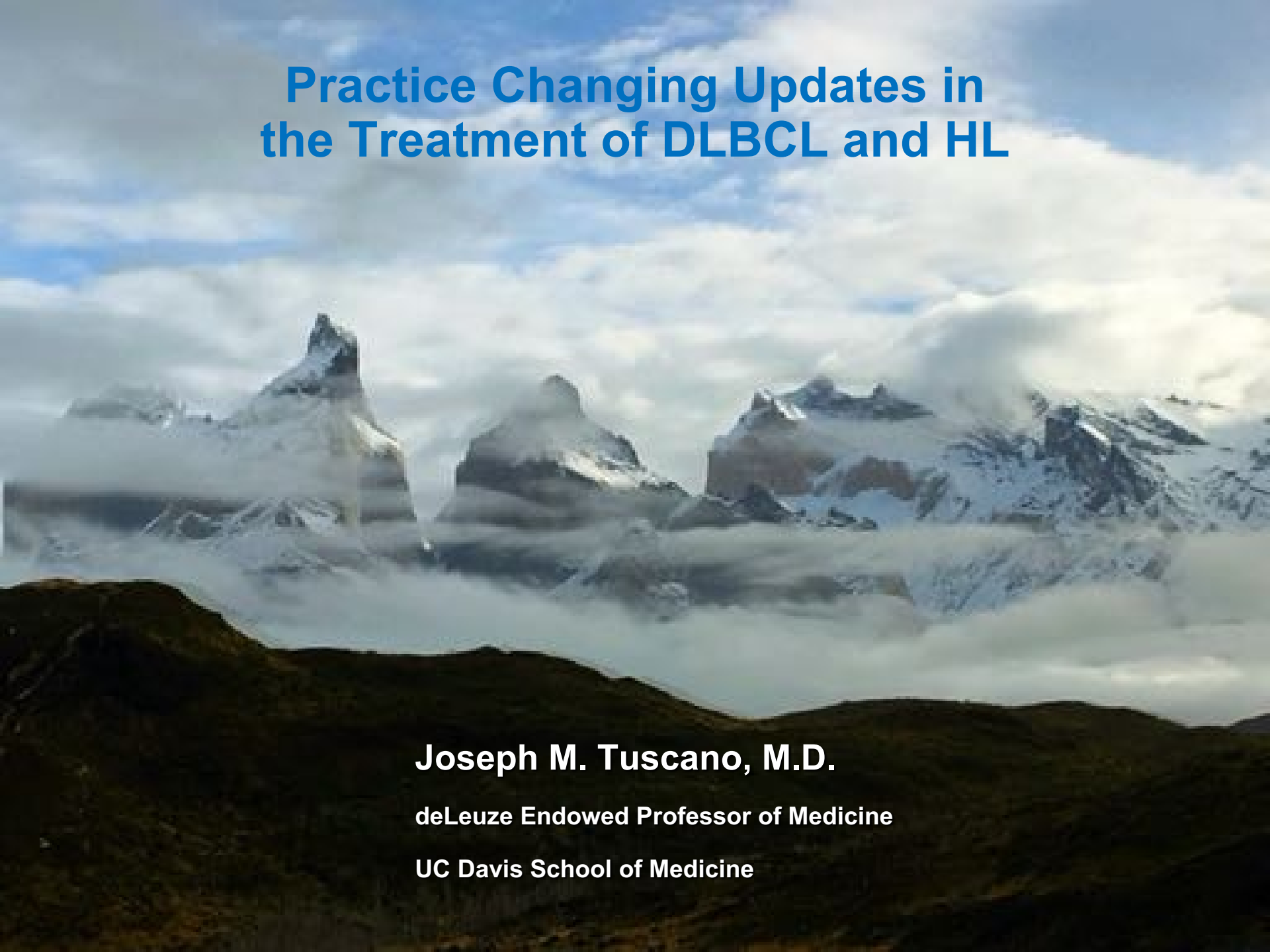
Practice Changing Updates in the Treatment of DLBCL and HL



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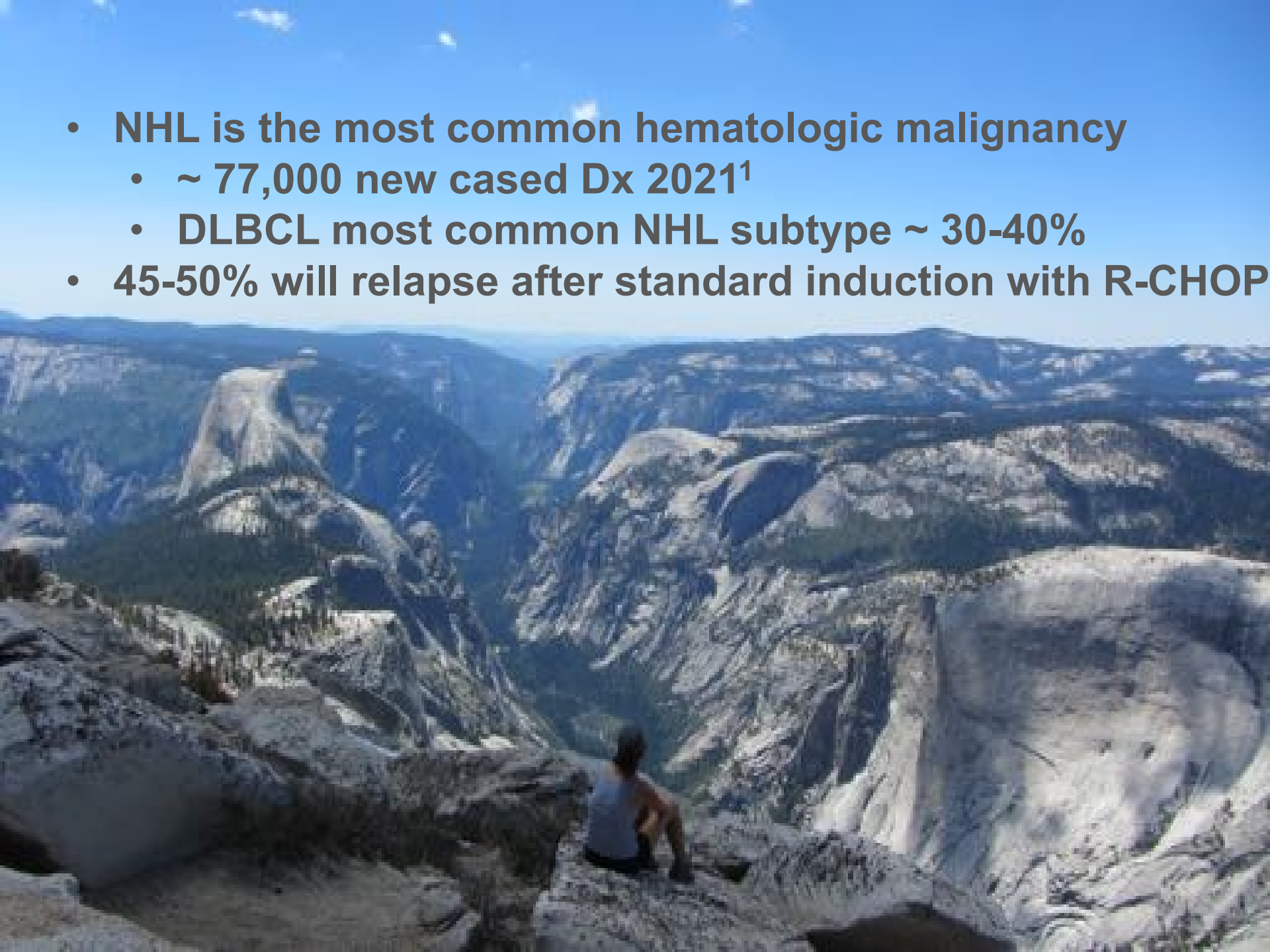
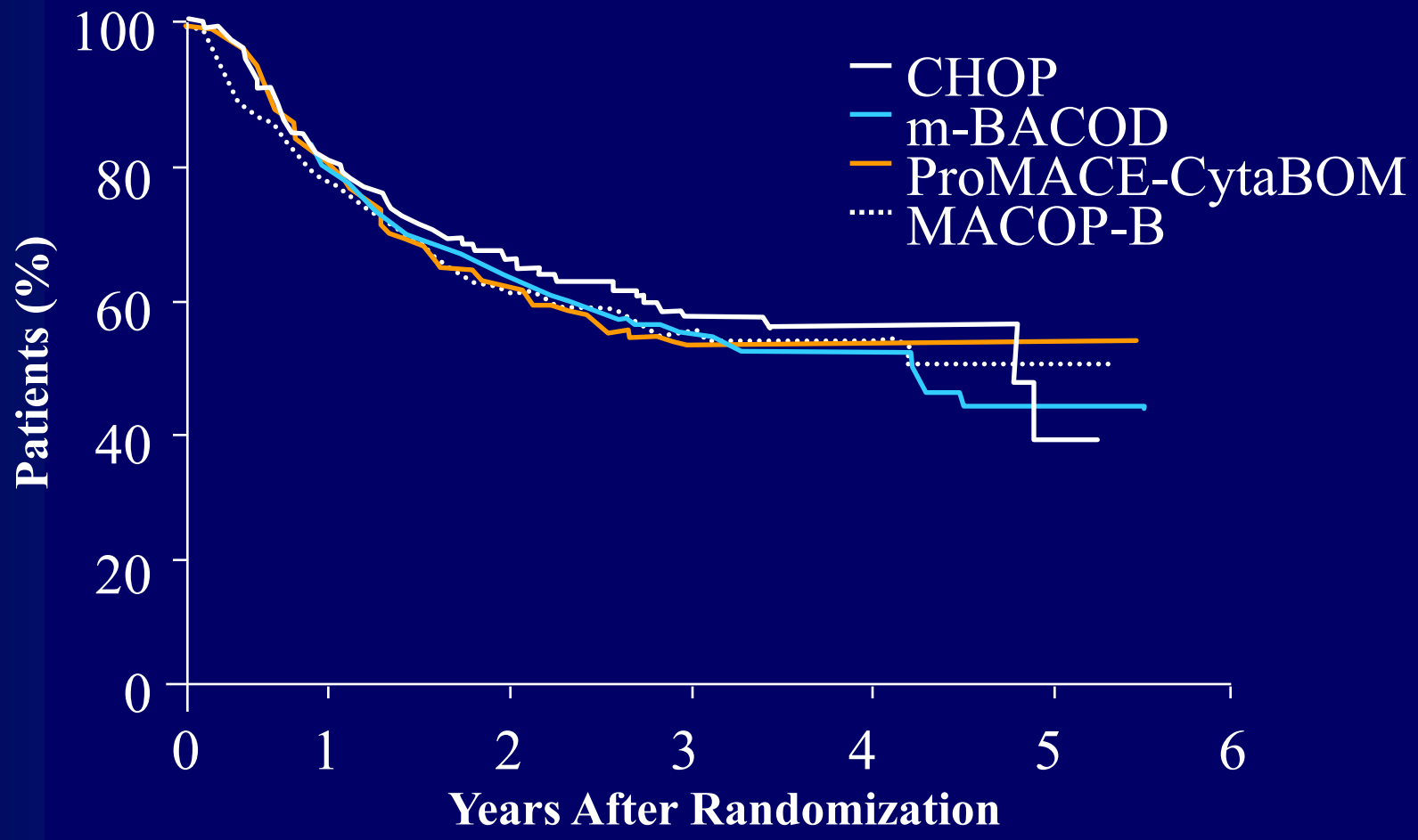


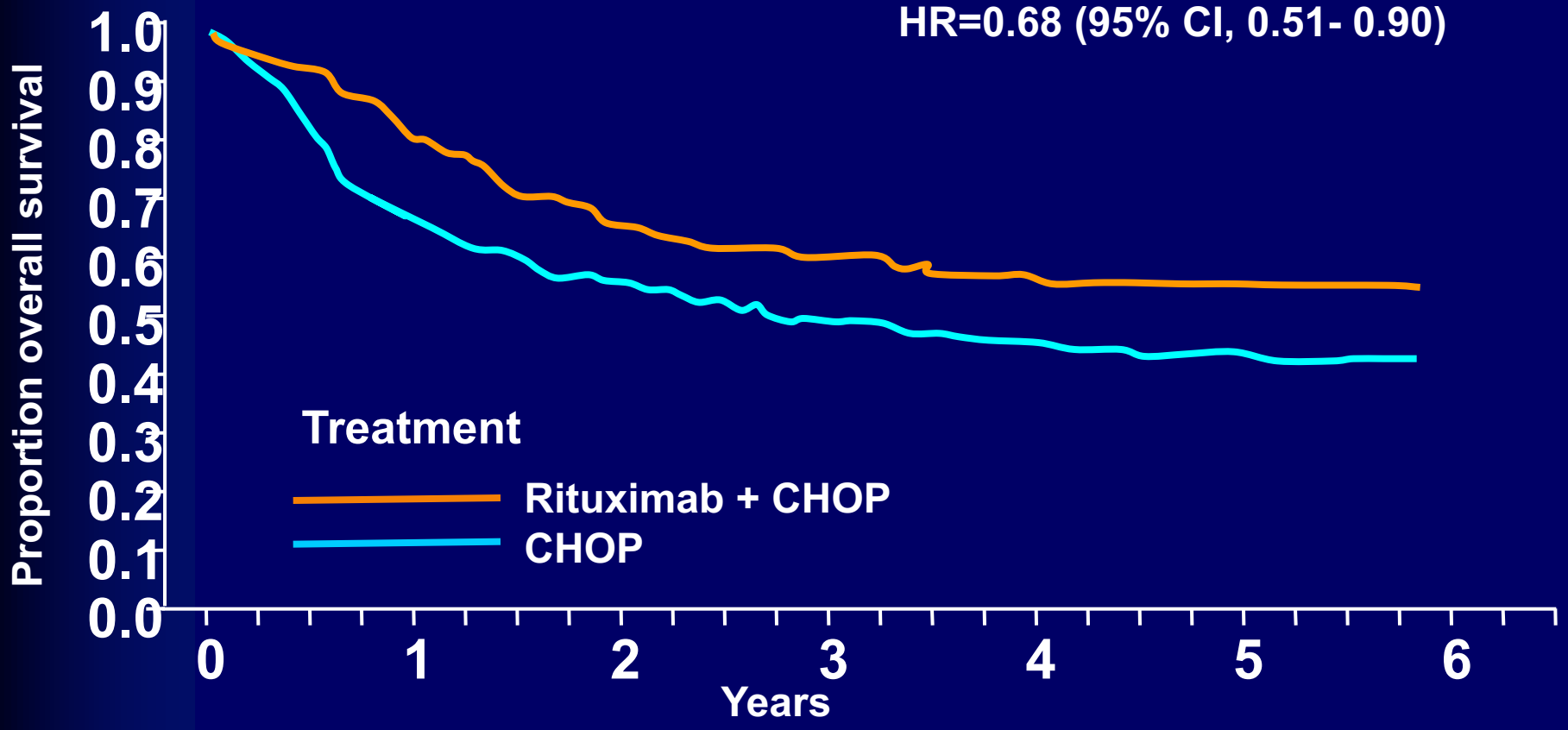
- NHL is the most common hematologic malignancy
  - ~ 77,000 new cased Dx 2021[1]
  - DLBCL most common NHL subtype ~ 30-40%
- 45-50% will relapse after standard induction with R-CHOP

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



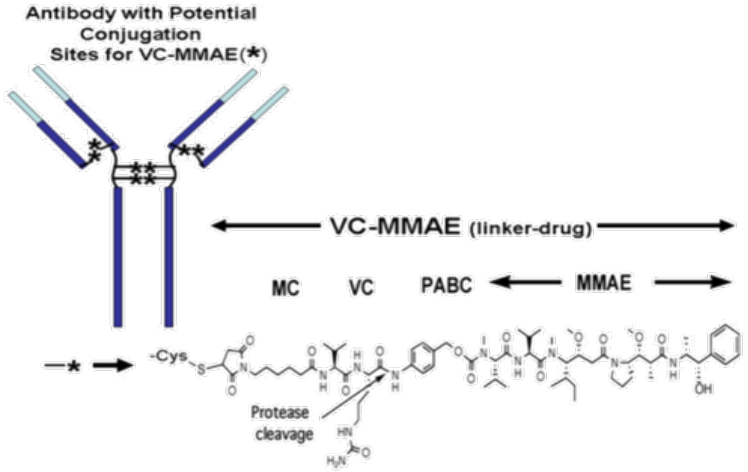
Coiffier et al. *N Engl J Med*. 2002;346:235.

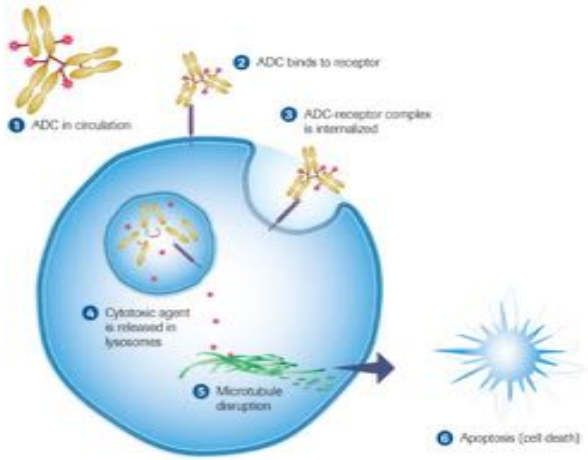
CHOP/R-CHOP has been the SOC for 20-30 years

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



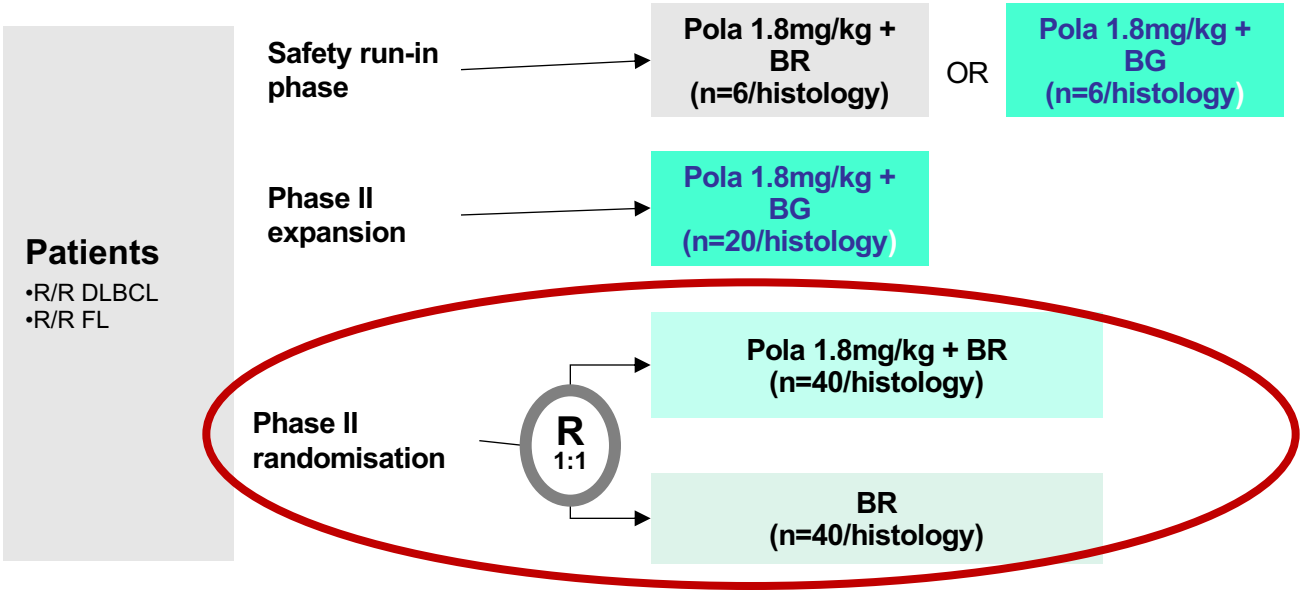


- Pola has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2]

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

Pola-BR vs BR: Study Design



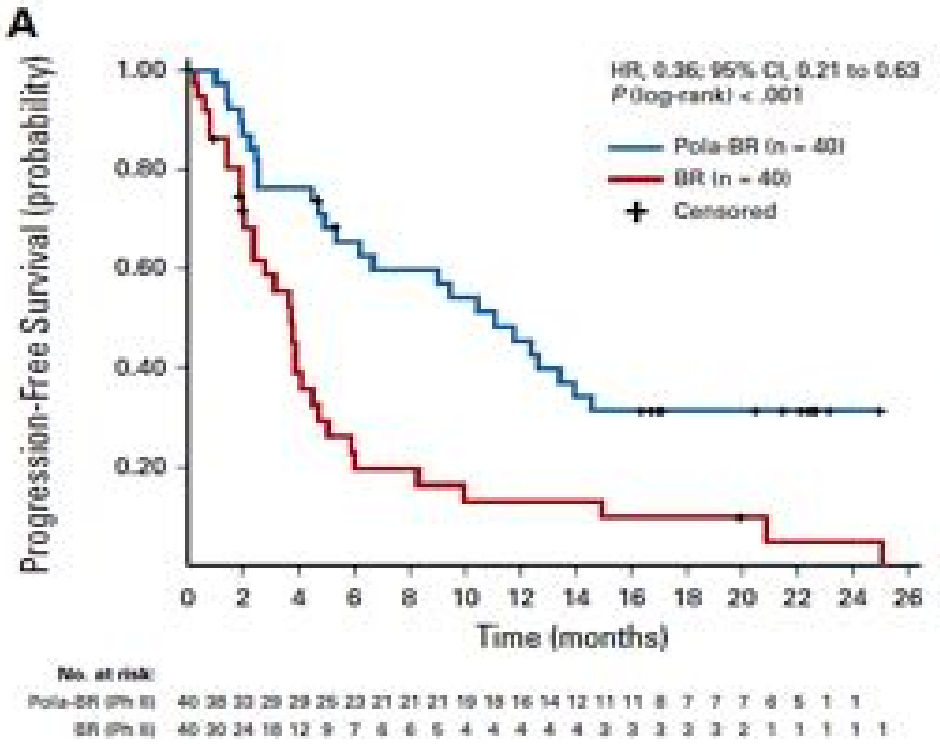
Primary endpoint (Phase II): PET-CR rate according to modified Lugano criteria

BG, bendamustine and obinutuzumab; BR, bendamustine and rituximab; FL, follicular lymphoma; PET-CR, positron electron tomography–complete response; pola, polatuzumab vedotin; R, randomisation; R/R, relapsed/refractory

Sehn L, et al. Abstract #1683, ASH 2018

Polatuzumab vedotin added to bendamustine/rituximab

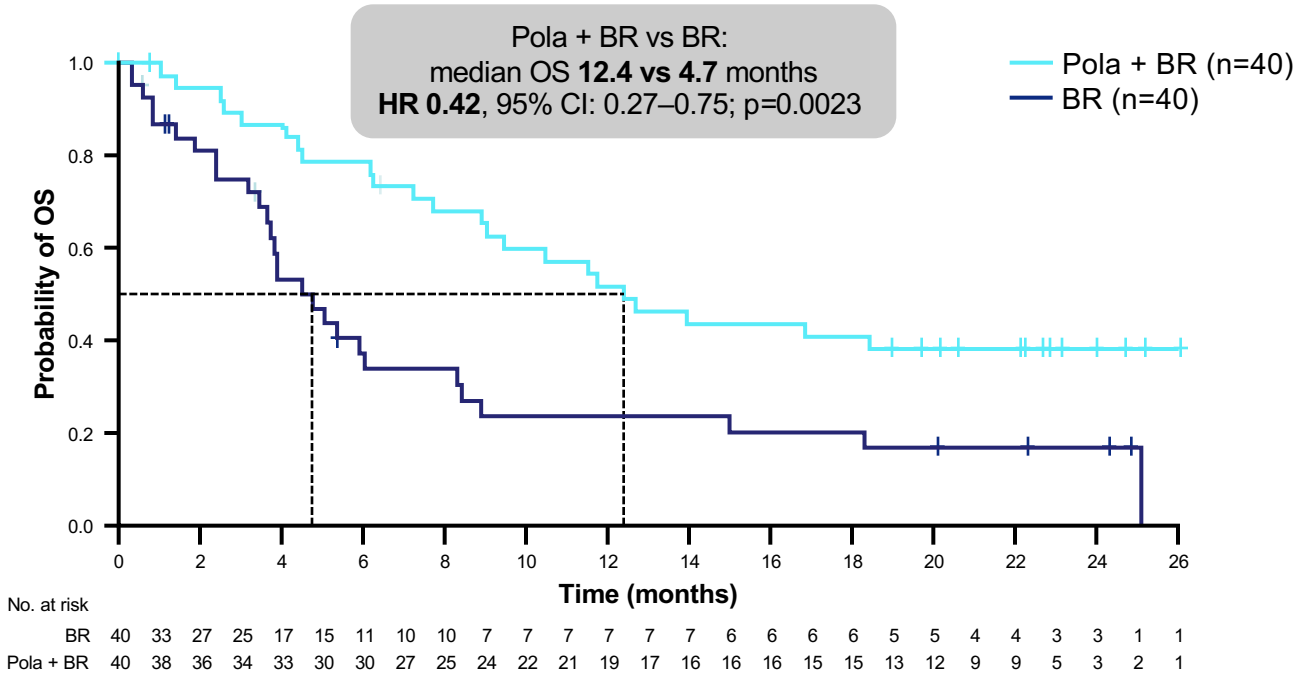
Progression Free Survival (IRC)



- Few patients with durable responses
- Toxicity: hematological, infectious, neurological

Sehn, JCO 2019

OS was significantly longer with pola + BR versus BR



Median follow-up: 22.3 months

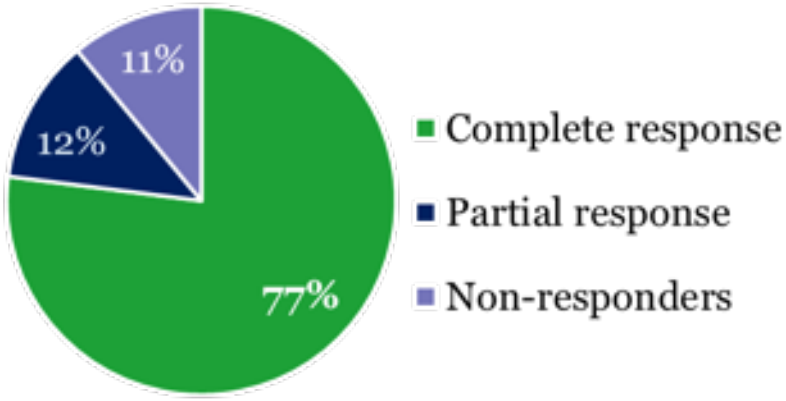
Sehn L, et al. Abstract #1683, ASH 2018

Data cut-off: 30 April 2018
BR, bendamustine and rituximab; pola, polatuzumab vedotin

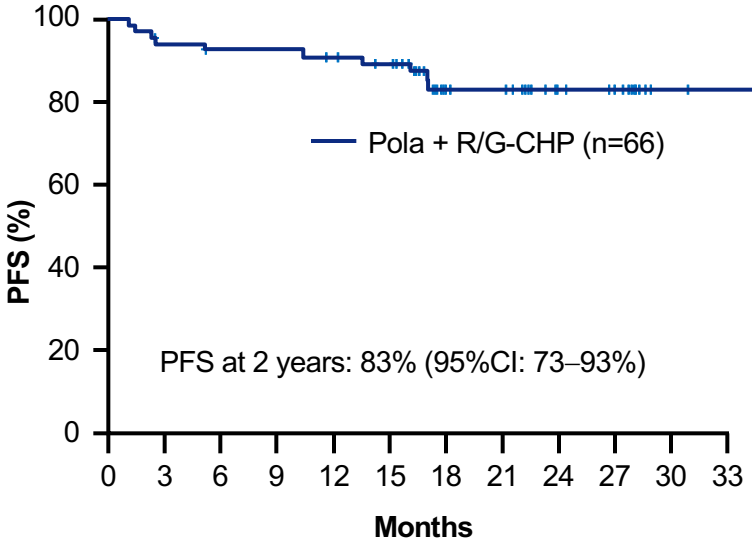
In frontline: Pola-R-CHP in a phase 1b/2 trial

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



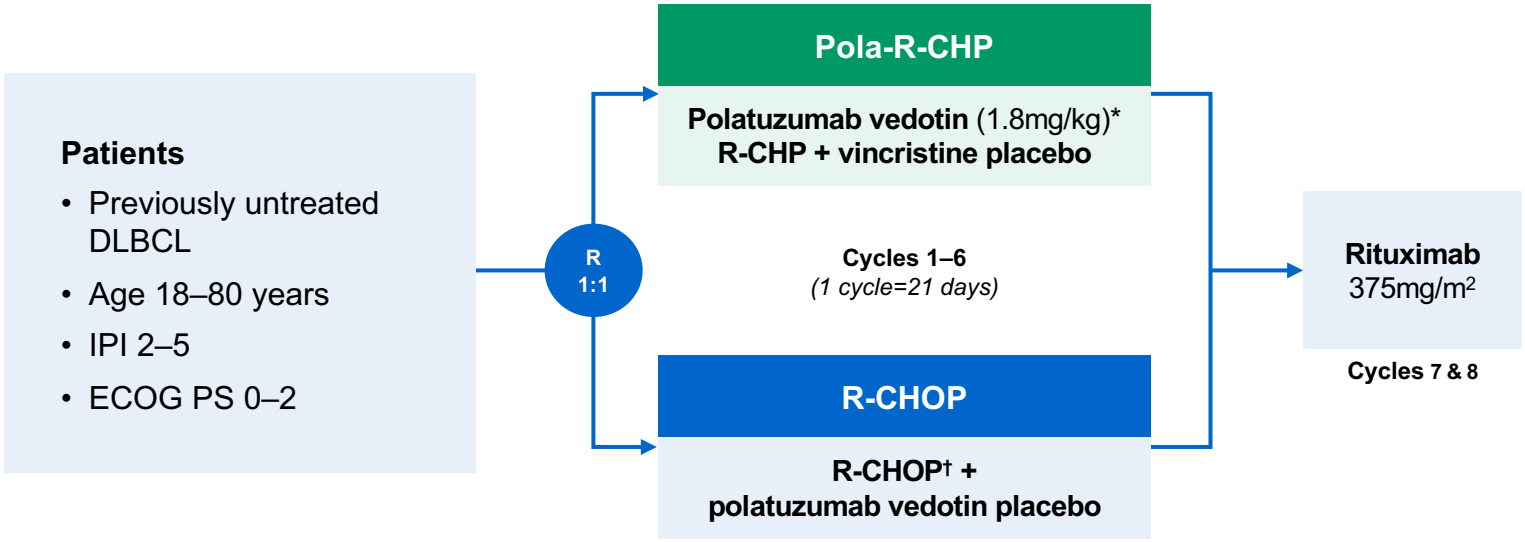
3. PFS in patients with 1L DLBCL receiving pola + R/G-CHP



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)

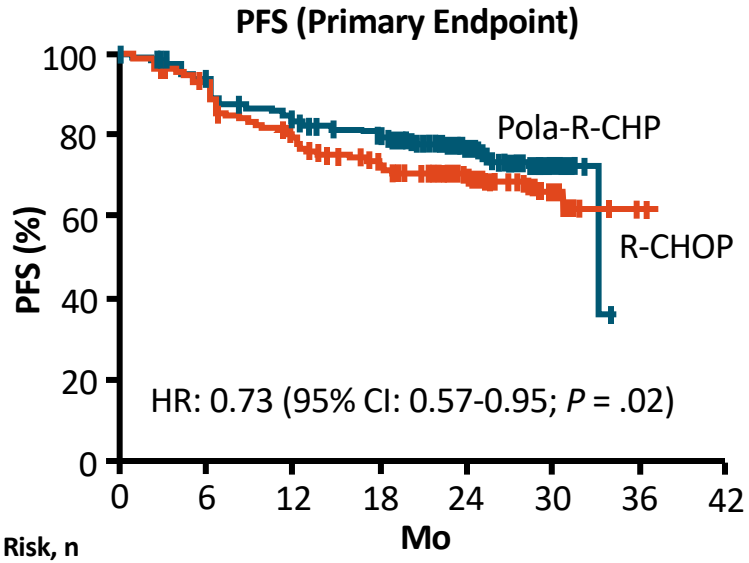
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub]

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

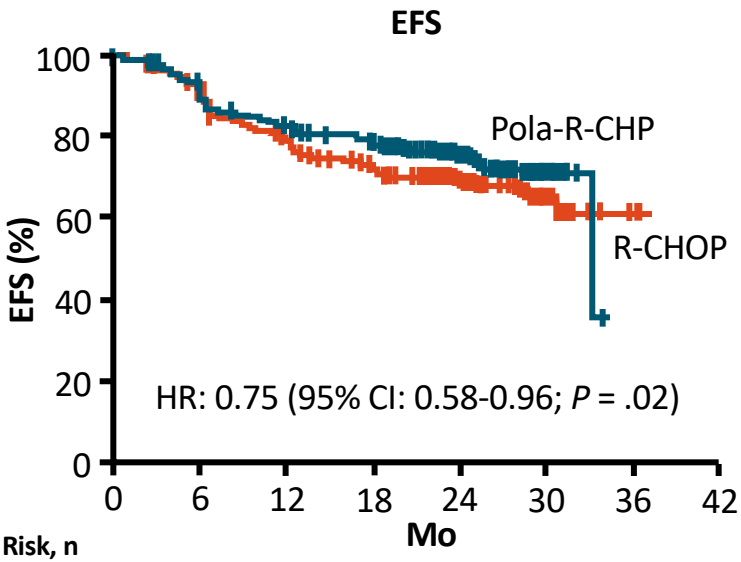
Best ORR, %	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
CR	86.6	82.7
PR	9.3	11.4

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

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS and EFS



Patients at Risk, n							
Pola-R-CHP	440	404	353	327	246	78	NE
R-CHOP	NE 439	389	330	296	220	78	3
	NE						

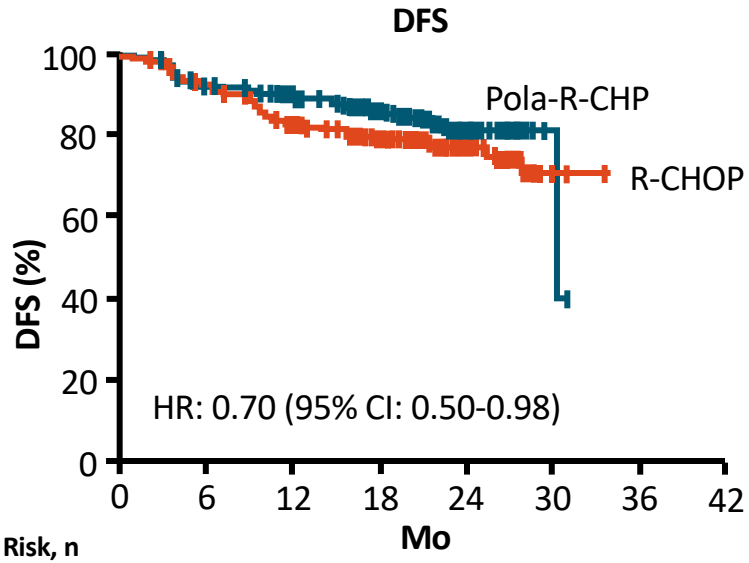


Patients at Risk, n							
Pola-R-CHP	440	402	348	323	243	78	NE
R-CHOP	NE 439	386	327	294	218	78	3
	NE						

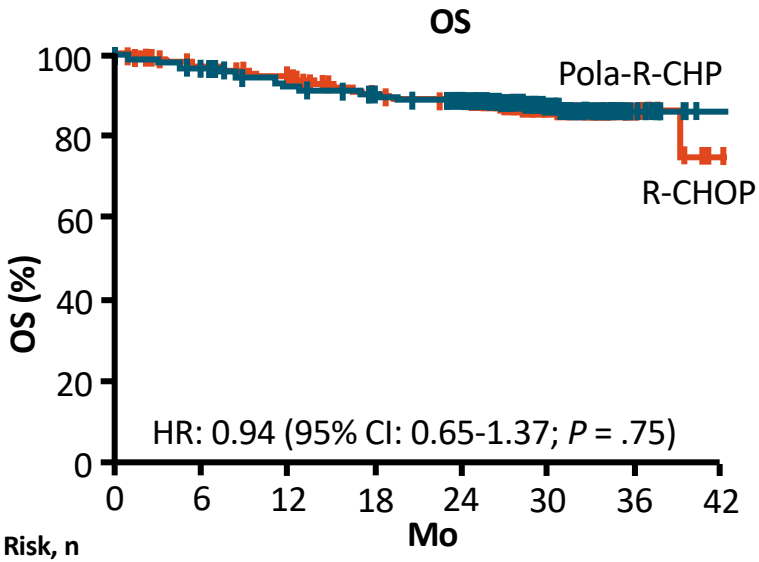
- **Median follow-up: 28.2 mo**
- **24-mo PFS: 76.7% polatuzumab vedotin + R-CHP vs 70.2% R-CHOP**
- **27% reduction in risk of progression, relapse or death with Pola-R-CHP**

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

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP DFS and OS



Patients at Risk, n							
Pola-R-CHP	381	342	322	266	106	2	NE
R-CHOP	NE						
	363	326	282	238	96	5	NE
	NE						



Patients at Risk, n								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	2

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

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]

POLARIX: Polatuzumab Vedotin + R-CHP Vs R-CHOP AEs

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	28.7	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	25.7	1.1	29.0	0.2
Fatigue	24.4	0.9	26.5	2.5
Alopecia	16.3	0	24.0	0.2
Dec appetite	15.6	1.1	14.2	0.7

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8.0	8.0
Headache	12.9	0.2	13.0	0.9
Cough	12.9	0	12.1	0
Dec weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13.0	0

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

POLARIX: Safety

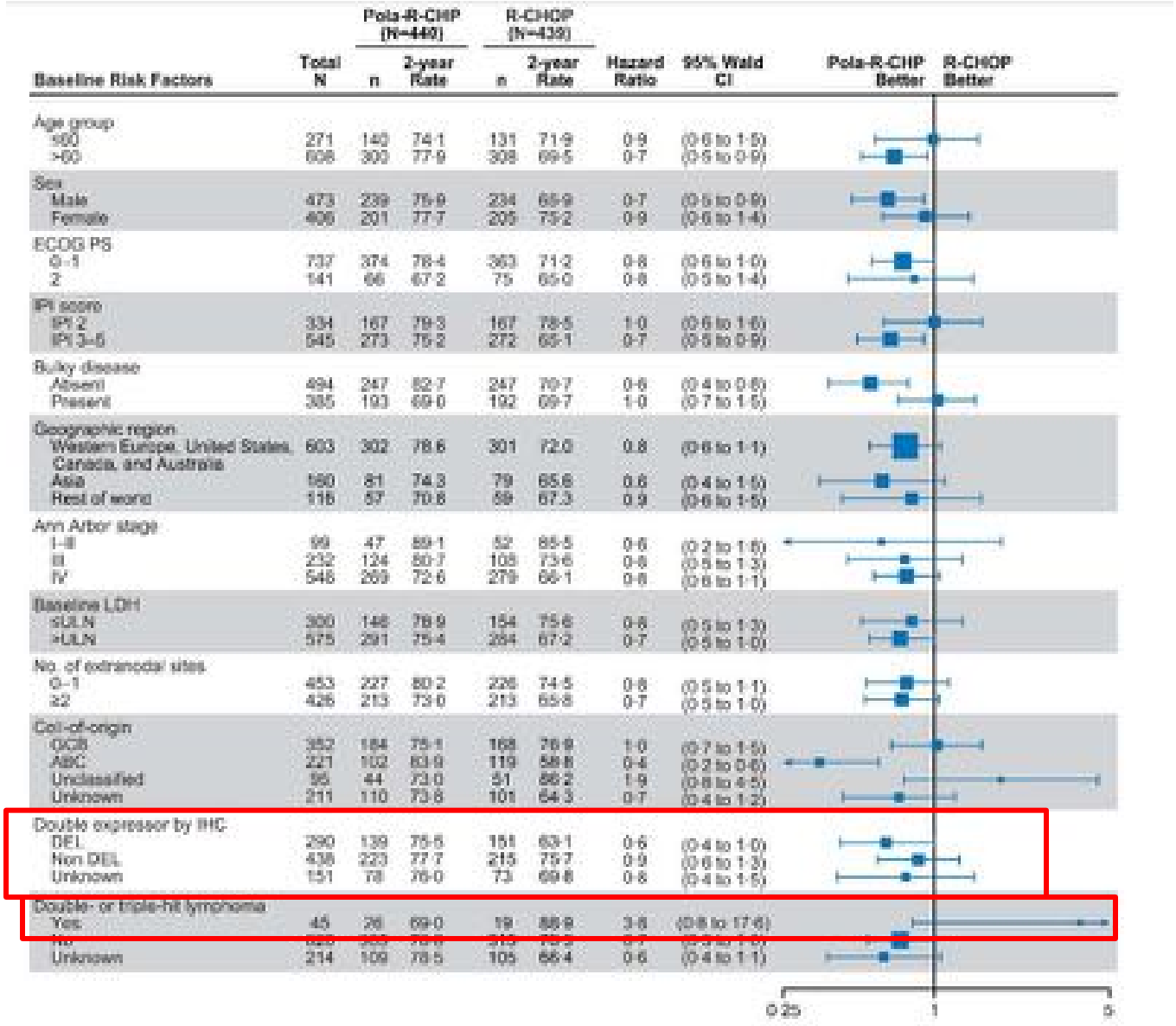
AEs, n (%)	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Any grade AEs	426 (97.9)	431 (98.4)
▪Grade ≥3*	264 (60.7)	262 (59.8)
Serious AEs	148 (34.0)	134 (30.6)
AEs leading to:		
▪D/c of any study drug†	27 (6.2)	29 (6.6)
▪Dose reduction of any study drug	40 (9.2)	57 (13.0)

*Grade 5 AEs: 13 patients (3.0%) and 10 patients (2.3%), respectively.
†19 patients (4.4%) d/c PV in PV arm, 22 patients (5.0%) d/c vincristine in R-CHOP arm.

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

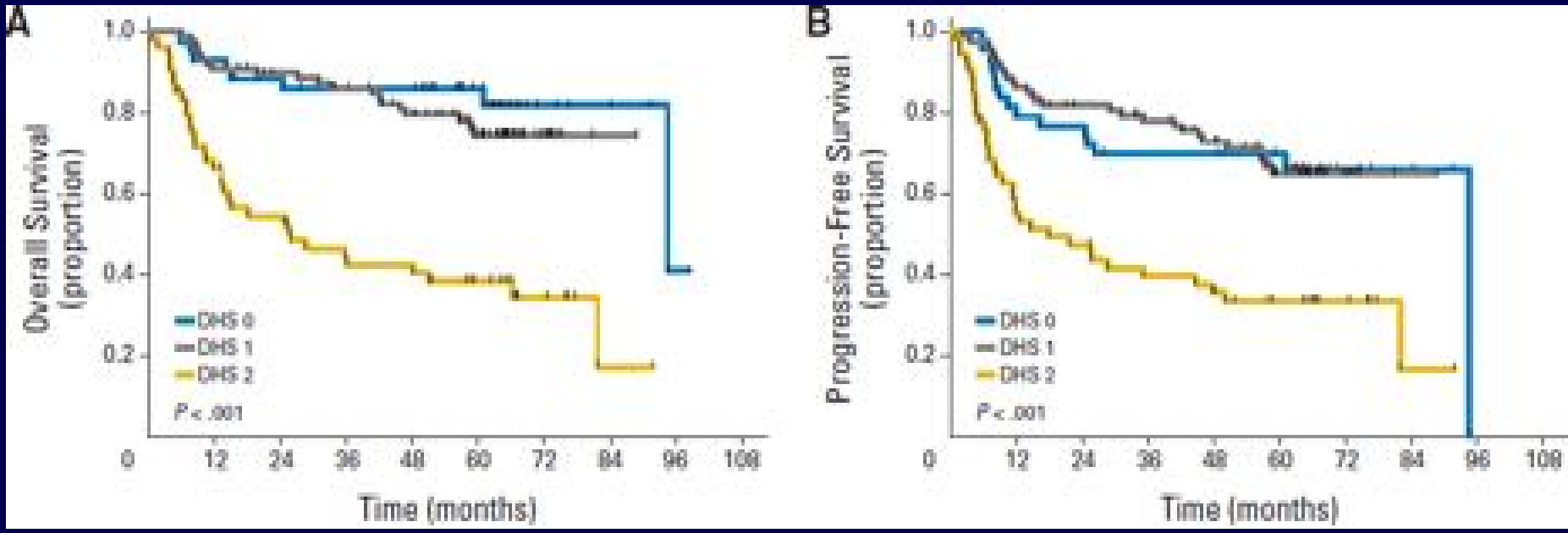
Phase 3 POLARIX Study: PFS (INV) by Subgroup

Exploratory Analysis



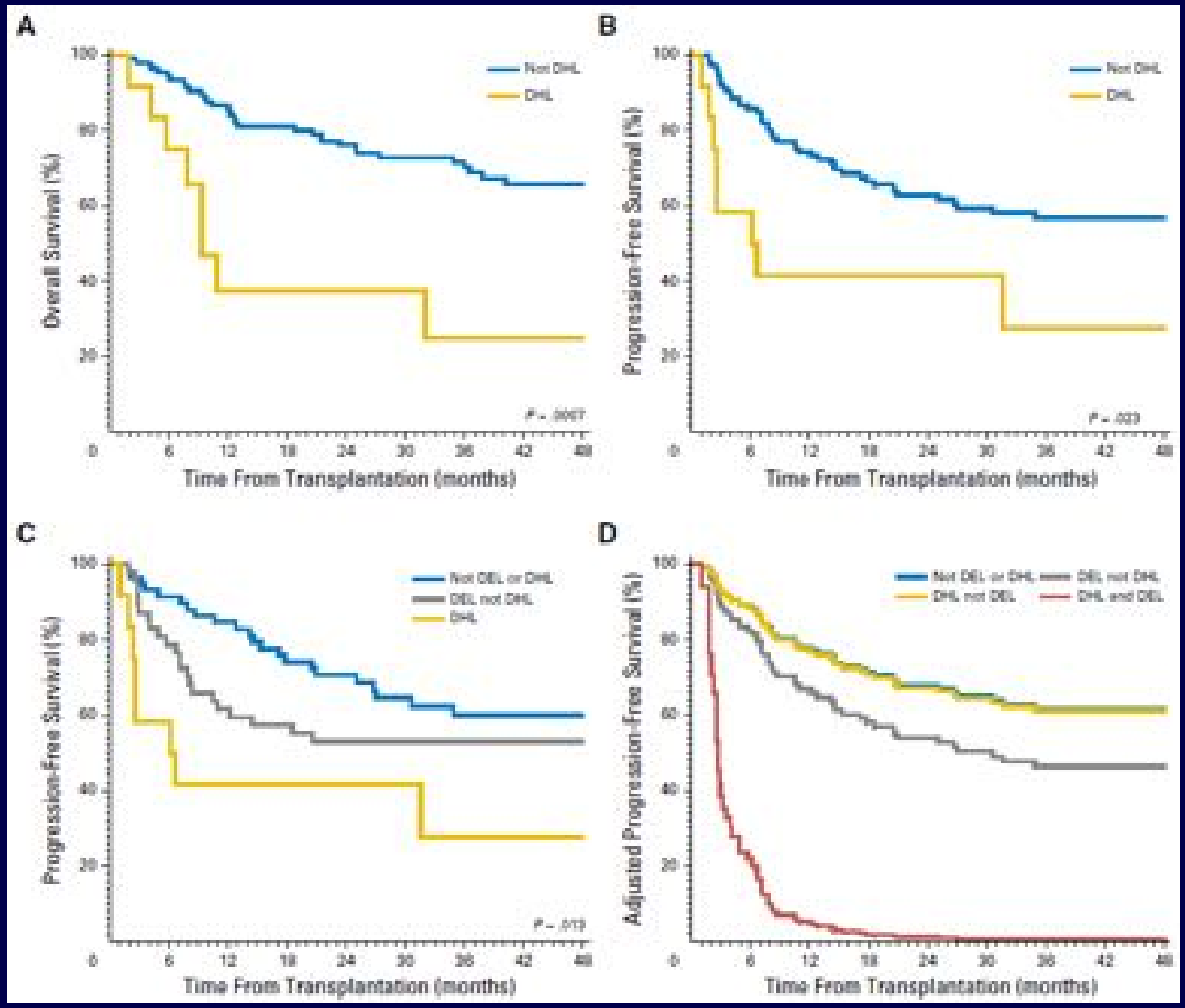
Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	69·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	76·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·6	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78·6	301	72·0	0·8	(0·6 to 1·1)
Asia	160	81	74·3	79	65·6	0·6	(0·4 to 1·0)
Rest of world	116	57	70·8	59	67·3	0·9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·6)
III	232	124	80·7	108	73·6	0·6	(0·3 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	148	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·6	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	63·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	72·0	51	66·2	1·5	(0·8 to 4·5)
Unknown	211	110	73·6	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·6	(0·8 to 17·6)
No	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

Double Expression - Prognosis



Green et al. J Clin Oncol 2012

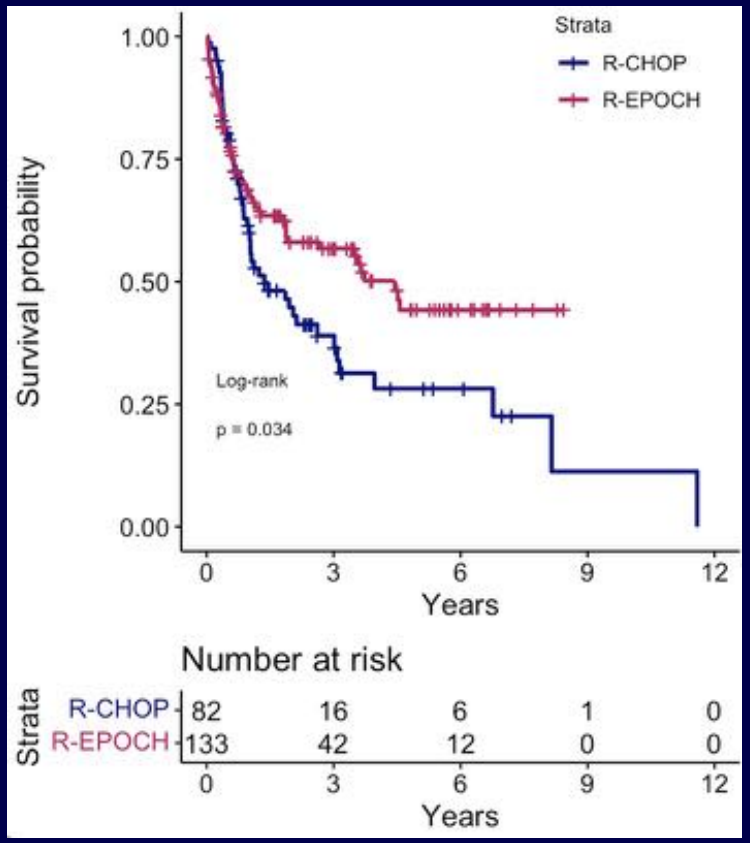
Relapsed DEL/DHL and AutoPSCT



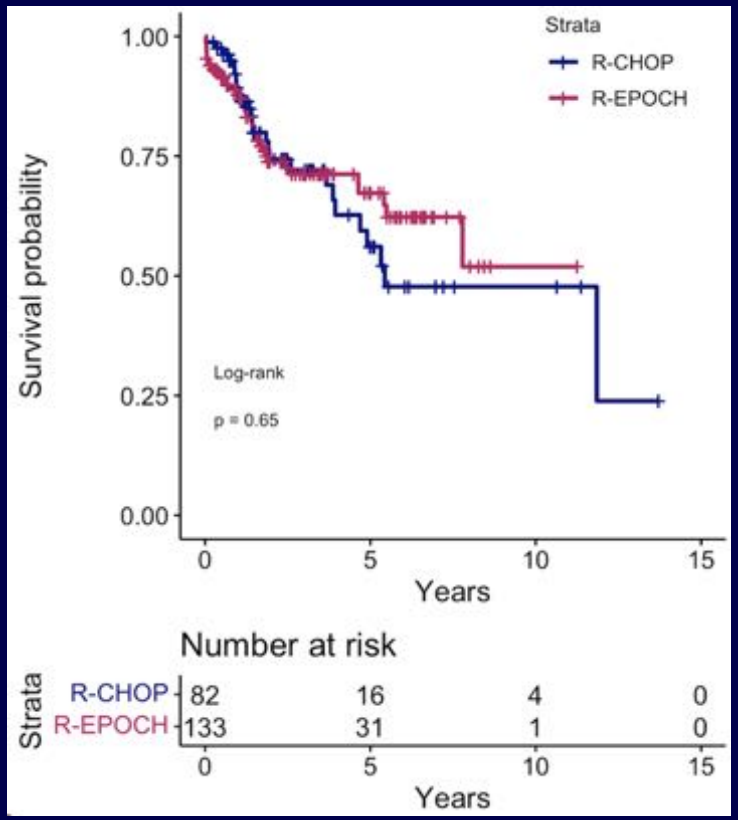
Herrera et al J Clin Oncol 2016

R-DA-EPOCH for DEL

PFS



OS



Othman T et al Clin Myel and Leuk 2022

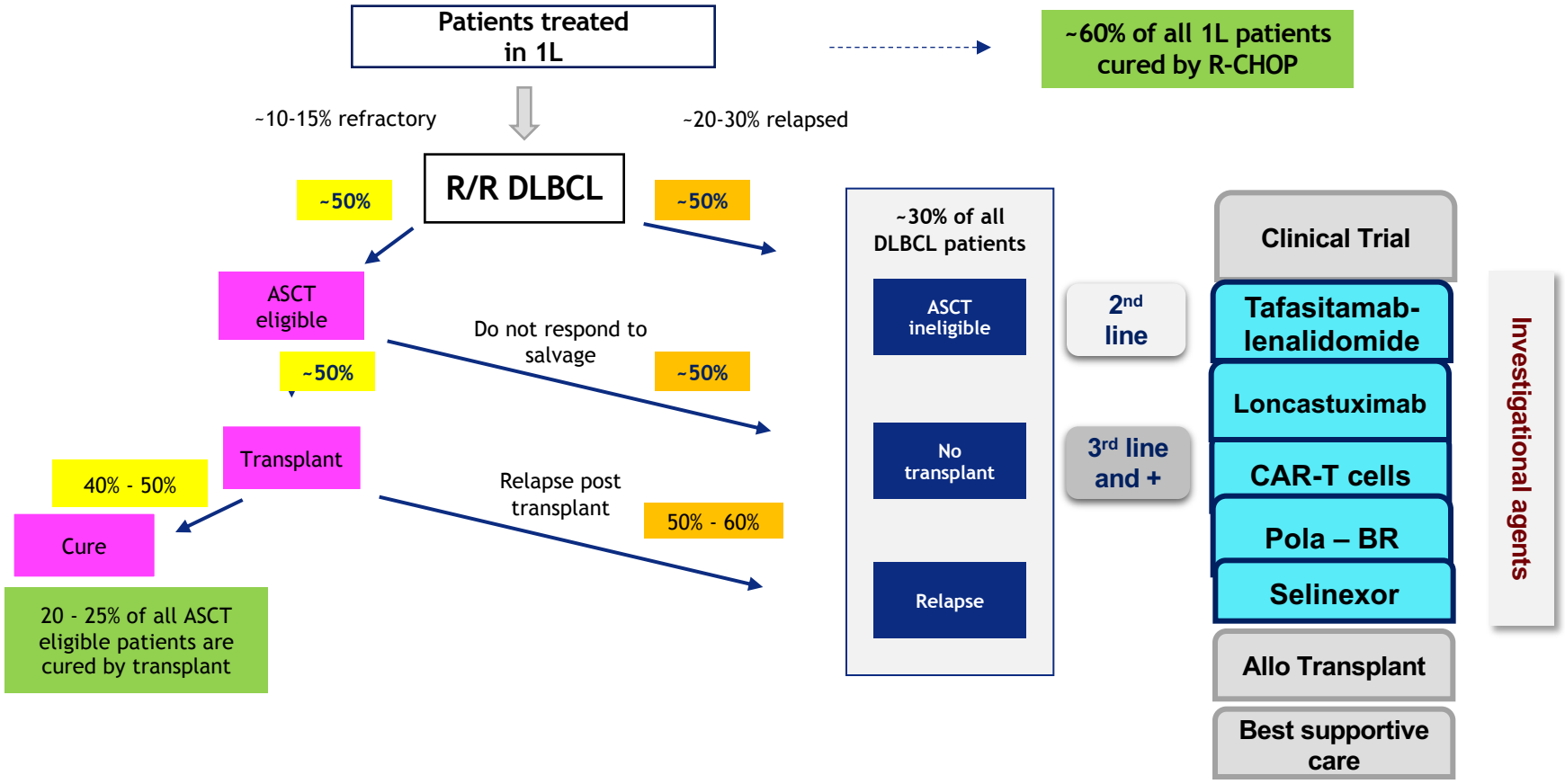
POLARIX: Conclusions

- 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

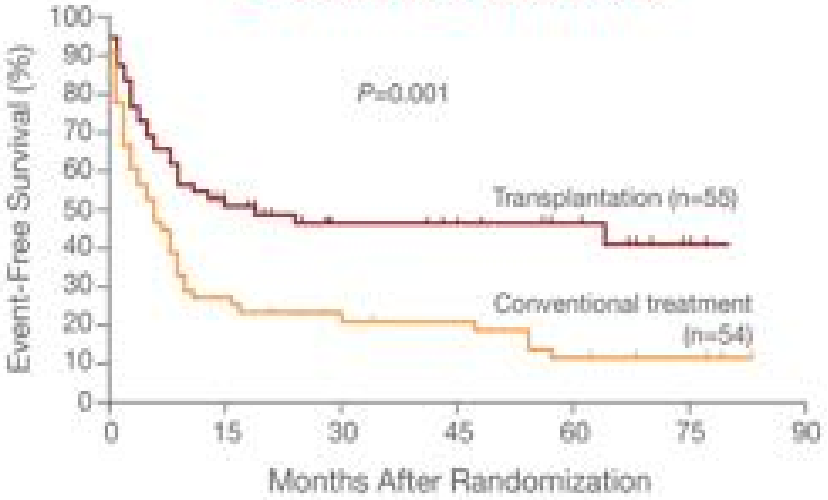
Relapsed and refractory DLBCL



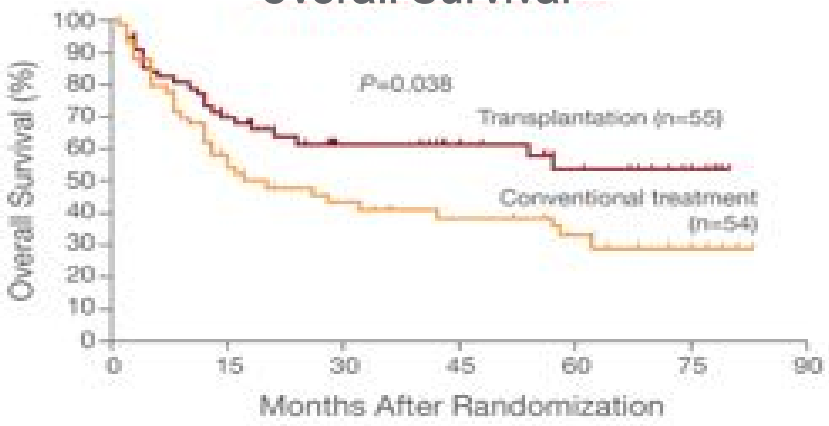
Exciting New Developments for R/R DLBCL Cellular Therapy

Standard of Care for Chemosensitive R/R DLBCL Is ASCT

Event-Free Survival[1]



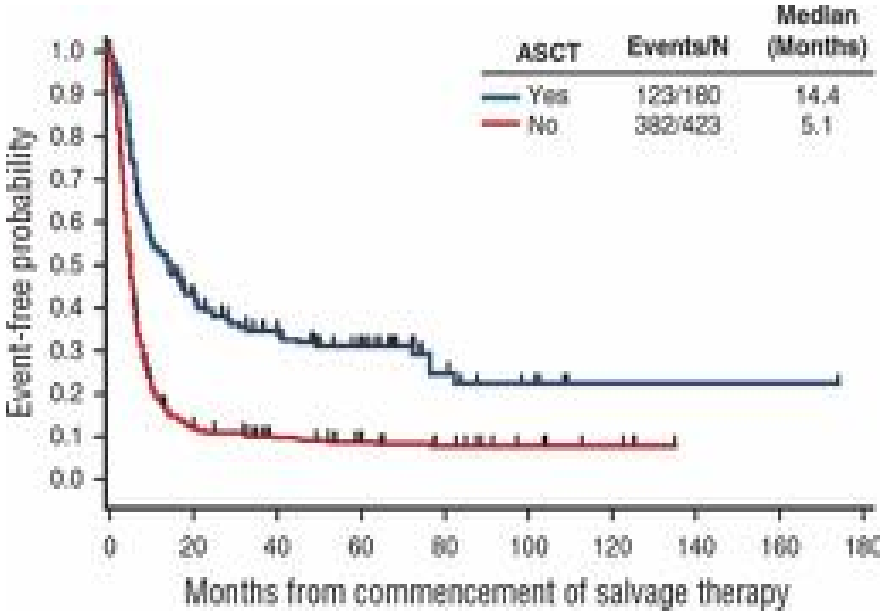
Overall Survival[1]

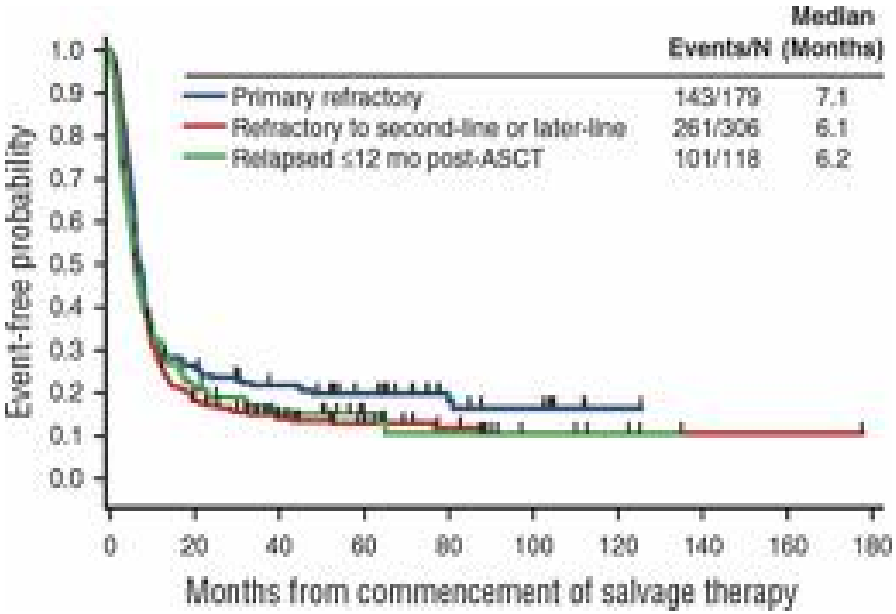


- 20% to 50% of patients will relapse or be refractory to R-CHOP, depending on IPI[2]
- 30% to 40% of patients will respond to salvage chemotherapy and proceed to ASCT[2]
  - Relative equivalency with intensive salvage regimens
- 50% will relapse after ASCT[2]

1. Philip T, et al. *N Engl J Med.* 1995;333(23):1540-1545. 2. Crump M, et al. *Blood*. 2017;130(16):1800-1808.

Outcomes for Patients With Refractory Disease: SCHOLAR-1 Event-Free Probability





Crump M, et al. *Blood.* 2017;130(16):1800-1808.

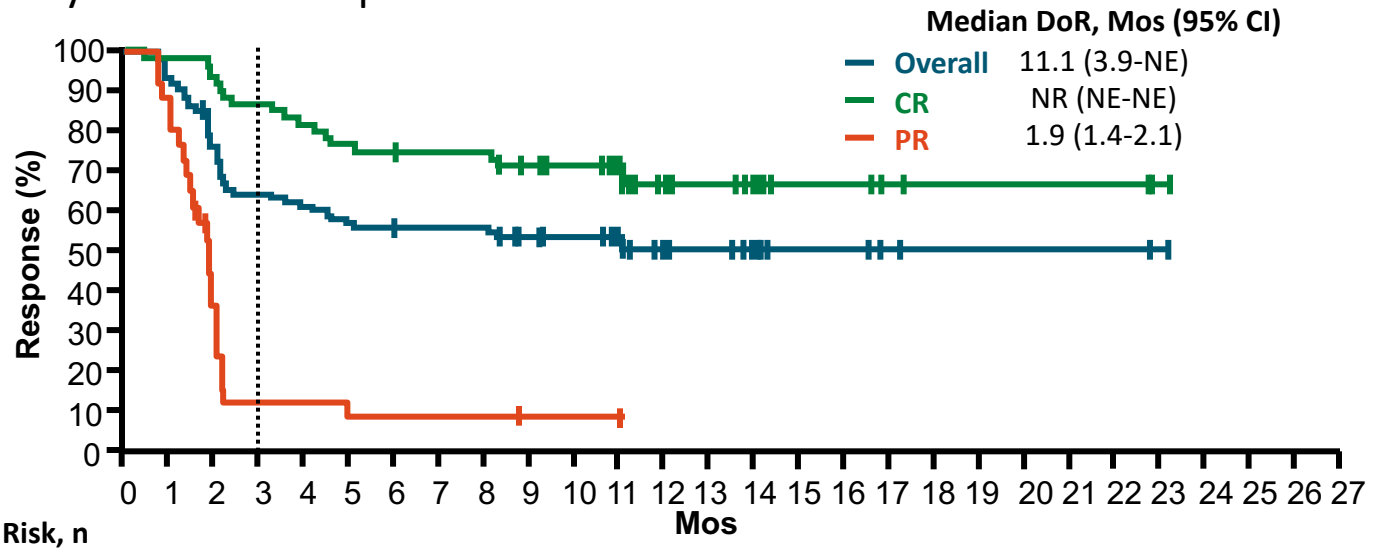
Axicabtagene Ciloleucel in Patients With Refractory DLBCL (ZUMA-1): Background

- Axi-cel: autologous second-generation CD19-directed CAR T-cell therapy[1,2]
  - FDA approved for use in adult R/R large B-cell lymphoma after ≥ 2 lines of therapy based on the results of ZUMA-1
- ZUMA-1: multicenter, multicohort phase I/II trial in patients with refractory DLBCL, PMBCL, or transformed FL (N = 111)[2]
  - After median follow-up of 15.4 mos, ORR of 82%, CR rate of 54% in 108 patients with minimum 1-yr follow-up
    - Responses ongoing in 42% at time of primary analysis, with 40% in CR
- Current report of long-term follow-up data from ZUMA-1 evaluated durability of responses with axi-cel treatment over time and the prognostic value of PR and CR at Month 3 for long-term remissions[3]

1. Axicabtagene ciloleucel [package insert]. 2017. 2. Neelapu SS, et al.
N Engl J Med. 2017;377:2531-2544. 3. Locke FL, et al. ASCO 2018. Abstract 3003.

ZUMA-1: Duration of Response by Best Objective Response (Primary Analysis)

- More than one half of patients with PR progressed by Month 3, defining Month 3 as a clinically relevant timepoint



Patients at Risk, n

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

Neelapu SS, et al. N Engl J Med. 2017;377:2531-2544.

ZUMA-1 Long-term Follow-up: Conclusions

- Long-term analysis of phase II ZUMA-1 trial demonstrated high, durable response rates in patients with refractory large B-cell lymphoma treated with axi-cel
- ORR and CR rate increased during long-term follow-up, with patients achieving CRs up to 1 yr after a single infusion of axi-cel
- Patients with an ongoing response at 3 months had ~ 80% probability of maintaining response at 12 months
- Investigators concluded that achieving PR or CR by 3 months may be prognostic of long-term response to axi-cel
- **At 18 mon med F/U PFS is ~ 37%**

Locke FL, et al. ASCO 2018. Abstract 3003.

ASH 2021: Three Randomized Phase III Trials Comparing CART to SOC APSCT in patients with Primary Refractory DLBCL *OR* Relapsed within 12 Months

ZUMA-7, TRANSFORM, and BELINDA in 2L DLBCL: Study Summary

Variable	Axi-Cel (ZUMA-7)[1]	Liso-Cel (TRANSFORM)[2]	Tisa-Cel (BELINDA)[3,4]
Study design	Axi-cel vs salvage Chemo before HDT-ASCT	Liso-cel vs salvage Chemo before HDT-ASCT	Tisa-cel vs salvage Chemo before HDT-ASCT
Bridging therapy regimens allowed	Steroids	Protocol-defined SOC regimen	R-DHAP, R-ICE, R-GemOx, or R-GDP
Primary endpoint	EFS	EFS	EFS
Secondary endpoints	ORR, OS, PFS, safety, PROs	CR rate, PFS, OS, DOR, ORR, PFS, safety, PROs	ORR, safety, cellular kinetics
Crossover to CAR T-cell therapy allowed?	No Nonresponders could receive additional treatment off protocol	Yes	Yes

ZUMA-7, TRANSFORM, and BELINDA in 2L DLBCL: Efficacy Results

Factor	Axi-Cel (ZUMA-7)[1]		Liso-Cel (TRANSFORM)[2]		Tisa-Cel (BELINDA)[3]	
	Axi-Cel (n=180)	SOC (n=179)	Liso-Cel (n=92)	SOC (n=92)	Tisa-Cel (n=162)	SOC (n=160)
Median follow-up, months	24.9		6.2		10.0	
Median EFS, months (95% CI)	8.3 (4.5-15.8)	2.0 (1.6-2.8)	10.1 (6.1-NR)	2.3 (2.2-4.3)	3.0 (2.9-4.2)	3.0 (3.0-3.5)
HR *P* value	0.398 (0.31-0.51) <0.0001		0.349 (0.23-0.53) <0.0001		1.07 (0.82-1.40) 0.69	
ORR, % CR, %	83 65	50 32	86 66	48 39	46 28	43 28

- ZUMA-7 and TRANSFORM met their primary endpoint of EFS
- BELINDA failed to meet its primary endpoint of EFS and had no advantage over SOC

1. Locke FL, et al. ASH 2021. Abstract 2. 2. Kamdar M, et al. ASH 2021. Abstract 91. 3. Bishop M, et al. ASH 2021. Abstract LBA-6.

ZUMA-7, TRANSFORM, and BELINDA in 2L DLBCL: Safety Results

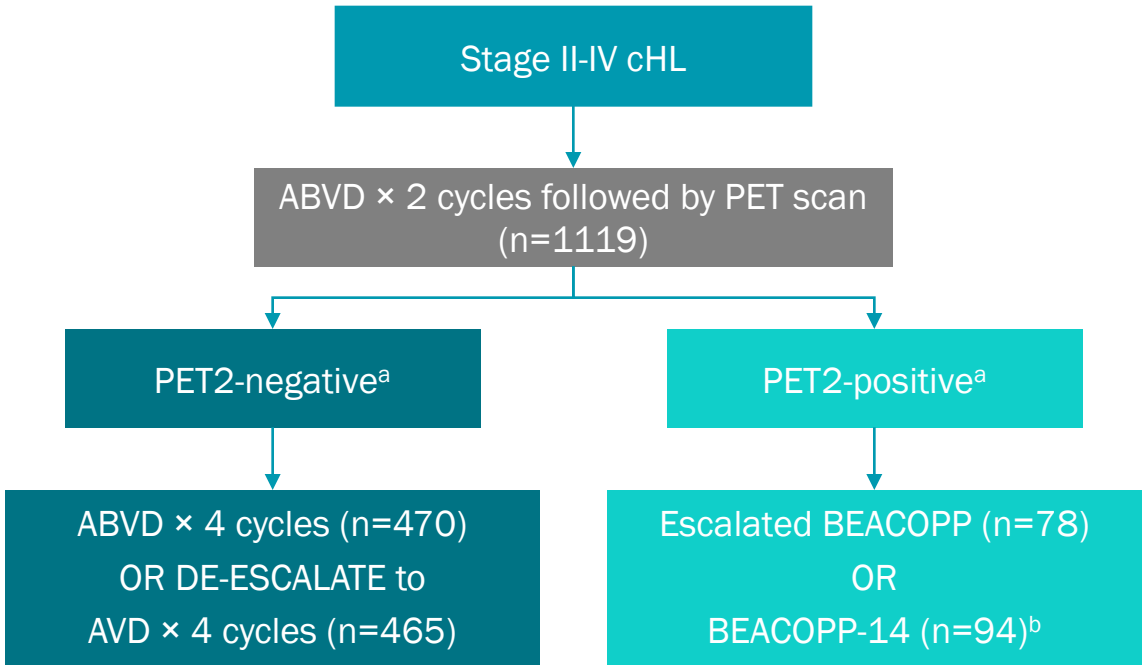
Factor	Axi-Cel (ZUMA-7)[1]		Liso-Cel (TRANSFORM)[2]		Tisa-Cel (BELINDA)[3]	
	Axi-Cel (n=180)	SOC (n=179)	Liso-Cel (n=92)	SOC (n=92)	Tisa-Cel (n=162)	SOC (n=160)
Grade AE, % Grade ≥3 AE	100 91	100 83	100 92	99 87	99 84	99 90
Grade ≥3 CRS, % Median time to onset, day Median duration, day	6 3 7	-	1 5 Not reported	-	5 Not reported Not reported	-
Grade ≥3 NE, % Median time to onset, day Median duration, day	21 7 9	1 23 23	4 11 Not reported	-	2 Not reported Not reported	-

- Across all studies, AEs between the CAR T-cell therapy and SOC were generally comparable with a low incidence of grade ≥3 CRS and NE

Treatment of Newly Diagnosed Hodgkin's Lymphoma

Recent Developments

RATHL: Response-Adapted Therapy for Advanced cHL



Primary Endpoint
Difference in 3-year PFS between groups (noninferiority comparison)

[a] PET2-negative = Deauville score of 1-3; PET2-positive = Deauville score of 4-5.

[b] PET2-positive patients received 3 cycles of escalated BEACOPP or 4 cycles of BEACOPP-14 and underwent an additional PET scan. Patients who were still PET-positive received radiotherapy or a salvage regimen; those who were PET-negative received either 1 cycle of escalated BEACOPP or 2 cycles of BEACOPP-14.

Johnson P, et al. *N Engl J Med*. 2016;374(25):2419-2429.

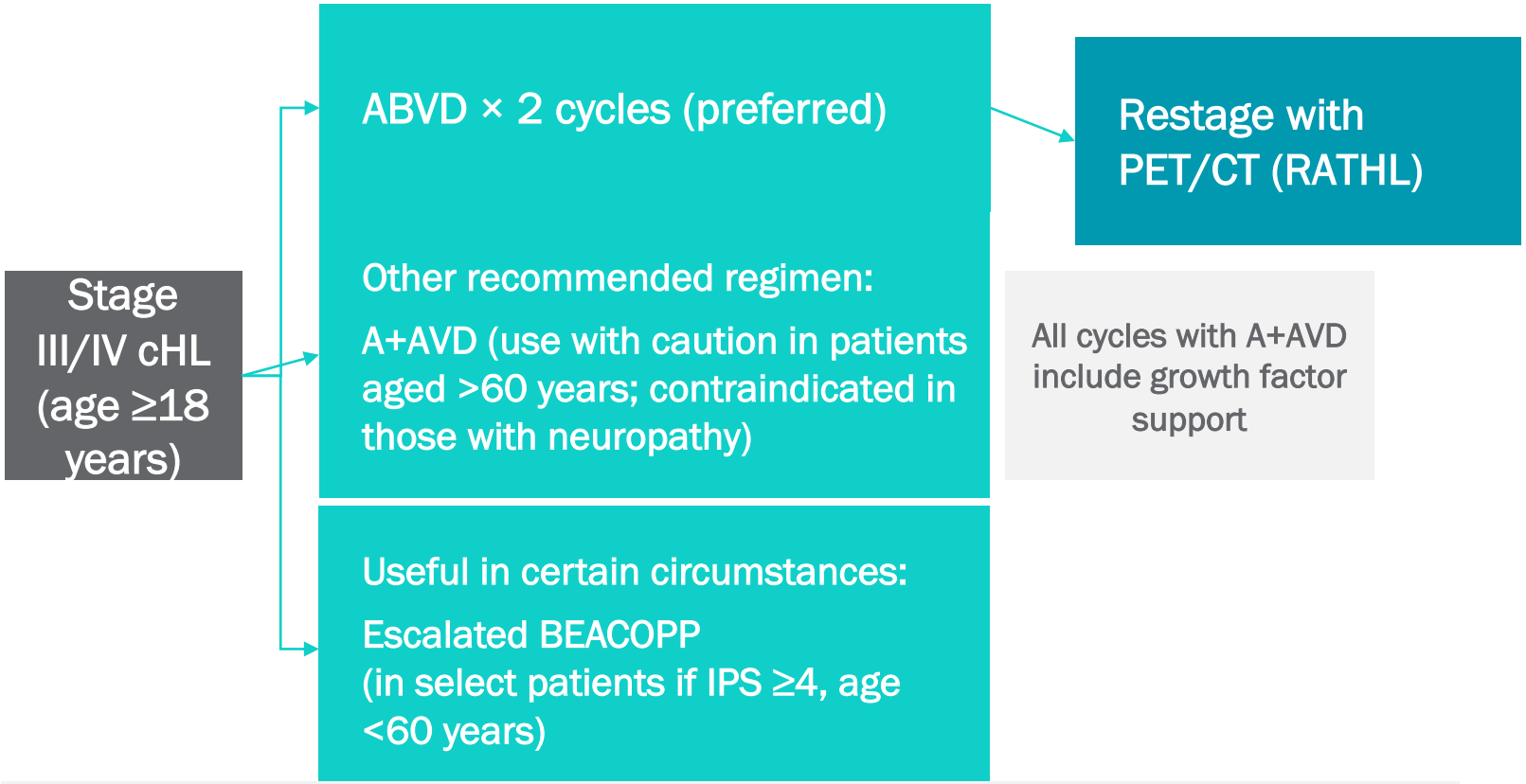
RATHL Outcomes[1,2]

Outcome, %	ABVD (n=470)	AVD (n=465)	BEACOPP (n=172)
3-year PFS (95% CI)	85.7 (82.1, 88.6)	84.4 (80.7, 87.5)	67.5 (59.7, 74.2)
Ann Arbor stage III or IV and age ≤60 years			
3-year PFS (95% CI)	82.1 (76.5, 86.5)	82.1 (76.3, 86.4)	63.9 (52.9, 72.9)
5-year PFS (95% CI)	82.7 (78.8, 86.0)	80.6 (76.2, 84.2)	65.7 (57.9, 72.5)

- De-escalation to AVD was associated with lower pulmonary toxicity risk compared with ABVD

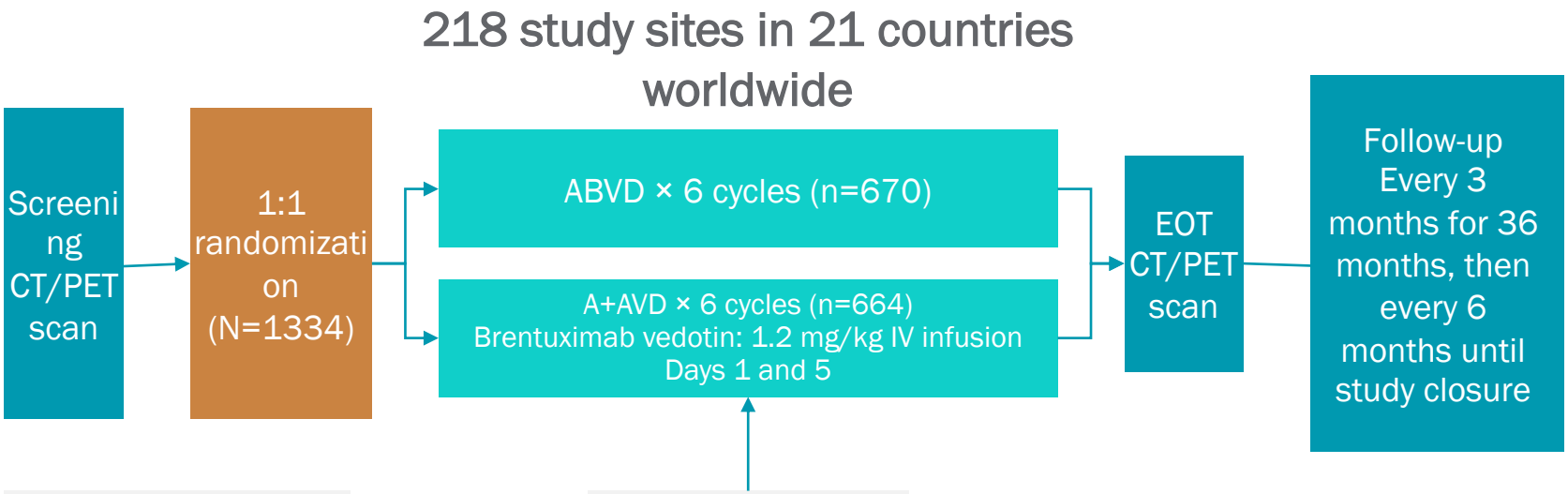
1. Johnson P, et al. *N Engl J Med*. 2016;374(25):2419-2429. 2. Trotman J, et al. *Hematol Oncol*. 2017;35(S2):65-67.

NCCN Guidelines® in Stage III-IV cHL (Last Updated February 2022)



National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 2.2022). Accessed February 23, 2022. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

ECHELON-1: A+AVD vs ABVD in Advanced cHL



Inclusion Criteria

- cHL stage III or IV
- ECOG PS 0, 1, or 2
- Age ≥18 years
- Measurable disease
- Adequate liver and renal function

PET 2 Scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

Primary Endpoint

- Modified PFS[a] per IRF

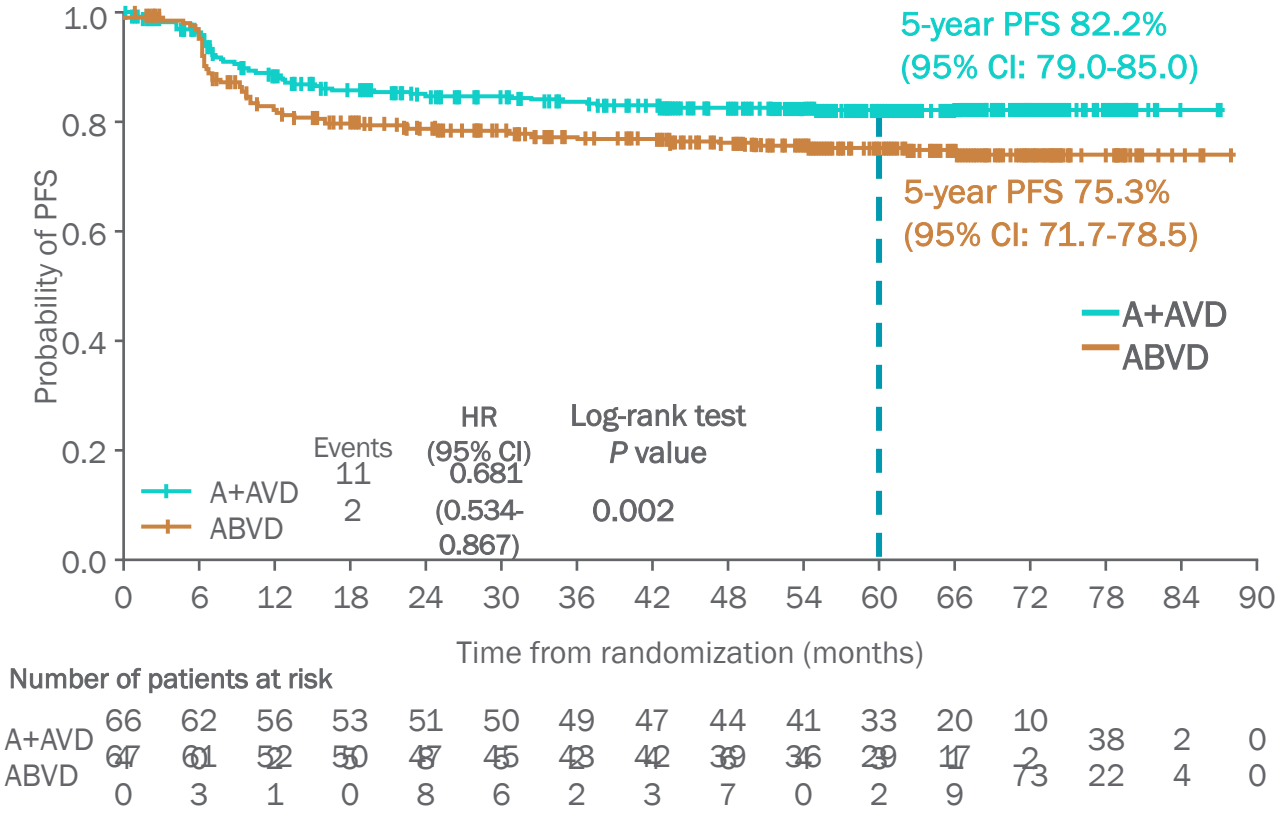
Key Secondary Endpoint

- Overall survival

[a] Modified PFS: Progression, death from any cause, or receipt of additional anticancer therapy for patients not in CR after completion of frontline therapy.

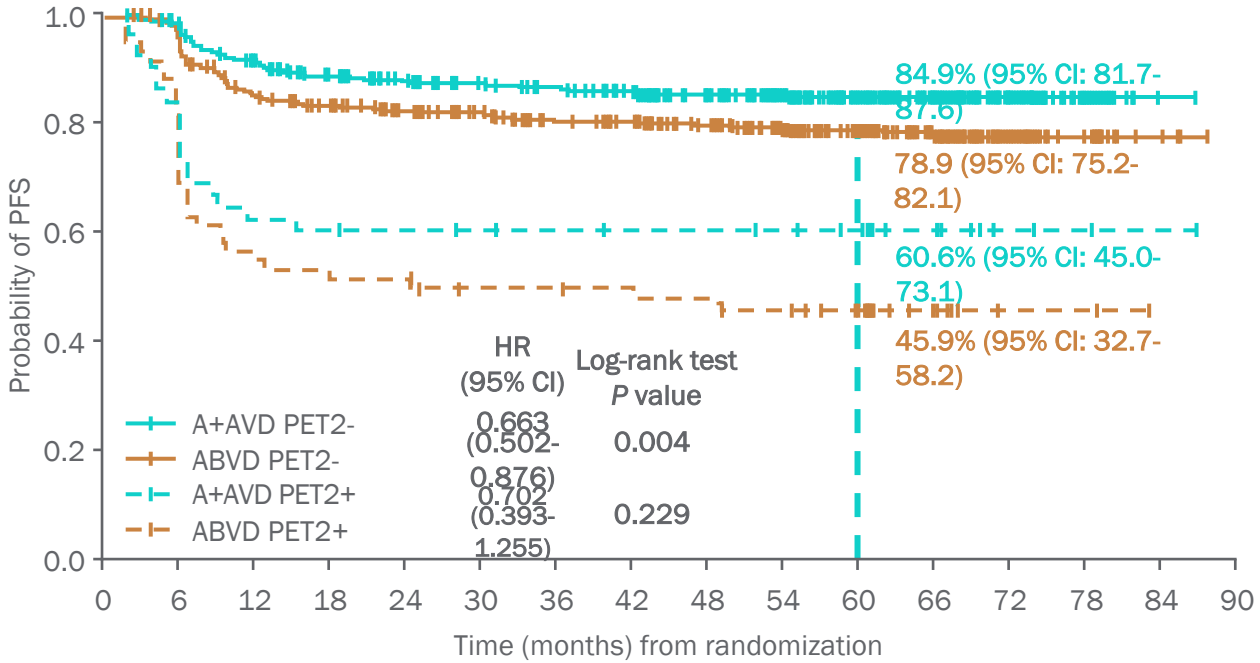
Connors JM, et al. *N Engl J Med*. 2018;378(4):331-344.

ECHELON-1: PFS Per Investigator at 5-Year Follow-Up



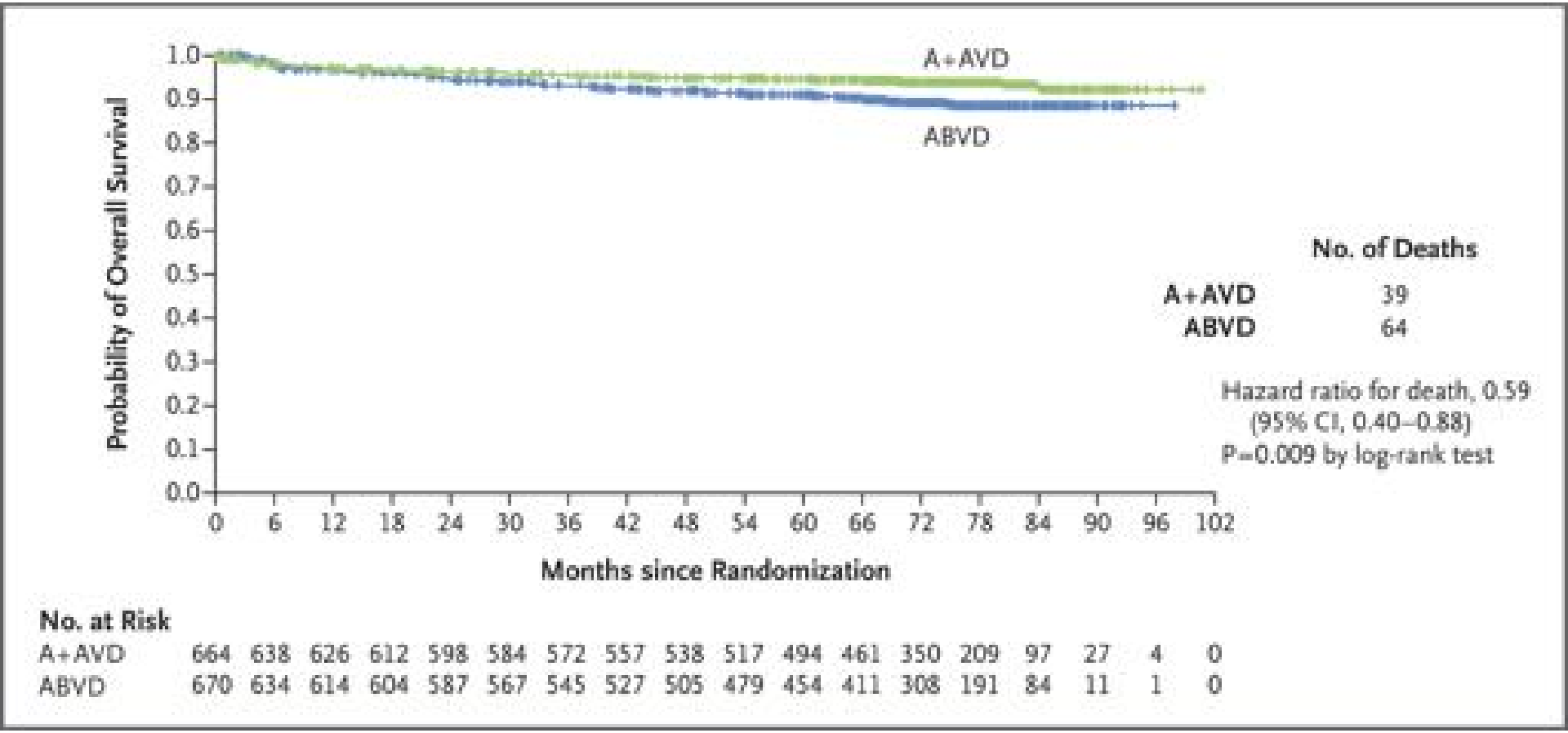
Straus DJ, et al. ASH 2020. Abstract 2973.

ECHELON-1: 5-Year PFS Rates by PET2 Status



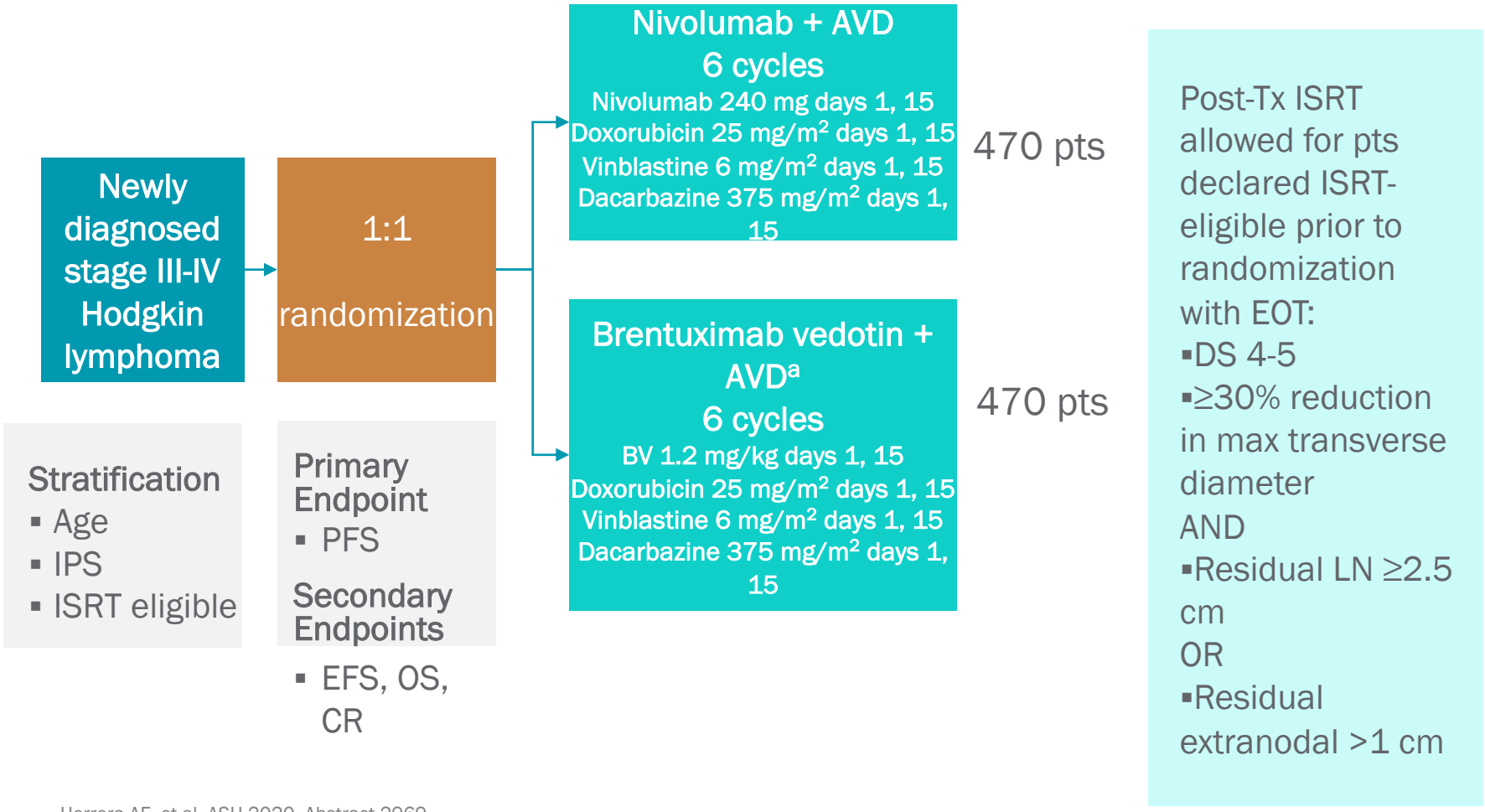
Straus DJ, et al. ASH 2020. Abstract 2973.

ECHELON-1: LTFU Overall Survival Analysis



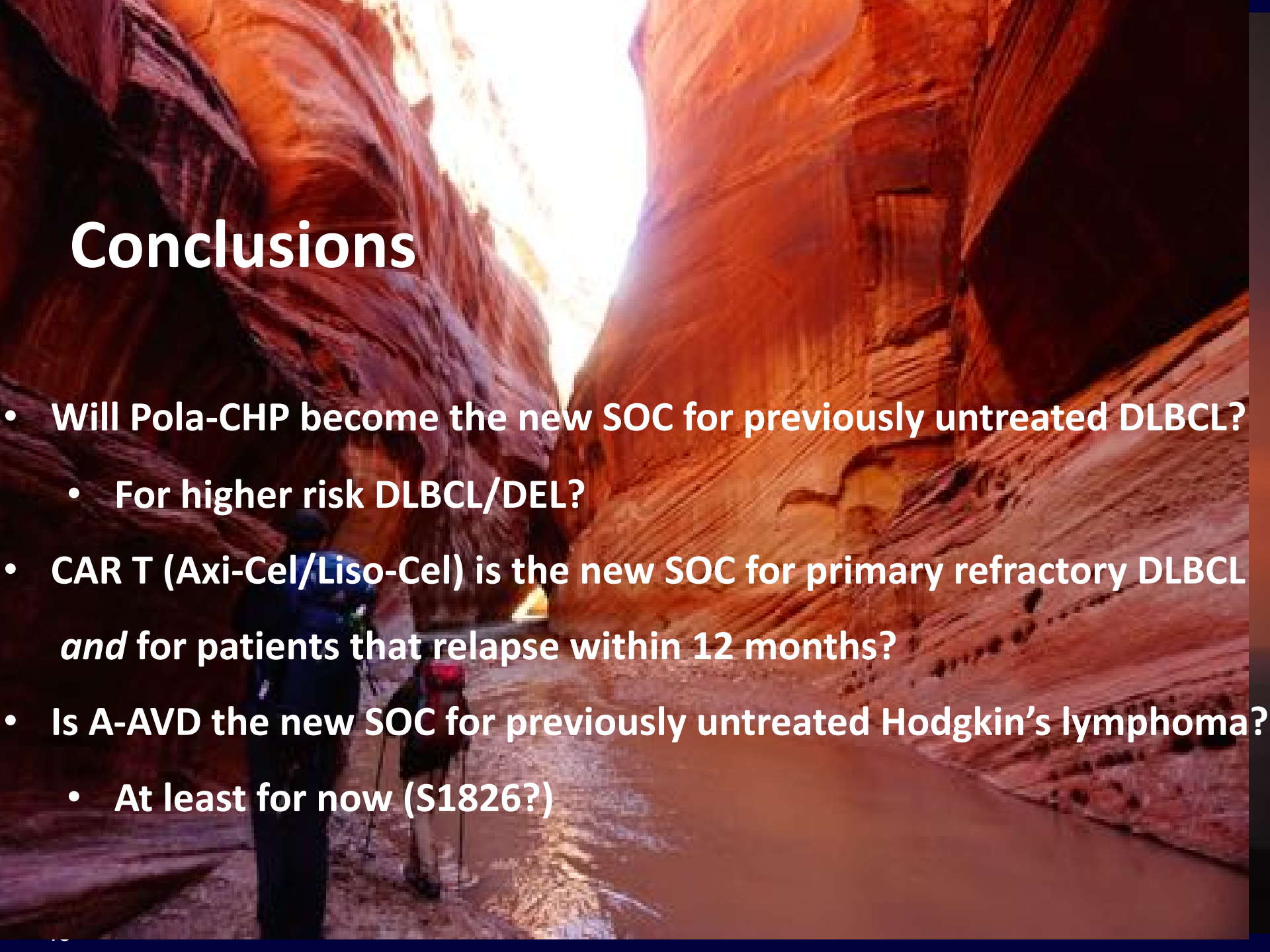
Ansell et al NEJM 2022

S1826 Intergroup Study: Accrual Nearly Complete



Herrera AF, et al. ASH 2020. Abstract 2969.

[a] G-CSF is mandatory in BV-AVD arm, optional in N-AVD arm



Conclusions

- Will Pola-CHP become the new SOC for previously untreated DLBCL?
  - For higher risk DLBCL/DEL?
- CAR T (Axi-Cel/Liso-Cel) is the new SOC for primary refractory DLBCL *and* for patients that relapse within 12 months?
- Is A-AVD the new SOC for previously untreated Hodgkin's lymphoma?
  - At least for now (S1826?)