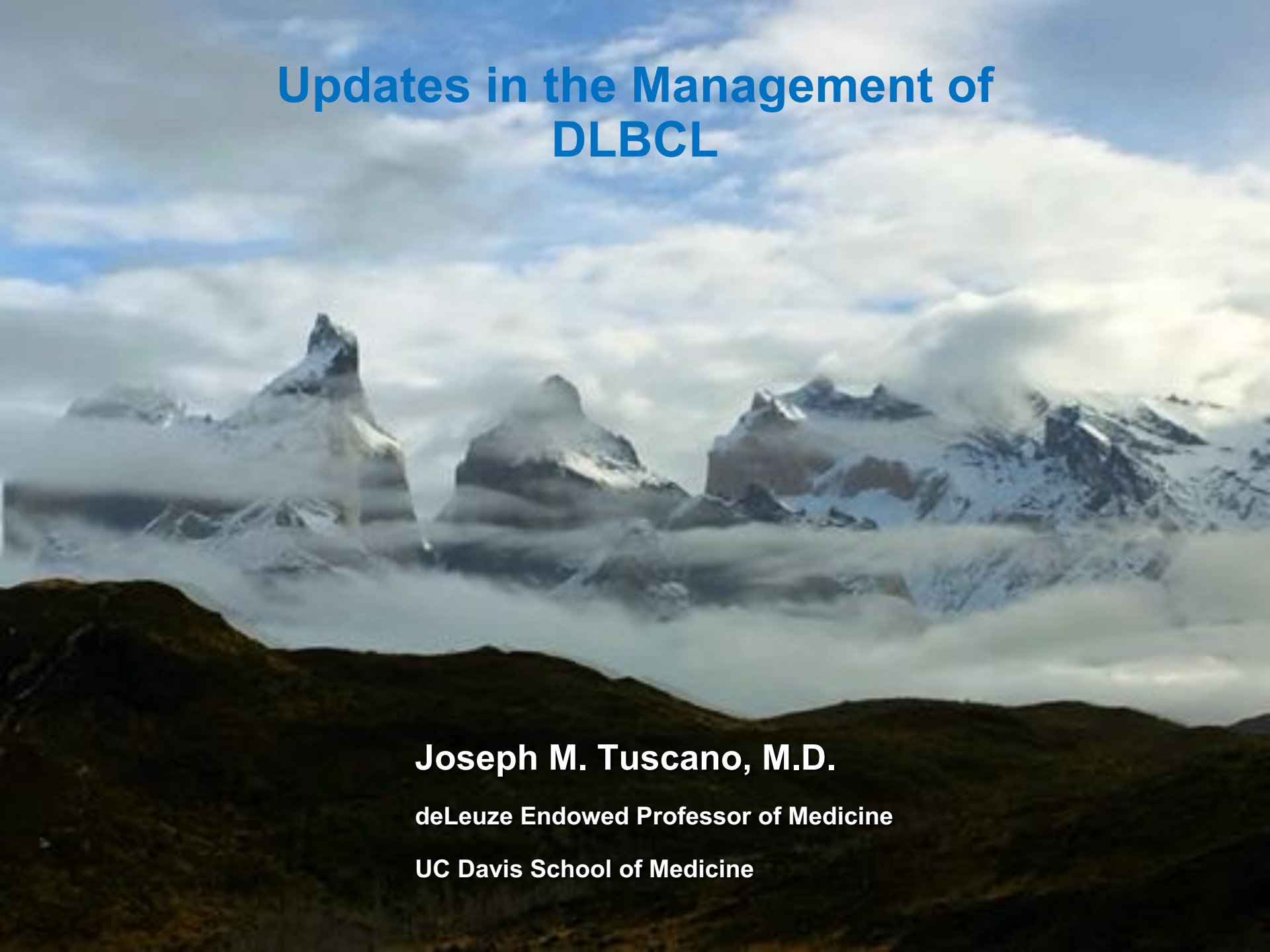
Updates in the Management of DLBCL

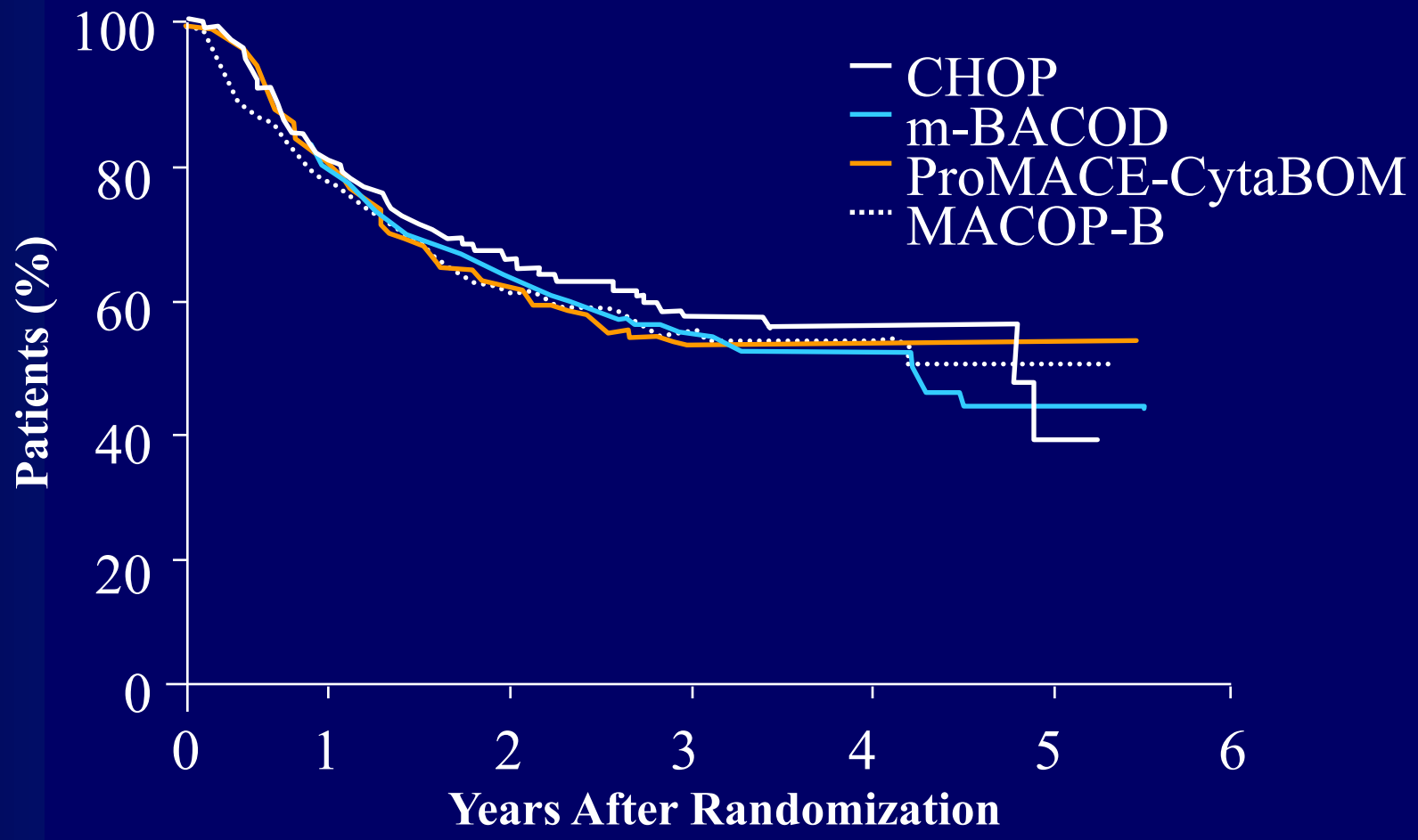


Joseph M. Tuscano, M.D.

deLeuze Endowed Professor of Medicine

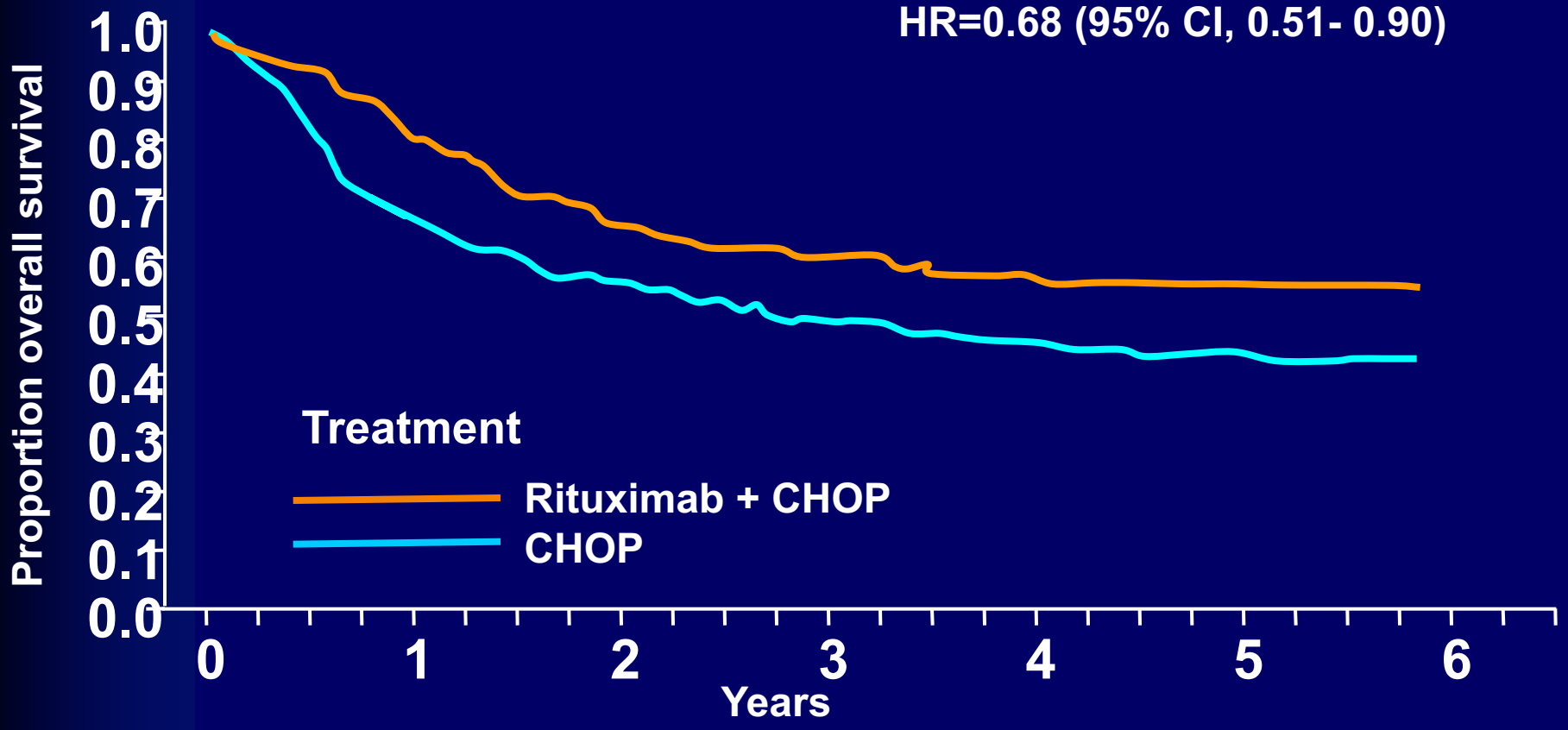
UC Davis School of Medicine

National High Priority Lymphoma Study: Progression-Free Survival



Adapted from Fisher. *N Engl J Med.* 1993;328:1002.

LNH 98-5 Trial: Overall Survival
Median 5-Year Follow-up



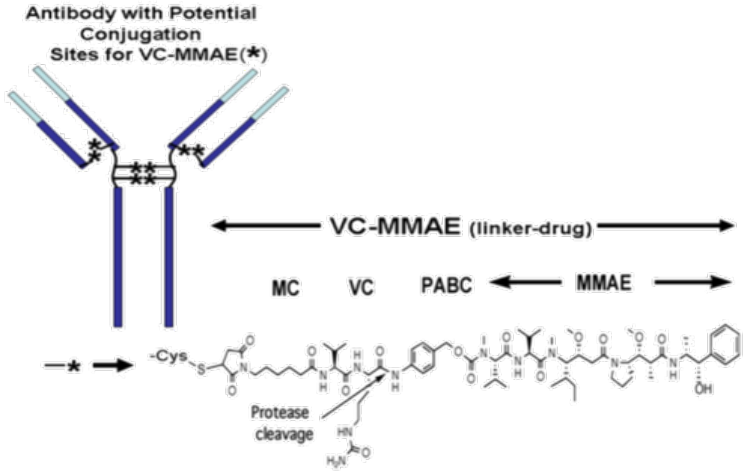
Coiffier et al. *N Engl J Med*. 2002;346:235.

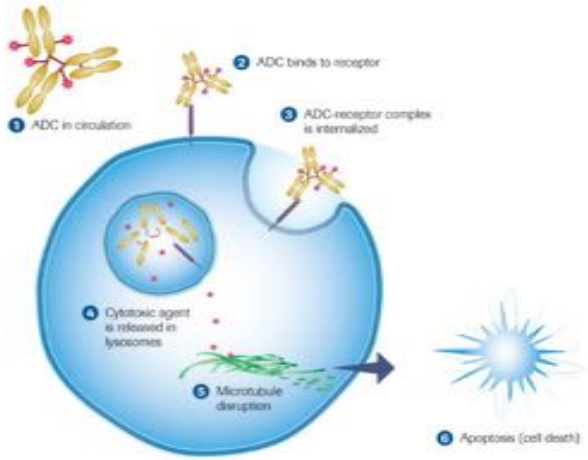
CHOP/R-CHOP has been the SOC for 20-30 years

Can we do better?

Polatuzumab vedotin

- Polatuzumab vedotin (pola) is an antibody drug conjugate (ADC) consisting of a potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker





- Pola has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2]

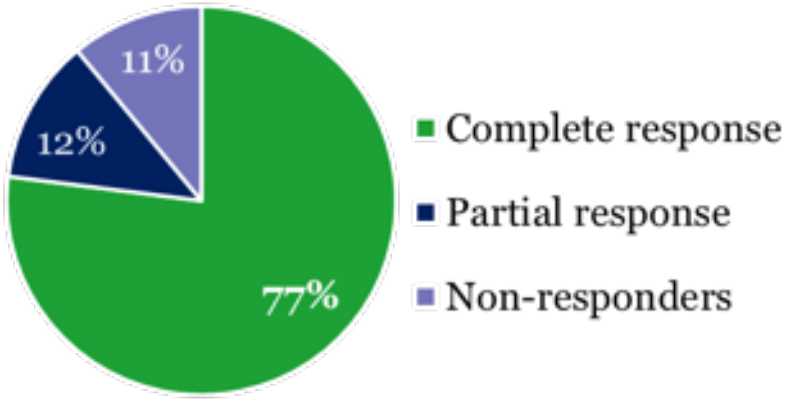
Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]

1. Palanca-Wessels A, et al. Lancet Oncol, 2015;16:704–15
2. Morschhauser F, et al. Lancet Hematology, 2019;6:e254 –65

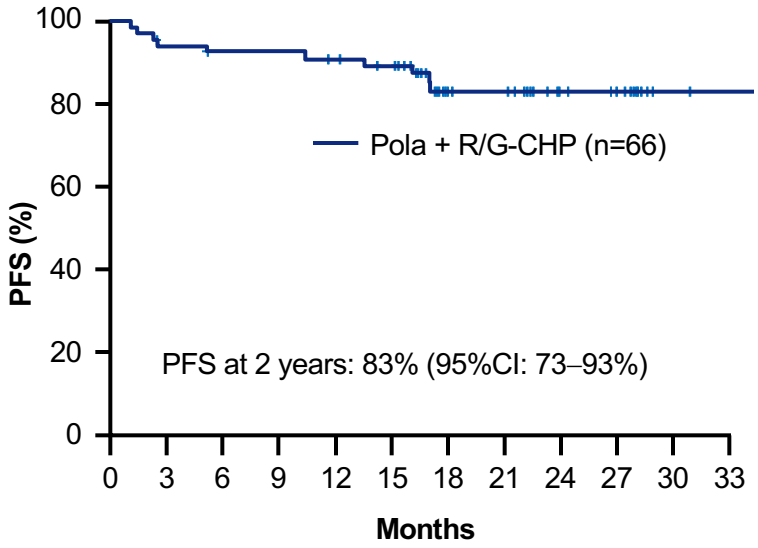
In frontline: Pola-R-CHP in a phase 1b/2 trial

1. The safety and tolerability of pola-R-CHP is similar to that of R-CHOP

2. Tumour responses to pola-R-CHP assessed by PET



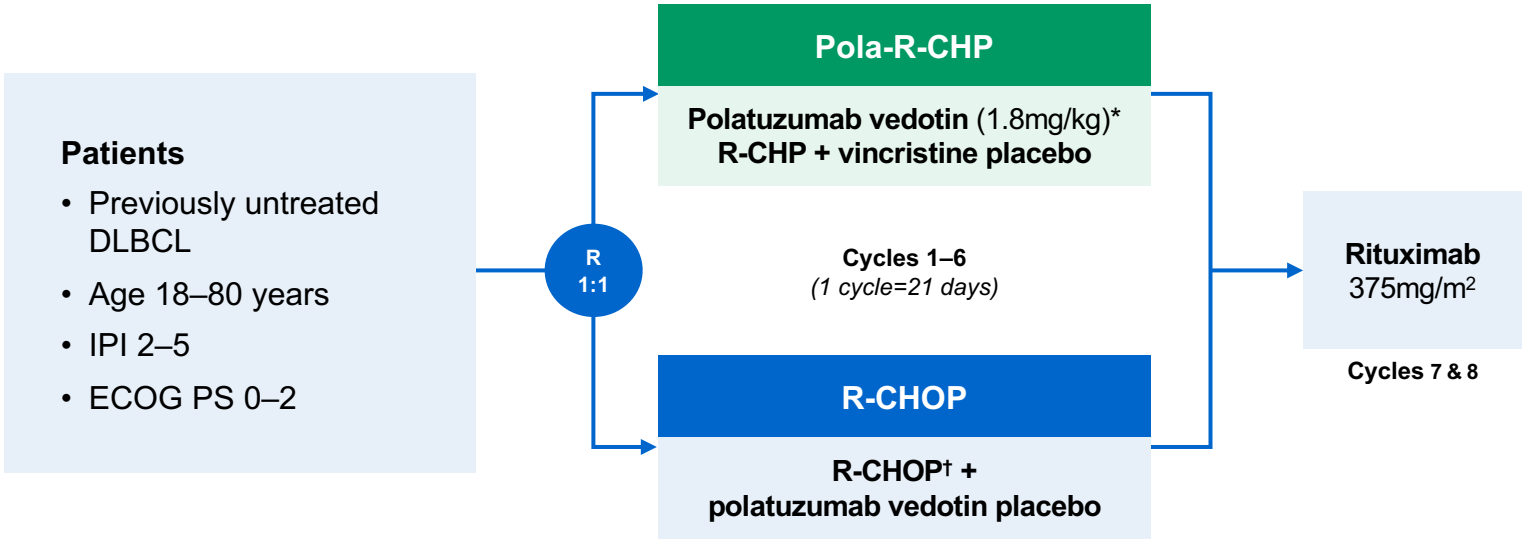
3. PFS in patients with 1L DLBCL receiving pola + R/G-CHP



G, obinutuzumab; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Tilly H, et al. Lancet Oncol 2019; [Epub ahead of print]

Phase 3 POLARIX Study: Polatuzumab Vedotin + R-CHP Versus R-CHOP for Newly Diagnosed DLBCL—Study Design



Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

- Primary endpoint: PFS (INV)
- Secondary endpoints: EFS, CR at EOT, DFS, OS, safety

Median follow up, 28.2 mo; data cut off: 28 JUN 2021.

Tilly H, et al. *N Engl J Med*. 14 Dec 2021. Tilly H, et al. ASH 2021 LBA1.

POLARIX: Baseline Characteristics

Characteristic	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Median age, yr (range)	65 (19-80)	66.0 (19-80)
Male, n (%)	239 (54)	234 (53)
ECOG PS 0/1, n (%)	374 (85)	363 (83)
Bulky disease (≥7.5 cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Median time from diagnosis to treatment initiation, days	26	27
Ann Arbor stage III/IV, n (%)	393 (89)	387 (88)
Extranodal sites (≥2), n (%)	213 (48)	213 (49)

Characteristic, n (%)	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
IPI score		
▪ 2	167 (38)	167 (38)
▪ 3-5	273 (62)	272 (62)
Cell of origin		
▪ ABC	102 (31)	119 (35)
▪ GCB	184 (56)	168 (50)
▪ Unclassified	44 (13)	51 (15)
MYC/BCL2 expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement	26 (8)	19 (6)

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP Response

Best ORR, %	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
CR	86.6	82.7
PR	9.3	11.4

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

Table 1. **Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).***

Characteristic	Pola-R-CHP (N = 440)	R-CHOP (N = 439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)
ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

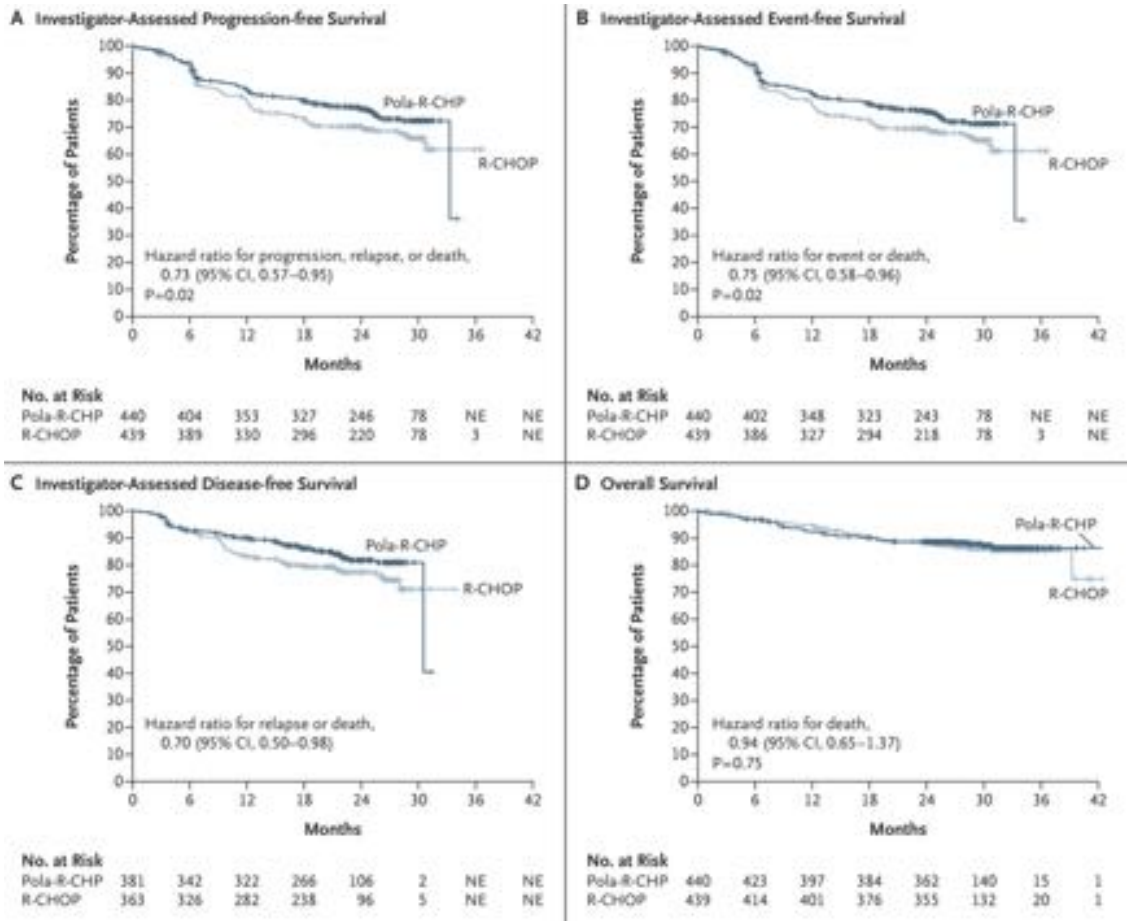


Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP Subsequent Therapy Not Specified in the Protocol

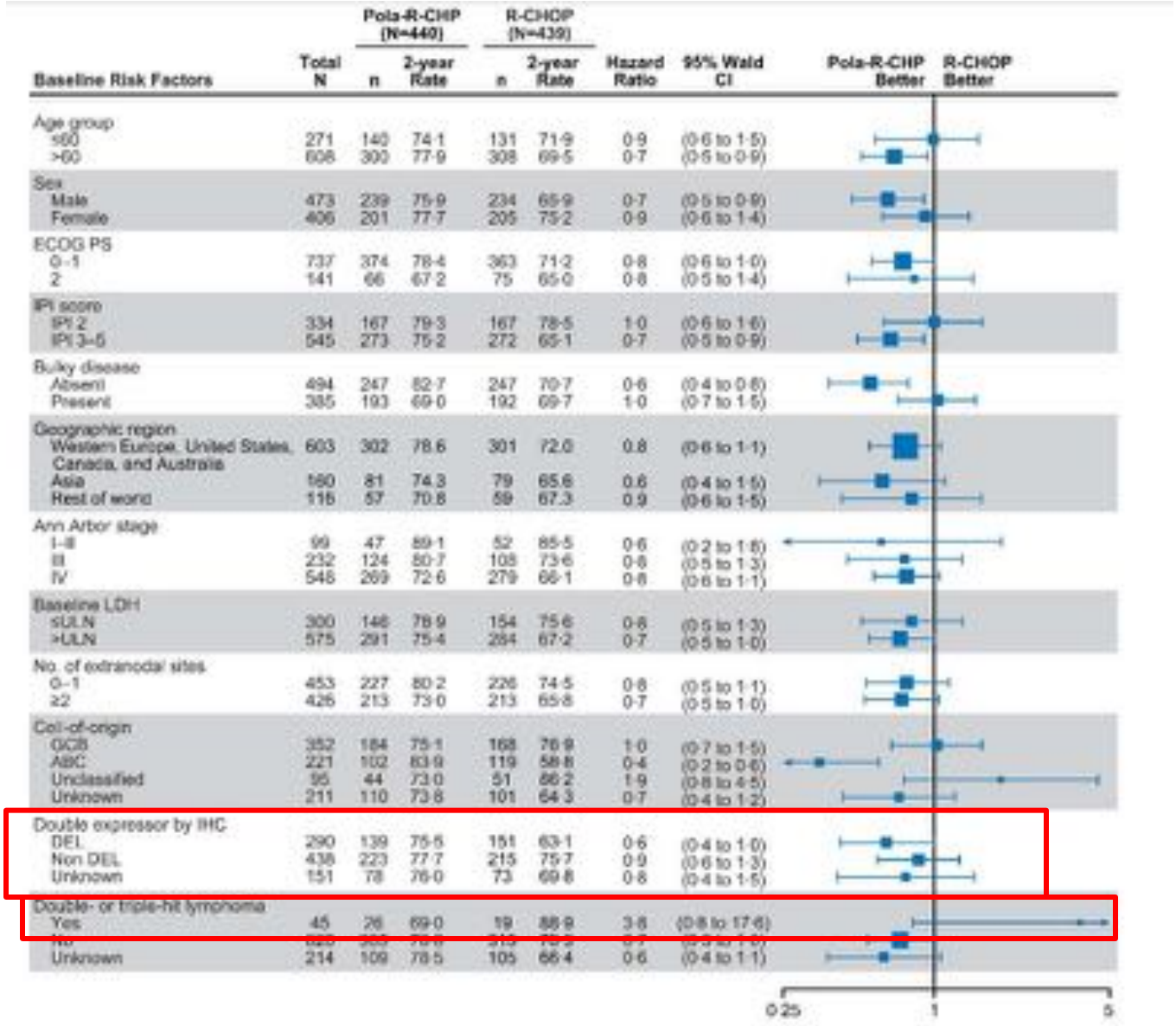
Subsequent Therapy at Data Cutoff, %	Polatuzumab Vedotin + R-CHP (n = 99)	R-CHOP (n = 133)
Radiotherapy	9.3	13.0
Systemic therapy	17.0	23.5
SCT	3.9	7.1
CAR T-cell	2.0	3.6

- At data cutoff, 99 of 440 patients (22.5%) in the polatuzumab vedotin arm and 133 of 439 patients (30.3%) in the R-CHOP arm had received ≥1 subsequent course of therapy not specified in the trial protocol
- Unblinding was permitted for individual patients after disease progression, with 8 patients in the R-CHOP arm receiving polatuzumab vedotin as part of subsequent therapy

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

Phase 3 POLARIX Study: PFS (INV) by Subgroup

Exploratory Analysis



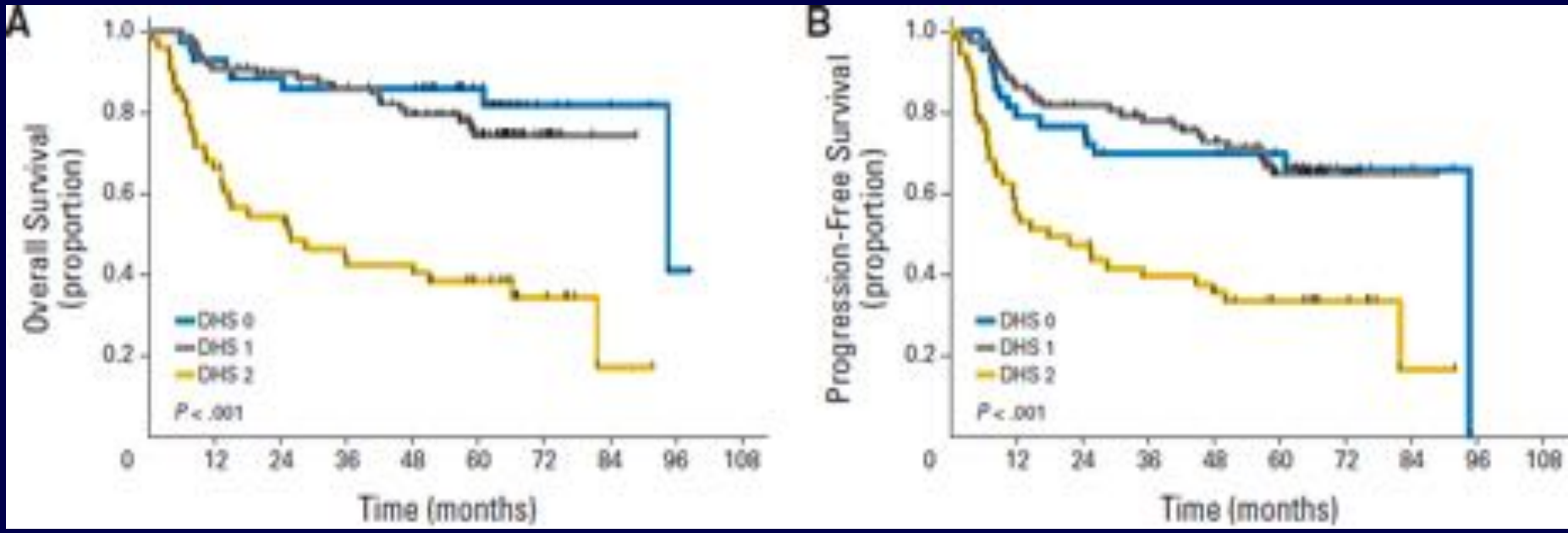
	Pola-R-CHP		R-CHOP		Univariate PFS HR (95% CI)
	Prevalence (%)	2-year PFS (%)	Prevalence (%)	2-year PFS (%)	
BCL2 IHC	N=359		N=365		
BCL2+	56	75	55	63	0.65 (0.46–0.92)
BCL2–	44	79	45	80	0.97 (0.60–1.56)
MYC IHC	N=366		N=368		
MYC+	64	78	70	69	0.68 (0.48–0.96)
MYC–	36	75	30	74	0.92 (0.57–1.51)
BCL2-R	N=332		N=334		
Yes	28	77	23	76	0.90 (0.51–1.59)
No	72	76	77	70	0.78 (0.55–1.09)
MYC-R	N=331		N=336		
Yes	12	77	10	71	0.86 (0.36–2.08)
No	88	76	90	71	0.78 (0.57–1.06)
BCL6-R*	N=38		N=34		
Yes	26	70	29	100	Not evaluable
No	74	79	71	58	0.46 (0.17–1.26)

*BCL6-R only tested in patients with *MYC*-R; N=patients with central lab results

- DEL vs non-DEL in the R-CHOP arm (UVA HR 1.53, 95% CI 1.06–2.21; MVA HR 1.29, 95% CI 0.88–1.91)
- No prognostic difference between DEL and non-DEL in the Pola-R-CHP arm
- BCL2+ associated with inferior PFS vs BCL2– in the R-CHOP arm (UVA HR 1.96, 95% CI 1.31–2.93; MVA HR 1.74, 95% CI 1.14–2.66)
- No prognostic difference between BCL2+ and BCL2- in the Pola-R-CHP arm
- No prognostic impact of MYC+ vs MYC– was detected in either arm

Morschhauser et al, EHA 2022

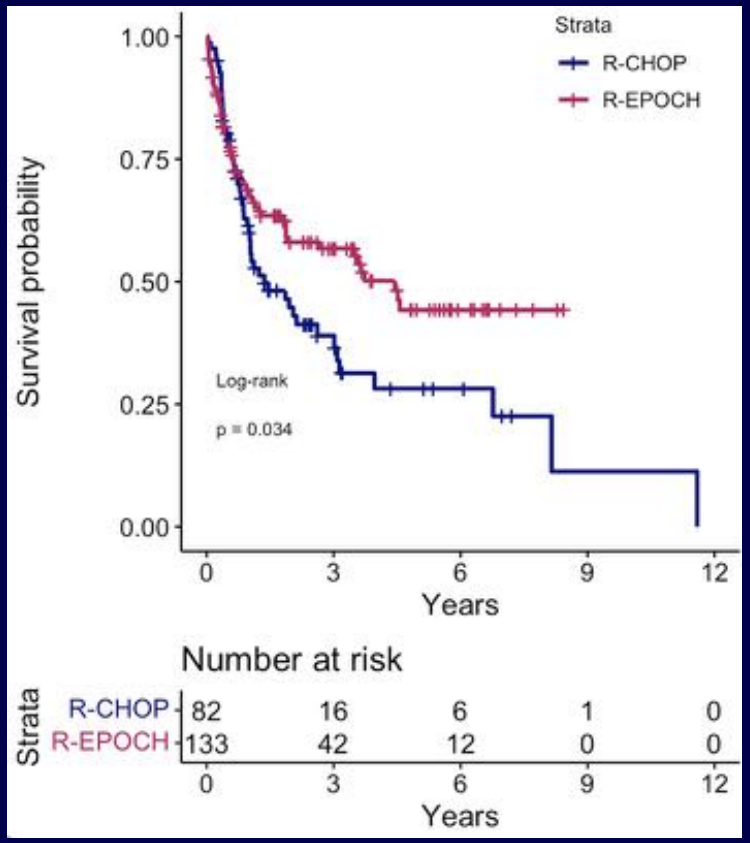
Double Expression - Prognosis



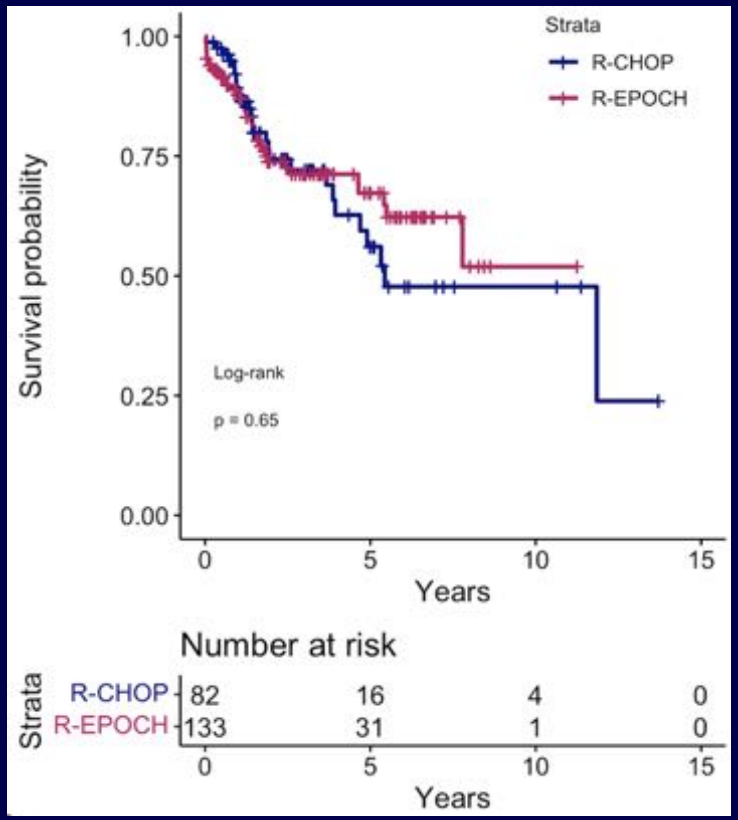
Green et al. J Clin Oncol 2012

R-DA-EPOCH for DEL

PFS



OS



Othman T et al Clin Myel and Leuk 2022

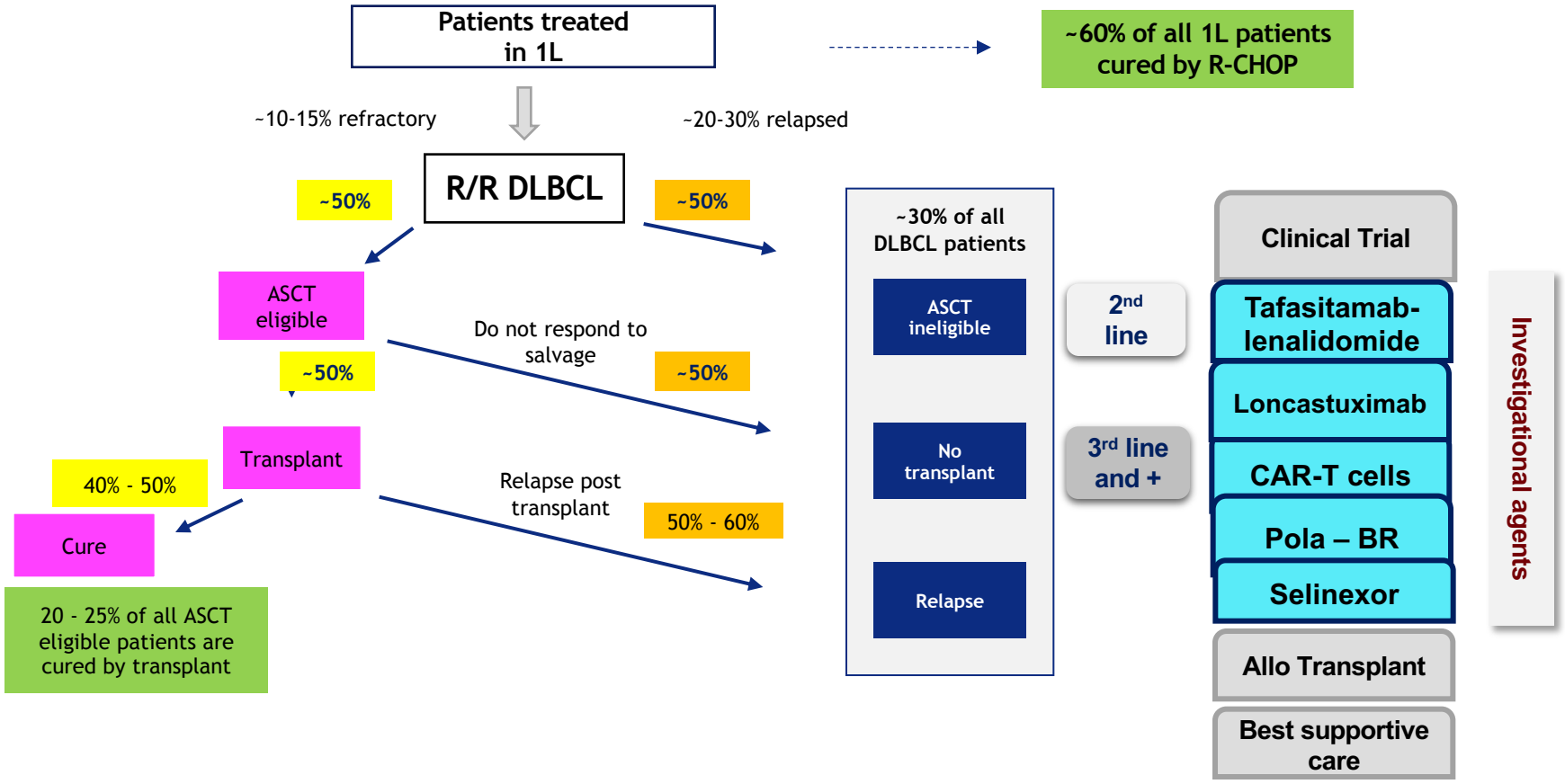
POLARIX: Conclusions

- In patients with intermediate-risk or high-risk untreated DLBCL, polatuzumab vedotin + R-CHP significantly increased PFS vs R-CHOP
  - HR: 0.73 (95% CI: 0.57-0.95; *P* <.02)
- Frequency of AEs similar between treatment arms
- Exploratory analyses of various subgroups and other prognostic classification systems are ongoing
- Investigators conclude these data support use of polatuzumab vedotin + R-CHP in patients with untreated DLBCL and may represent a new SOC for previously untreated DLBCL ?

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

Relapsed/Refractory DLBCL

Relapsed and refractory DLBCL



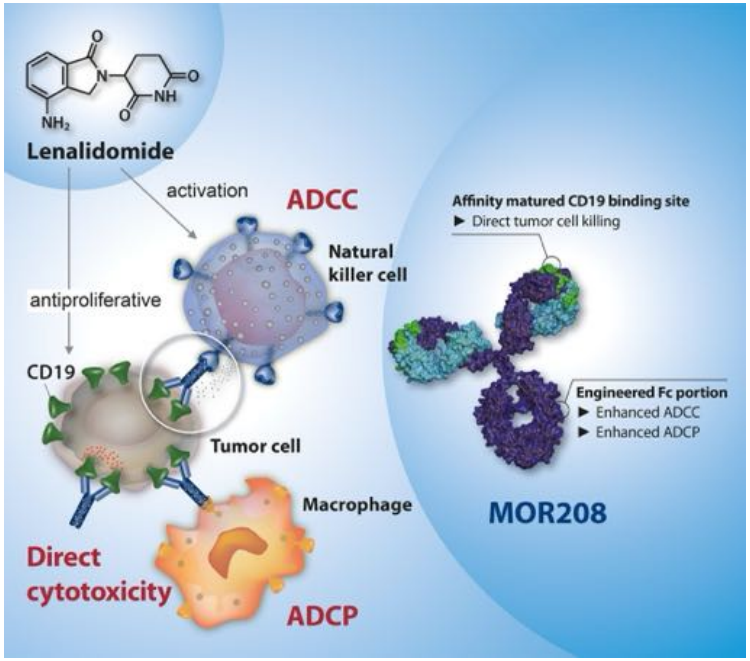
Tafasitamab (MOR208) and Lenalidomide: A Novel Immunological Combination

Tafasitamab (MOR208: Fc-engineered, anti-CD19 mAb)

- ↑ ADCC
- ↑ ADCP
- Direct cell death
- Encouraging single-agent activity in R/R DLBCL and iNHL patients

Lenalidomide

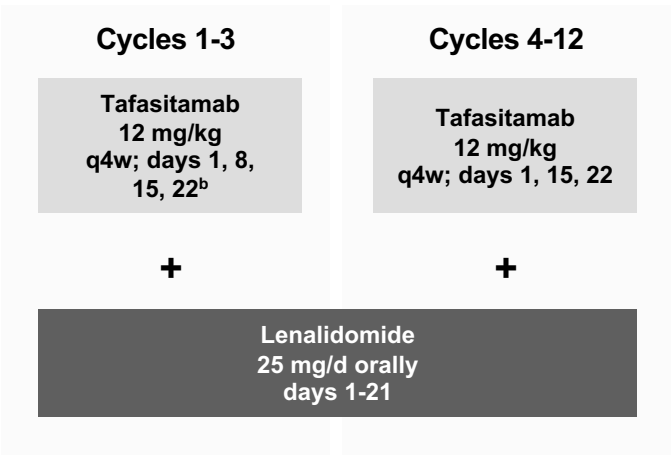
- T and NK cell activation/expansion
- Direct cell death
- Has been well studied as an antilymphoma agent, alone or in combination



Salles GA, et al. ASH 2018. Abstract 227.

L-MIND Study Design[1,2]

- **R/R DLBCL**
- **Not eligible for HDC + ASCT**
- **1-3 prior regimens**
- **Primary refractory patients were not eligible[a]**
- **Patients with double/triple-hit DLBCL were excluded**
- **ECOG PS 0-2**



Primary endpoint
- **ORR (central read)**

Secondary endpoints
- **PFS**
- **DOR**
- **OS**
- **Safety of the tafasitamab + Len combination**
- **Exploratory and biomarker-based assays**

- Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab/lenalidomide combination vs lenalidomide monotherapy at 85% power, two-sided alpha of 5%
- Safety data from the first 6 patients were evaluated in a safety run-in to determine the starting dose of lenalidomide for the remainder of the study

[a] Primary refractory defined as no response to, or progression/relapse during or within 6 months of frontline therapy.
[b] A loading dose of tafasitamab was administered on day 4 of cycle 1.

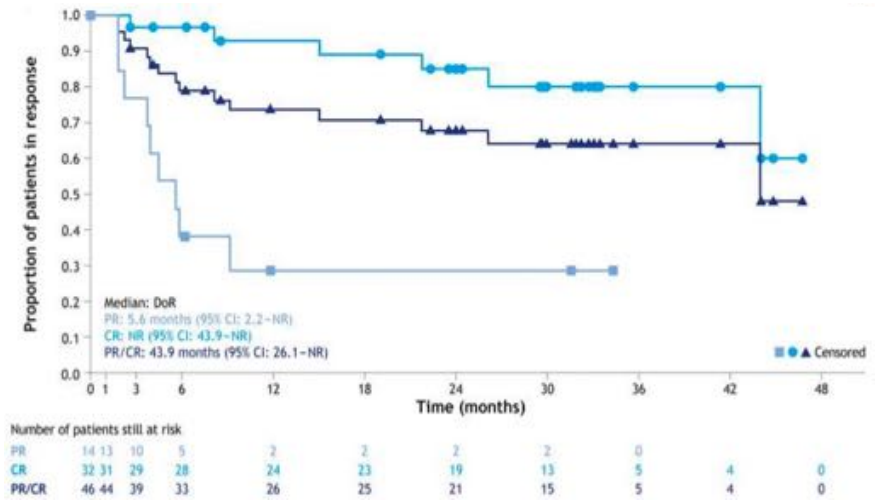
1. Duell J, et al. ASCO 2021. Abstract 7513. 2. ClinicalTrials.gov. NCT02399085. Accessed March 28, 2022. https://clinicaltrials.gov/ct2/show/NCT02399085

L-MIND ≥35 Months of Follow-Up: Response Rate and DOR by Best Response

Response, n (%)	Follow-Up Analysis[a] (n=80)
ORR (CR+PR)	46 (57.5)
CR	32 (40.0)
PR	14 (17.5)
SD	13 (16.3)
PD	13 (16.3)
NE[b]	8 (10.0)

- Of 34 patients who received tafasitamab monotherapy after discontinuing lenalidomide (30/34 patients had completed 12 cycles of tafasitamab plus lenalidomide), 19 remained on therapy as of the data cutoff date

IRC-Assessed DOR by Best Response



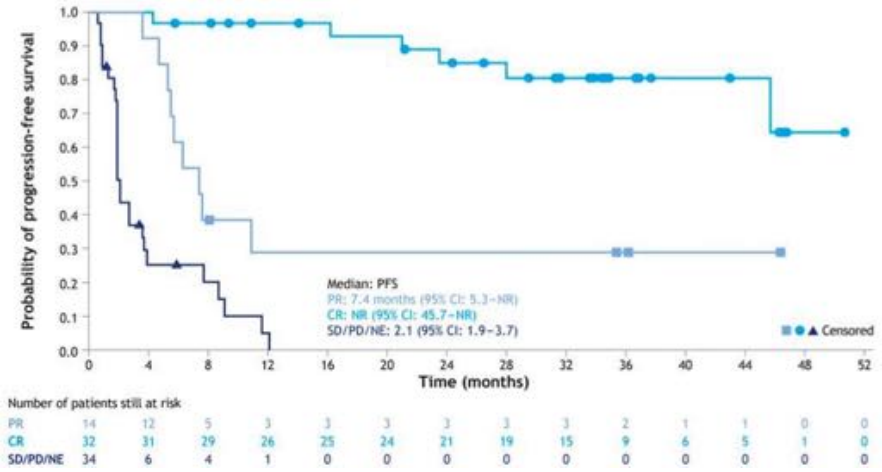
- Of responders, the median DOR was 43.9 months

Data cutoff: October 30, 2020. [a] One patient received tafasitamab only. [b] Nonevaluable patients had no valid postbaseline response assessments.

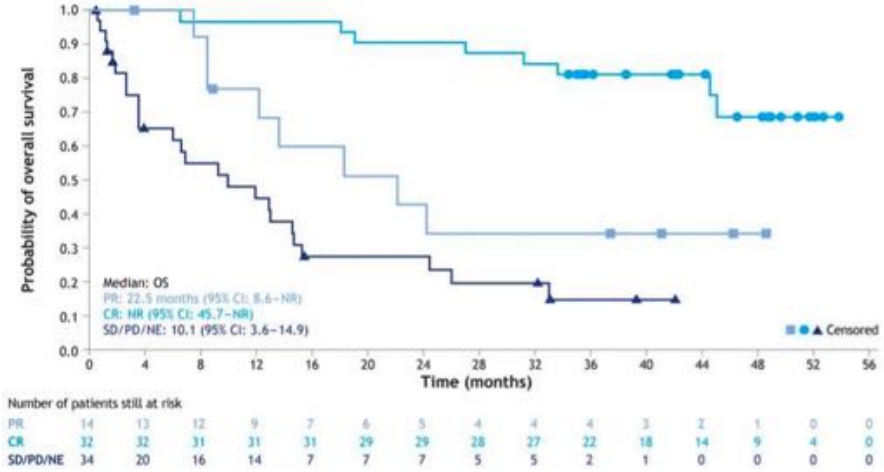
Duell J, et al. *Haematologica*. 2021;106(9):2417-2426.

L-MIND ≥35 Months of Follow-Up: PFS and OS by Best Response

IRC-Assessed PFS by Best Response



IRC-Assessed OS by Best Response



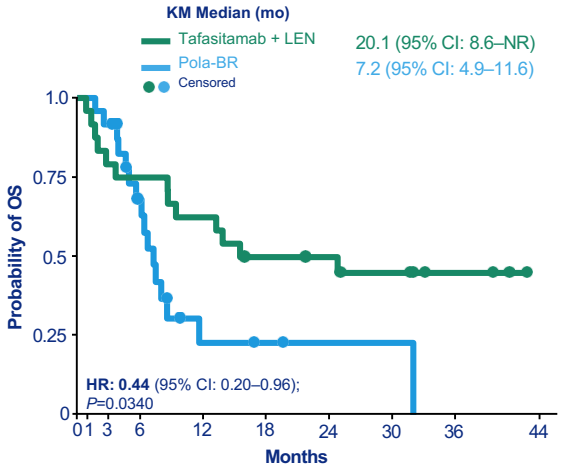
- Of responders, the median PFS was 11.6 months and median OS was 33.5 months

Data cutoff: October 30, 2020.

Duell J, et al. *Haematologica*. 2021;106(9):2417-2426.

Retrospective Analysis
Tafasitamab vs R2 vs CAR T
Primary Endpoint: Overall Survival*

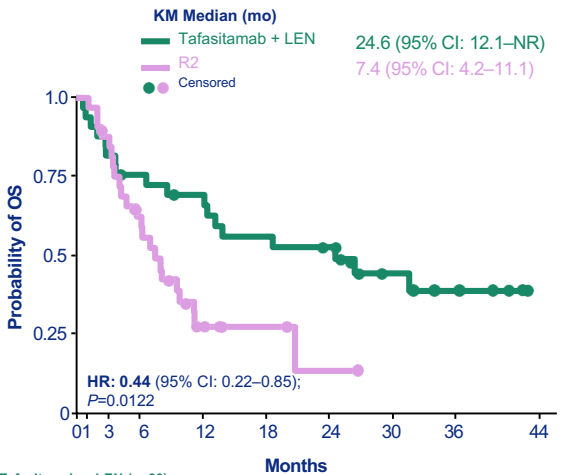
Tafasitamab + LEN vs Pola-BR Cohort



Tafasitamab + LEN (n=24)											
At risk	24	23	19	18	15	11	10	8	4	0
Event(s)	0	1	5	6	9	12	12	13	3	13
Censored	0	0	0	0	0	1	2	3	7	11
Pola-BR (n=24)										
At risk	24	24	22	13	3	2	1	1	0	0
Event(s)	0	0	2	7	15	15	15	15	16	16
Censored	0	0	0	4	6	7	8	8	8	8

Median duration of follow-up: tafasitamab plus + LEN: 32 months; Pola-BR: 16.6 months

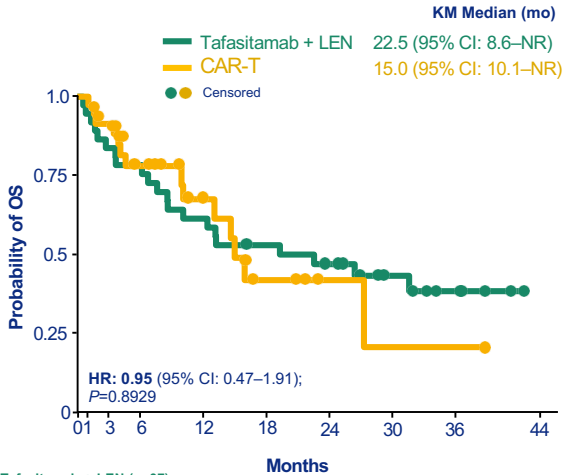
Tafasitamab + LEN vs R2 Cohort



Tafasitamab + LEN (n=33)											
At risk	33	31	27	24	21	17	15	8	5	0
Event(s)	0	2	6	8	10	14	15	17	18	18
Censored	0	0	0	1	2	2	3	8	10	15
R2 (n=33)										
At risk	33	33	28	19	5	3	1	0	0	0
Event(s)	0	0	4	12	22	22	23	23	23	23
Censored	0	0	1	2	6	8	9	10	10	10

Median duration of follow-up: tafasitamab plus + LEN: 32 months; R2: 13.4 months

Tafasitamab + LEN vs CAR-T Cohort



Tafasitamab + LEN (n=37)											
At risk	37	35	31	28	22	18	15	9	5	0
Event(s)	0	2	6	8	14	17	19	20	21	21
Censored	0	0	0	1	1	2	3	8	11	16
CAR-T (n=37)										
At risk	37	37	30	22	11	5	2	1	1	0
Event(s)	0	0	3	7	9	13	13	14	14	14
Censored	0	0	4	8	17	19	22	22	22	23

Median duration of follow-up: tafasitamab plus + LEN: 32 months; CAR-T: 10.2 months

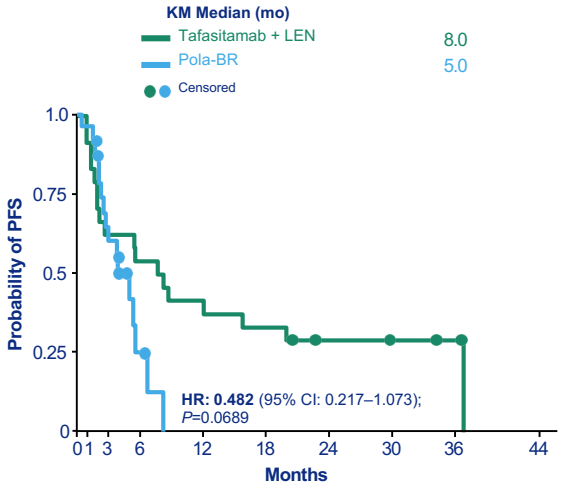
***This study compares the L-MIND population with matching real-world cohorts and therefore contains limitations that may affect the interpretation of the results**

P values were calculated using log-rank test.

Nowakowski GS, et al. ASH 2021. Oral Presentation: Abstract 183.

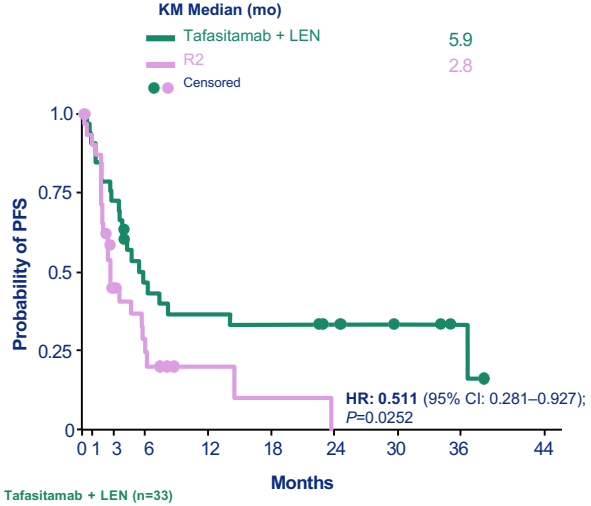
Retrospective Analysis
Tafasitamab vs R2 vs CAR T
Primary Endpoint: PFS*

Tafasitamab + LEN vs Pola-BR Cohort



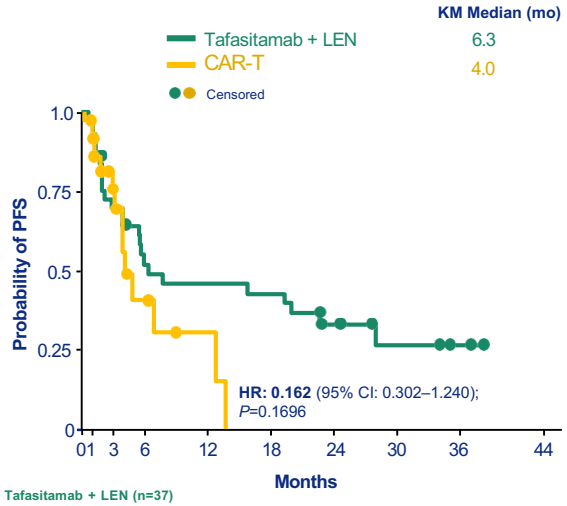
Tafasitamab + LEN (n=24)												
At risk	24	22	15	13	10	8	5	4	2	0		
Event(s)	0	2	9	11	14	16	17	17	17	18		
Censored	0	0	0	0	0	0	2	3	5	6		
Pola-BR (n=24)												
At risk	24	23	13	3	0	0	0	0	0	0		
Event(s)	0	1	9	14	16	16	16	16	16	16		
Censored	0	0	2	7	8	8	8	8	8	8		

Tafasitamab + LEN vs R2 Cohort



Tafasitamab + LEN (n=33)												
At risk	33	30	24	14	11	10	7	5	2	0		
Event(s)	0	3	9	17	20	21	21	21	21	22		
Censored	0	0	0	2	2	2	5	7	10	11		
R2 (n=33)												
At risk	33	30	11	7	2	1	0	0	0	0		
Event(s)	0	2	17	21	23	24	25	25	25	25		
Censored	0	1	5	5	8	8	8	8	8	8		

Tafasitamab + LEN vs CAR-T Cohort



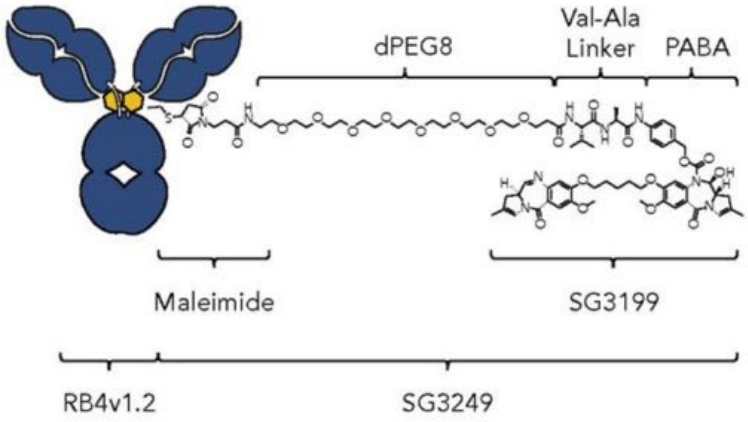
Tafasitamab + LEN (n=37)												
At risk	37	33	25	17	15	14	7	4	2	2		
Event(s)	0	3	11	17	19	20	23	24	24	24		
Censored	0	1	1	3	3	3	7	9	11	13		
CAR-T (n=37)												
At risk	37	33	12	5	2	0	0	0	0	0		
Event(s)	0	3	7	12	13	15	15	15	15	15		
Censored	0	1	18	20	22	22	22	22	22	22		

***This study compares the L-MIND population with matching real-world cohorts and therefore contains limitations that may affect the interpretation of the results**

Loncastuximab Tesirine

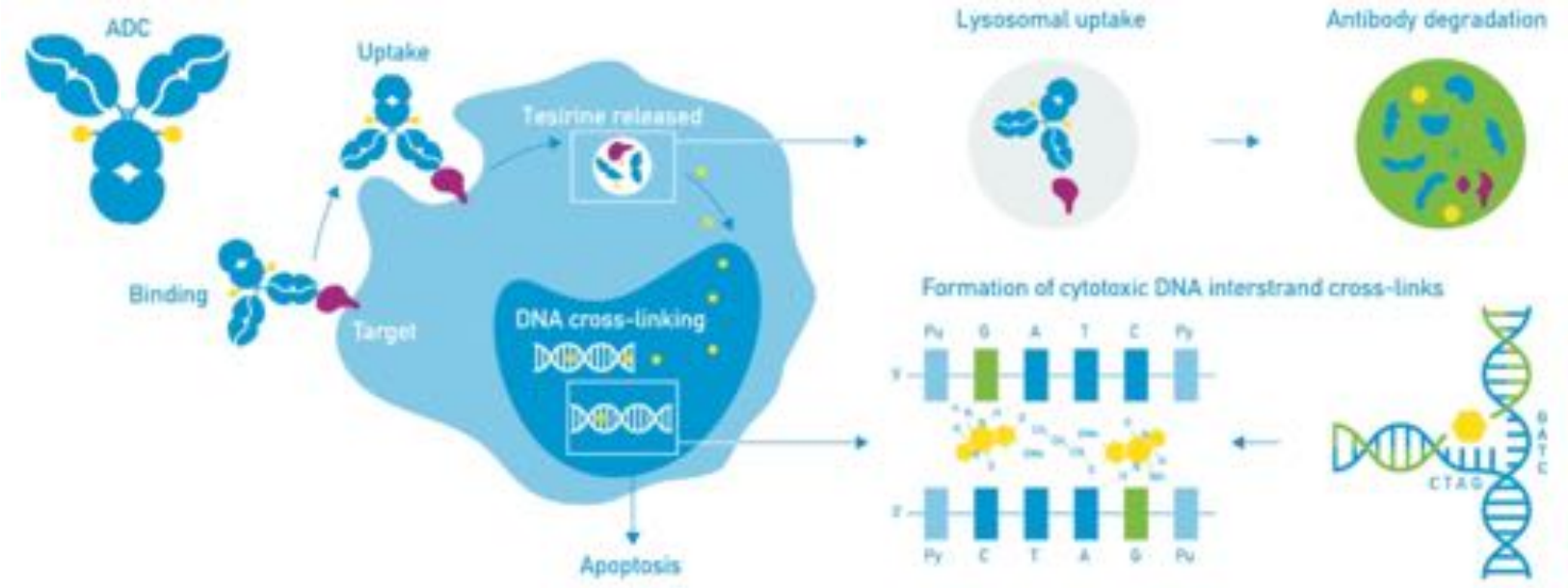
- Loncastuximab tesirine is an FDA-approved CD19-directed antibody-drug conjugate indicated for adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including patients with HGBCL[1]

- ADC delivering SG3199, a cytotoxic minor groove interstrand cross-linkin dimer payload[1,2]
  - Anti-CD19
  - Payload is a PBD toxin
  - DNA cross-linking agent



1. Loncastuximab tesirine. Package insert. ADC Therapeutics, SA; 2021. 2. Zammarchi F, et al. *Blood*. 2018;131(10):1094-1105.

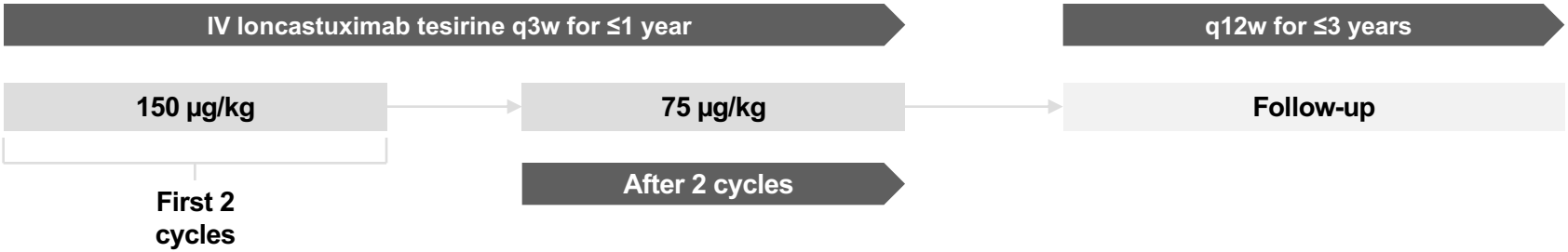
Loncastuximab Tesirine: Mechanism of Action



Our Science. ADC Therapeutics. Accessed March 28, 2022. https://www.adctherapeutics.com/our-science/

LOTIS-2: Study Design

- Patients with R/R DLBCL for whom salvage chemotherapy/SCT is unsuccessful and who have a poor prognosis and limited treatment options[1,2]
- Loncastuximab tesirine comprises a humanized anti-CD19 antibody conjugated to a potent PBD dimer toxin[3]
- LOTIS-2 is a multicenter, open-label, single-arm, phase 2 study in patients aged ≥18 years with pathologically defined R/R DLBCL and ≥2 prior systemic treatments[4-6]
  - Included patients with high-risk characteristics such as double-hit, triple-hit, transformed, or primary refractory DLBCL[4]

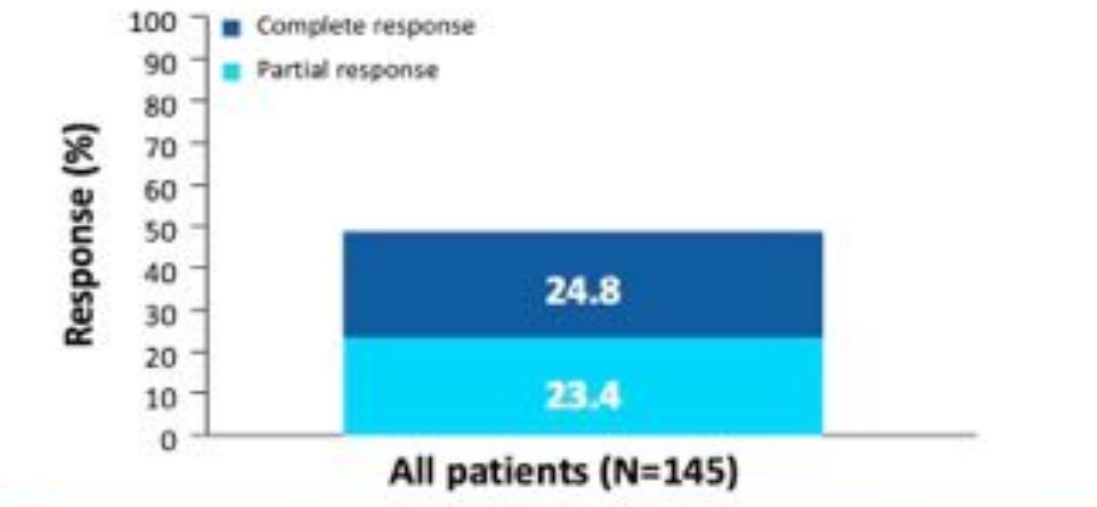


- Primary efficacy and safety data have been published (**≥6 months** since first dose)[4]
- Presented are updated results (**≥17 months** since first dose)

Study findings were previously presented as a poster at the International Conference on Malignant Lymphoma (ICML) Virtual Congress, June 18-22, 2021.

1. Crump M, et al. *Blood.* 2017;130(16):1800-1808. 2. Gisselbrecht C, et al. *Br J Haematol.* 2018;182(5):633-643.
3. Zammarchi F, et al. *Blood.* 2018;131(10):1094-1105. 4. Caimi PF, et al. *Lancet Oncol.* 2021;22(6):790-800.
5. Caimi PF, et al. ASH 2020. Abstract 1183. 6. Caimi PF, et al. ASCO 2021. Abstract 7546.

LOTIS-2: Efficacy Results – ORR and DOR



Loncastuximab tesirine ORR:

48.3%

Loncastuximab tesirine DOR in responders (CR+PR):

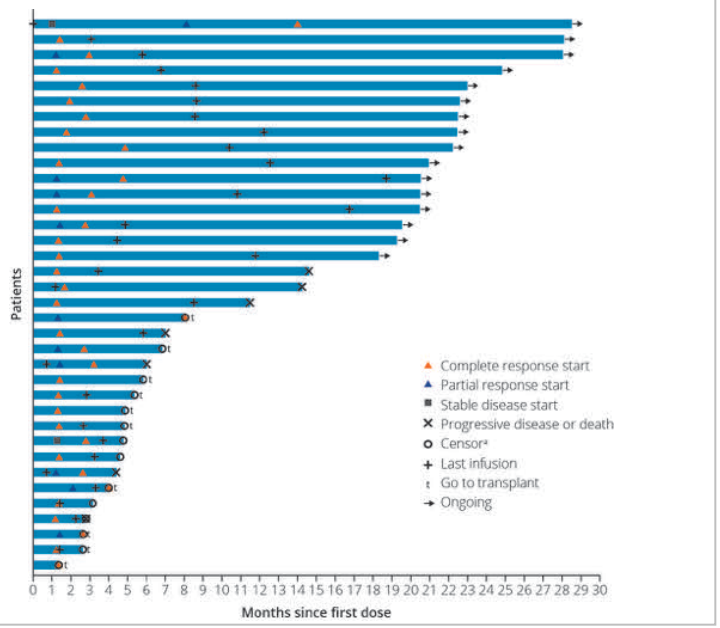
13.4 mo

Data cutoff: March 01, 2021. All-treated population.

Kahl BS, et al. SOHO 2021. Abstract ABCL-022.

LOTIS-2: Efficacy Results – Complete Responders

Swimmer Plot of Complete Responders

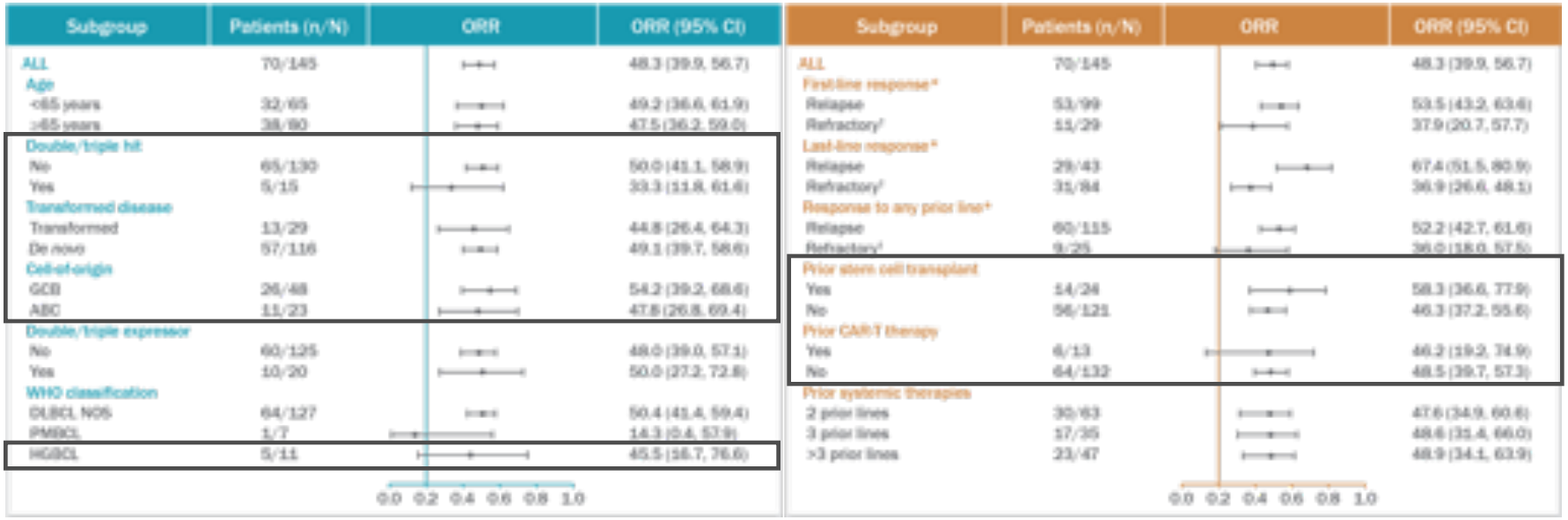


Response	Remained in CR With No Further Treatment	PD or Death
CR, % (n/N)	44.4 (16/36)	36.1 (13/36)
CR excluding 10 patients censored due to SCT, % (n/N)	61.5 (16/26)	34.6 (9/26)

Data cutoff: March 01, 2021. All-treated population. Each bar represents 1 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.
Kahl BS, et al. SOHO 2021. Abstract ABCL-022.

LOTIS-2 Trial: Focus on High-Risk Groups

High-Risk Subgroup Analysis of ORR



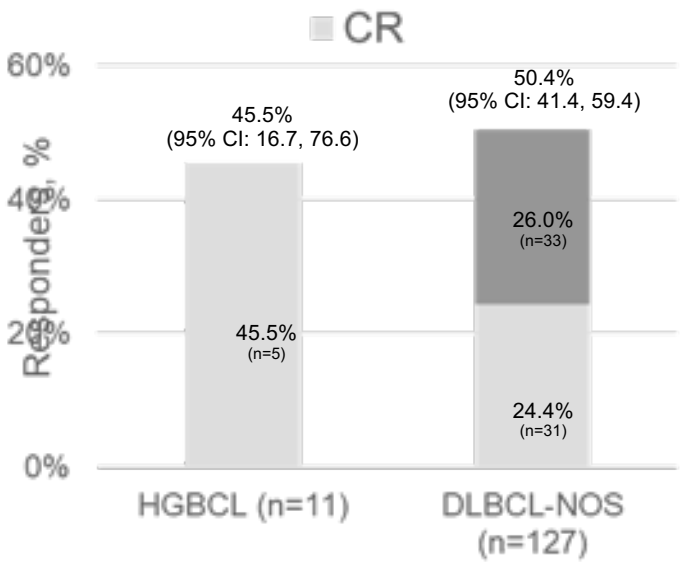
Data cutoff: August 06, 2020. ORR was assessed by independent reviewer.

* Prior systemic therapies. † Refractory disease defined as no response to therapy.

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

LOTIS-2: High-Grade BCL and Sequencing Around CAR T-Cell Therapy

HGBCL/DLBCL NOS Response Rates[1]



Lonca After CAR T-Cell Therapy Relapse[2]

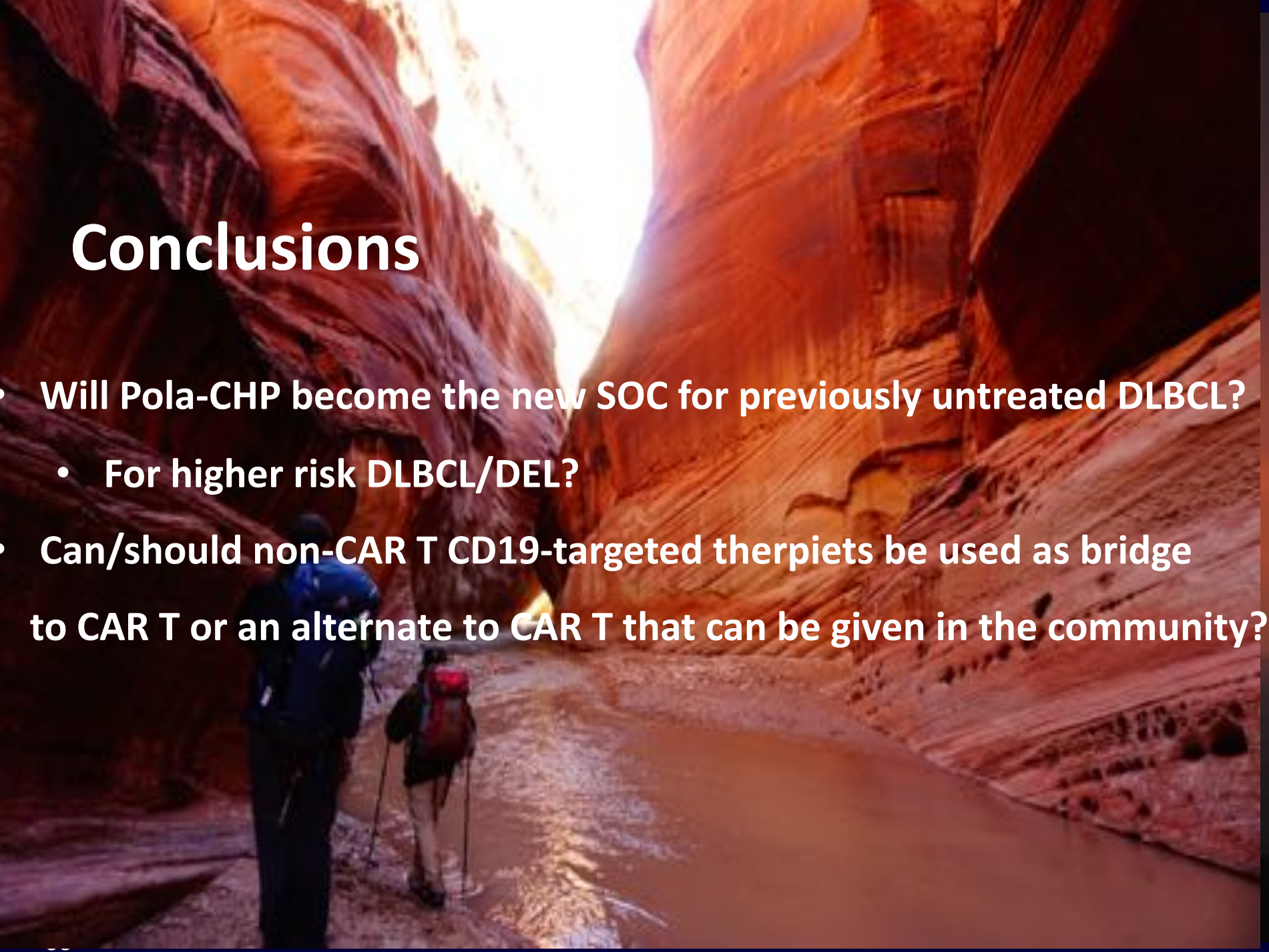
		n=13
Best response to CAR T-cell therapy, n (%)	CR	7 (54)
	PR	2 (15)
	No response	4 (31)
Best response to Lonca post–CAR T-cell therapy,[a] n (%)	CR	2 (15)
	PR	4 (31)
	SD	1 (8)
	PD	2 (15)

CAR T-Cell Therapy After Lonca Failure[3]

		n=14
Best response to Lonca, n (%)	CR	1 (7)
	PR	5 (36)
	Refractory	8 (57)
Best response to CAR T-cell therapy post-Lonca, n (%)	CR	6 (43)
	PR	1 (7)
	Refractory	7 (50)

[a] 4 patients were not evaluable (30.8%).

1. Alderuccio J, et al. ASH 2021. Abstract 3575. 2. Caimi PF, et al. *Clin Lymphoma Myeloma Leuk*. 2021 Nov 12:S2152-2650(21)02437-X. Online ahead of print. 3. Thapa B, et al. *Blood Adv*. 2020;4(16):3850-3852.



Conclusions

- Will Pola-CHP become the new SOC for previously untreated DLBCL?
  - For higher risk DLBCL/DEL?
- Can/should non-CAR T CD19-targeted therpiets be used as bridge to CAR T or an alternate to CAR T that can be given in the community?