Novel immunotherapies in Rel/Ref DLBCL

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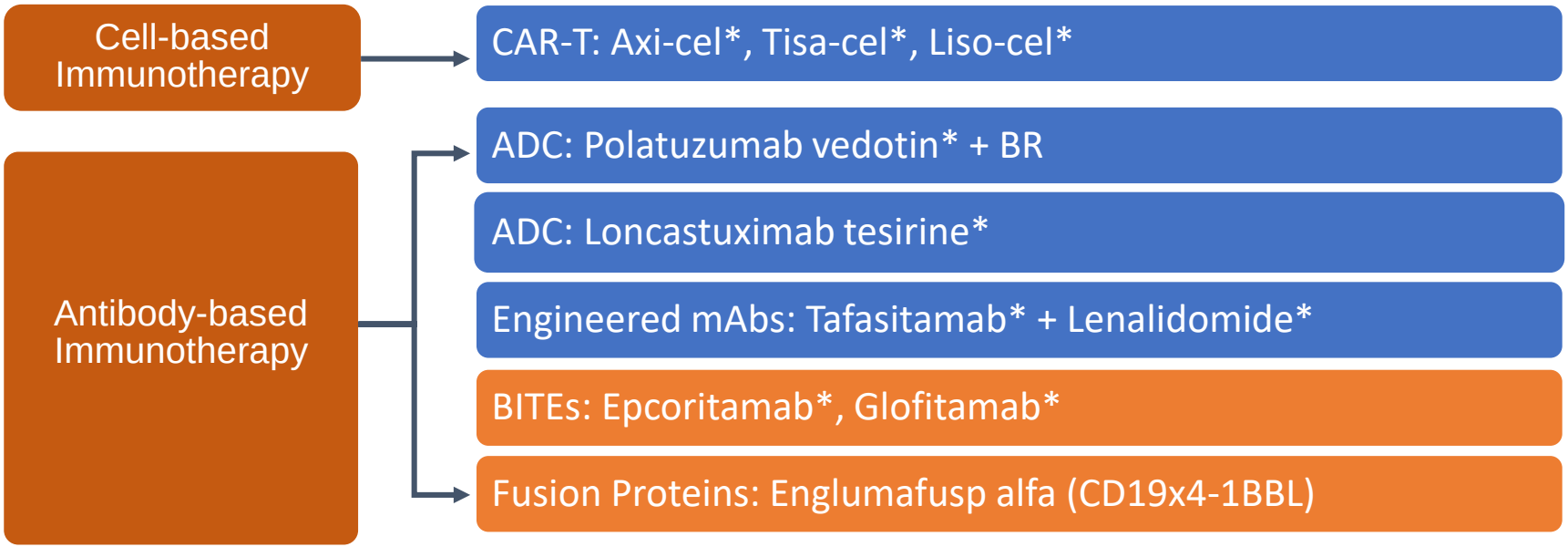
Unmet challenges in high-risk hematological malignancies: from benchside to clinical practice
Turin, September 21-22, 2023

Disclosures – Carmelo Carlo-Stella

- Advisory Board
  - Sanofi, ADC Therapeutics, Bristol-Myers Squibb/Celgene, Roche, Karyopharm, Novartis, Scenic Biotech, Janssen Oncology, SOBI, AbbVie
- Consultancy
  - Sanofi, ADC Therapeutics
- Honoraria
  - Janssen Oncology, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Takeda, Roche, Incyte, ADC Therapeutics, Gilead
- Research Support
  - Sanofi, ADC Therapeutics, Roche

Immunotherapy Treatments for r/r DLBCL



* FDA and/or EMA approved

CART-cell Therapy Pivotal Ph 2 Trials

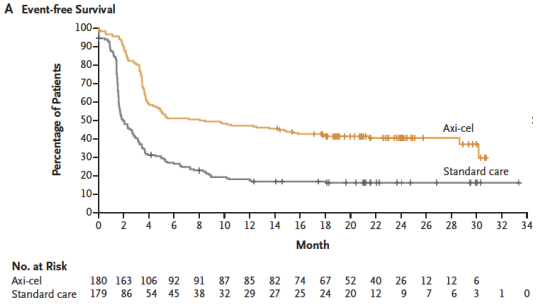
All 3 CAR T-cell products demonstrated capacity to induce durable remissions in approximately one-third of treated patients (including patients who had not had a durable remission with a prior ASCT) and have been US Food and Drug Administration approved for patients with R/R LBCL after at least 2 lines of therapy

	Axi-cel	Tisa-cel	Liso-cel
Pivotal trial	ZUMA-1	Juliet	Transform
Most mature follow up (m)	63.1	40.3	24
Median duration of response (m)	11.1	NE	23.1
ORR/CR (%)	83/58	52/39	73/53
Median PFS (m)	5.9	2.9	6.8
PFS, 24 m (%)	36	33*	40.6
Median OS (m)	25.8	11.1	27.3
OS, 24 m (%)	50.5	40*	50.5
CRS: Any/Gr3+ (%)	93/13	57/23	42/2
Neuro tox: Any/Gr3+ (%)	64/28	20/11	30/10

Westin, Blood, 139:2737, 2022

Randomized Ph 3 Trials CART-cells vs ASCT

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

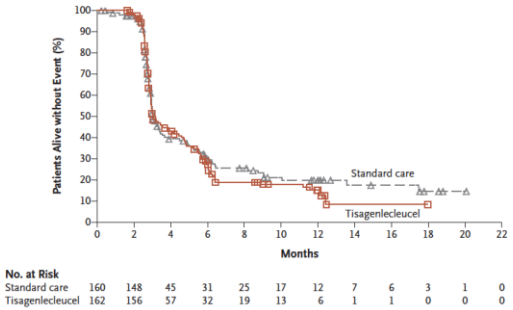


	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

F.L. Locke, NEJM, 386:640, 2022

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

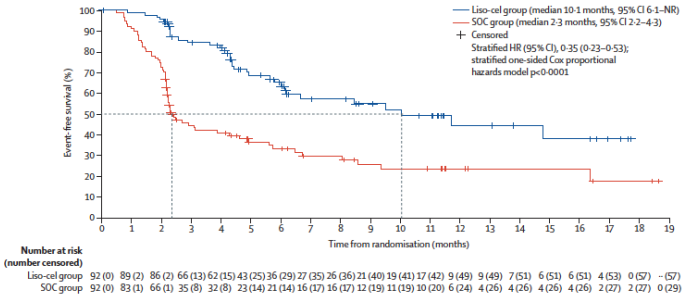


	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

M.R. Bishop, NEJM, 386:629, 2022

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial



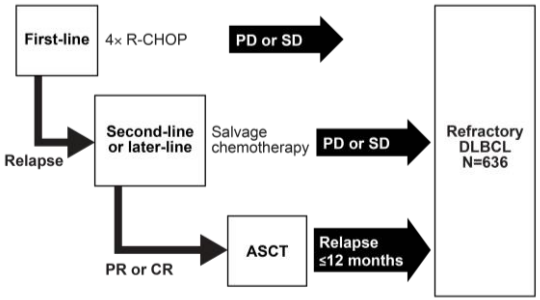
Kamdar, Lancet, 399:2294, 2022

Outcome of Randomized Ph 3 Trials
CART-cells vs ASCT

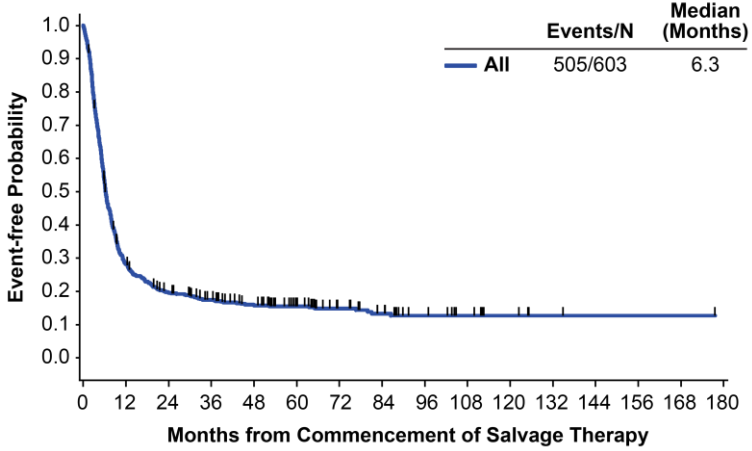
	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
Received bridging corticosteroids (%)	36	—	—	—	—	—
Received bridging chemotherapy (%)	0	—	83	—	63	—
Received >1 SOC chemotherapy regimen (%)	—	0	—	54	—	0
Received intended CAR T cell (%)	94	—	96	—	97.8	—
Median time to CAR T-cell infusion in days, (interquartile range* or range†)	29 (27-34)*	—	52 (31-135)†	—	NR	—
Received intended ASCT (%)	—	36	—	32.5	—	45.6
Crossover pn protocol (%)	—	—	—	51	—	51
Received cellular therapy off protocol (%)	—	56	—	—		—
Follow up, median in months	24.9		10		6.2	
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
PFS, median in months	14.7	3.7	NR	NR	14.8	5.7
PFS HR (95% CI)	0.49 (0.37-0.65)		NR		0.406 (0.21-0.66)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

Sehn & Westin, Blood, 139:2737, 2022

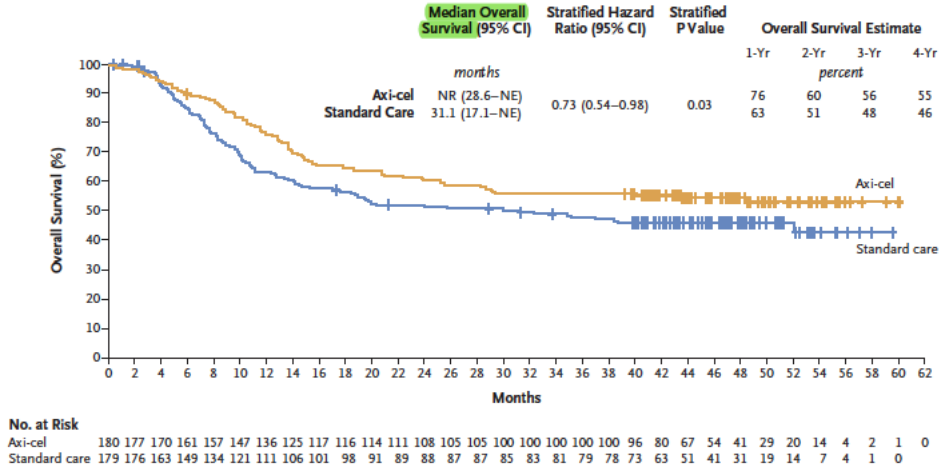
Outcome of r/r DLBCL - Scholar-1

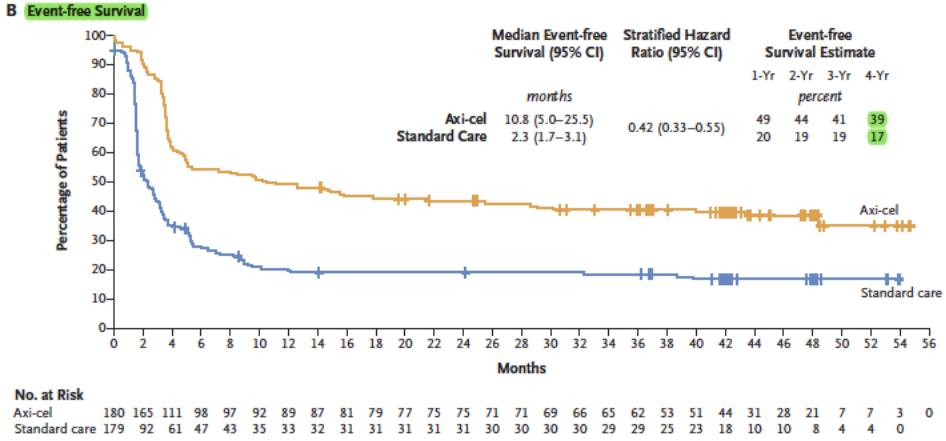


- ORR to NLT: 26% (CR 7%)
- Median OS: 6.3 months
- Only 20% of patients alive at 2 years



Crump, Blood 130:1800, 2017

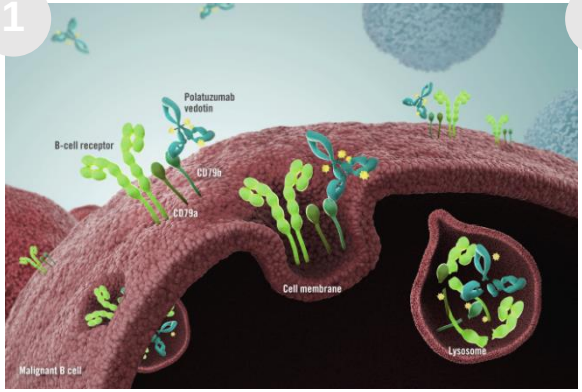




Westin, NEJM, 2022

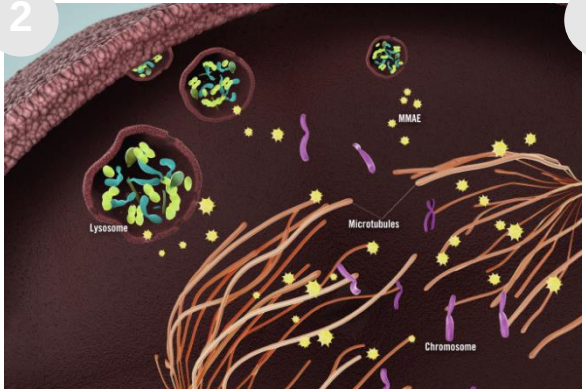
Polatuzumab Vedotin Mechanism of Action

1



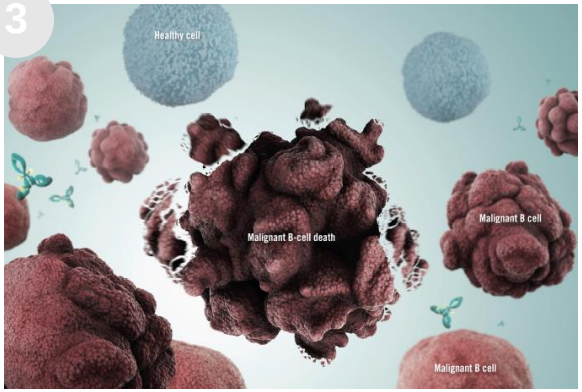
Pola binds to cell surface antigen CD79b, a component of the B-cell receptor, which is expressed only on B-cells and in most NHLs[1-3]

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]

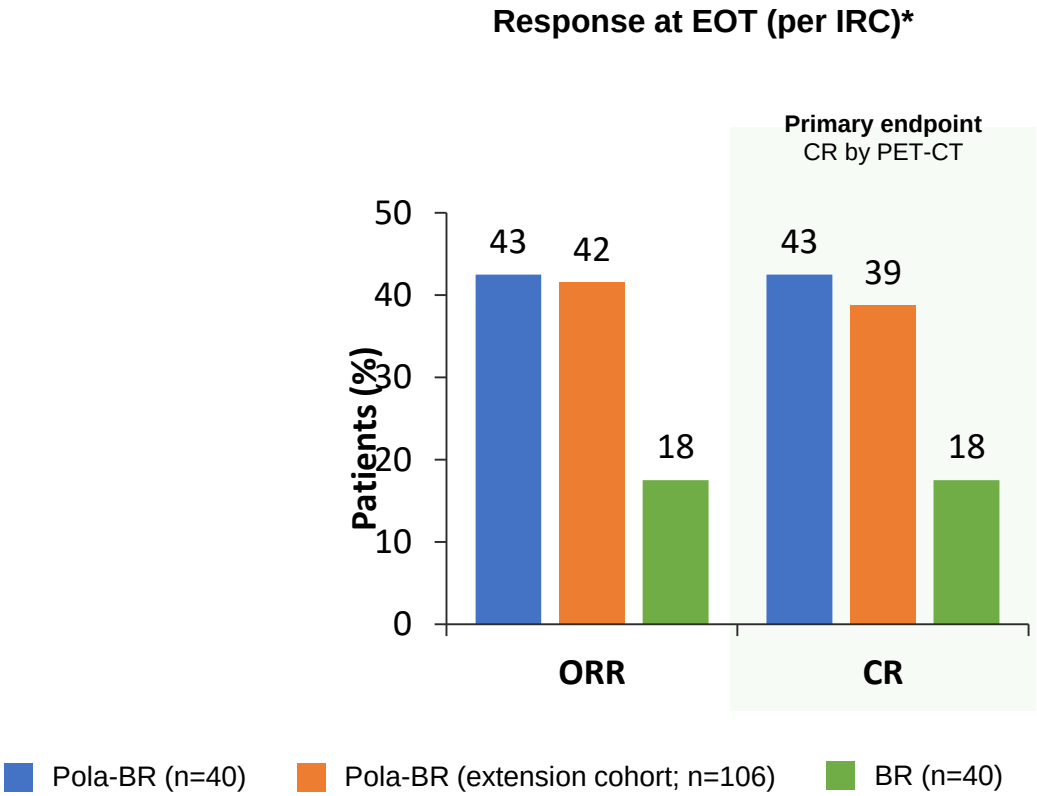
Sehn LH, et al. Blood Adv 2022;6(2):533–543.

Pola + BR: Baseline characteristics

	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)

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

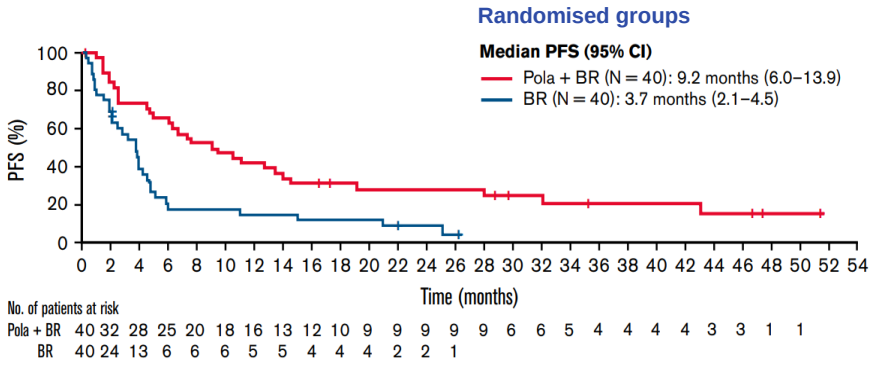
Pola + BR: Efficacy

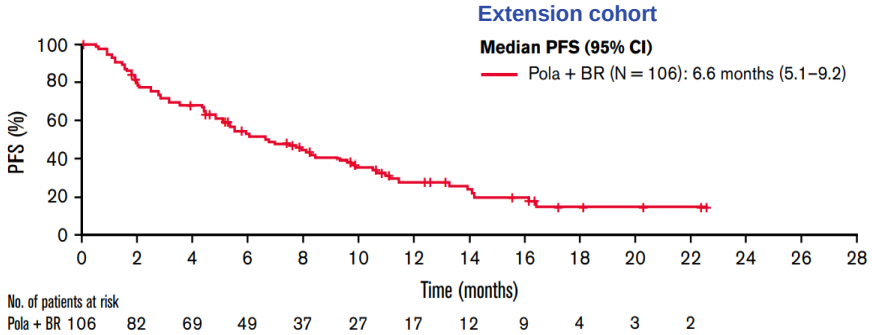


Sehn LH, et al. Blood Adv 2022;6(2):533–543.

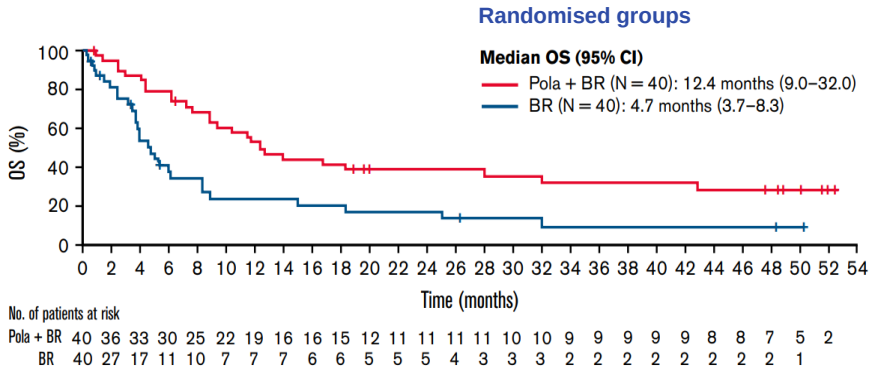
GO29365: Efficacy

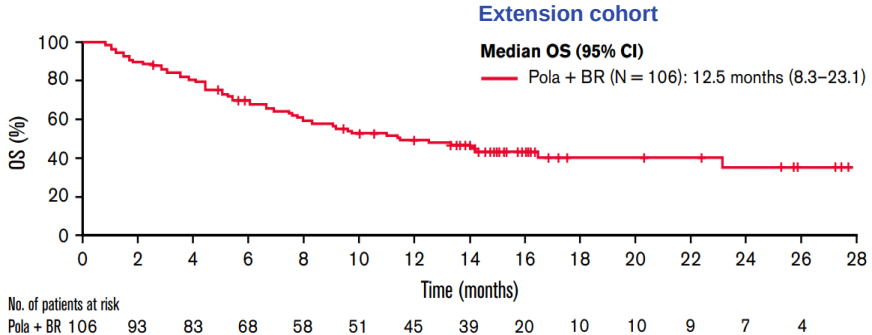
Progression-free Survival





Overall Survival





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.

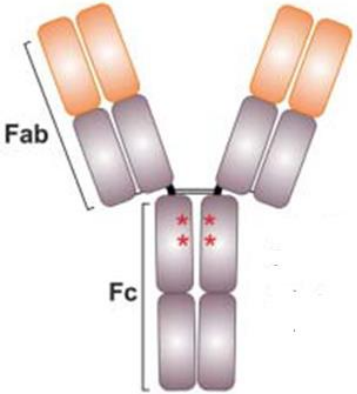
Polatuzumab-(B)R

- Bridging therapy
- Combo with Glofitamab

Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma

Johannes Duell,[1] Kami J. Maddocks,[2] Eva González-Barca,[3] Wojciech Jurczak,[4] Anna Marina Liberati,[5] Sven de Vos,[6] Zsolt Nagy,[7] Aleš Obr,[8] Gianluca Gaidano,[9] Pau Abrisqueta,[10] Nagesh Kalakonda,[11] Marc André,[12] Martin Dreyling,[13] Tobias Menne,[14] Olivier Tournilhac,[15] Marinela Augustin,[16] Andreas Rosenwald,[17] Maren Dirnberger-Hertweck,[18] Johannes Weirather,[18] Sumeet Ambarkhane[18] and Gilles Salles[19*]

Duell, Haematologica, 106:2417, 2021



- Fc engineered to increase its affinity for FcγR to increase ADCC and ADCP

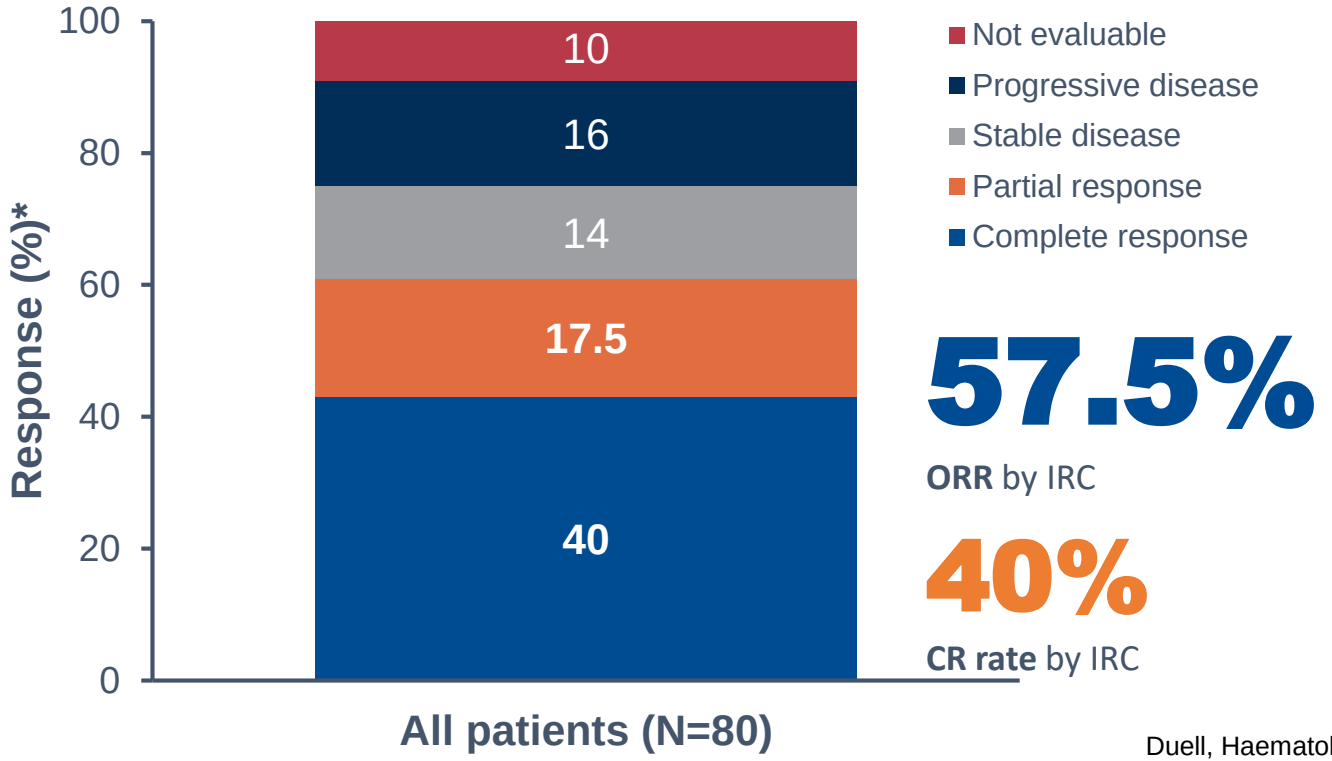
Baseline Characteristics

Characteristic n (%), unless otherwise stated	Total (N=81*)
Sex	
Male	44 (54)
Female	37 (46)
Age, years: median (range)	72 (62–76)
ECOG PS	
0	29 (36)
1	45 (56)
2	7 (9)
IPI score at screening	
0–2 (low and low–intermediate risk)	40 (49)
3–5 (intermediate–high and high risk)	41 (51)
Cell of origin by IHC	
GCB	38 (47)
Non-GCB	21 (26)
Unknown	22 (27)

Characteristic n (%), unless otherwise stated	Total (N=81*)
Primary refractory	
Yes	15 (19)
No	66 (81)
Refractory to most recent prior therapy	
Yes	36 (44)
No	45 (56)
Prior lines of systemic therapy	
Median (range)	2 (1–4)
1	40 (50)
2	35 (43)
3	5 (6)
4	1 (1)
Prior anti-CD20 therapy	
Yes	81 (100)
No	0
Prior AHCT	
Yes	9 (11)
No	72 (89)

Duell, Haematologica, 106:2417, 2021

Tafa/Lena ORR



57.5%

ORR by IRC

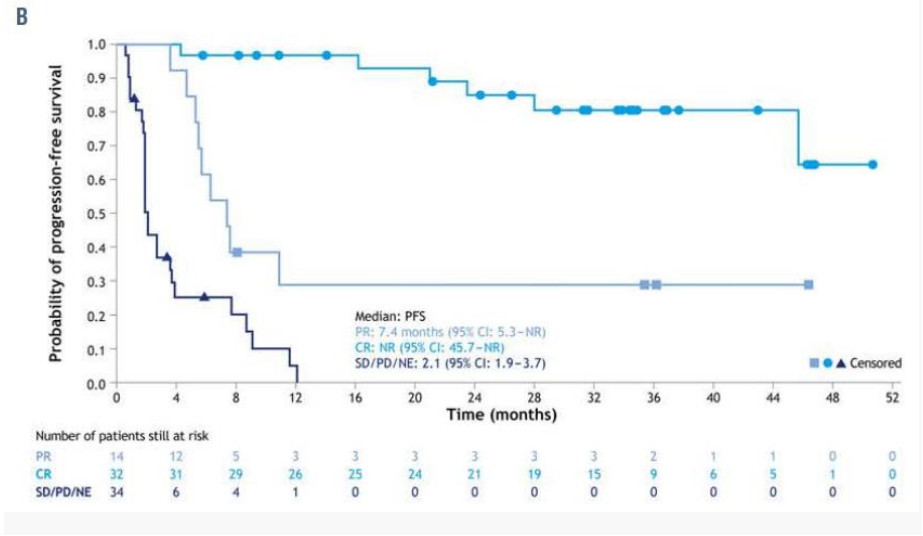
40%

CR rate by IRC

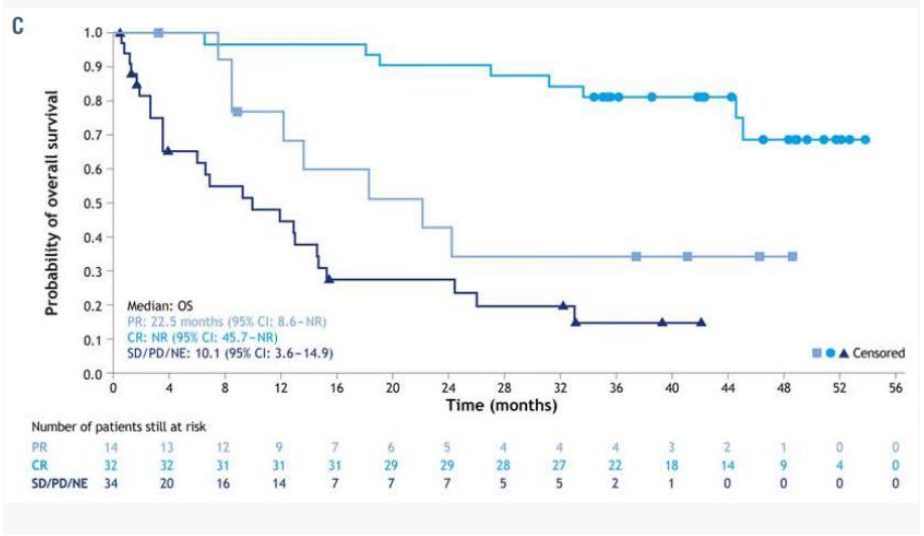
Duell, Haematologica, 106:2417, 2021

PFS and OS

Median PFS: 11.6 months



Median OS: 33.5



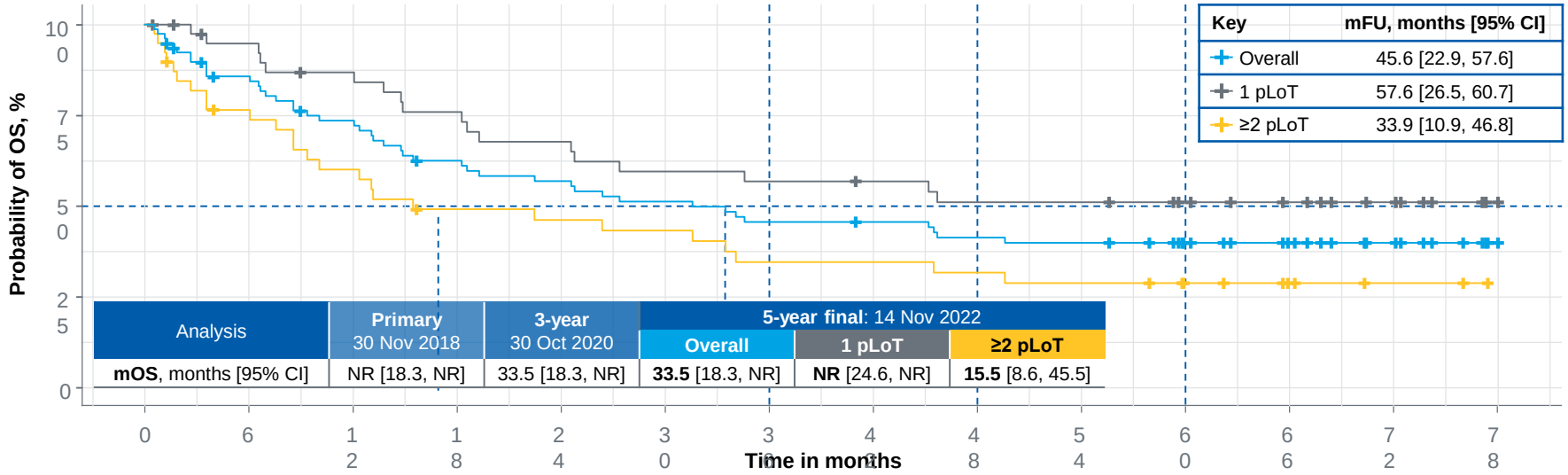
mDOR

43.9 mos among the 46 **responders**

NR, among patients **achieving a CR**

Duell, Haematologica, 106:2417, 2021

Efficacy Results: OS at 5-year Follow-up



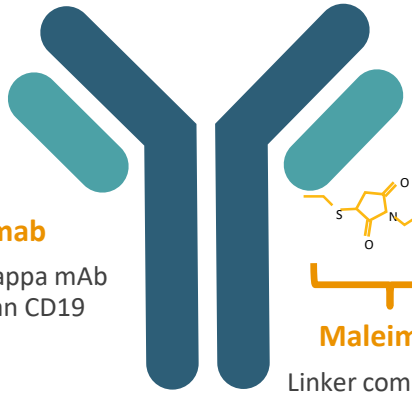
Number at

Overall	80	64	54	45	41	37	33	32	29	28	21	15	9	1
1 pLoT	40	36	32	28	25	22	21	20	18	18	14	11	7	1
≥2 pLoT	40	28	22	17	16	15	12	12	11	10	7	4	2	0

mFU, median follow-up; mOS, median OS; NR, not reached; OS, overall survival; pLoT, prior line of therapy.

Duell J, et al. AACR 2023. Abstract 9810.

Molecular Structure of Lonca[1,2]



Loncastuximab

Humanised IgG1 kappa mAb specific for human CD19

8-polyethylene glycol

Valine-alanine dipeptide

Para-amino-benzoic acid

Self-immolative group

Maleimide

Linker component

SG3199

PBD dimer cytotoxin

Tesirine/SG3249

PBD linker comprising the PBD dimer SG3199 and all linker components

CD19-specific IgG1

Caimi et al. *Lancet Oncol* 2021

Baseline Characteristics[1-3]

Patient characteristics* (N=145)	
Sex, n (%)	
Female	60 (41)
Male	85 (59)
Age, years, median (min, max)	66.0 (23, 94)
Histology, n (%)	
DLBCL NOS	127 (88)
HGBL	11 (8)
PMBCL	7 (5)
Double/triple hit DLBCL†, n (%)	15 (10)
Double/triple expressor DLBCL, n (%)	20 (14)
Transformed DLBCL, n (%)	29 (20)
Disease stage‡, n (%)	
I–II	33 (23)
III–IV	112 (77)
ECOG performance status[4], n (%)	
0	58 (40)
1	78 (54)
2	9 (6)

Patient treatment history (N=145)	
No. of previous systemic therapies§, median (range)	3 (2–7)
First-line systemic therapy response, n (%)	
Relapse	99 (68)
Refractory‖	29 (20)
Other¶	17 (12)
Last-line systemic therapy response,# n (%)	
Relapse	43 (30)
Refractory‖	84 (58)
Other¶	18 (12)
Refractory to all prior therapies,‖ n (%)	
Yes	25 (17)
No	115 (79)
Other¶	5 (3)
Prior stem cell transplant, n (%)	
Allogeneic	2 (1)
Autologous	21 (14)
Both	1 (1)
Prior CAR T-cell therapy, n (%)	
Yes	13 (9)
No	132 (91)

* Data cut-off: March 1, 2021. † Some patients had a diagnosis of double-hit or triple-hit lymphoma based on institutional pathology before the WHO classification of HGBCL with *MYC* and *BCL2* or *BCL6* rearrangements, or with *MYC* and *BCL2* and *BCL6* rearrangements. ‡ Disease stage at study entry. § Prior SCT is included. For patients who received an autologous transplant, the mobilisation regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. ‖ Refractory disease defined as no response to therapy. ¶ Other defined as unknown, not evaluable or missing. # If SCT is most recent line, the variable is defined as response to the therapy immediately preceding SCT.

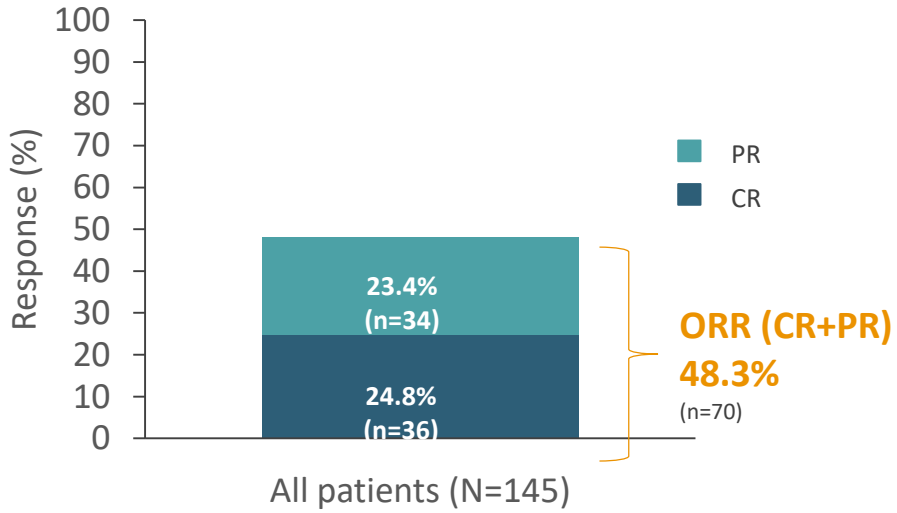
CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplant; WHO, World Health Organization.

1. Zinzani et al. ICML 2021 **2.** Caimi et al. *Lancet Oncol* 2021 **3.** Caimi et al. ASCO 2021 **4.** Data on file.

Caimi et al. *Lancet Oncol* 2021

Efficacy: ORR data[1]

Follow-up analysis



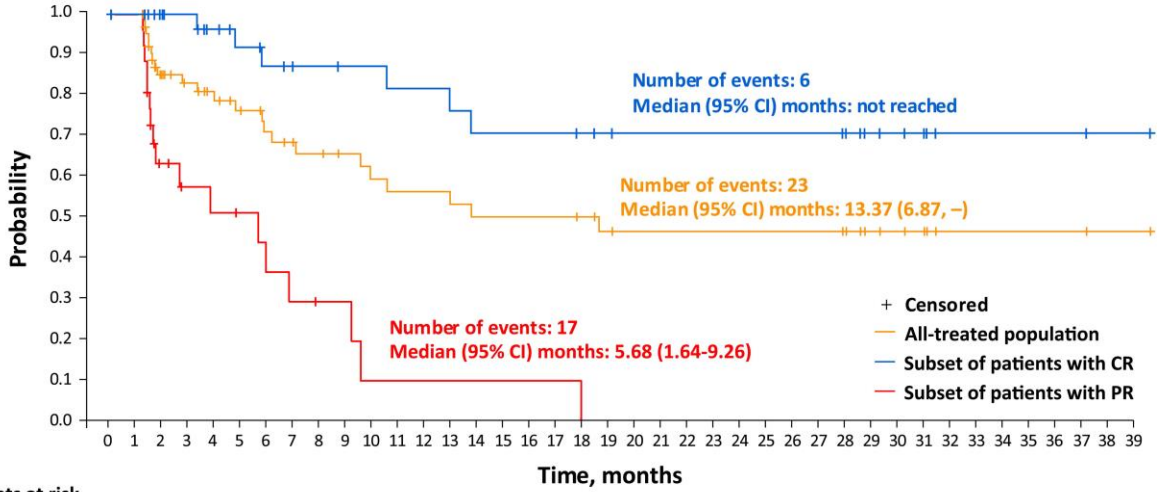
- **ORR** by central review was 70/145 **48.3%** (95% CI:[2] 39.9–56.7)
- CR rate 24.8% (95% CI:[2] 18.0–32.7)
- PR rate 23.4% (95% CI:[2] 16.8–31.2)

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)

Response was assessed by central independent review. Data cut-off: March 1, 2021. Updated results ≥17 months since patients received their first dose.
CR, complete response; Lonca, loncastuximab tesirine; ORR, overall response rate; PR, partial response; SD, stable disease.
1. Zinzani et al. ICML 2021 **2.** Data on file.

Duration of response by best overall response



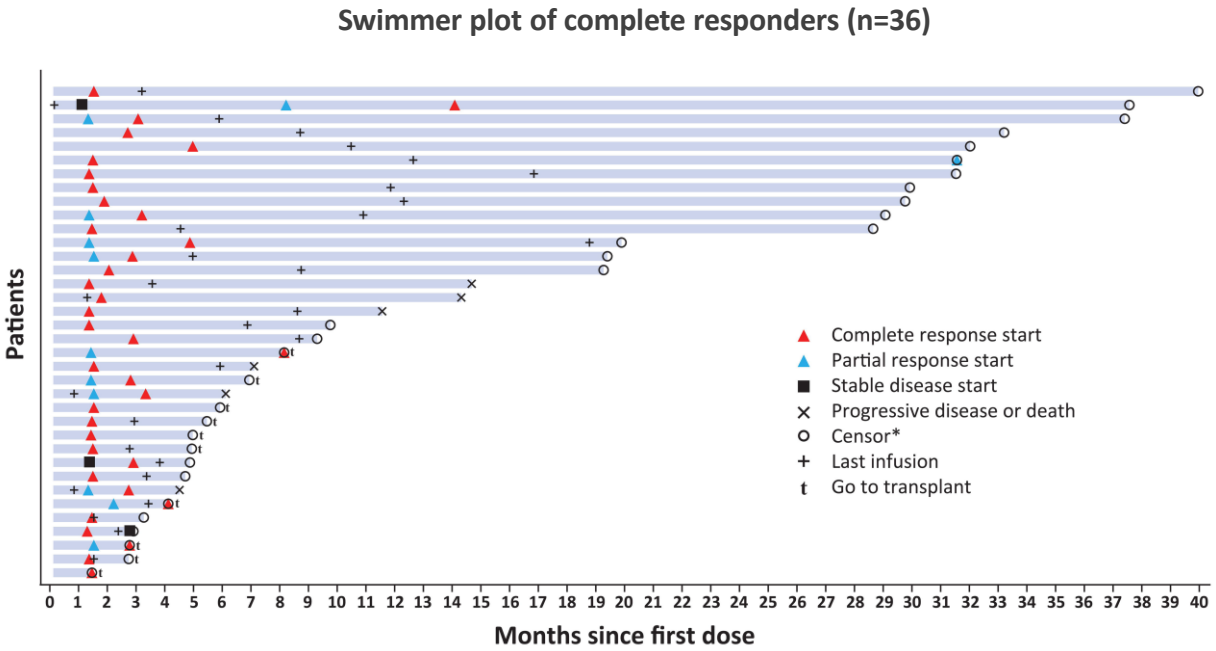
mDOR for patients with a **CR**
Not reached

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

Follow-up of complete responders[1]



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

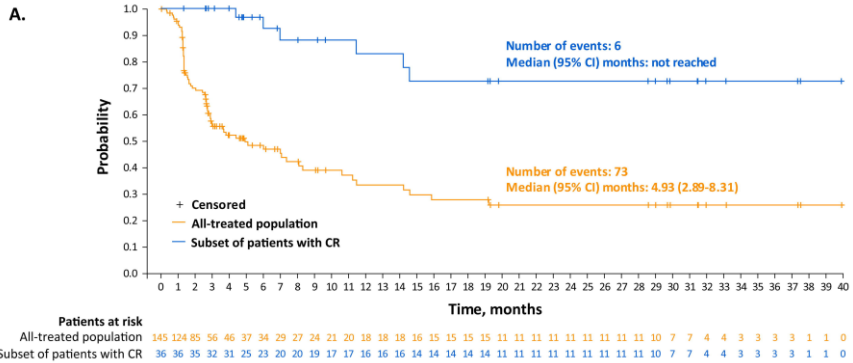
36.1% (13/36) were censored; of them, 10 patients were censored due to transplant while in CR

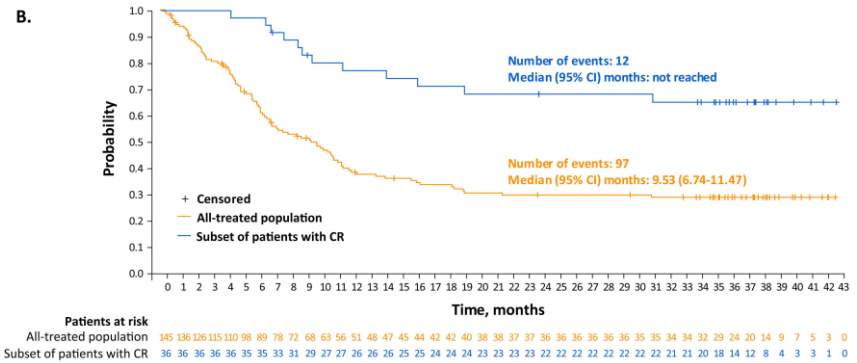
19.4% (7/36) patients had PD or death

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

Caimi et al. *Haematologica* 2023

PFS and OS





mPFS was 4.9 months

mOS was 9.5 months

Caimi et al. *Haematologica* 2023

Loncastuximab-Tesirine

- Bridging therapy to Allo-SCT
- Combo with BITEs
- Elderly patients