of indolent disease to DLBCL
- Current grade >1 peripheral neuropathy
- Eligible for autologous transplant if DLBCL



FDA Accelerated Approval - June 10, 2019 - in combination with BR for DLBCL NOS after ≥ 2 prior therapies

a. biopsy-confirmed R/R DLBCL (excluding transformed lymphoma)
ASCT, autologous stem cell transplant.

Sehn L, et al. ASCO 2018. Abstract 7507. Sehn L, et al. *J Clin Oncol*. 2020;38:155-165.

Phase 2 Study of Polatuzumab Vedotin + BR

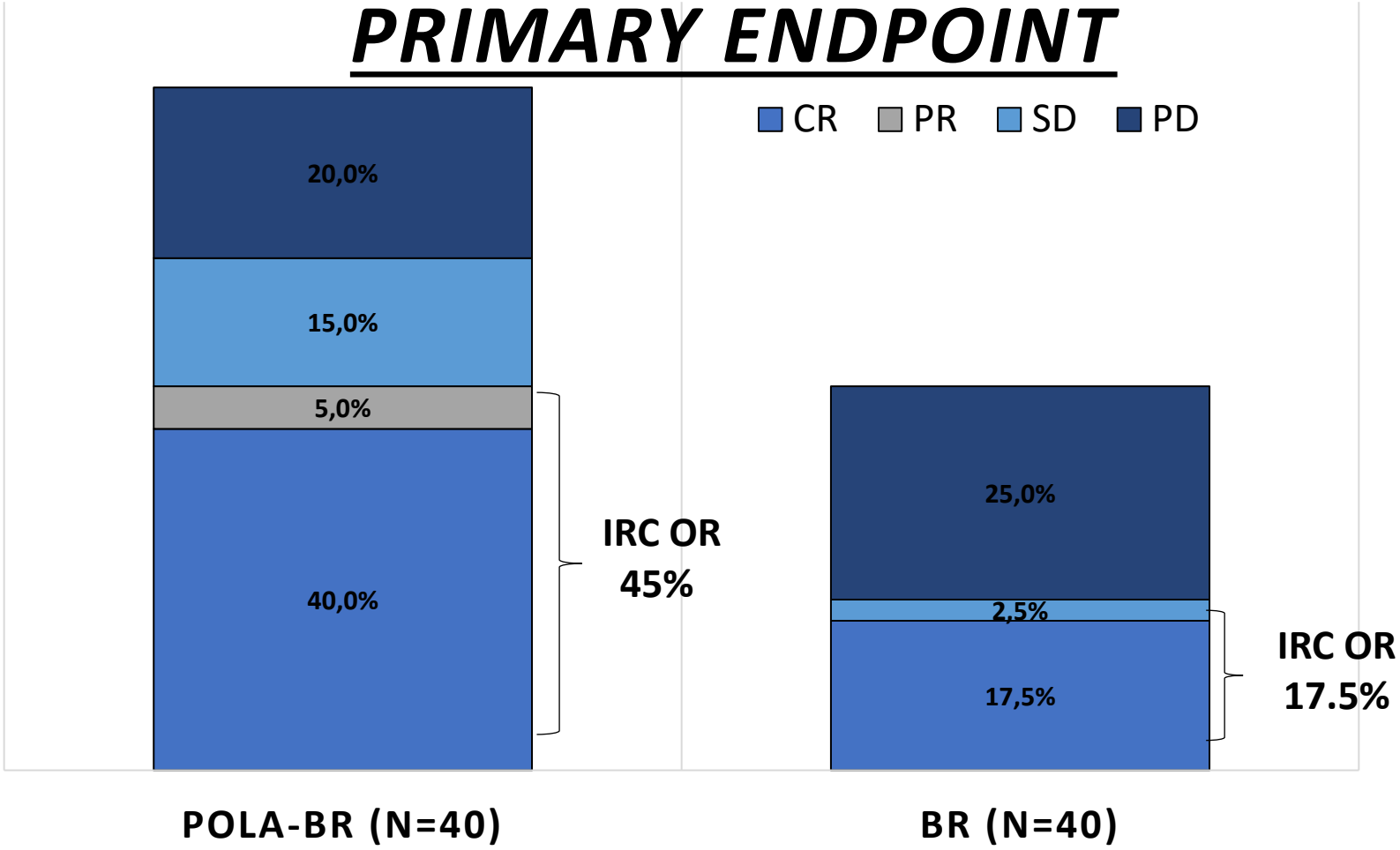
Characteristic	Pola-BR (n=40)	BR (n=40)
Sex, % (M)	70	62.5
Median age (range), years	67 (33-86)	71 (30-84)
IPI risk score, % (0-2/3-5)	45/55	27.5/72.5
Ann Arbor Stage III-IV, %	85	90
Median prior LOT (range)	2 (1-7)	2 (1-5)
No. Prior Lines, % (1/2/≥3)	27.5/27.5/45	30/22.5/47.5
DOR of last treatment ≤ 12 mo, %	80	82.5
Refractory to last prior therapy, %	75	85
Prior SCT, % (Y/N)	25	15
GCB, %	37.5	42.5

Median time to first response: 2 mo (range 1.8-5.3)

Sehn L, et al. ASCO 2018. Abstract 7507. Sehn L. et al. ASH 2019. Abstract 4081.
Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

IRC OBJECTIVE RESPONSE

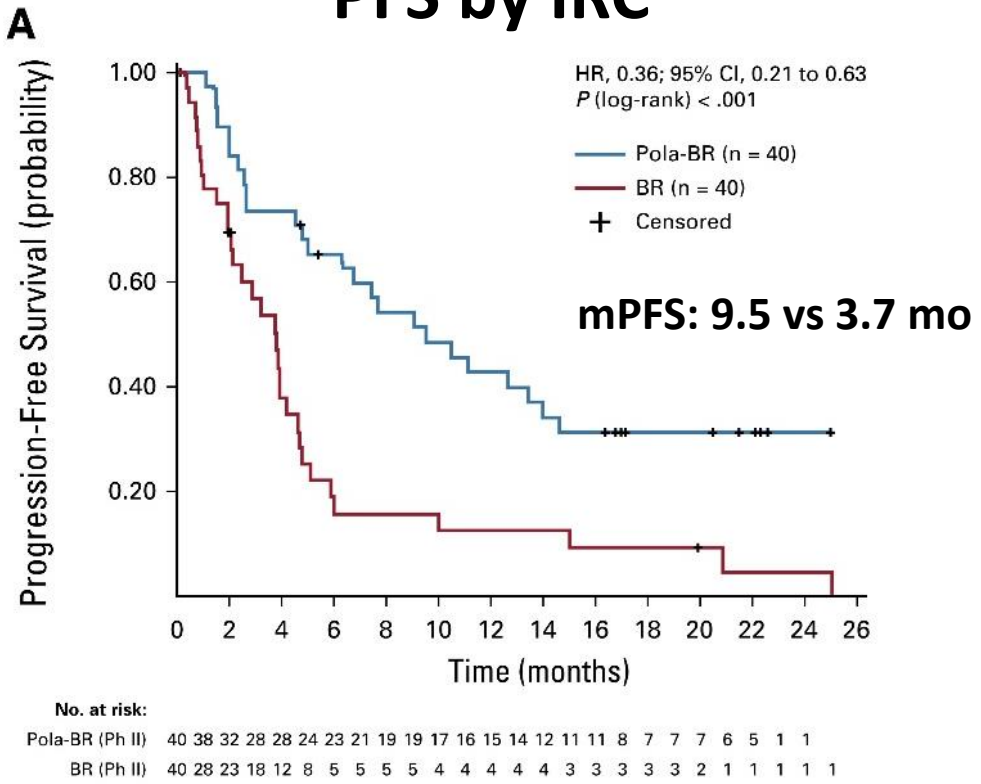
PRIMARY ENDPOINT



Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

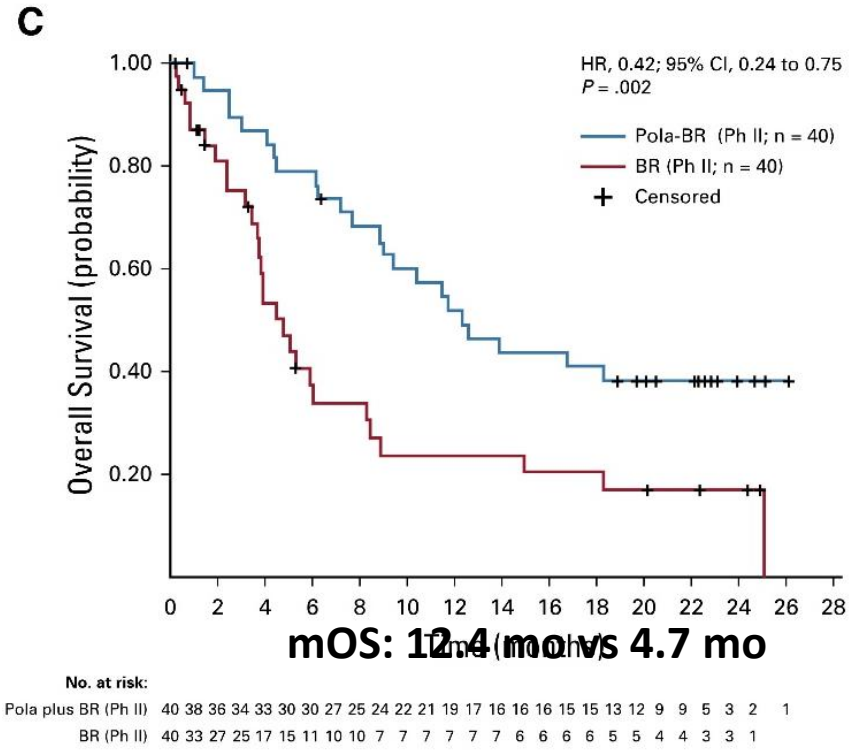
Phase 2 mDOR by IRC (Pola + BR vs BR): 12.6 mo vs 7.7 mo

PFS by IRC



mPFS: 9.5 vs 3.7 mo

OS



mOS: 12.4 mo vs 4.7 mo

Median follow-up, 22.3 mo

Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165. Sehn L, et al. ASH 2020. Abstract 3020.

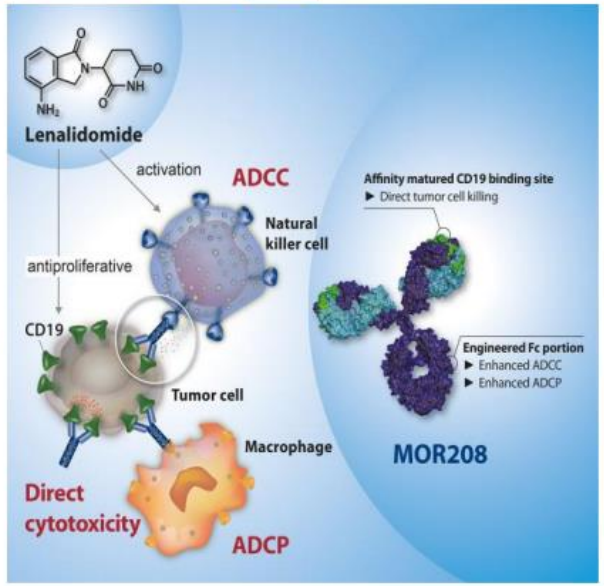
Combination Tafasitamab and Lenalidomide

MOR208
Fc-enhanced, anti-CD19 mAb

+

Lenalidomide

- ADCC ↑
- ADCP ↑
- Direct Cell Death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL



- T and NK Cell Activation/Expansion
- Direct Cell Death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

Potentiation of activity by combining Tafasitamab & LEN in vivo and in vitro

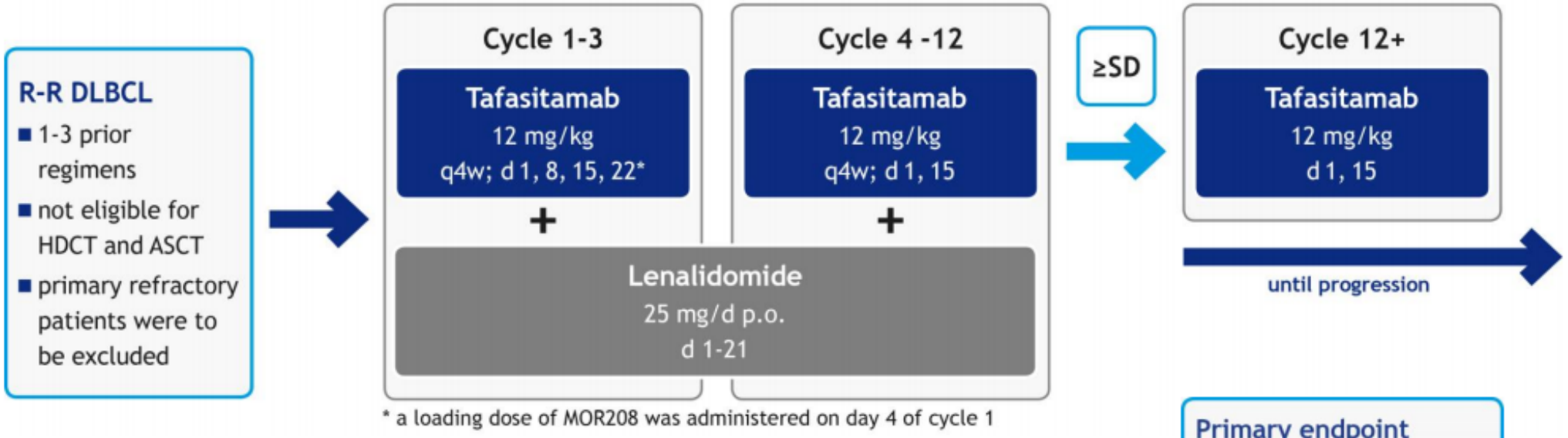
Horton et al., 2008; Awan et al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al, 2018

FDA Accelerated Approval – July 31, 2020 – RR DLBCL NOS (including DLBCL arising from low-grade lymphoma), and who are not eligible for autologous stem cell transplant.

ICML 2019 #124. Salles G, et al. L-MIND. June 22, 2019.

Phase 2 L-MIND: Tafasitamab plus Lenalidomide

phase 2, single-arm, open-label, multicenter study (NCT02399085)



* a loading dose of MOR208 was administered on day 4 of cycle 1

- 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

-Primary refractory DLBCL was defined as no response to or progression/relapse during or within 6 months of frontline therapy.
-Response assessment (Cheson 2007 Criteria) was after cycles 2, 4, 6, 9 and 12, thereafter every 3 cycles.
-ASCT, autologous stem cell transplant; HDCT, high-dose chemotherapy; SD, stable disease, p.o., per os.

ICML 2019 #124. Salles G, et al. L-MIND. June 22, 2019.
Salles G, et al. *Lancet Oncol*. 2020;21(7):978-988.

Phase 2 L-MIND: Baseline Characteristics

Characteristic	Patients (n=81)
Median age (range), years	72 (41-86)
IPI risk score, % (0-2/3-5)[a]	49/51
Ann Arbor Stage, % (I-II/III-IV)	25/75
Elevated LDH, % (Y/N)[a]	56/44
Median prior LOT (range)[a]	2 (1-4)
No. Prior Lines, % (1/2/3/4)[a]	50/43/6/1
Primary refractory, % (Y/N)	19/81
Refractory to last prior therapy, % (Y/N)[a]	44/56
Prior SCT, % (Y/N)	11/89
Cell of Origin, % (GCB/non-GCB/other[b])[c]	10/25/65

[a]At study entry. [b] Unclassified or unknown. [c]Centrally assessed, Hans algorithm.

Duell J, et al. *Haematologica*. 2021;106:2417-2426; Salles G, et al. *Lancet Oncol.* 2020;21(7):978-988.

Phase 2 L-MIND: Response

	Tafa + Len (N = 80)
Best Response (≥ 35 Mo)	
CR	40% (32)
PR	17.5% (14)
SD	16.3% (13)
PD	16.3% (13)
NE	10% (8)
ORR	57.5% (46)
Median DOR	43.9 mo

Median time to response was 2.1 months (range 1.7–34.7)

DOR, duration of response; OR, overall response rate; NE, not evaluable.

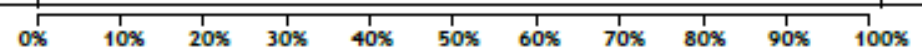
Data cutoff: Oct 30, 2020.

Salles G, et al. *Lancet Oncol.* 2020;21(7):978-988.

Duell J, et al. ASCO 2021. Abstract 7513; Duell J, et al. *Haematologica*. 2021;106:2417-2426.

Phase 2 L-MIND: Response by Subgroup

Subgroup		N	Objective response rate (%) (95% CI)	Objective response rate (%)	95% CI
Age	>70 years	45		58	42–72
	≤70 years	35		63	45–79
Ann-Arbor stage	I–II	20		60	36–81
	III–IV	60		60	47–72
LDH elevated	Yes	44		57	41–72
	No	36		64	46–79
IPI score	Low risk and low–intermediate risk	40		70	54–83
	Intermediate–high risk and high risk	40		50	34–66
Cell of origin, phenotype*	Non-GCB	21		71	48–89
	GCB	37		49	32–66
Rituximab refractory	Yes	33		58	39–75
	No	46		61	45–75
Refractory to last line	Yes	35		60	42–76
	No	45		60	44–74
Primary refractory	Yes	15		60	32–84
	No	65		60	47–72
Number of prior lines	1	40		70	54–83
	≥2	40		50	34–66



Median follow-up, 13.2 mo; data cutoff on Nov 30, 2018.

Salles G, et al. *Lancet Oncol*. 2020;21:978-988.

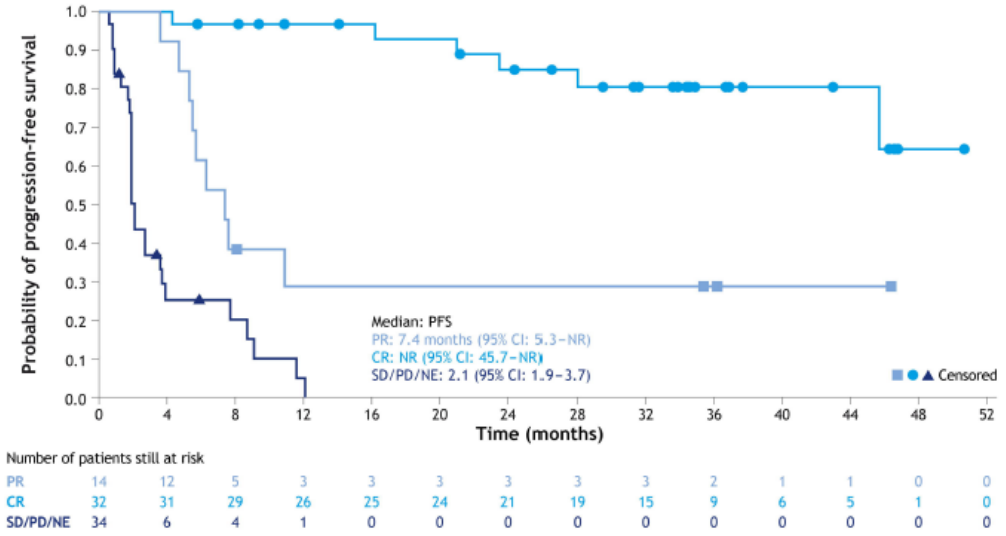
Phase 2 L-MIND: PFS and OS

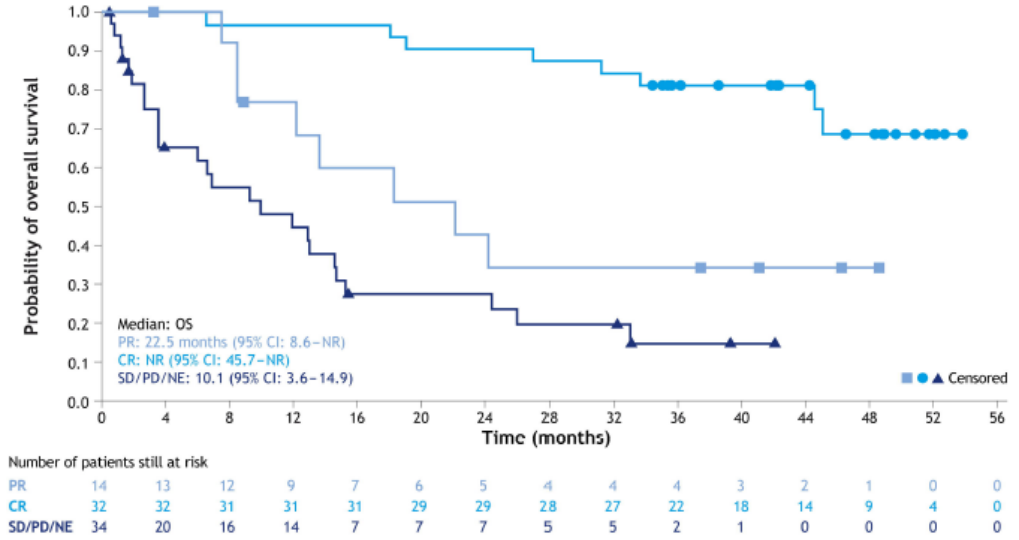
- **Median PFS**
  - **At median 33.9 mo follow up: 11.6 mo**

    12-mo PFS, 50%
    18-mo PFS: 46%

- **Median OS**
  - **At median 42.7 mo follow up: 33.5 mo**

    12-mo OS: 74%
    18-mo OS: 64%

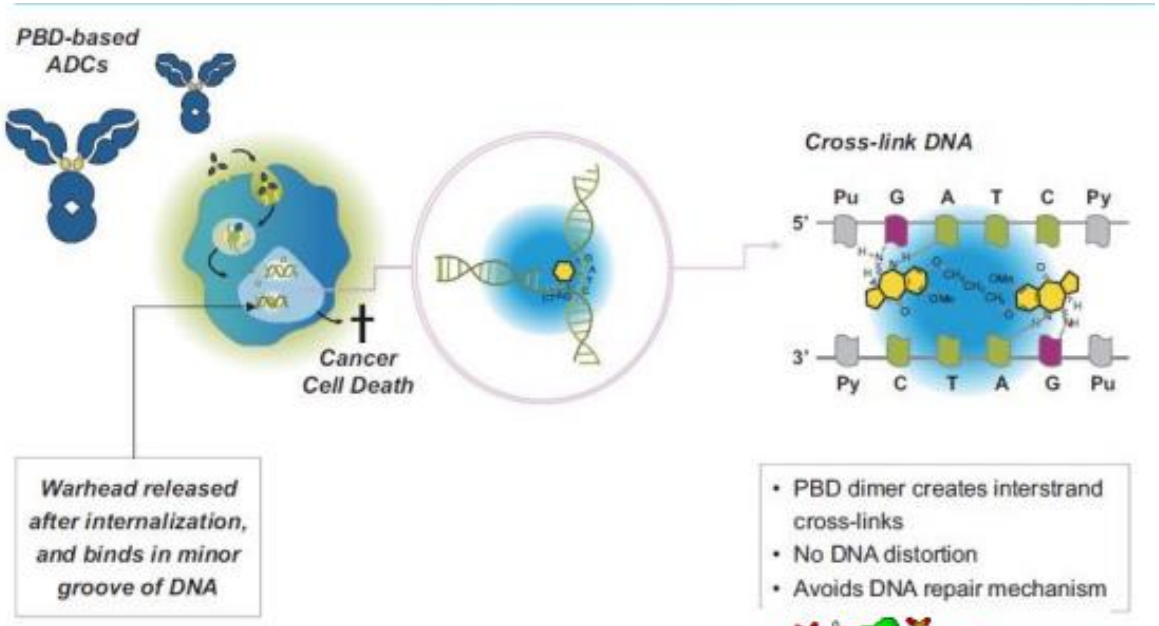




a Full analysis set.

Duell J, et al. *Haematologica*. 2021;106:2417-2426. Duell J, et al. ASCO 2021. Abstract 7513.

Loncastuximab Tesirine: Novel Anti-CD19 Antibody-Drug Conjugate



- First-in-class PBD-based ADCs
- Improved preclinical therapeutic index

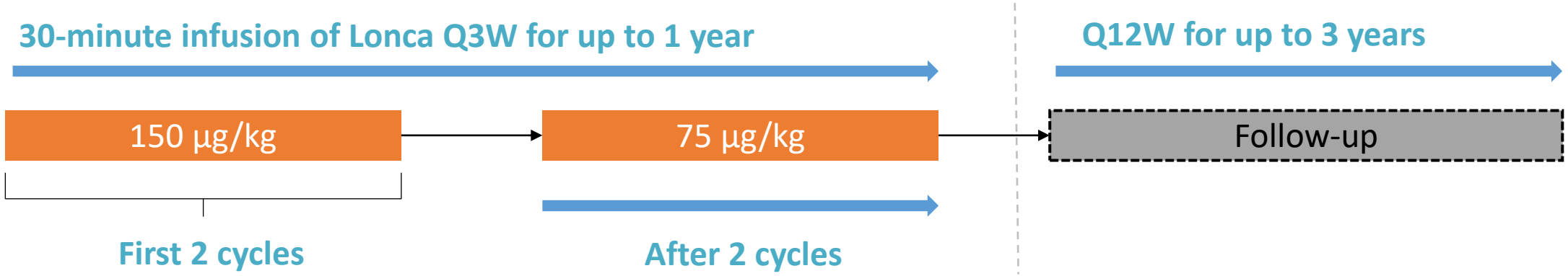
CD19-targeted ADC delivering SG3199, a cytotoxic DNA minor groove interstrand crosslinking pyrrolobenzodiazepine (PBD) dimer payload

FDA Accelerated Approval – April 23, 2021 - DLBCL after ≥ 2 lines of systemic therapy (including DLBCL NOS, DLBCL arising from low-grade lymphoma, and high-grade BCL

Zammarchi F, et al. *Blood.* 2018;131(10):1094-1105.

Single-Arm, Phase 2 LOTIS-2 Study of Loncastuximab Tesirine for R/R DLBCL

Eligibility: Adults with R/R DLBCL after 2 or more lines of systemic therapy, CD19+ biopsy if prior anti-CD19 therapy received, ECOG PS 0-2, ASCT 30+ days prior or alloSCT 60+ days prior permitted



Primary endpoint: ORR
Secondary endpoints: DOR, CR, RFS, PFS, OS, Safety, PK/PD, HRQoL

Primary antitumour activity/safety analyses done in as-treated population (patients who received ≥ 1 dose of loncastuximab tesirine), when all responding patients had ≥ 6 mo follow-up after initial documented response.

Carlo-Stella C, et al. EHA Congress 2020. Abstract S233.
Caimi PF, et al. *Lancet Oncol*. 11 May 2021. DOI: 10.1016/S1470-2045(21)00139-X

LOTIS-2 Trial: Baseline Characteristics

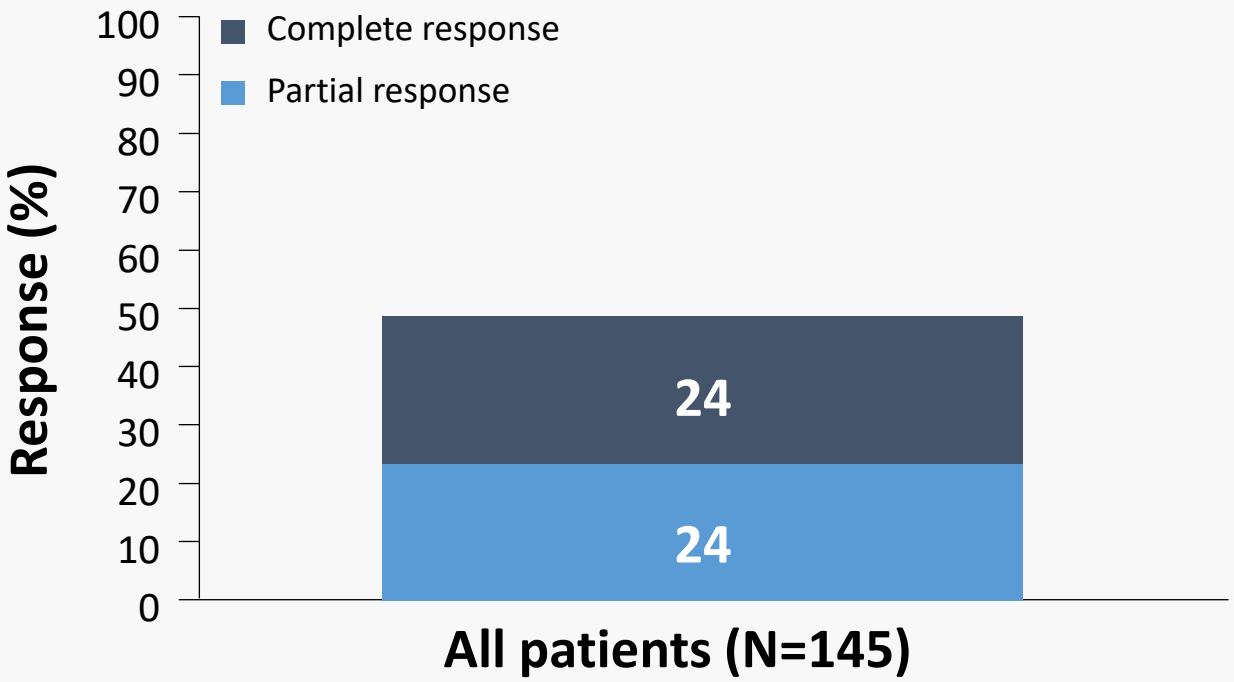
Treatment history	Total (N = 145)
Female/Male, n (%)	60 (41)/85 (59)
Median age, y (IQR)	66 (56-71)
Histology	
DLBCL	127 (88)
HGBCL	11 (8)
PMBCL	7 (5)
Double/triple hit, n (%)	15 (10)
Double/triple expressor, n (%)	20 (14)
Transformed disease, n (%)	29 (20)
Stage I-II / III-IV, n (%)	33 (23) / 112 (77)
Cell of Origin, % (GCB/non-GCB/other	33/16/51
Median no. prior systemic therapies (IQR)	3 (2-4)
No. Prior Lines, % (2/3/>3)[a]	43/24/32

Treatment history	Total (N = 145)
First-line systemic therapy response, n (%)[b]	
Relapse	99 (68)
Refractory	29 (20)
Last-line systemic therapy response, n (%)[c]	
Relapse	43 (30)
Refractory	84 (58)
Refractory to all prior therapies (Y/N), n (%)	25 (17) / 115 (79)
Prior allogeneic SCT, n (%)	2 (1)
Prior autologous SCT	21 (14)
Prior allo + auto SCT	1 (1)
Prior CAR T-cell therapy	13 (9%)

a. Previous HSCT is included; for patients who received auto transplant, mobilization regimen was considered a LOT if it was chemotherapy-based and distinct from the other previous LOT. B Other: 17 (12%). c. Other: 18 (13%)

Carlo-Stella C, et al. EHA Congress 2020. Abstract S233; Caimi PF, et al. *Lancet Oncol*. 2021;22:790-800.

LOTIS-2 Trial: Efficacy Results – ORR



Lonca ORR

48%

(95% CI, 39.9-56.7)

Median time to first response

41.0 days

(IQR, 38-44)

ASCO 2021

Response rates reported from March 1, 2021 data cutoff were consistent with earlier reports.

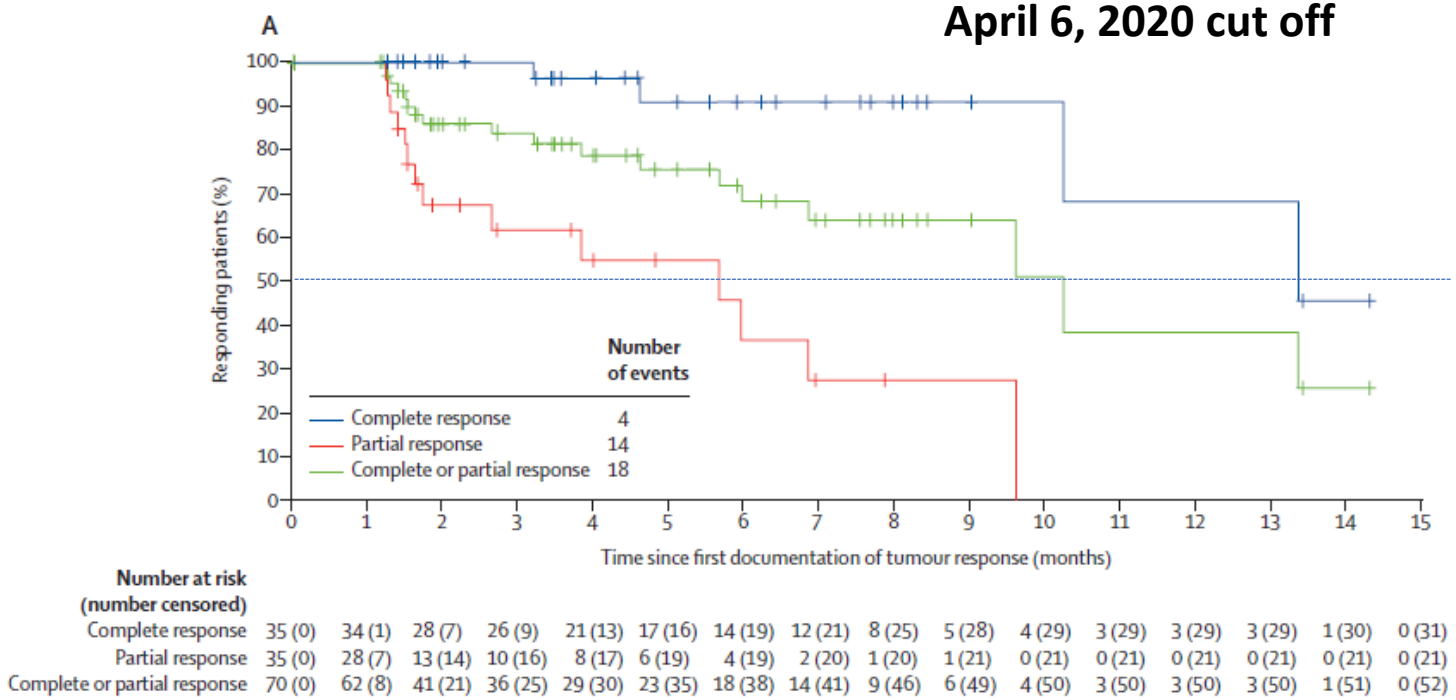
- **Of 35 CRs, 57% were maintained at data cut off**
- **Most responders had a response after 2 cycles**
- **Mean Lonca cycles: 4.5 (Std: ± 3.89) (Min, max: 1, 18)**

ORR was assessed by independent reviewer. Data cut-off: 06 Apr 2020.

Carlo-Stella C, et al. EHA Congress 2020. Abstract S233.
1. Caimi PF, et al. *Lancet Oncol*. 11 May 2021. DOI: 10.1016/S1470-2045(21)00139-X. Caimi PF, et al. ASCO 2021 Abstract 7546.

LOTIS-2 Trial: Efficacy Results – DoR

April 6, 2020 cut off



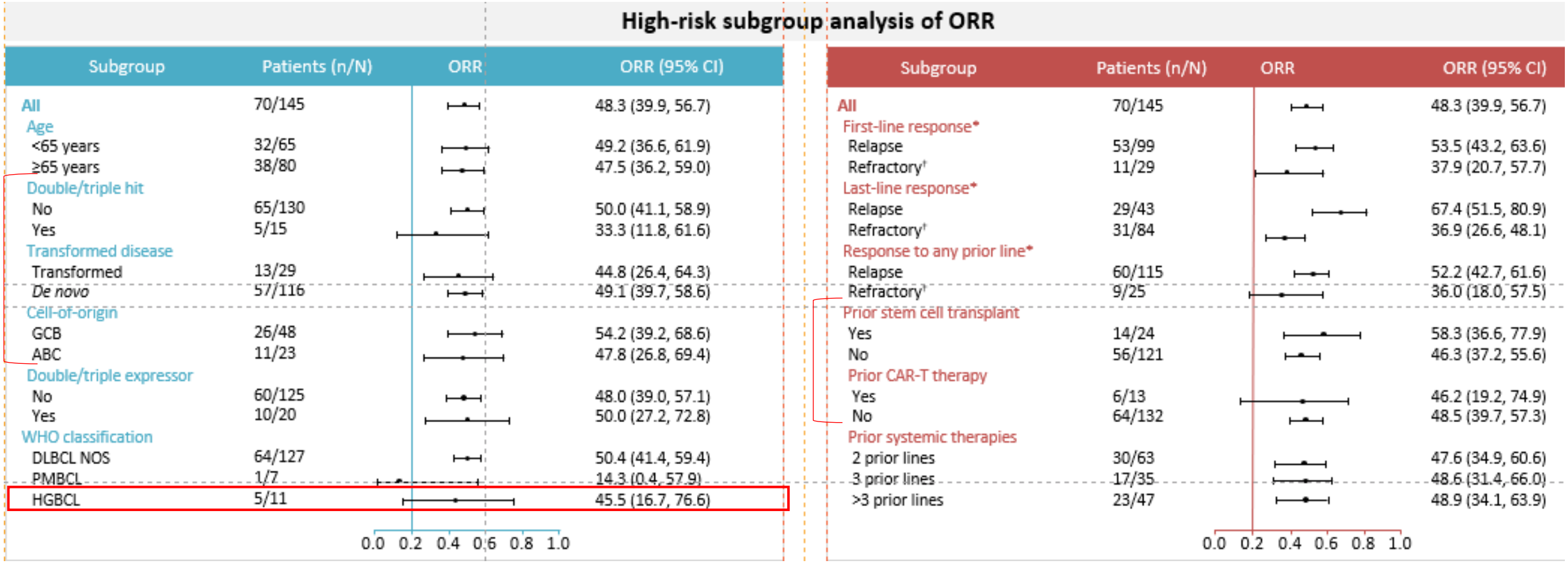
	APR 6 2020[1]	MAR 1 2021[2,a]
mDoR (n = 70), mo (95% CI)	**10.3** (6.9-NE)	**13.4** (NR)
mDoR for patients with CR, mo (95% CI)	**13.4** **n = 35** (10.3-NE)	**Not reached,** n = 36 (NR)

mDoR comparable to whole study population in subgroups at high risk of poor prognosis; follow up for DOR continuing.

NE, not estimable; NR, not reported. a. Median followup, 7.8 mo (0.3-31 mo). b. mDoR for patients with a PR: 5.7 mo (at both cutoffs).

1. Caimi PF, et al. *Lancet Oncol*. 11 May 2021. DOI: 10.1016/S1470-2045(21)00139-X.
2. Caimi PF, et al. ASCO 2021 Abst 7546.

LOTIS-2 Trial: Efficacy Results – ORR by Subgroup



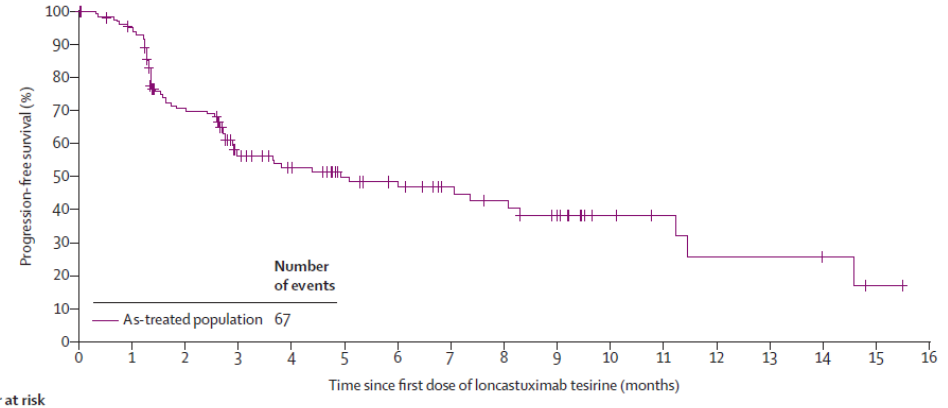
ORR was assessed by independent reviewer. *Prior systemic therapies. †Refractory disease defined as no response to therapy. Data cut-off: 06 Aug, 2020.

Caimi PF, et al. ASH 2020. Abstract 1183.

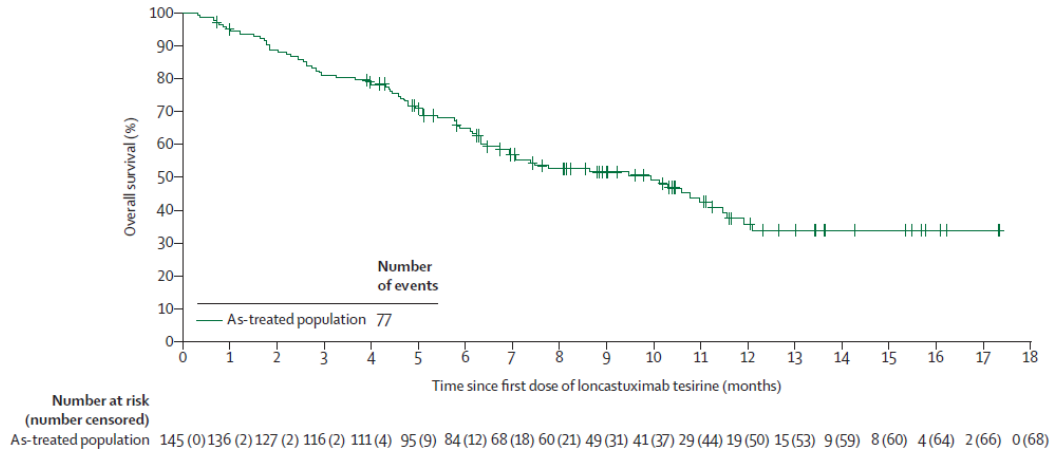
Caimi PF, et al. *Lancet Oncol*. 11 May 2021. DOI: 10.1016/S1470-2045(21)00139-X

LOTIS-2: PFS, OS, and Subsequent Treatment Results

Median PFS:
Apr 6 2020 Cut Off: 4.9 mo (95% CI, 2.9-8.3)[1]
Aug 6 2020 Cut Off: 5.1 mo (95% CI, 2.9-8.3)[2]



Median OS:
Apr 6 2020 Cut Off: 9.9 mo (95% CI, 6.7-11.5)[1]
Aug 6 2020 Cut Off: 9.5 mo (95% CI, 6.9-11.3)[2]

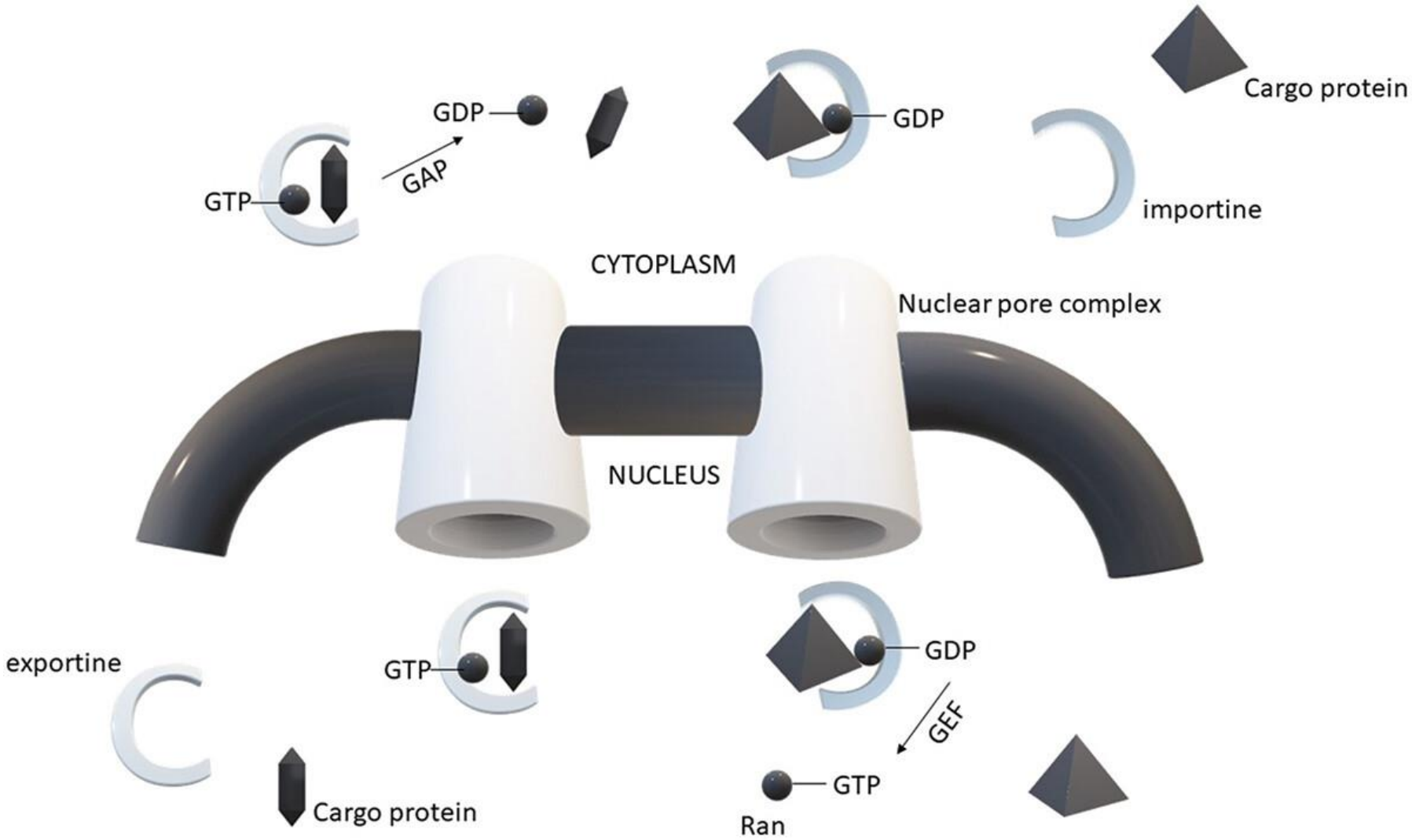


Subsequent Treatment[2]

- **15 patients** received CD19-directed CAR-T therapy with an investigator-assessed ORR of 46.7% (6 CR; 1 PR)
- **9 patients** proceeded to SCT as consolidation after response to lonca

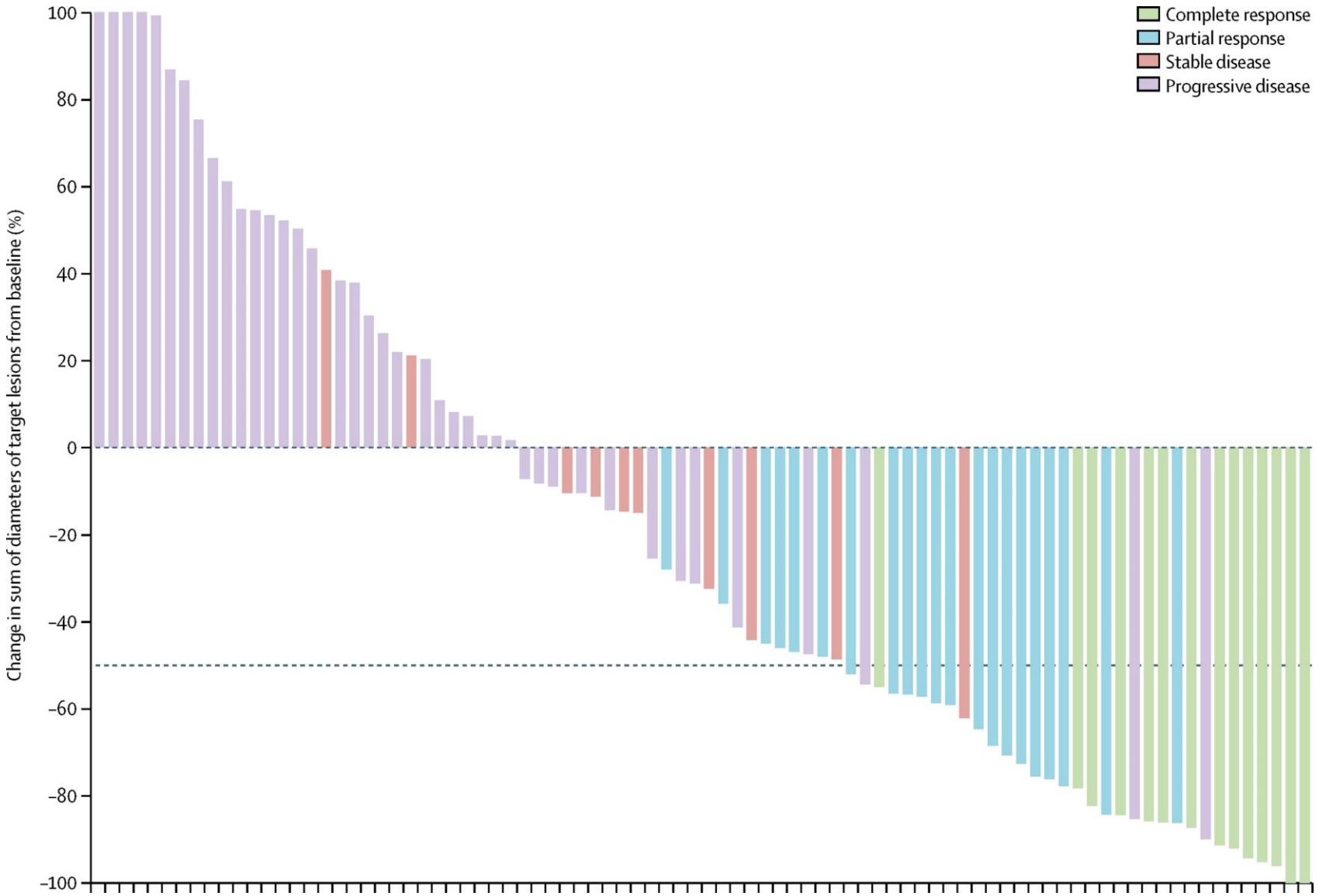
1. Caimi PF, et al. *Lancet Oncol*. 11 May 2021. DOI: 10.1016/S1470-2045(21)00139-X.
2. Caimi PF, et al. ASH 2020. Abstract 1183.

Transport of macromolecules between the nucleus and the cytoplasm



Sylvain et al. Expert Rev Hematol. 2022 Mar;15(3):195-201.

SADAL Trial: Overall response rate



267 patients

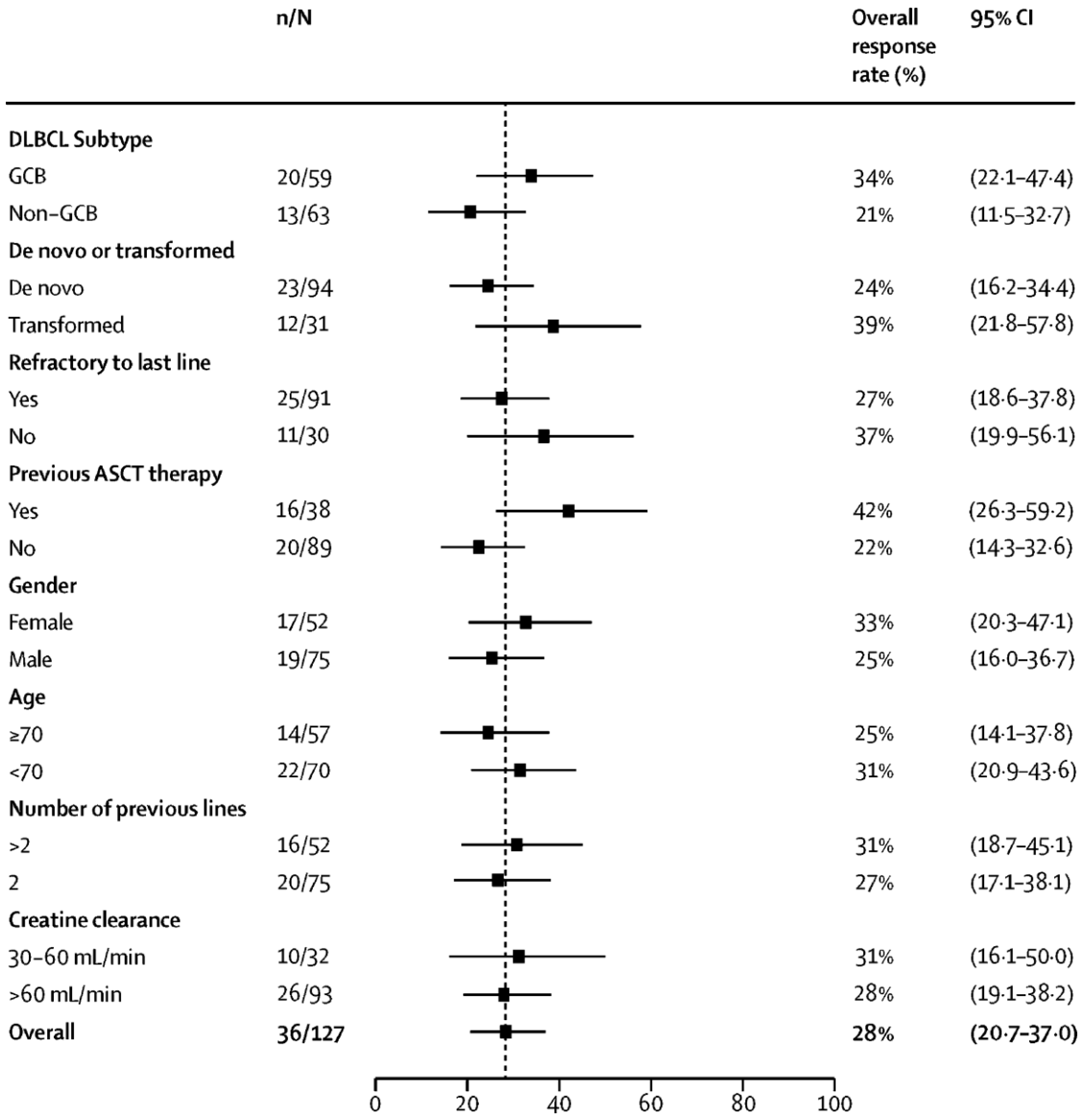
175 allocated to the 60 mg selinexor group and 92 to the 100 mg selinexor group.

Overall response rate was 28%

15 (12%) achieved a complete response and 21 (17%) a partial response.

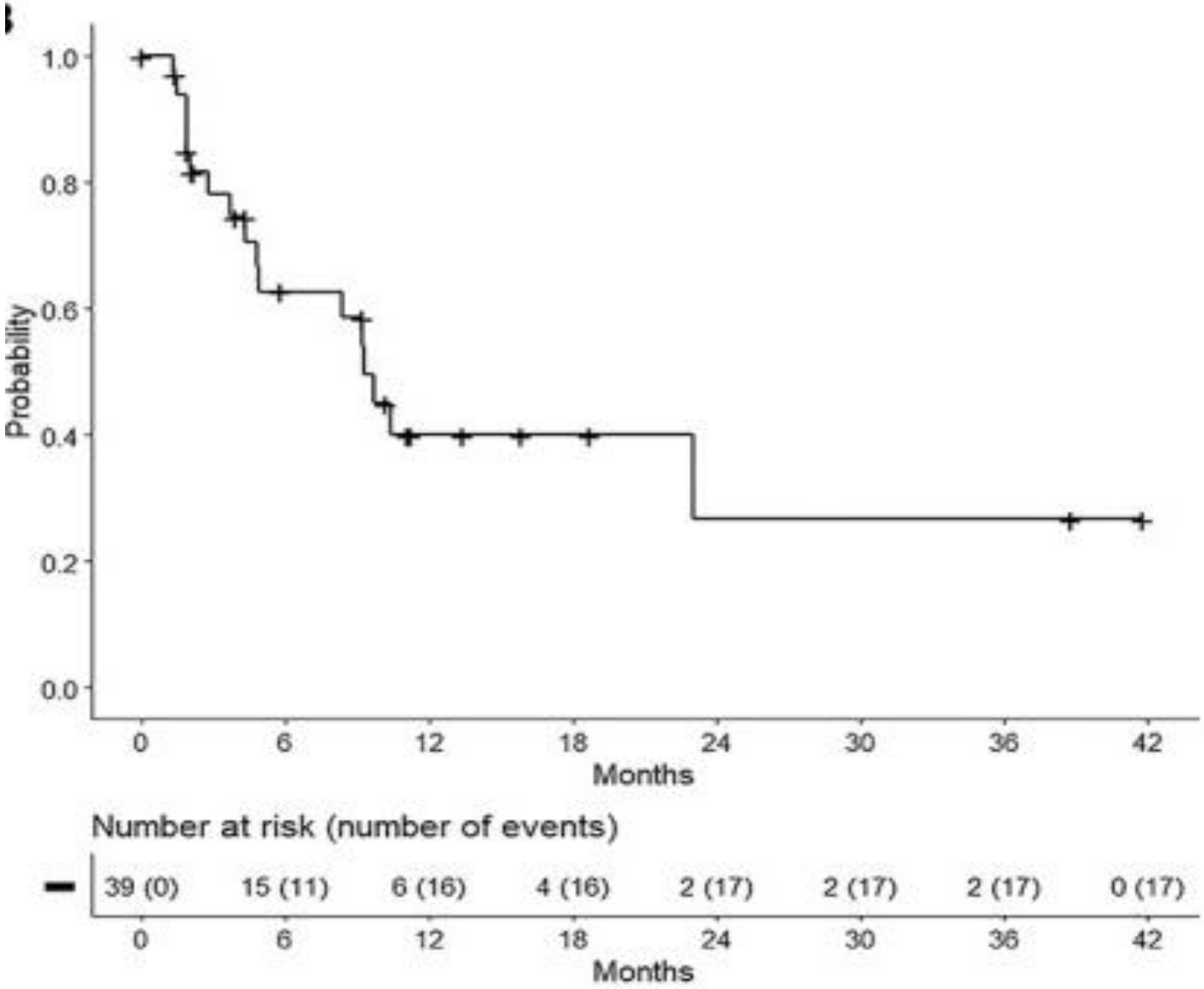
Kalakonda et al. Lancet Haematol. 2020 Jul;7(7):e511-e522.

SADAL Trial: Overall response rate



Kalakonda et al. Lancet Haematol. 2020 Jul;7(7):e511-e522.

Duration of response



Kasamon et al. Oncologist. 2021 Oct;26(10):879-886.

Diffuse large B-cell lymphoma – Conclusions

Relapsed/refractory patients

Effective approved combinations/agents include polatuzumab vedotin +BR, tafasitamab + lenalidomide and loncastuximab tesirine

Selinexor is also approved and effective

Bispecific antibodies and CAR T-cells are highly effective