IN PURSUIT OF *YOUR CURE.*™

North Carolina Symposium

Craig Moskowitz, MD
Physician in Chief
Sylvester Comprehensive Cancer Center
Professor of Medicine, Miller School of Medicine
University of Miami Health System

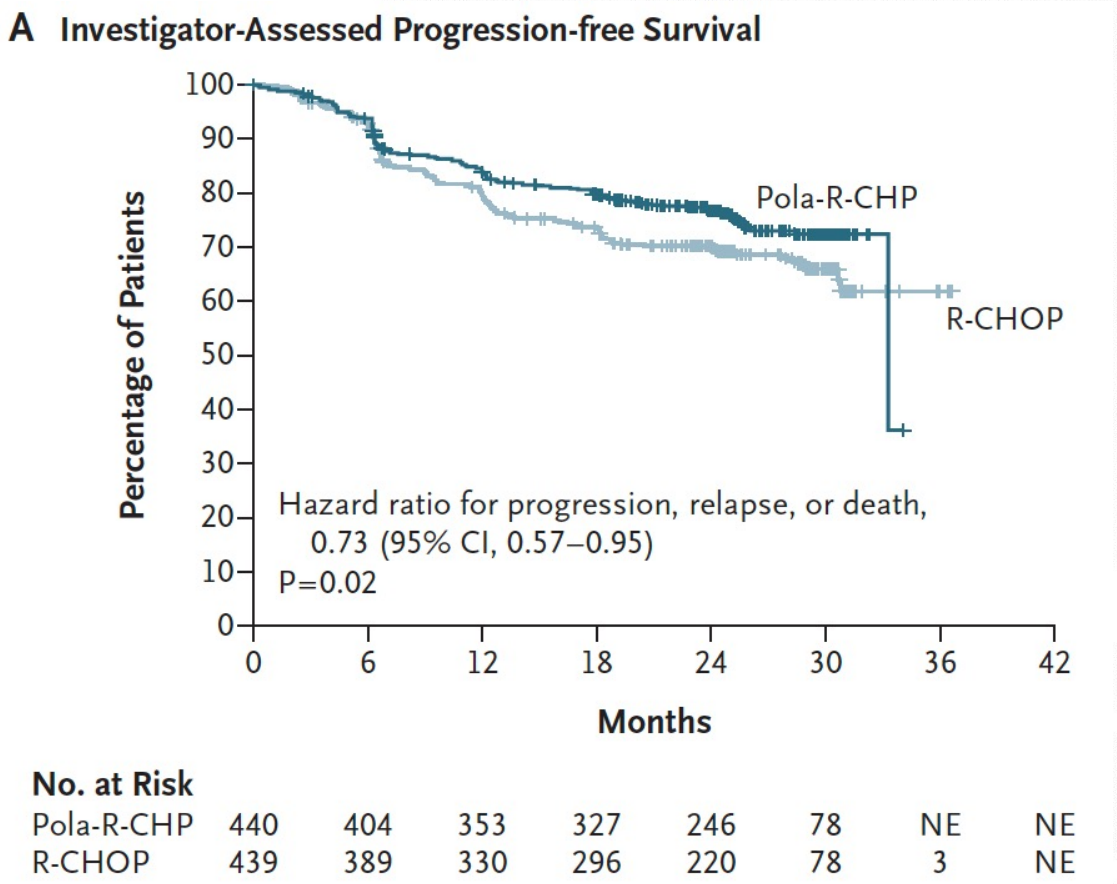
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

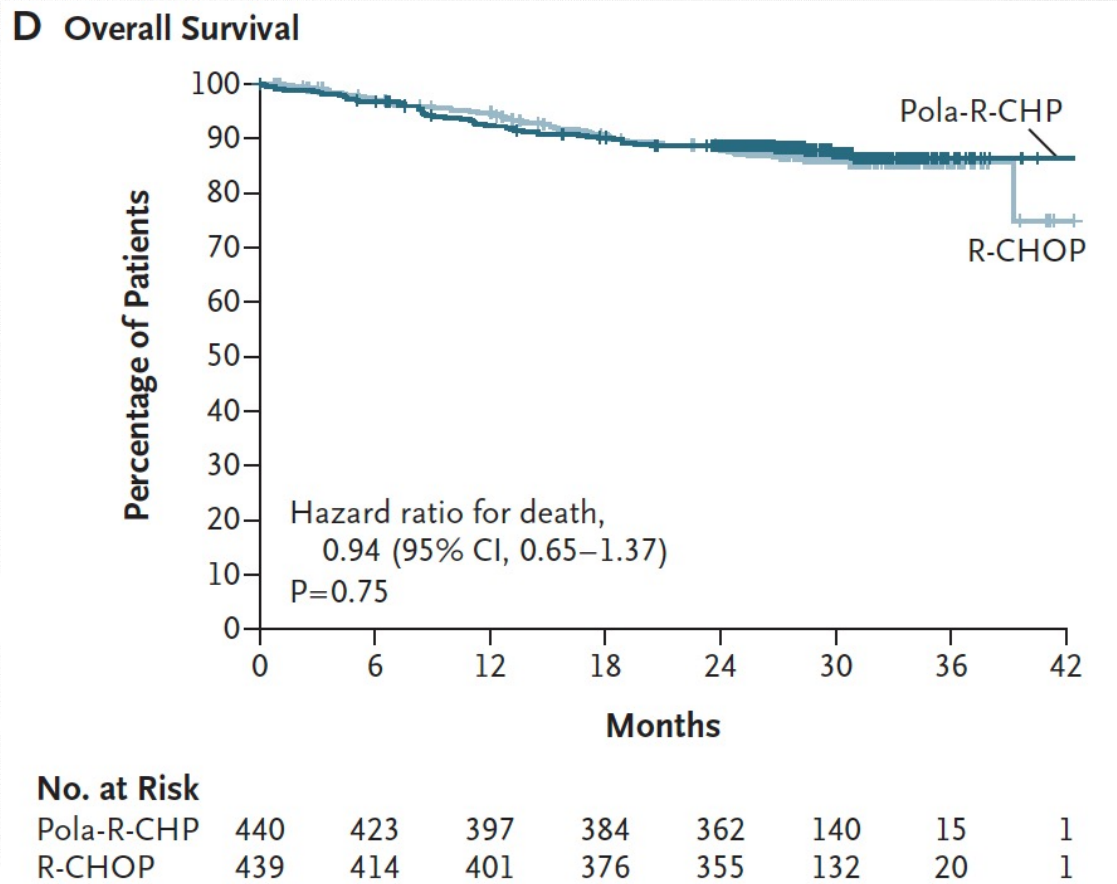
NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Discussion Question

In which situations, if any, do you feel it would be beneficial to administer polatuzumab vedotin/R-CHP as first-line therapy for diffuse large B-cell lymphoma (DLBCL)?

POLARIX: Polatuzumab Vedotin-R-CHP vs R-CHOP in 1L DLBCL



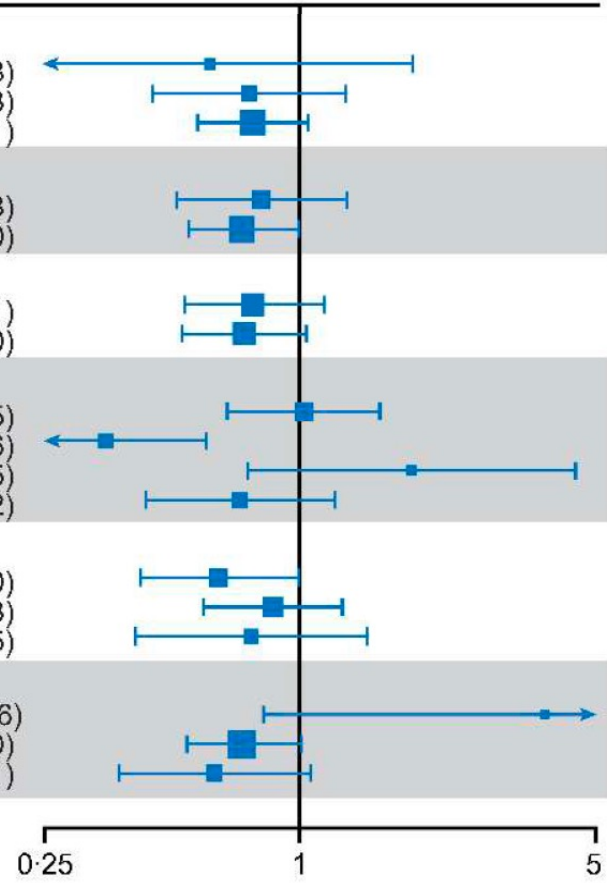


Tilly H et al. N Engl J Med 2022;386(4):351-363; Mehta-Shah N et al. Pan Pacific Lymphoma Conference 2022.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

POLARIX: Polatuzumab Vedotin-R-CHP vs R-CHOP in 1L DLBCL

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
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	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	73·0	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	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	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	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Tilly H et al. N Engl J Med 2022;386(4):351-363.

Discussion Question

For patients with relapsed/refractory (R/R) DLBCL, how do you usually sequence CAR T-cell therapy, polatuzumab vedotin, tafasitamab/lenalidomide, loncastuximab tesirine and selinexor?

Lancet Haematol 2020;7:e511-22.

Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Nagesh Kalakonda, Marie Maerevoet*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima De la Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales*

	ORR	CRR
All patients	36/127 **(28%)**	15/127 (12%)
GCB subtype	20/59 (34%)	8/59 (14%)
Non-GCB subtype	13/63 (21%)	6/63 (10%)
Unclassified	3/5 (60%)	1/5 (20%)

Maerevoet *et al. J Hematol Oncol* (2021) 14:111
https://doi.org/10.1186/s13045-021-01122-1

Journal of Hematology & Oncology

LETTER TO THE EDITOR Open Access

Survival among patients with relapsed/refractory diffuse large B cell lymphoma treated with single-agent selinexor in the SADAL study

Marie Maerevoet[1*], Josee M. Zijlstra[2], George Follows[3], Rene-Olivier Casasnovas[4], J. S. P. Vermaat[5], Nagesh Kalakonda[6], Andre Goy[7], Sylvain Choquet[8], Eric Van Den Neste[9], Brian Hill[10], Catherine Thieblemont[11,12], Federica Cavallo[13], Fatima De la Cruz[14], John Kuruvilla[15], Nada Hamad[16], Ulrich Jaeger[17], Paolo Caimi[18], Ronit Gurion[19,20], Krzysztof Warzocha[21], Sameer Bakhshi[22], Juan-Manuel Sancho[23], Michael Schuster[24], Miklos Egyed[25], Fritz Offner[26], Theodoros P. Vassilakopoulos[27], Priyanka Samal[28], Matthew Ku[29], Xiwen Ma[30], Kelly Corona[30], Kamal Chamoun[30], Jatin Shah[30], Sharon Shacham[30], Michael G. Kauffman[30] and Miguel Canales[31]

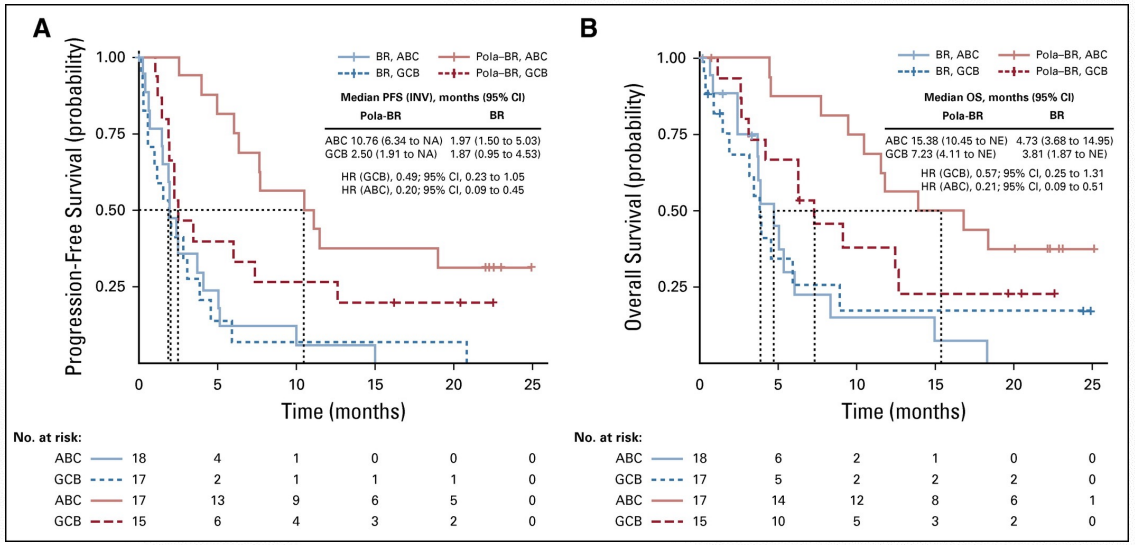
	Median OS
All patients (n = 134)	9 mo
Patients with CR/PR (n = 39)	Not reached
Nonresponders (n = 95)	4.9 mo

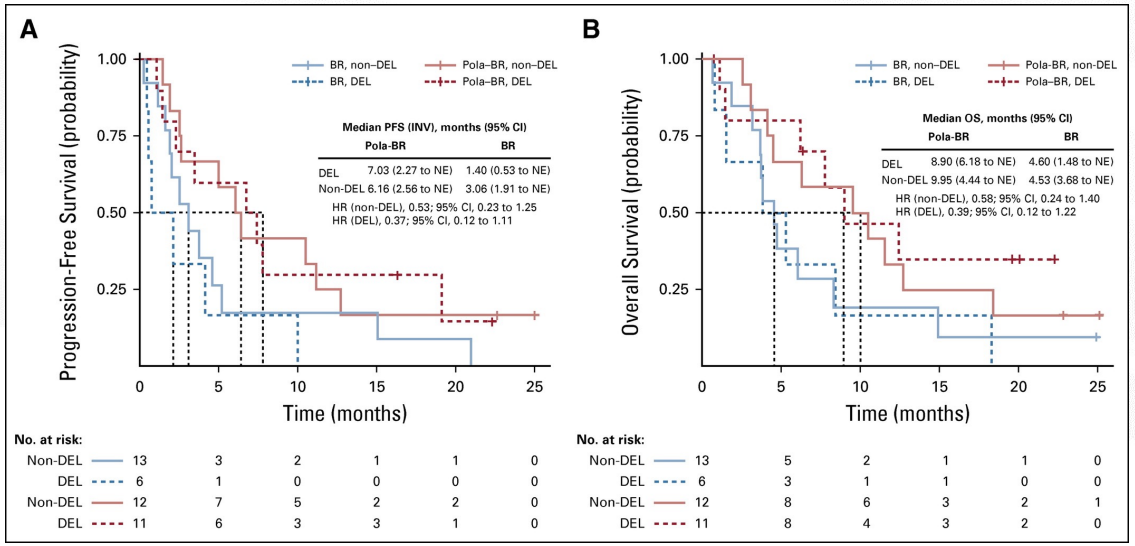
SADAL Post-Hoc Analysis: Effect of Prior Therapy and Disease Refractoriness on the Efficacy of Selinexor

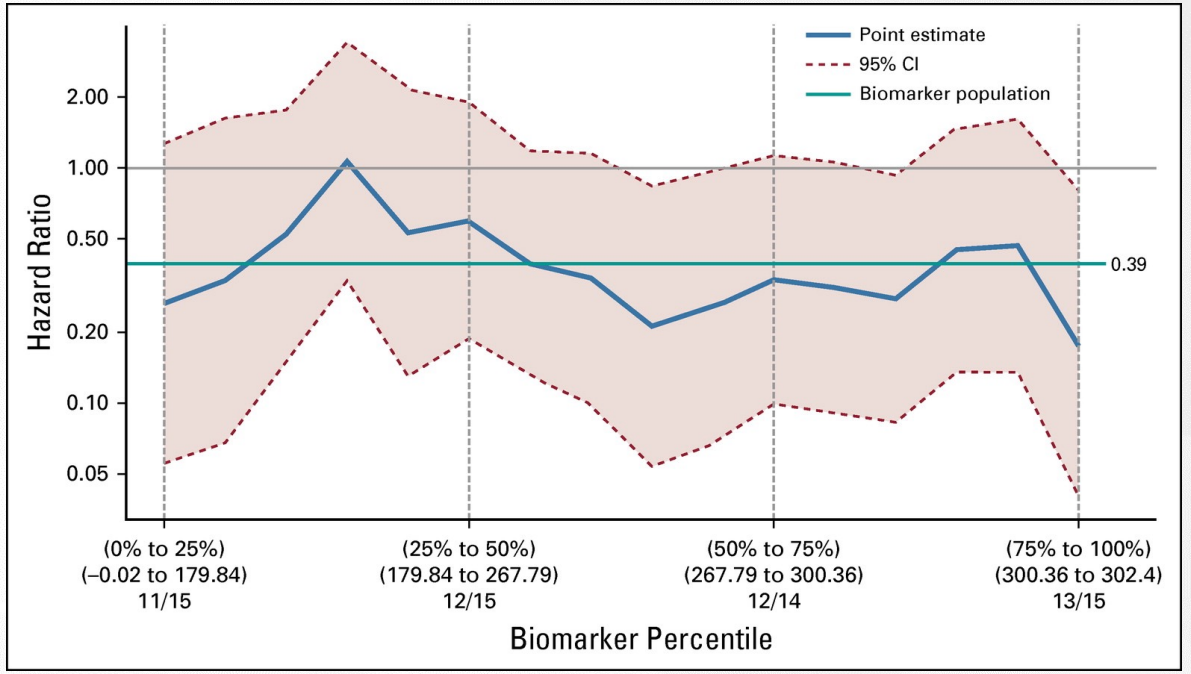
Patients	ORR, % (95% CI)	*P value*
Prior treatments		
2 Lines of Prior Therapies (n = 79)	27.8 (18.3, 39.1)	
3 or More Lines of Prior Therapies (n = 55)	30.9 (19.1, 44.8)	*.8490*
Prior ASCT (n = 40)	42.5 (27.0, 59.1)	
No Prior ASCT (n = 94)	23.4 (15.3, 33.3)	*.0435*
Response to Last Therapy		
PR or CR (n = 92)	35.9 (26.1, 46.5)	
No PR or CR (n = 37)	16.2 (6.2, 32.0)	*.0470*
Primary Refractory <6 Months (n = 55)	21.8 (11.8, 35.0)	
Primary Refractory ≥6 Months (n = 62)	37.1 (25.2, 50.3)	*.1098*

Schuster M et al. Clin Lymphoma Myeloma Leuk 2022;22(7):483-494.

Polatuzumab Vedotin + BR in R/R DLBCL – phase 2



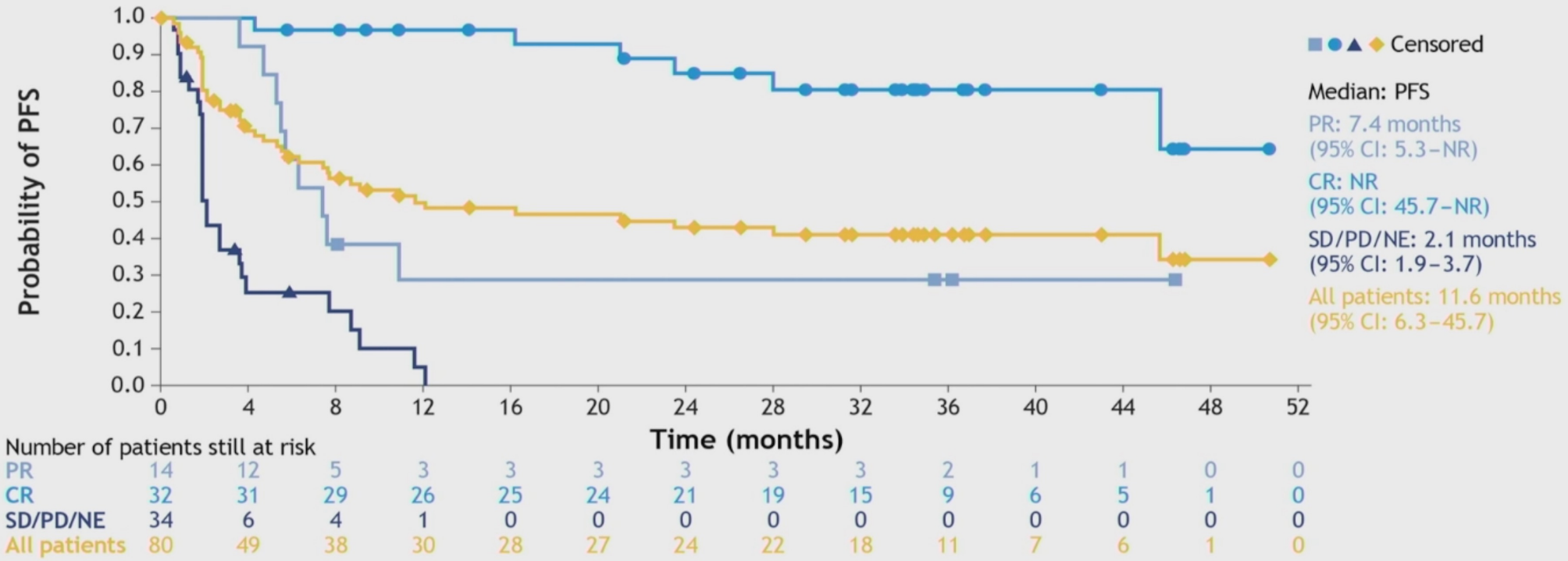




Sehn LH et al. J Clin Oncol 2020;38(2):155-165.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

L-MIND: prolonged PFS in a subset of patients



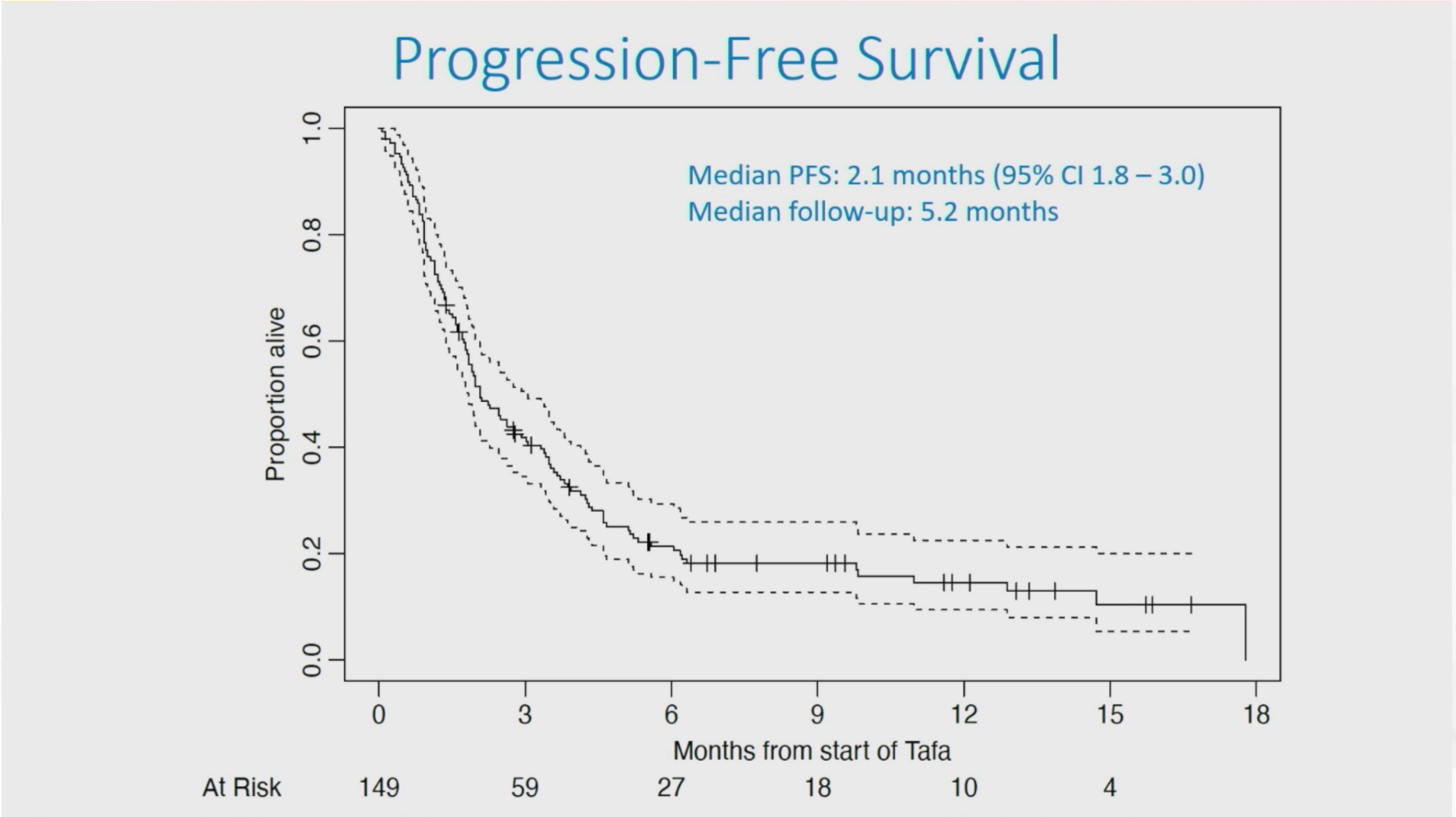
Number of patients still at risk

PR	14	12	5	3	3	3	3	3	3	2	1	1	0	0
CR	32	31	29	26	25	24	21	19	15	9	6	5	1	0
SD/PD/NE	34	6	4	1	0	0	0	0	0	0	0	0	0	0
All patients	80	49	38	30	28	27	24	22	18	11	7	6	1	0

Duell J et al., Haematologica 2021
Duell J et al., presented at ASCO 2021

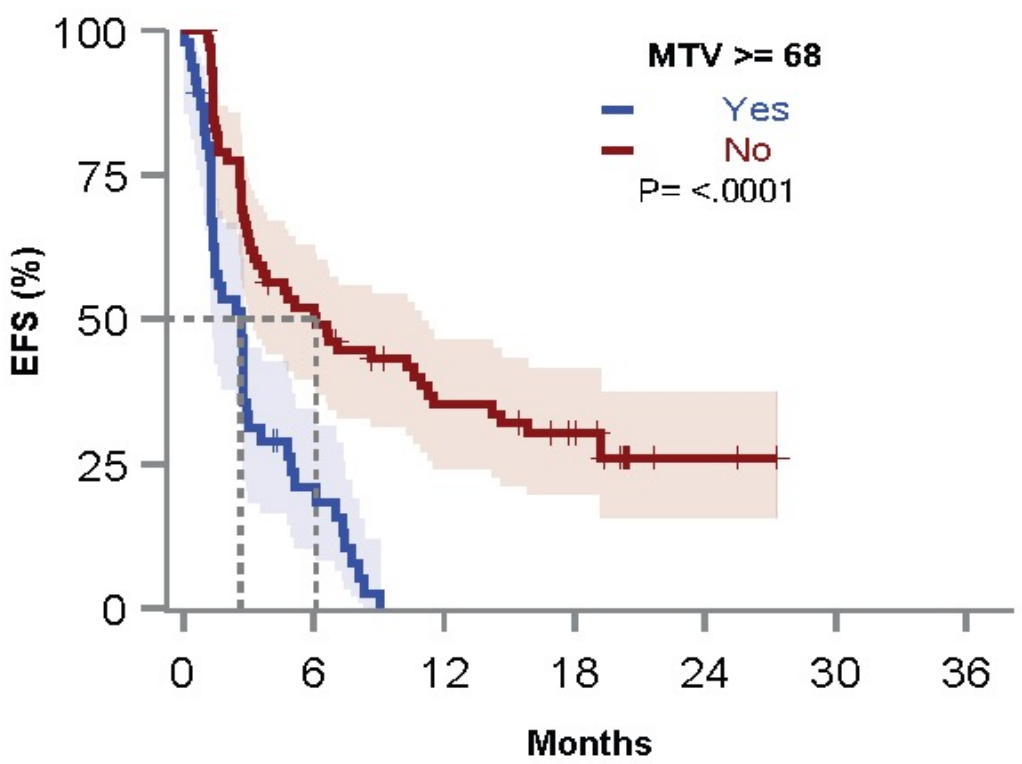
Qualls D et al. ASH 2022 abstract 323.

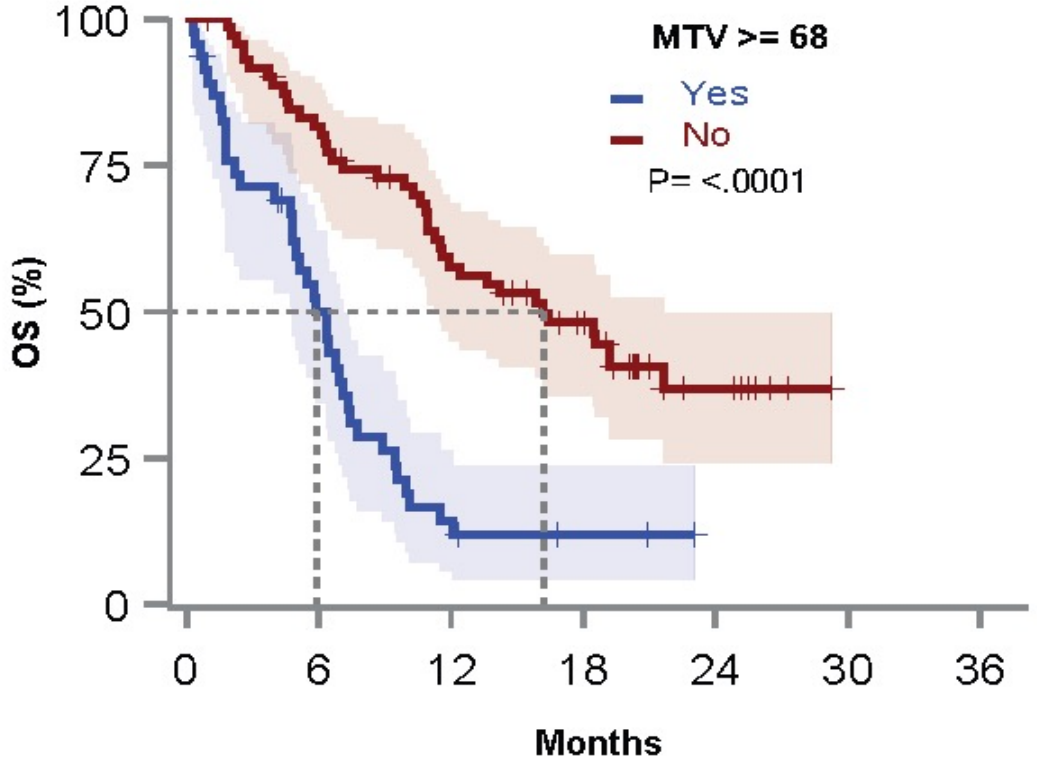
Tafasitamab-Lenalidomide Real World Data



Qualls D et al. ASH 2022 abstract 323.

Metabolic tumor volume predicts outcomes in patients with relapsed/refractory diffuse large B-cell lymphoma treated with loncastuximab tesirine in the LOTIS-2 trial





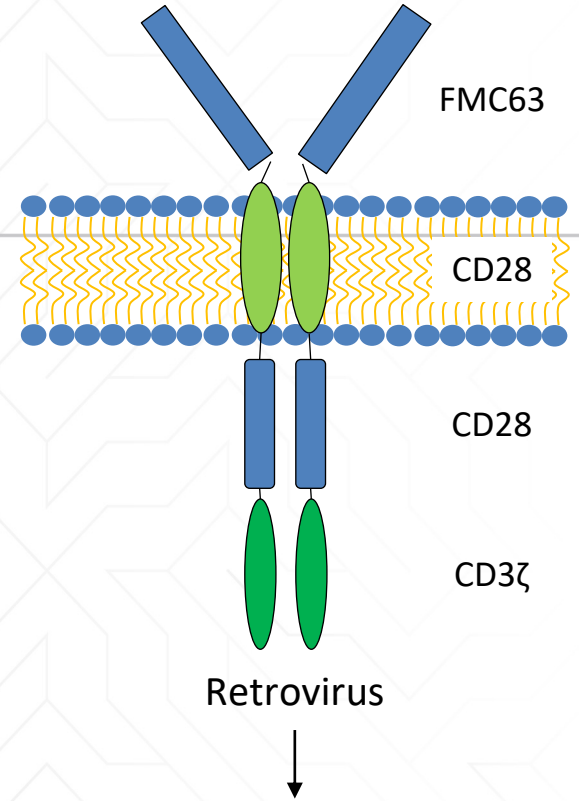
Cutpoints associated with shorter survival

SUVmax ≥ 18 (*EFS*: HR=1.65, 95%CI 1.06-2.55, P=0.027 & *OS*: HR=1.7, 95%CI 1.06-2.75, P=0.029)
MTV ≥ 68ml (*EFS*: HR=3.02, 95%CI 1.94-4.7, P<.0001 & *OS*: HR=3.26, 95%CI 2.05-5.19, P<.0001)
TLG ≥ 479 (*EFS*: HR=2.34, 95%CI 1.52-3.6, P=.0001 & *OS*: HR=2.46, 95%CI 1.54-3.91, P=.0001)

Alderuccio JP et al. ASH 2022; Abstract 2960

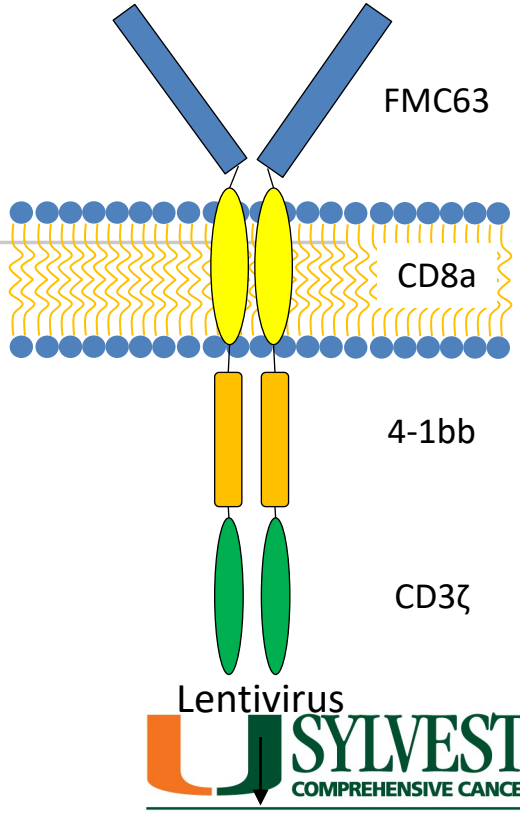
Three Anti-CD19 CAR T-cell Constructs are Currently FDA Approved for R/R DLBCL

Axicabtagene ciloleucel
(*aka* Axi-cel)
NCI



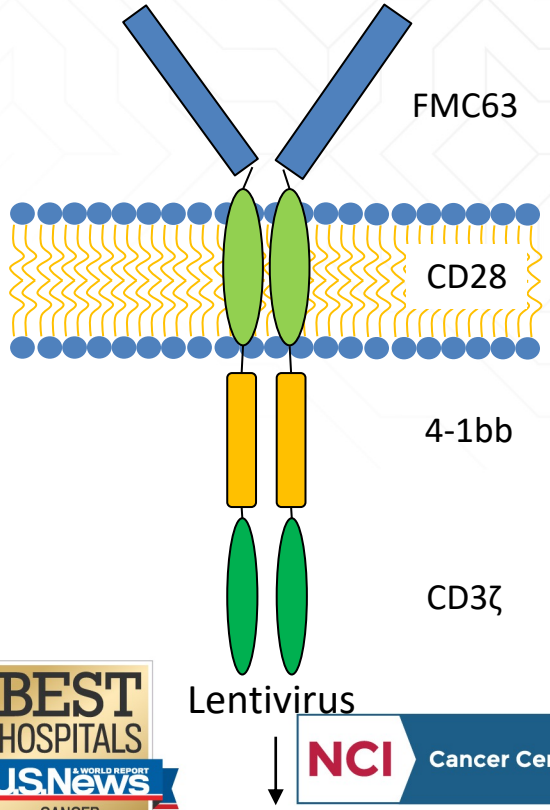
Kite Pharma - Gilead
KTE-C19

Tisagenlecleucel
UPenn



Novartis
CTL-019

Lisocabtagene maraleucel
(*aka* Liso-cel)
FHCR



Juno – Celgene - BMS
JCAR 017

[1] Adapted from: van der Stegen SJ et al. Nat Rev Drug Discov. 2015 Jul;14(7):499-509.

Phase 3 Trials of CAR-T vs Auto HCT in 2L LBCL

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell Product	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Tisagenlecleucel
CAR Construct	CD19.**CD28**.CD3z	CD19.**41BB**.CD3z	CD19.**41BB**.CD3z
# Enrolled	359	184	322
Median Follow Up	24.9 months	6.2 months	10 months
% Infused in CAR-T Arm	94%	98%	96%
% Received Bridging in CAR-T Arm	36%	63%	83%
% to HDT-ASCT in SOC Arm	36%	47%	33%
% SOC Crossover to CAR-T	56%	55%	51%
Median EFS	8.3 vs. 2 months	10.1 vs. 2.3 months	3 vs. 3 months
Hazard Ratio	0.398 (P < 0.0001)	0.349 (P < 0.0001)	1.07 (P = 0.69)
CR Rate	65% vs. 32%	66% vs. 39%	28% vs. 28%
Grade ≥3 CRS / ICANS	6% / 21%	1% / 4%	5% / 3%

] Locke F et al. NEJM 2021 [2] Kamdar M et al. Lancet 2022. [3] Bishop M et al. NEJM 2021.

Discussion Question

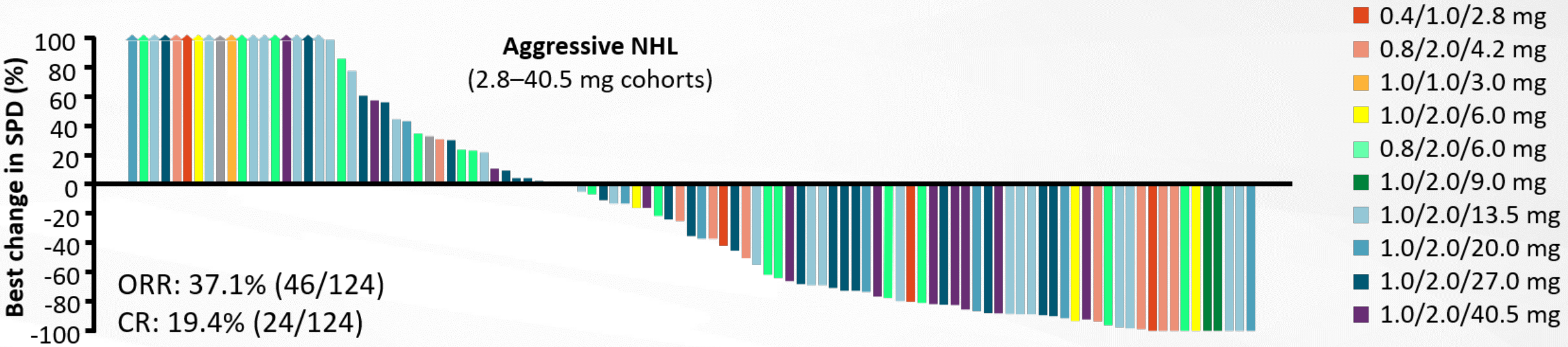
Based on available data, do you anticipate that bispecific antibodies will be widely used for R/R DLBCL in the near future? If so, how do you envision sequencing these drugs relative to currently available therapies?

CART or Bi-specific: What should we give first?

- CR rates to Epco/Glof: 40% and CR are durable out to 2+ years
- CR rates to CART: 50%-60% at 1 month post CART; 2/3 of CR patients that remain in CR at 1 year have not progressed
- CRS/ICANS: seen in both groups
- Easier-Bispecifics
- It is more likely that CART can salvage a bispecific failure than vice a versa

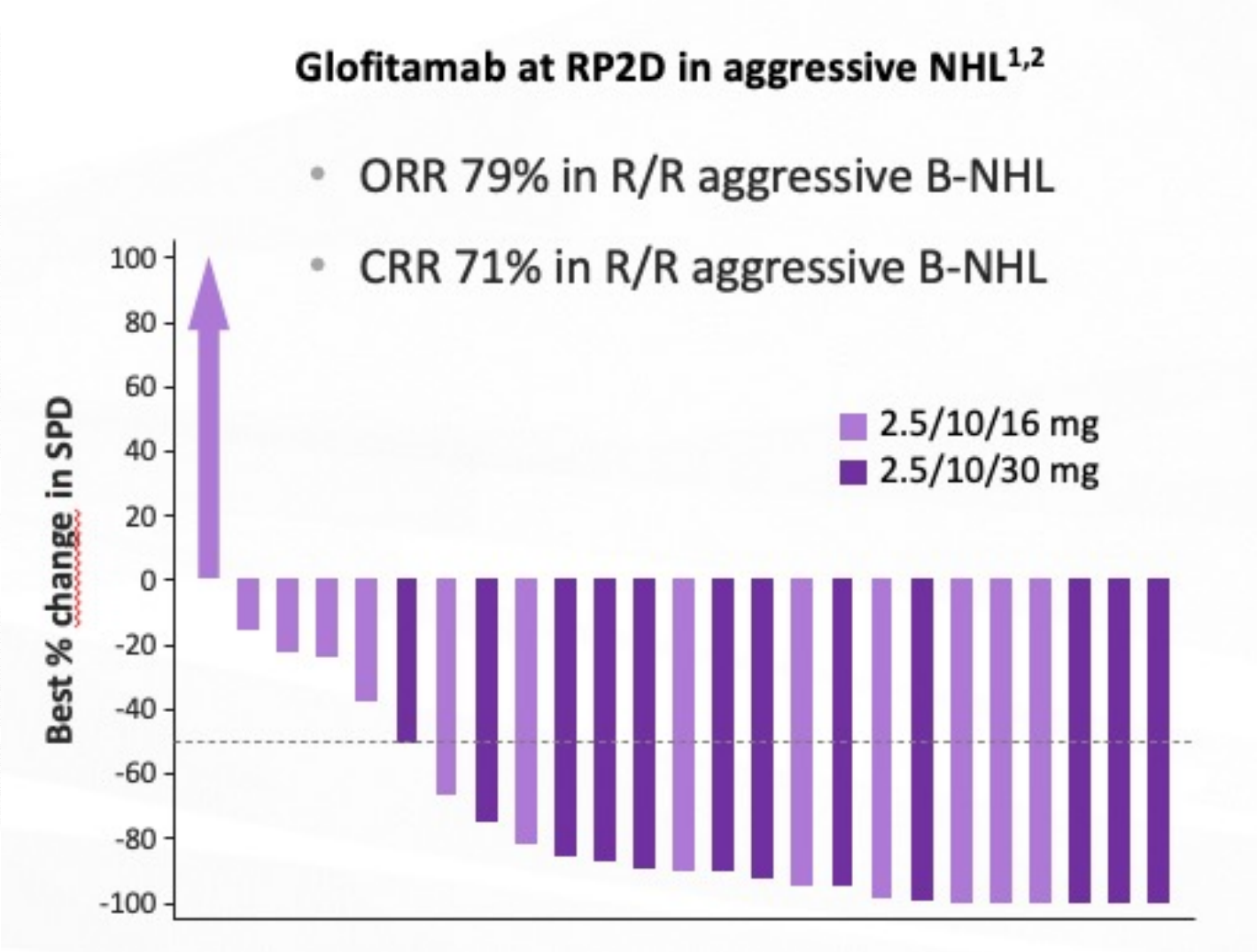
- When these 2 agents are approved I will use them before CART

Activity of Mosunetuzumab in R/R Aggressive B-NHL



1. Schuster SJ, et al. ASH 2019: Abstract 6 (oral presentation)

Activity of Glofitamab in R/R Aggressive B-NHL



1. Hutchings M, *et al. J Clin Oncol* 2021; **39**:1959–1970; 2. Carlo-Stella C, *et al.* ICML 2021. Abstract 15 (oral);

Pivotal Phase II Study of Glofitamab in R/R DLBCL and ≥2 prior therapies

Primary Endpoint Met

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

– At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater ($p<0.0001$) than 20% historical control CR rate‡

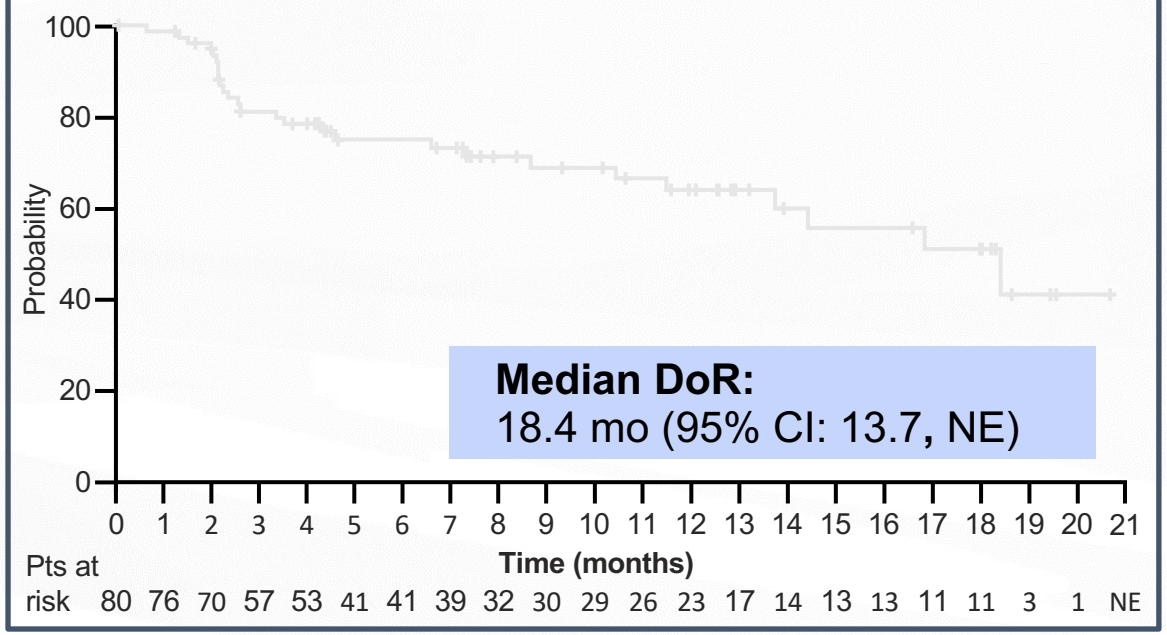
High CR/ORR rate at RP2D

*best response by intent-to-treat population; †the pivotal expansion cohort population; ‡the historical control CR rate was pre-specified based on a meta-analysis in patients with R/R DLBCL (where most [≥50%] had received ≥2 prior therapies) and compared with the CR rate in the primary efficacy-evaluable population using an exact binomial test (2-sided alpha level: 5%).

Dickinson M, et al. EHA 2022 oral presentation

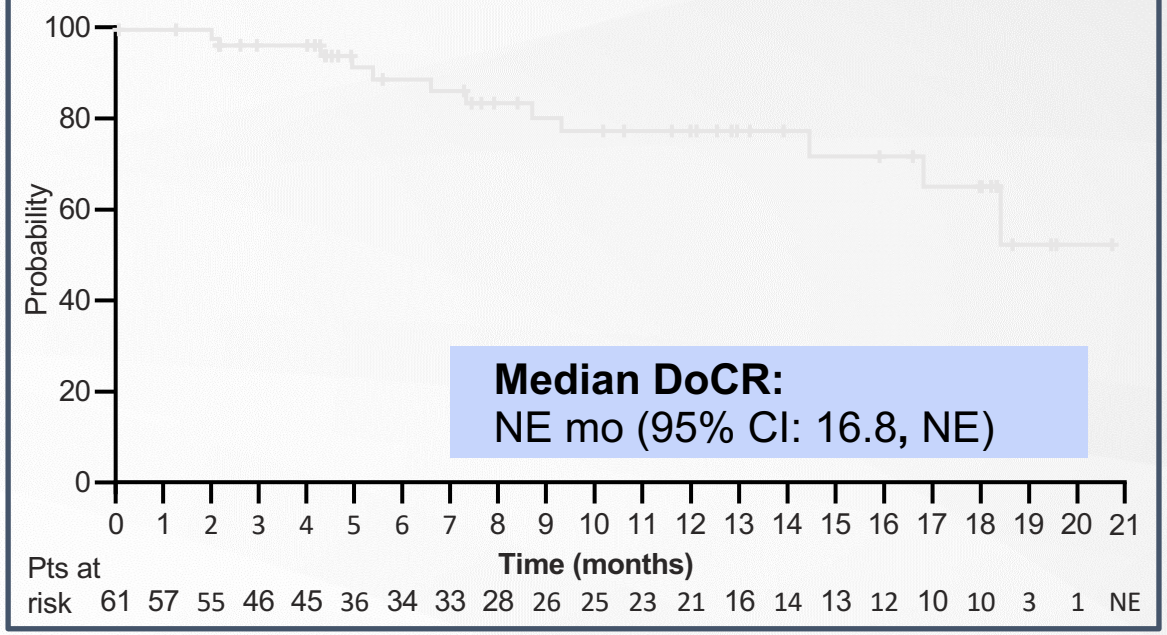
Pivotal Phase II Study of Glofitamab in R/R DLBCL and ≥2 prior therapies
Durable responses maintained after cessation of therapy

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

CCOD, clinical cut-off date; mo, months; NE, not estimable.

Dickinson M, et al. EHA 2022 oral presentation

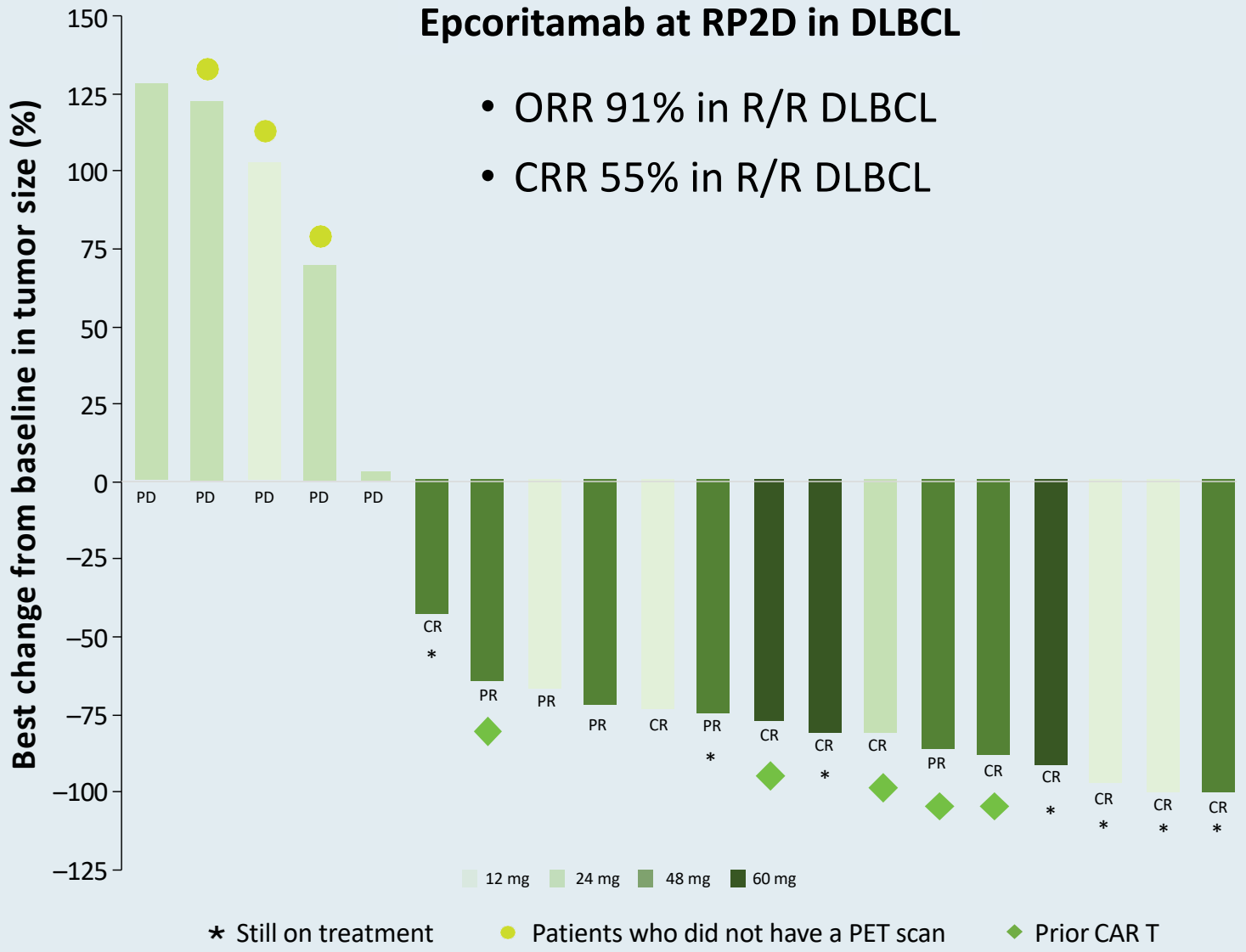
FDA Grants Priority Review for Bispecific Antibody Glofitamab for Relapsed or Refractory Large B-Cell Lymphoma

Press Release: January 6, 2023

"The US Food and Drug Administration (FDA) has accepted the company's Biologics License Application (BLA) and granted priority review for glofitamab, an investigational CD20xCD3 T-cell engaging bispecific antibody, for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. LBCL is an aggressive (fast-growing) type of non-Hodgkin lymphoma (NHL) and is one of the most prevalent types of blood cancer among adults in the U.S. The FDA is expected to make a decision on approval of this novel cancer immunotherapy by 1 July 2023. If approved, glofitamab would be the first fixed-duration, off-the-shelf CD20xCD3 T-cell engaging bispecific antibody available to treat people with an aggressive lymphoma who have previously received multiple courses of treatment."

https://www.globenewswire.com/news-release/2023/01/06/2584191/0/en/FDA-grants-priority-review-to-Roche-s-bispecific-antibody-glofitamab-for-people-with-relapsed-or-refractory-large-B-cell-lymphoma.html

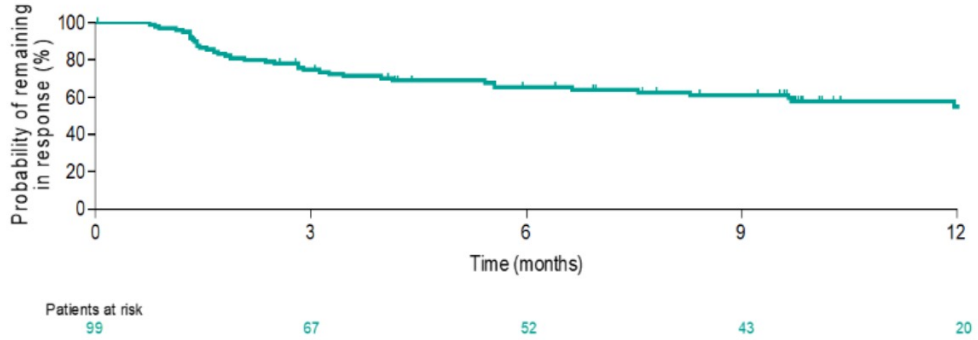
EPCORE NHL-1: Response to Epcoritamab in R/R DLBCL



Hutchings M, et al. *Lancet* 2021;398(10306):1157-69.

EPCORE NHL-1: Deep and Durable Responses Across Subgroups with Epcoritamab

	Overall LBCL N=157	Primary refractory n=96	CAR T–naive n=96	CAR T–exposed n=61	Refractory to prior CAR T n=46	DH/TH n=12	Non–DH/TH n=76	Non–DLBCL subtypes[a] n=30
ORR, %	63	55	69	54	46	50	63	63
CR rate, %	39	30	42	34	28	33	41	37
mDOR, mo	See update[b]	NR	12.0	9.7	NR	12.0	NR	12.0
mDOR in CR patients, mo	NR	NR	NR	NR	NR	12.0	NR	12.0
MRD-negativity rate, % (n/N)[c]	45 (54/119)	40 (29/72)	45 (33/74)	47 (21/45)	40 (14/35)	36 (4/11)	51 (32/63)	36 (9/25)



- As of a more recent data cutoff on June 30, 2022 (median follow-up, 15.7 mo):
  - An estimated 61% and 55% of responders remained in response at 9 and 12 mo, respectively
  - An estimated 89% and 79% of complete responders remained in response at 9 and 12 mo, respectively

Phillips T et al. ASH 2022;Abstract 4251.

FDA Grants Priority Review to Epcoritamab for Relapsed/Refractory LBCL

Press Release: November 21, 2022

The FDA has granted priority review for the biologics license application (BLA) of epcoritamab as a treatment for patients with relapsed/refractory large B-cell lymphoma (LBCL) after 2 or more lines of therapy, according to a press release.

The application is supported by findings from the LBCL cohort of the Phase I/II EPCORE NHL-1 trial (NCT03625037) which assessed epcoritamab in a population with relapsed, progressive, or refractory CD20-positive mature B-cell non-Hodgkin lymphoma. Topline data from the trial indicated that patients experienced an overall response rate of 63.1% by independent review committee with a median duration of response of 12 months. There were few incidences of high-grade cytokine release syndrome, with 49.7% of patients experiencing the toxicity in total.

https://www.cancernetwork.com/view/fda-grants-priority-review-to-epcoritamab-for-relapsed-refractory-lbcl

Discussion Question

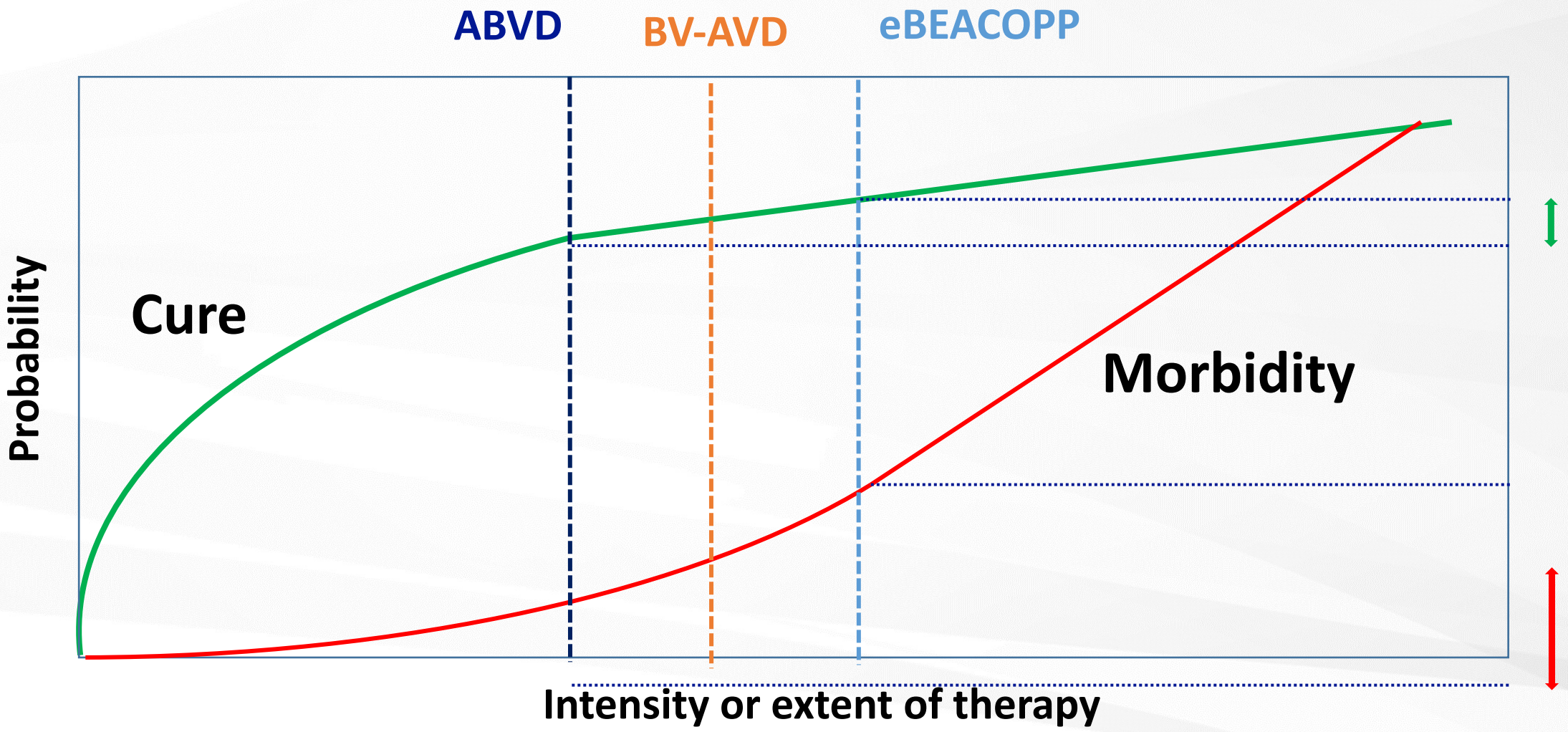
How do you approach first-line treatment for advanced Hodgkin lymphoma (HL), and how do patient age and risk status factor in?

How do you treat advanced stage HL?

- ABVD x 6
- Escalated BEACOPP x 4-6*
- BV-AVD x 6
- ABVD x 2 followed by an interim PET after 2 cycles to inform further therapy
- Escalated BEACOPP x 2 followed by an interim PET after 2 cycles to inform further therapy

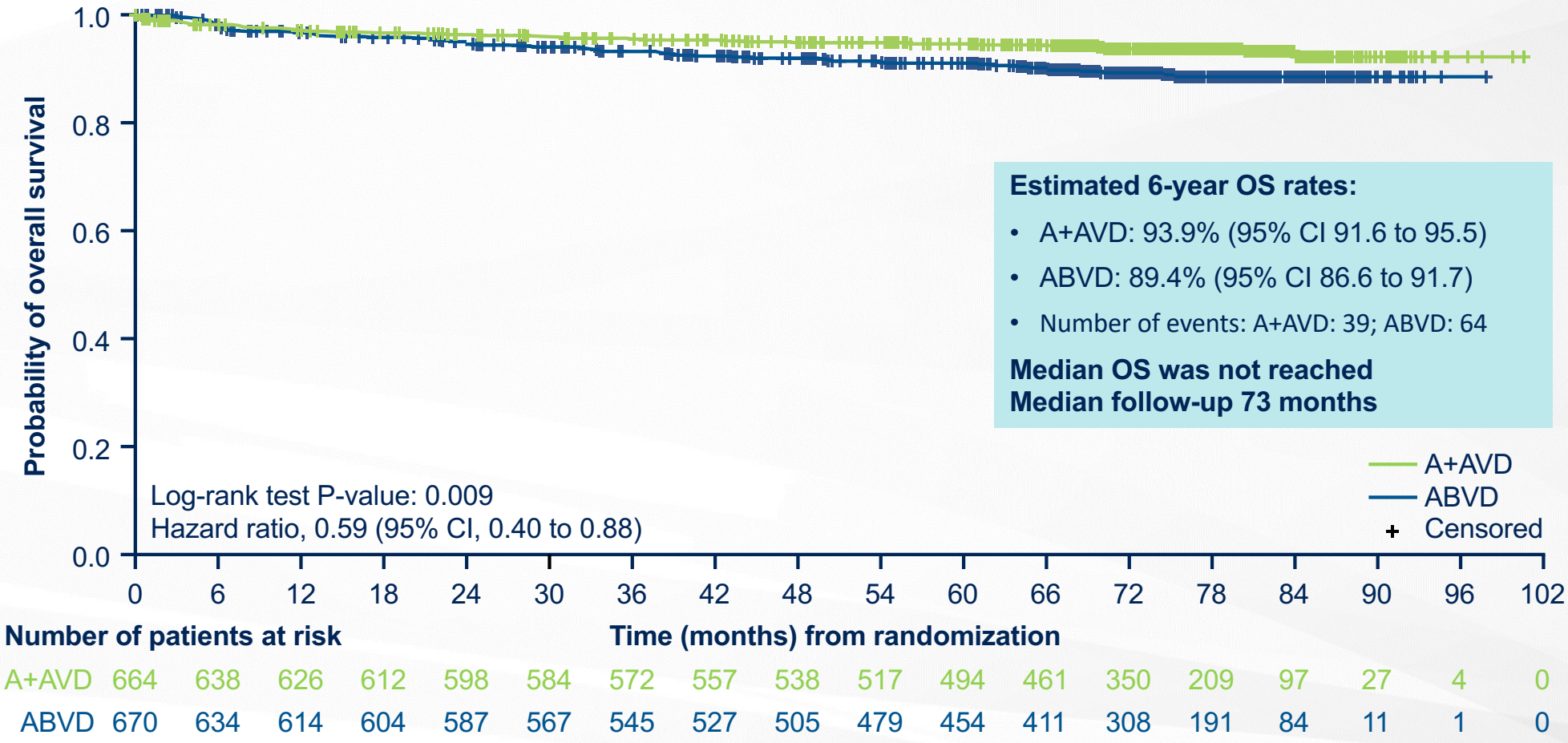
Many studies include stage IIA poor risk and IIB: This is not advanced stage HL!

The Dilemma Of Therapy



Courtesy Dr Johnson (modified)

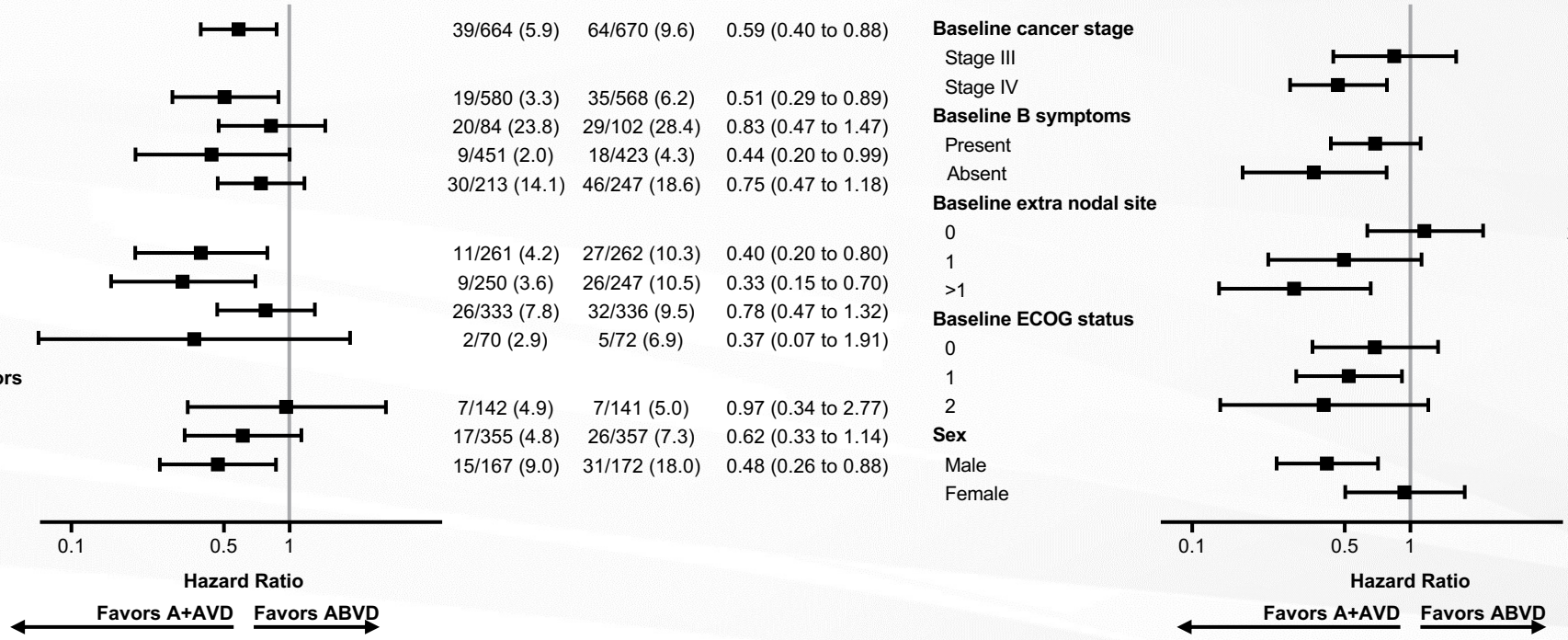
A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD



CI, confidence interval.

OS benefit was generally consistent across prespecified subgroups

Subgroup	Event/N (%) A+AVD	Event/N (%) ABVD	Hazard Ratio (95% CI)
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40 to 0.88)
Age			
<60 years	19/580 (3.3)	35/568 (6.2)	0.51 (0.29 to 0.89)
≥60 years	20/84 (23.8)	29/102 (28.4)	0.83 (0.47 to 1.47)
<45 years	9/451 (2.0)	18/423 (4.3)	0.44 (0.20 to 0.99)
≥45 years	30/213 (14.1)	46/247 (18.6)	0.75 (0.47 to 1.18)
Region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20 to 0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15 to 0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47 to 1.32)
Asia	2/70 (2.9)	5/72 (6.9)	0.37 (0.07 to 1.91)
Number of IPS risk factors			
0–1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34 to 2.77)
2–3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33 to 1.14)
4–7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26 to 0.88)
Baseline cancer stage			
Stage III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45 to 1.65)
Stage IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29 to 0.80)
Baseline B symptoms			
Present	30/400 (7.5)	39/381 (10.2)	0.71 (0.44 to 1.14)
Absent	9/264 (3.4)	25/289 (8.7)	0.37 (0.17 to 0.80)
Baseline extra nodal site			
0	22/217 (10.1)	19/228 (8.3)	1.18 (0.64 to 2.19)
1	9/217 (4.1)	17/223 (7.6)	0.51 (0.23 to 1.14)
>1	8/194 (4.1)	25/193 (13.0)	0.30 (0.14 to 0.67)
Baseline ECOG status			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36 to 1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31 to 0.94)
2	5/28 (17.9)	9/27 (33.3)	0.41 (0.14 to 1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25 to 0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51 to 1.80)



ECOG, Eastern Cooperative Oncology Group.

How do I treat ASHL

1. *Enroll on national study if available*
2. *Off protocol BV-AVD for stage IV and IIIB pts*
3. *Pet-adapted 3 for stage IIIA as well as stage 2B (not ASHL!)*
4. *Bulky stage II which is not ASHL! I give CMT 4-6 cycles of ABVD and ISRT*

Let's remember the intergroup study does not have an arm for PET-adapted therapy; the field is moving on

Discussion Question

Do you believe camidanlumab tesirine will gain FDA approval for HL in the near future, and if so, how do you envision using it relative to other evidence-based options?

Safety – Patients with Guillain–Barré Syndrome (GBS)/polyradiculopathy

- Baseline characteristics:
  - Median age: 35y (23-68)
  - 3/8 patients had prior SCT
  - Median days since last checkpoint inhibitor: 187 (50-377)
- Median number of Cami cycles (range): 3.5 (2-7)
  - 4/8 cases presented after 2 cycles; 3/8 had onset after 30 days post last-dose

Summary of Patients with GBS/polyradiculopathy

Patient	AE by preferred term	Max grade	Duration (days)	IVIG/PLEX/ Steroids	Outcome at last assessment
1	GBS	4	523	Y/Y/Y	Ongoing at grade 1
2	GBS	4	43	Y/Y/N	Recovered
3	GBS	3	50	Y/Y/Y	Not recovered; patient died of sepsis
4	GBS	3	287	Y/N/Y	Ongoing at grade 1
5	GBS	3	111	Y/Y/Y	Ongoing at grade 1[a]
6	GBS	2	119	Y/N/N	Recovered
7	Polyneuropathy[b], Meningitis, Facial paralysis, SIADH	4	72	Y/N/Y	Recovered
8	Radiculopathy	2	165	Y/Y/Y	Recovered

Data cut off: November 1, 2021

[a] Also received rituximab with clinical improvement. [b] Verbatim: polyradiculoneuritis.

IVIG, intravenous immunoglobulin; PLEX, plasma exchange; SCT, stem cell transplant; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Camidanlumab tesirine

The book is closed: will never get approved

Lymphoma Service-Sylvester Comprehensive Cancer Center, University of Miami Health System

- Izidore Lossos
- Juan Alderuccio
- Alvaro Alencar
- Georgio Pongas
- Juan Ramos
- Joe Rosenblatt
- Jonathan Schatz
- Craig Moskowitz

Special thanks to the
Lymphoma Service at MSKCC

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM