Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Diffuse Large B-Cell Lymphoma

Part 2 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024
7:30 PM – 8:30 PM CT

Faculty

Grzegorz S Nowakowski, MD
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

RTP RESEARCH TO PRACTICE

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RTP RESEARCH TO PRACTICE

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The program moderator will address as many cases or questions as possible with the faculty panel during the program.

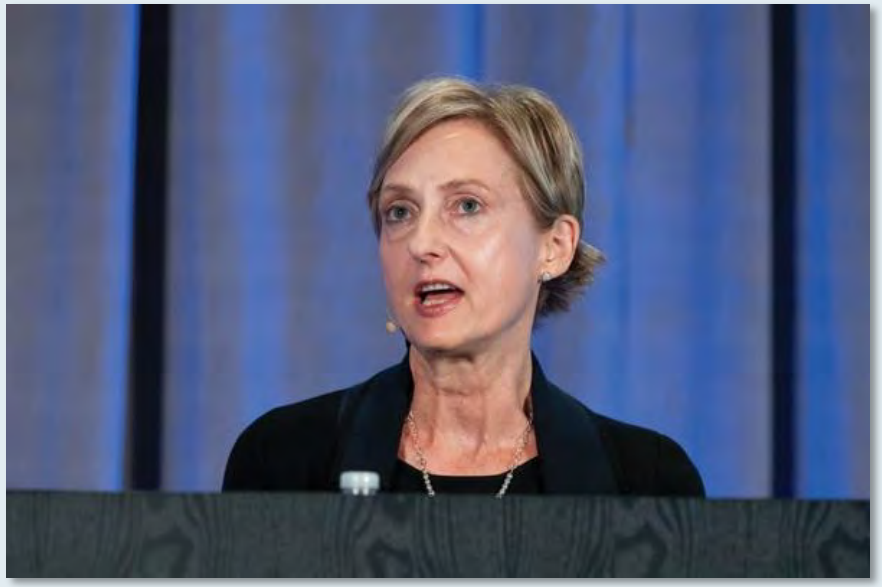
Download Program Slides Here

https://asset.researchtopractice.com/2024/Webinar/SOHO2024_DLBCL_Sep4.pdf

Slides are also available on our RTPLive app.

For Zoom attendees, the slides link is posted in the chat room.

About the Enduring Program



- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Module 1: Front-Line Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Sehn

Module 2: Integration of Novel Agents into the Care of Patients with Relapsed/Refractory DLBCL — Dr Flowers

Module 3: Bispecific Antibody Therapy for DLBCL — Dr Nowakowski

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Front-Line Management of Diffuse Large B-Cell Lymphoma (DLBCL)

Laurie H. Sehn, MD, MPH

Chair, Lymphoma Tumour Group

BC Cancer Centre for Lymphoid Cancer

Vancouver, Canada

BC CANCER

Provincial Health Services Authority

UBC

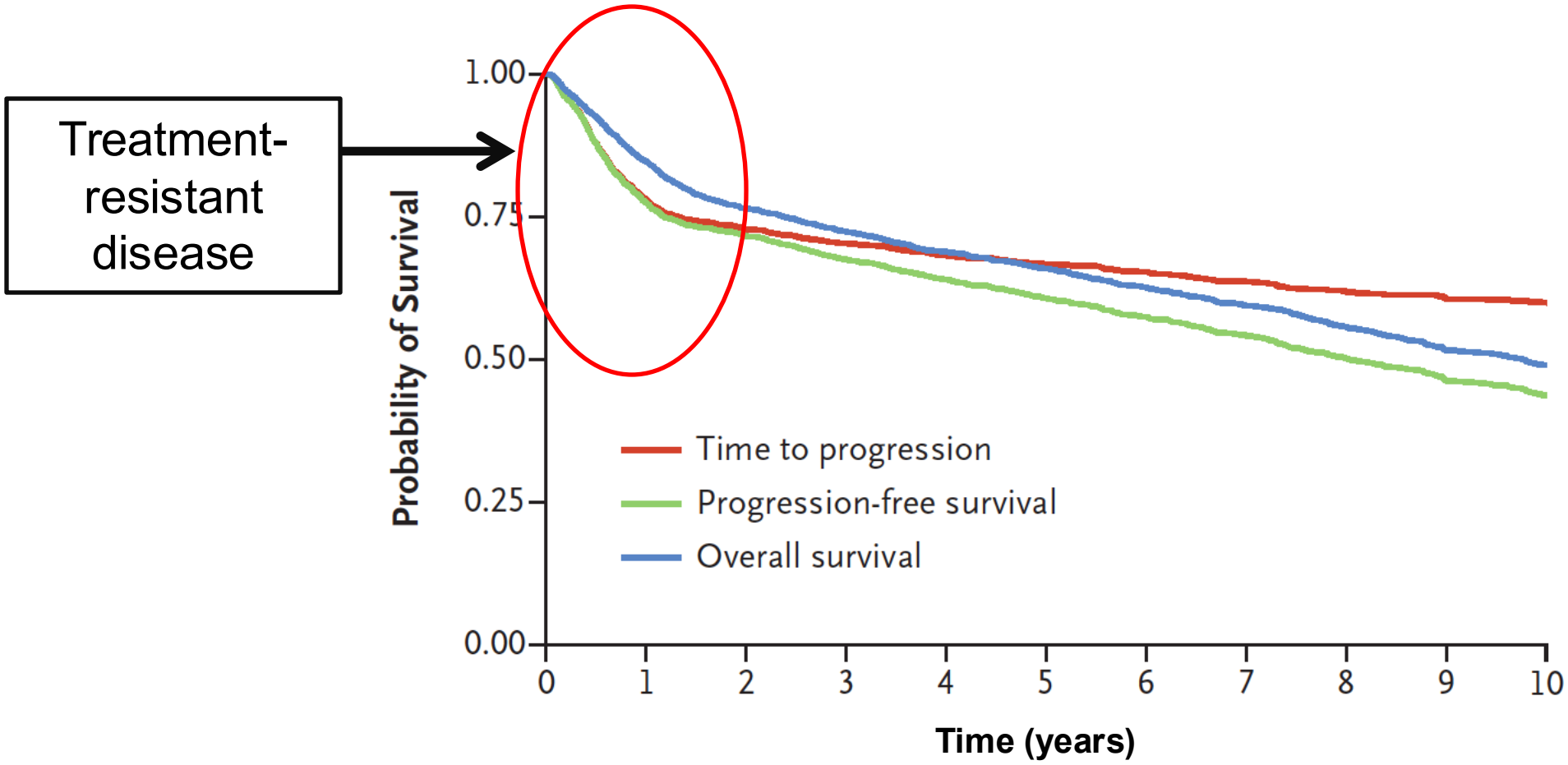
a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

Dr Sehn — Disclosures

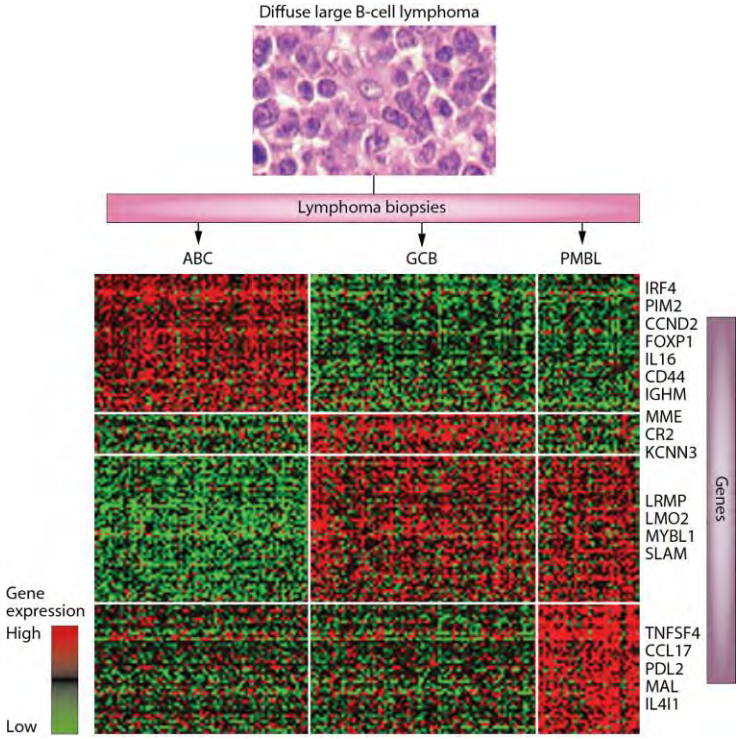
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Incyte Corporation, Janssen Biotech Inc, Kite, A Gilead Company, Merck, Novartis, Seagen Inc, Teva Oncology
Contracted Research	Genentech, a member of the Roche Group
Data and Safety Monitoring Board/Committee	CARGO Therapeutics

Outcomes with R-CHOP in Untreated DLBCL



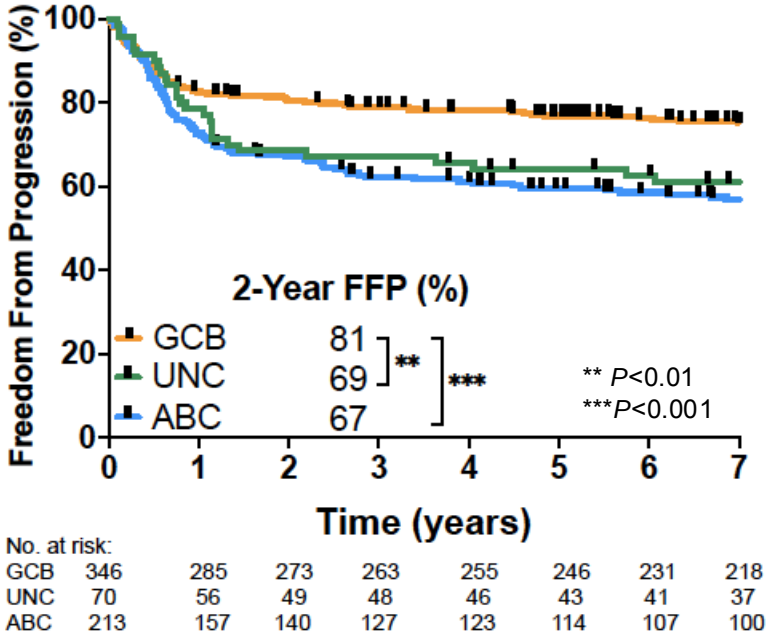
Sehn and Salles. *NEJM* 2021

Distinct Signaling Pathways and Outcomes According to Cell-of-Origin (ABC vs GCB)

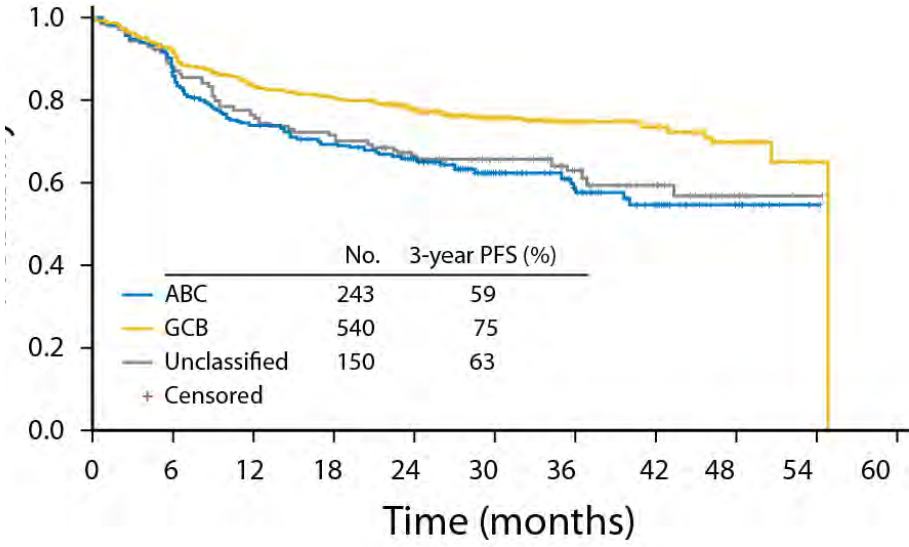


Alizadeh et al, *Nature* 2000
Rosenwald et al, *NEJM* 2002
Lenz et al, *NEJM* 2008

15%-20% difference in PFS

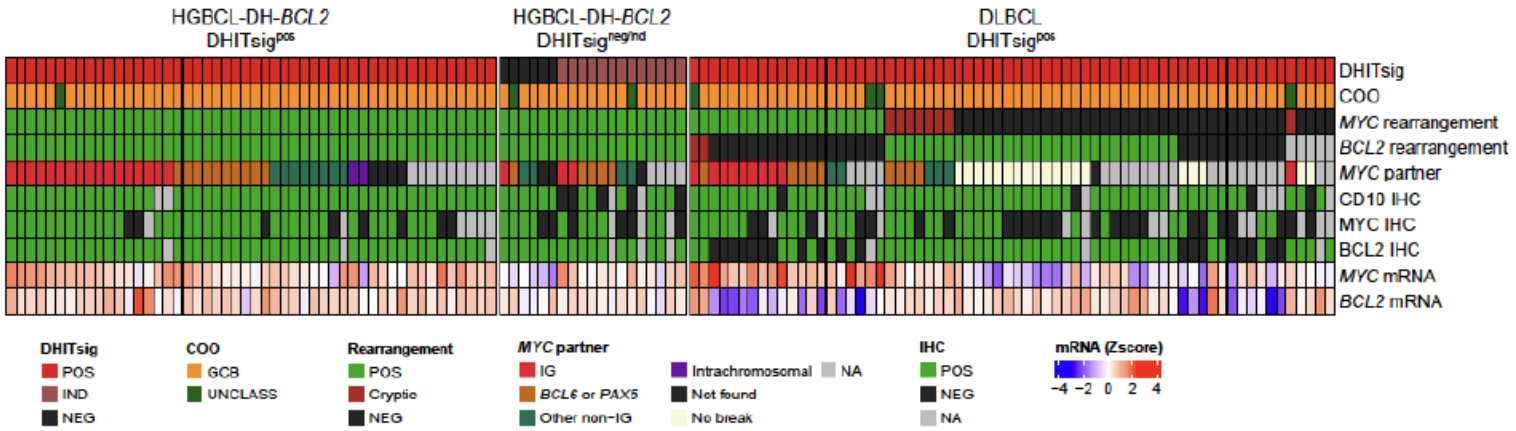


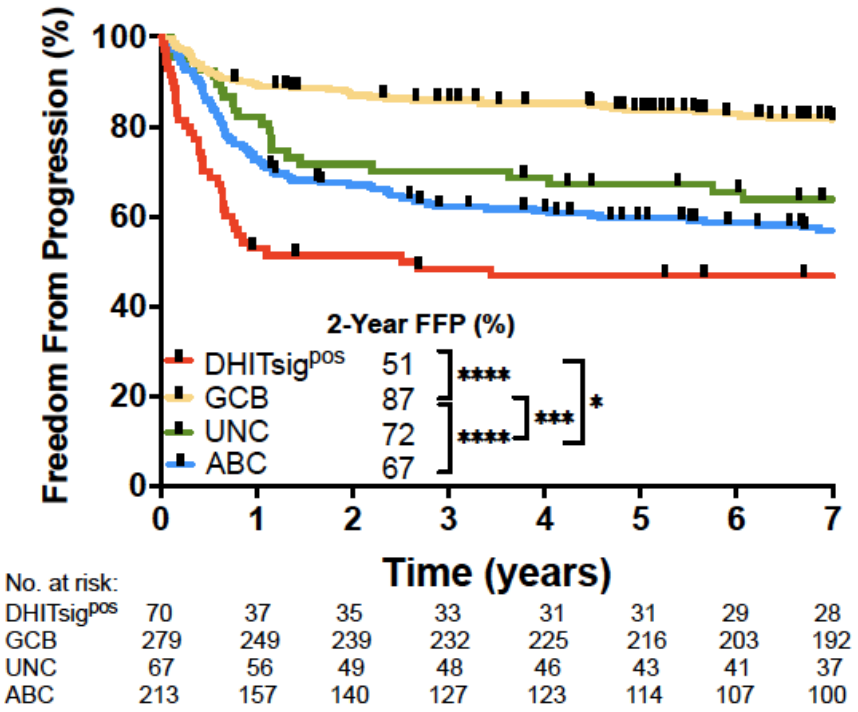
BC Cancer
R-CHOP treated
Alduaij et al *Blood* 2023



GOYA Trial
R-CHOP v G-CHOP
PFS including both arms
Vitolo et al *J Clin Oncol* 2017

Dark Zone Signature DLBCL

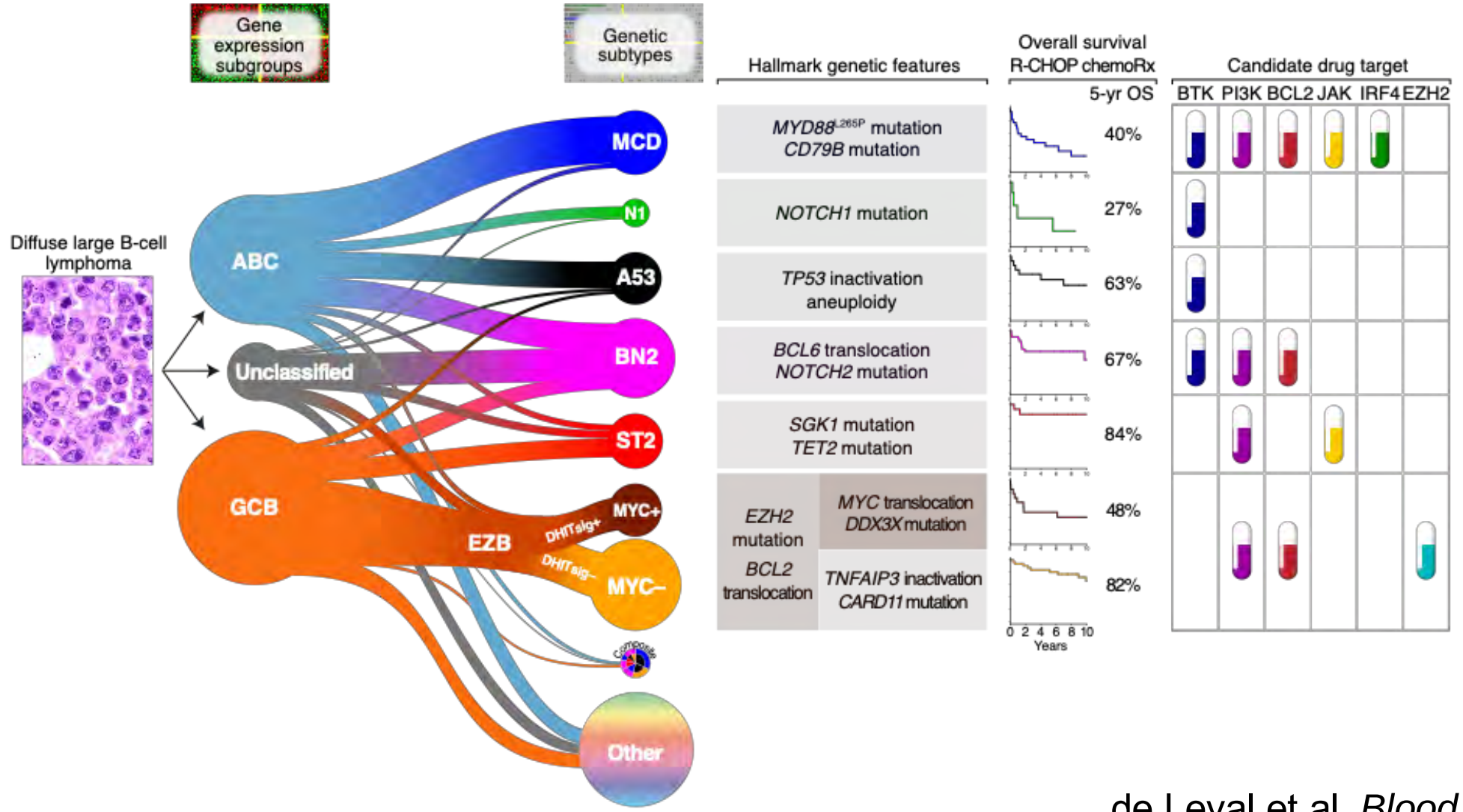




Subgroup of GCB DLBCL with molecular signature similar to high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements and have poor outcome with R-CHOP

Ennishi et al. *J Clin Oncol* 2019; Alduaij et al. *Blood* 2023

Novel DLBCL Genomic Subtypes

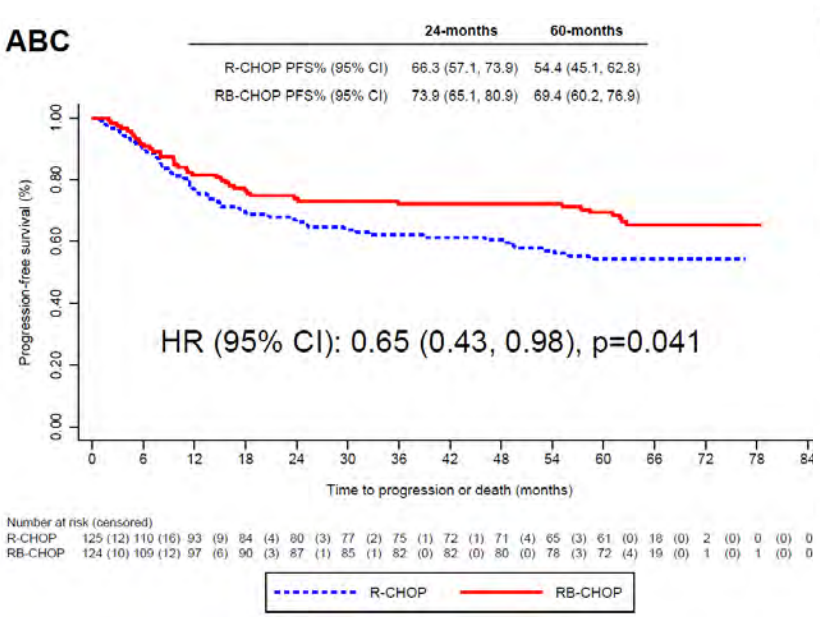


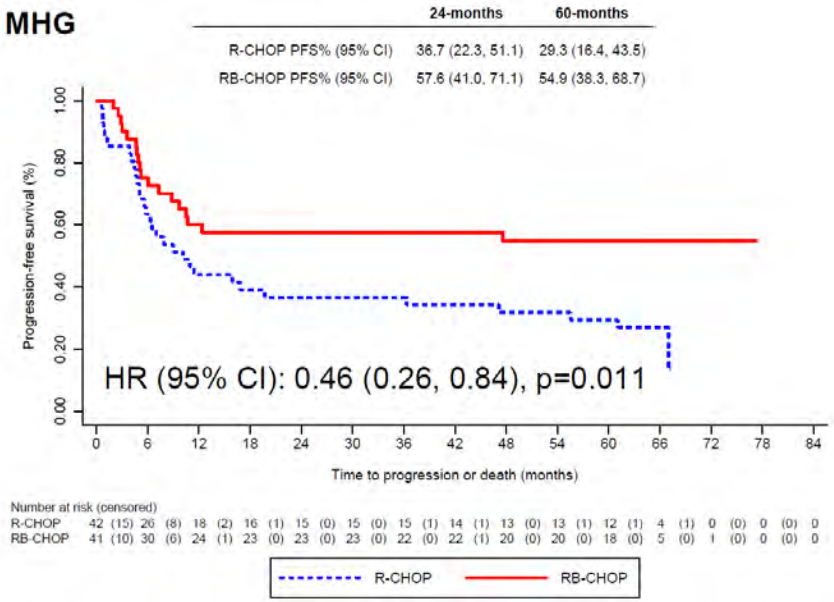
de Leval et al. *Blood* 2022

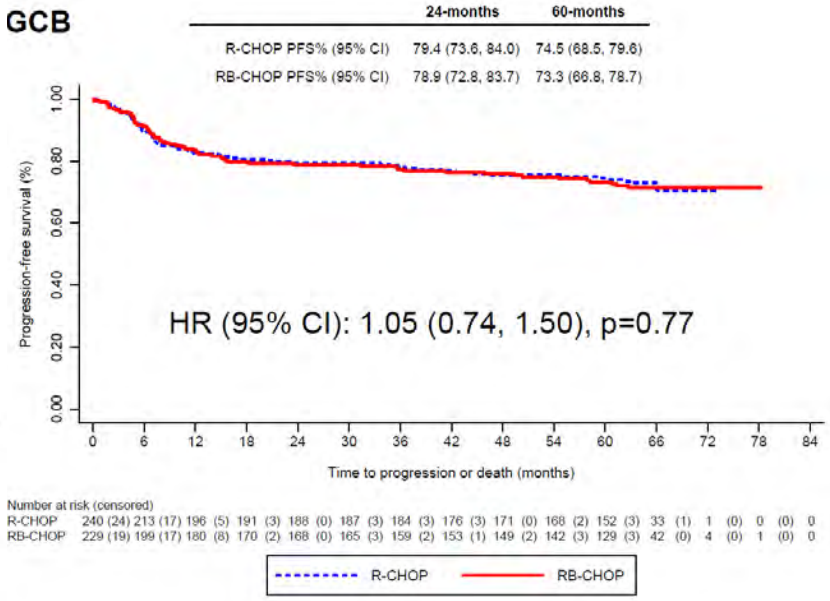
Randomized Trials of Novel Agents

Author	Therapy	Better than R-CHOP
Vitolo, JCO 2017	**Obinutuzumab-CHOP**	**No**
Leonard, JCO 2017	**R-CHOP- Bortezomib**	**No**
Davies, Lancet 2019	**R-CHOP- Bortezomib**	**No**
Younes, JCO 2019	**R-CHOP-Ibrutinib**	**? No**
Nowakowski, JCO 2021	**Lenalidomide-R-CHOP**	**? Yes (Phase II)**
Nowakowski, JCO 2021	**Lenalidomide-R-CHOP**	**No**

Five-Year Update of REMoDL-B: Improved PFS in Molecular Subgroups with Bortezomib-R-CHOP



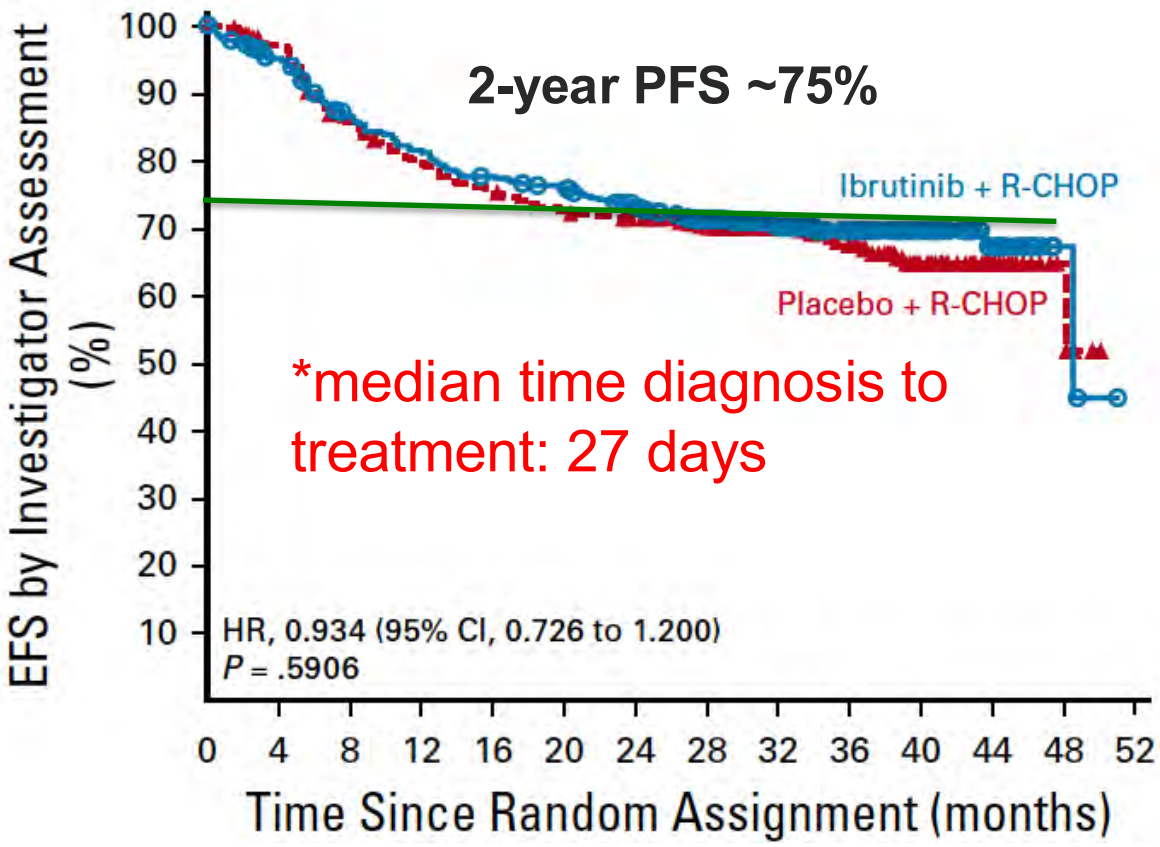




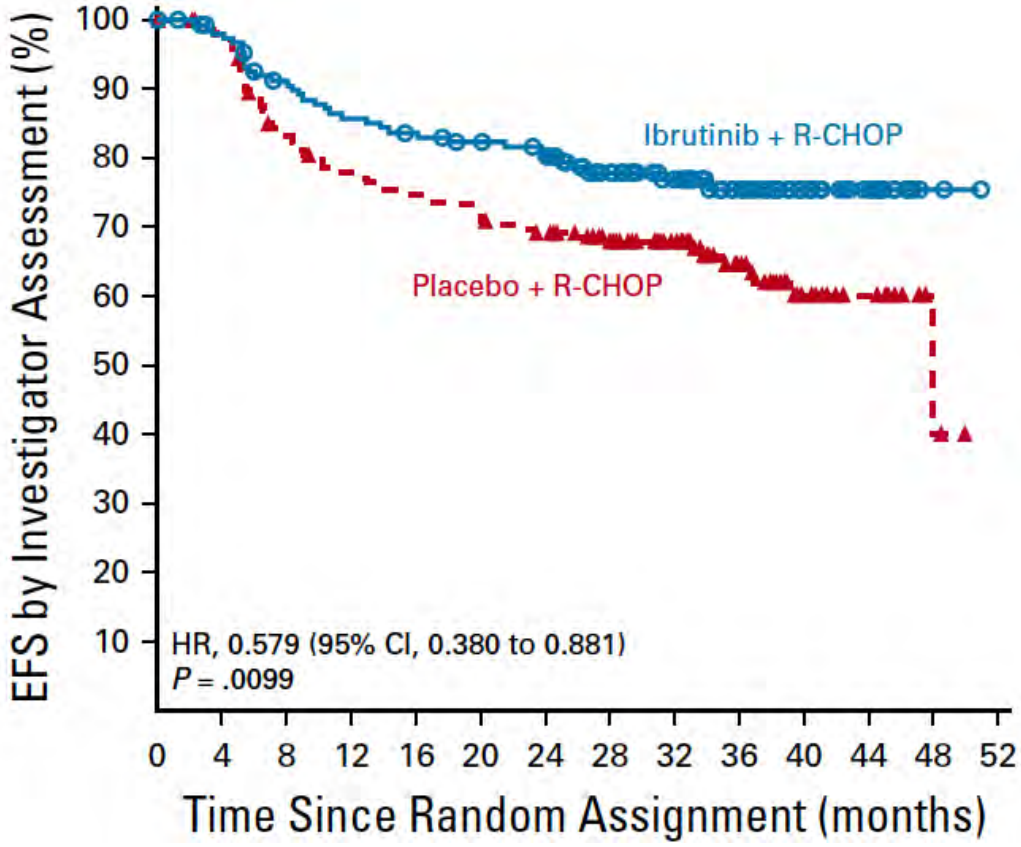
Significant improvement in PFS with Bortezomib-R-CHOP in ABC and Molecular High Grade subgroups, but not in GCB subgroup

Davies, A et al. *JCO* 2023

PHOENIX Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



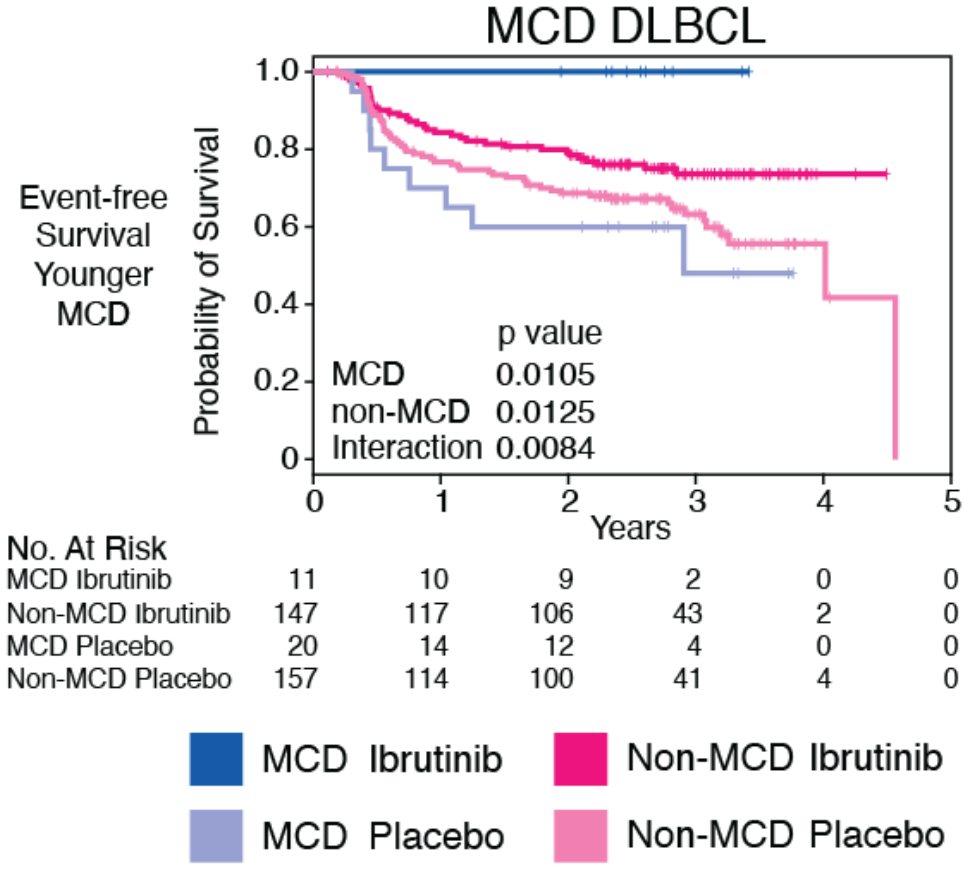
ITT Population

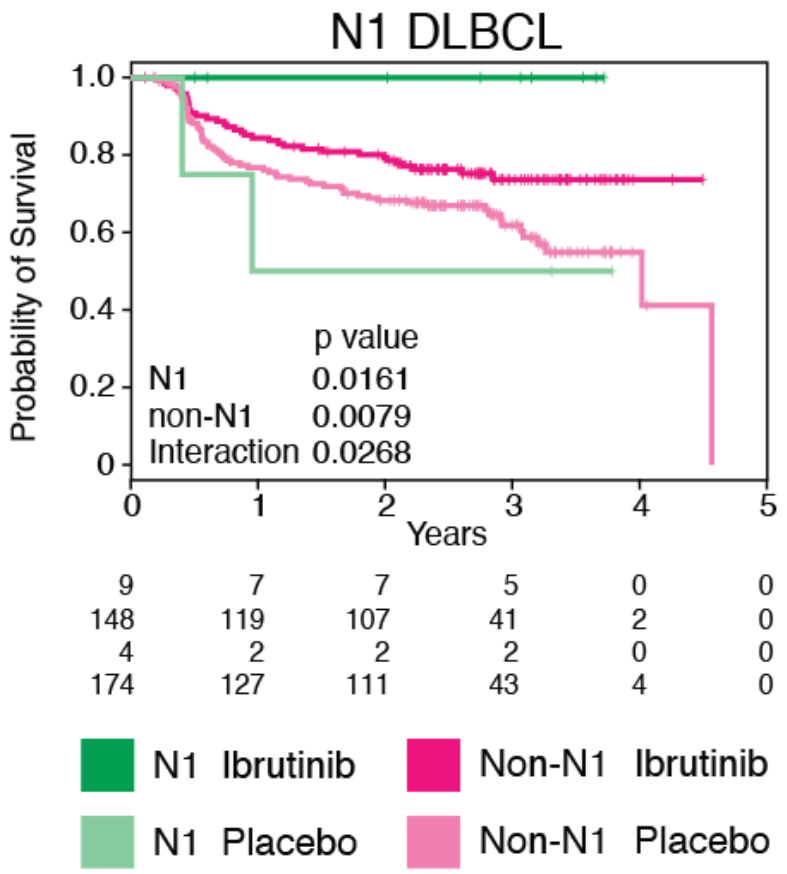


Age <60 years

Younes, A et al, *JCO* 2019

Genetic-Based Subtypes as a Predictive Marker
Retrospective Analysis of PHOENIX Trial

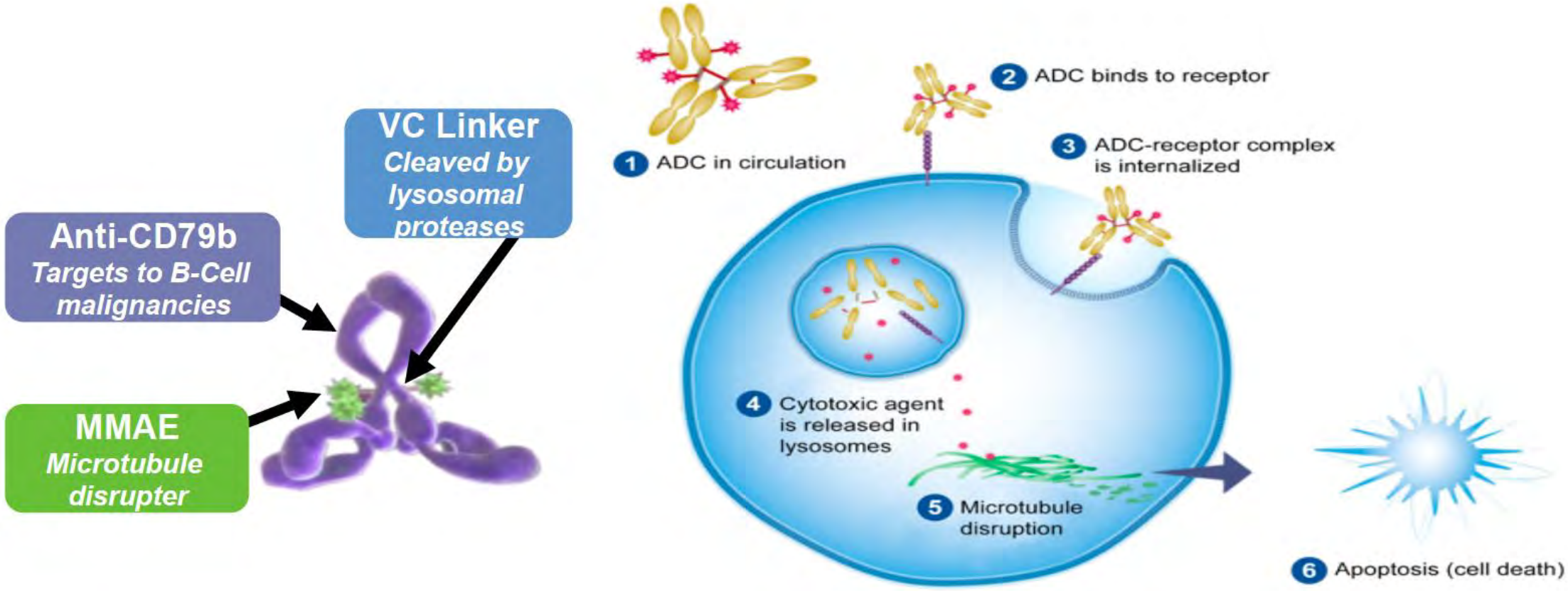




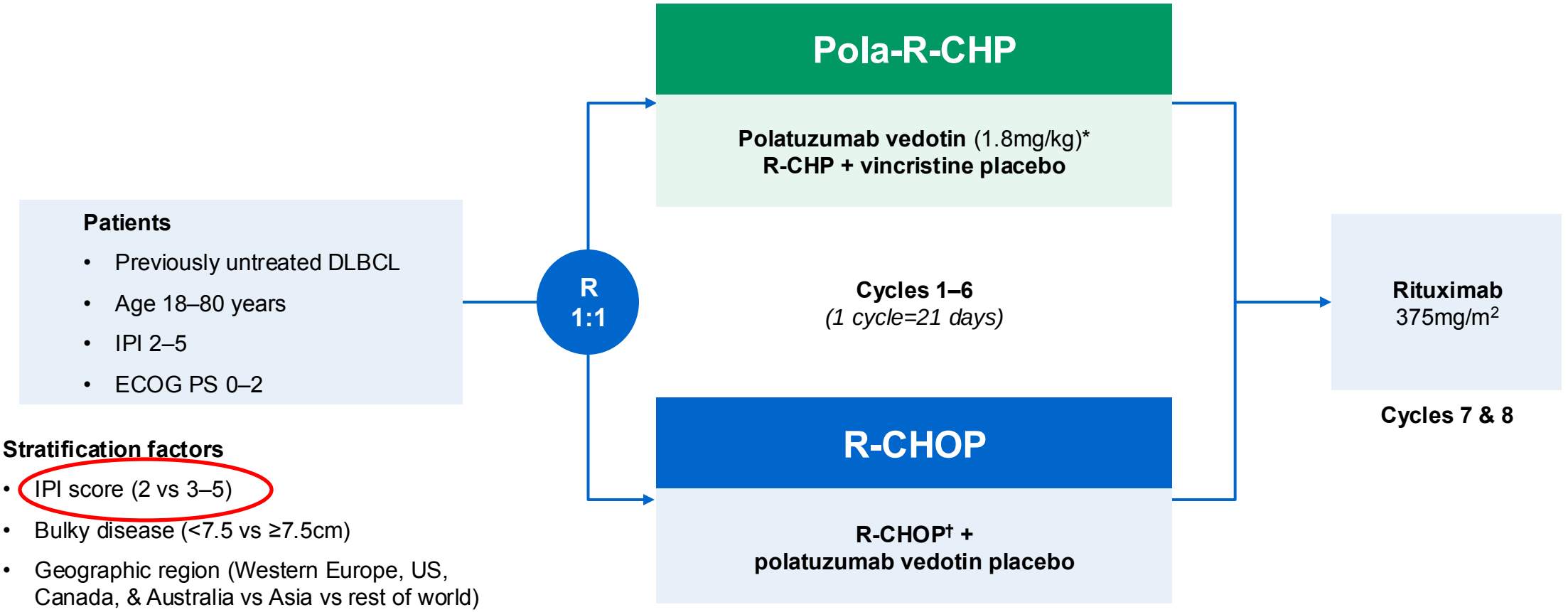
Wilson, WH et al. *Cancer Cell* 2021

Polatuzumab Vedotin: Anti-CD79b Drug Conjugate

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



POLARIX: A randomized double-blinded study

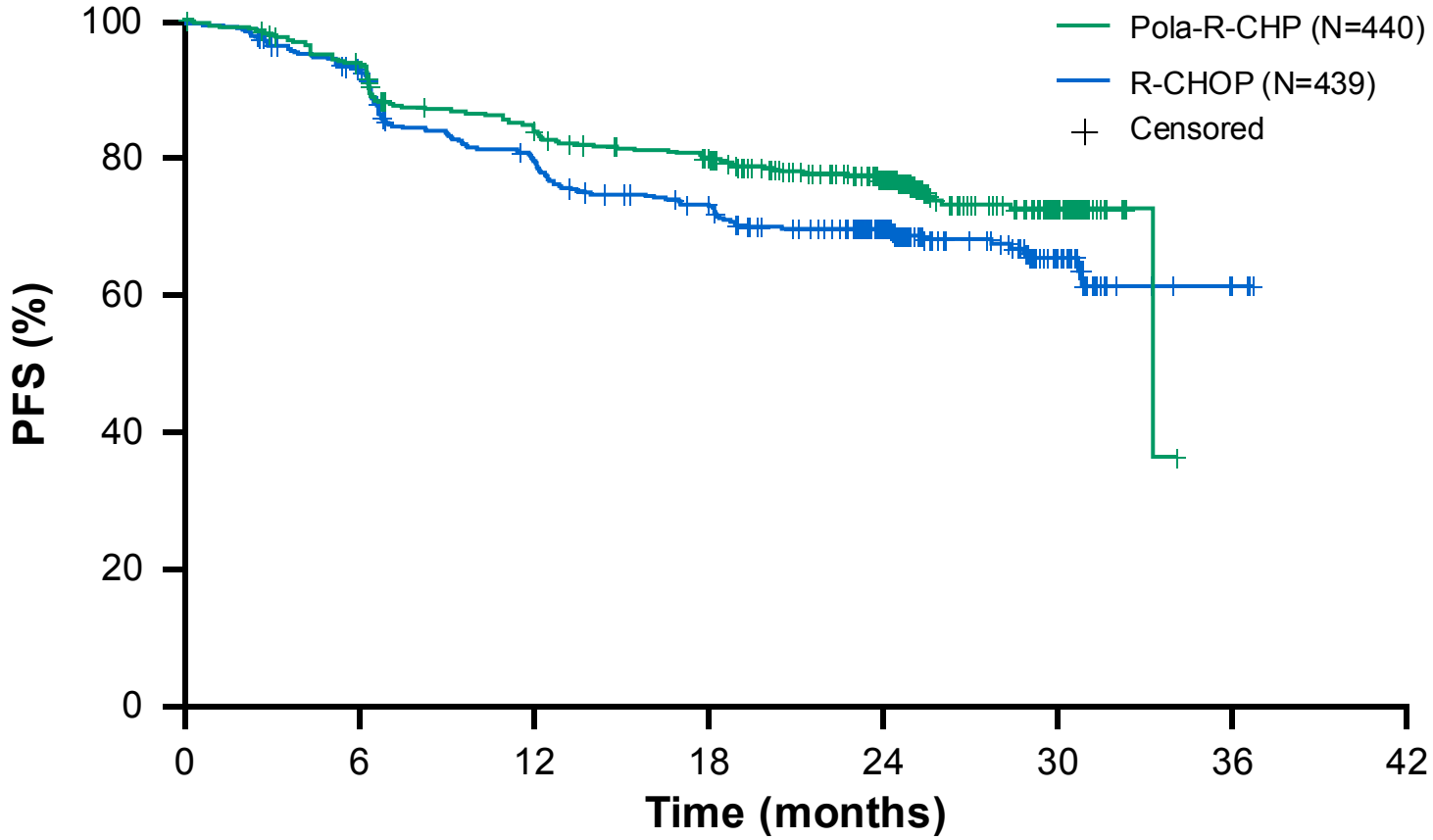


*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Tilly H et al. *NEJM* 2021

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 **(P=0.02)**

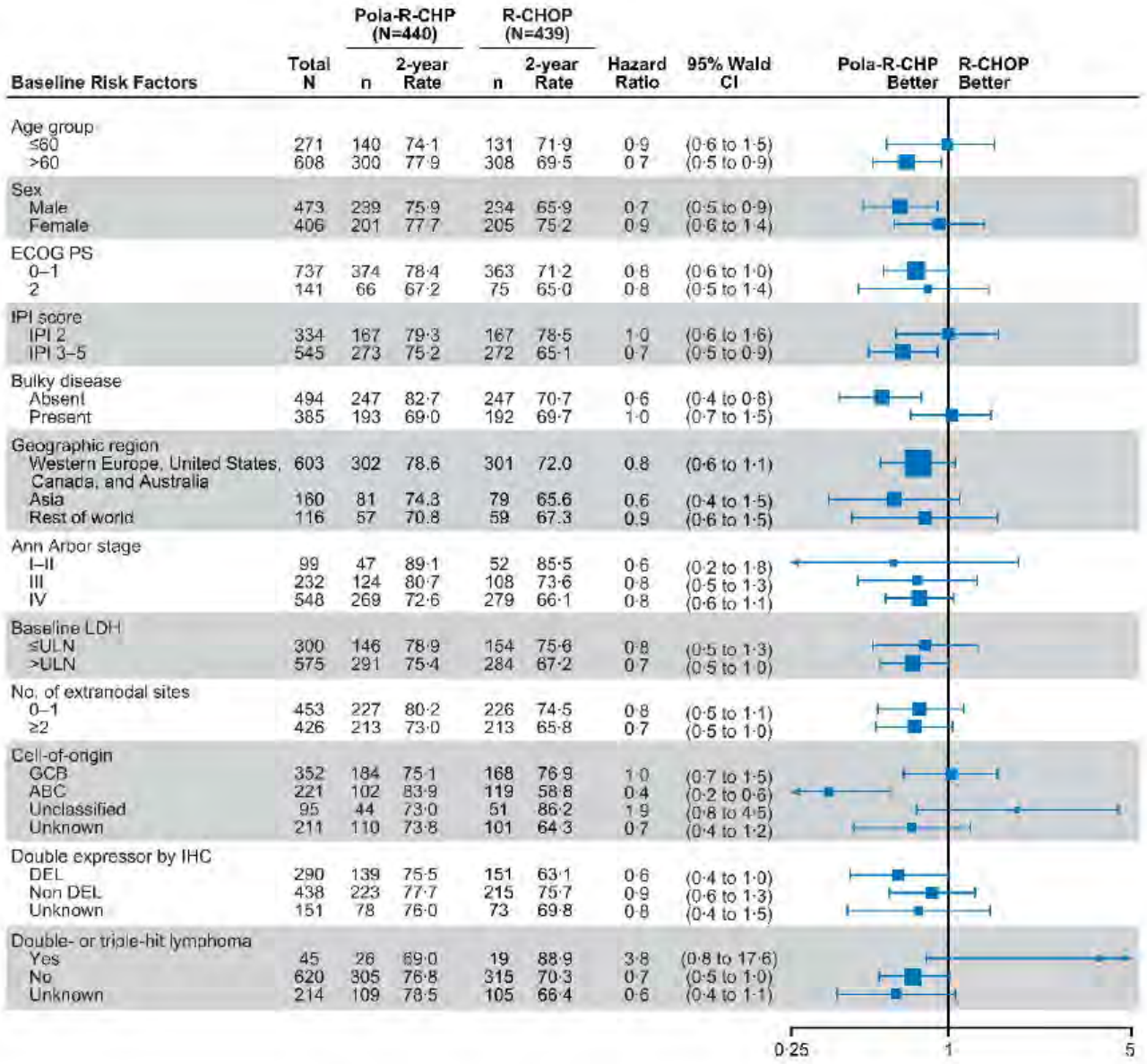
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Tilly H et al. *NEJM* 2021

Univariate Subgroup Analyses



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	65·9	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	78·4	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	69·0	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 1·5)
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 1·8)
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)

? Preferential Benefit

Older, >60 y

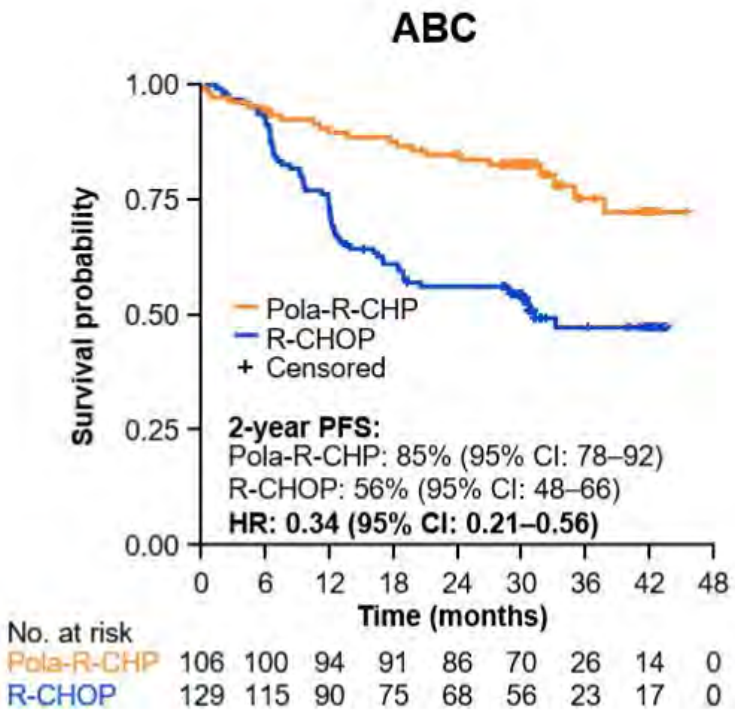
IPI = 3-5
Non-Bulky < 7.5 cm

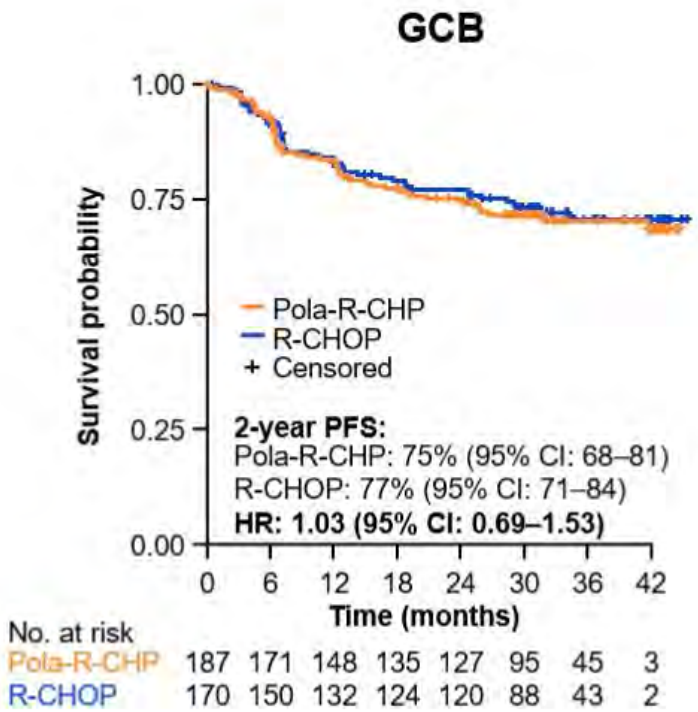
ABC Subtype

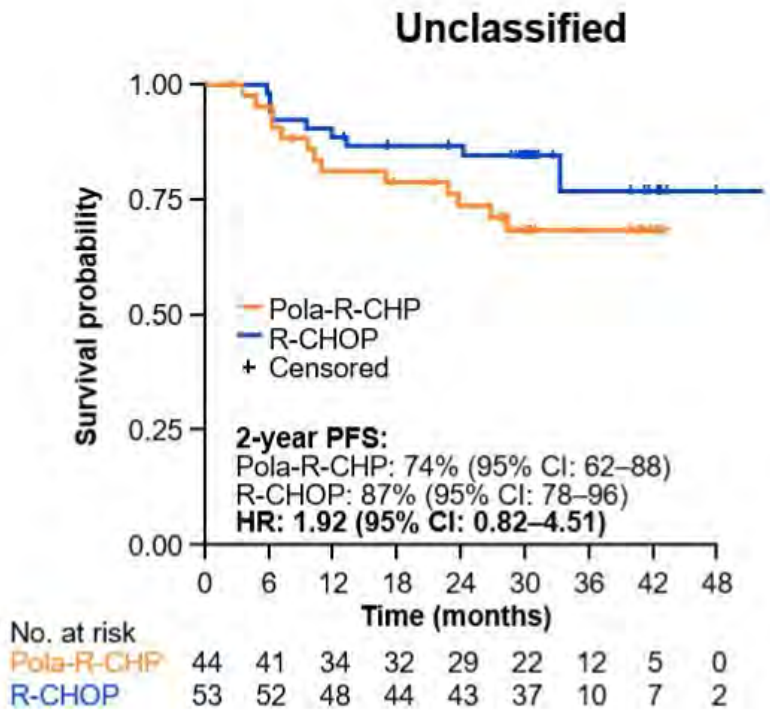
Tilly H et al. *NEJM* 2021

POLARIX Trial: PFS in COO Subgroups

Cell of origin (COO) determined in 689 patients (ABC n=235; GCB n=357; unclassified n=97)

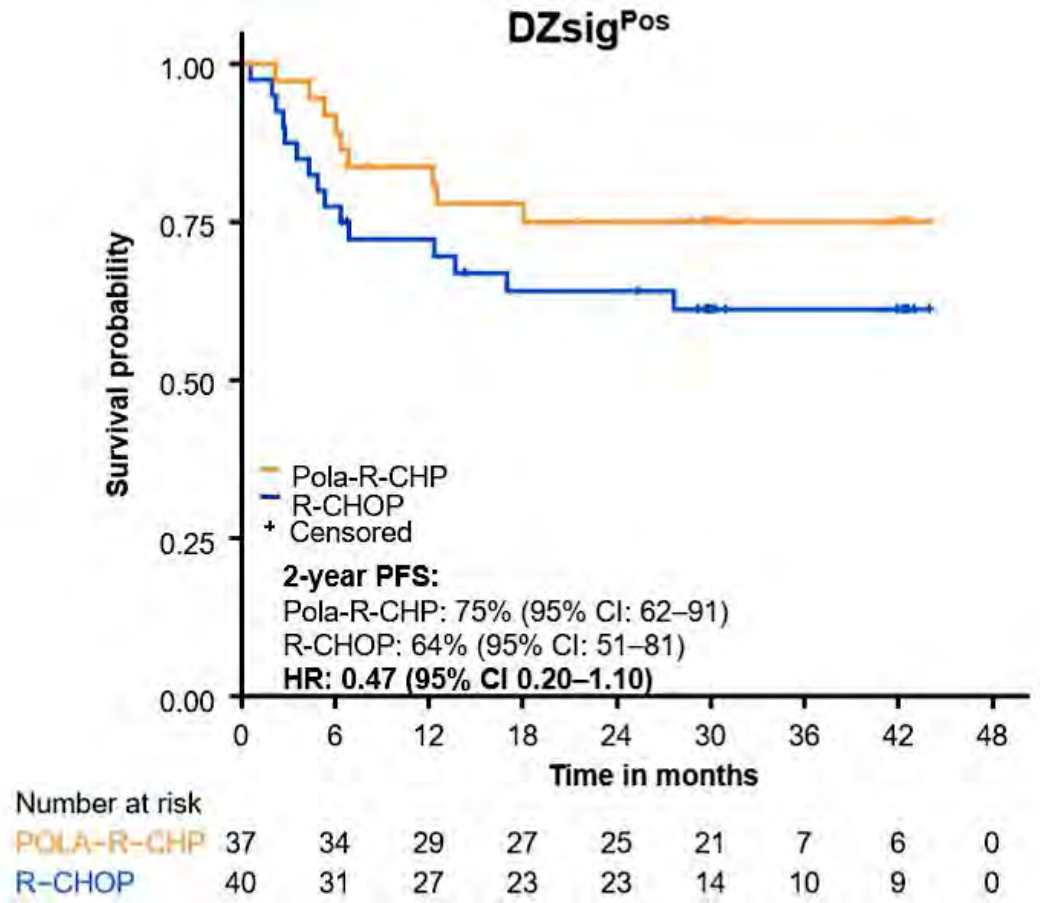


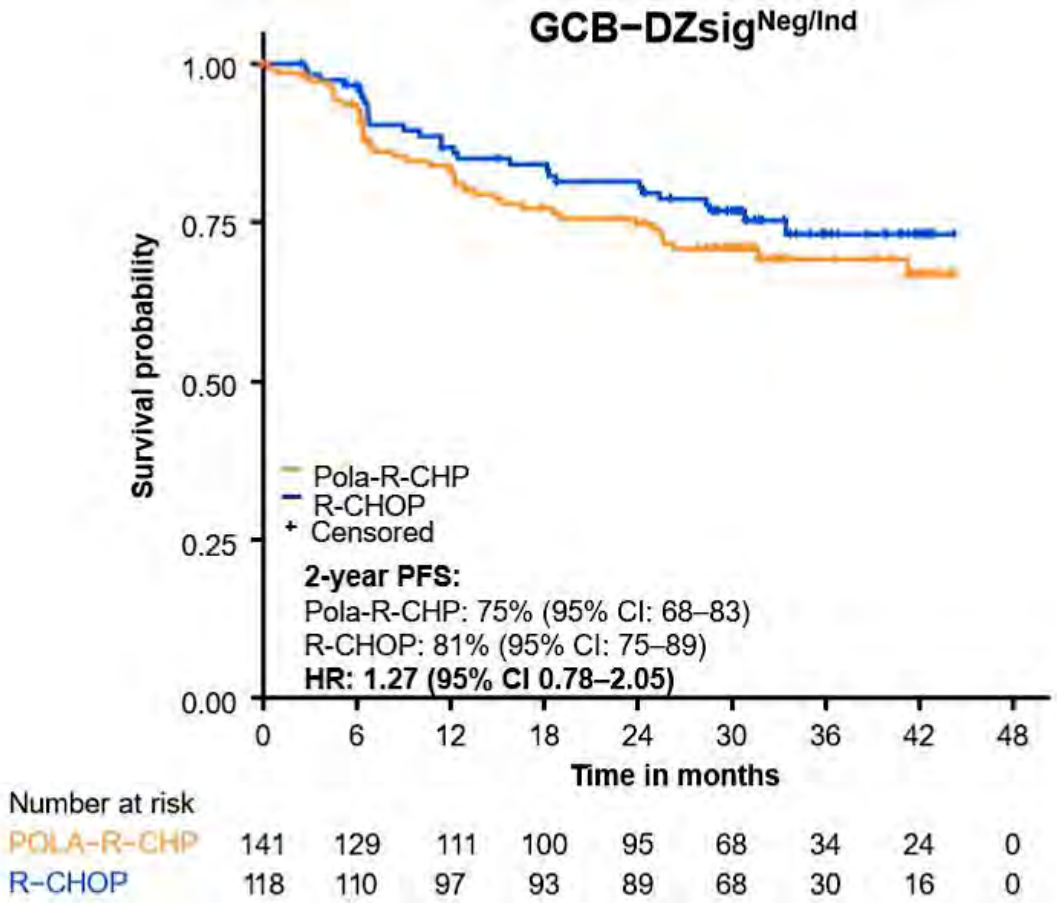




Morschhauser et al, ASH 2023 Abstract #3000

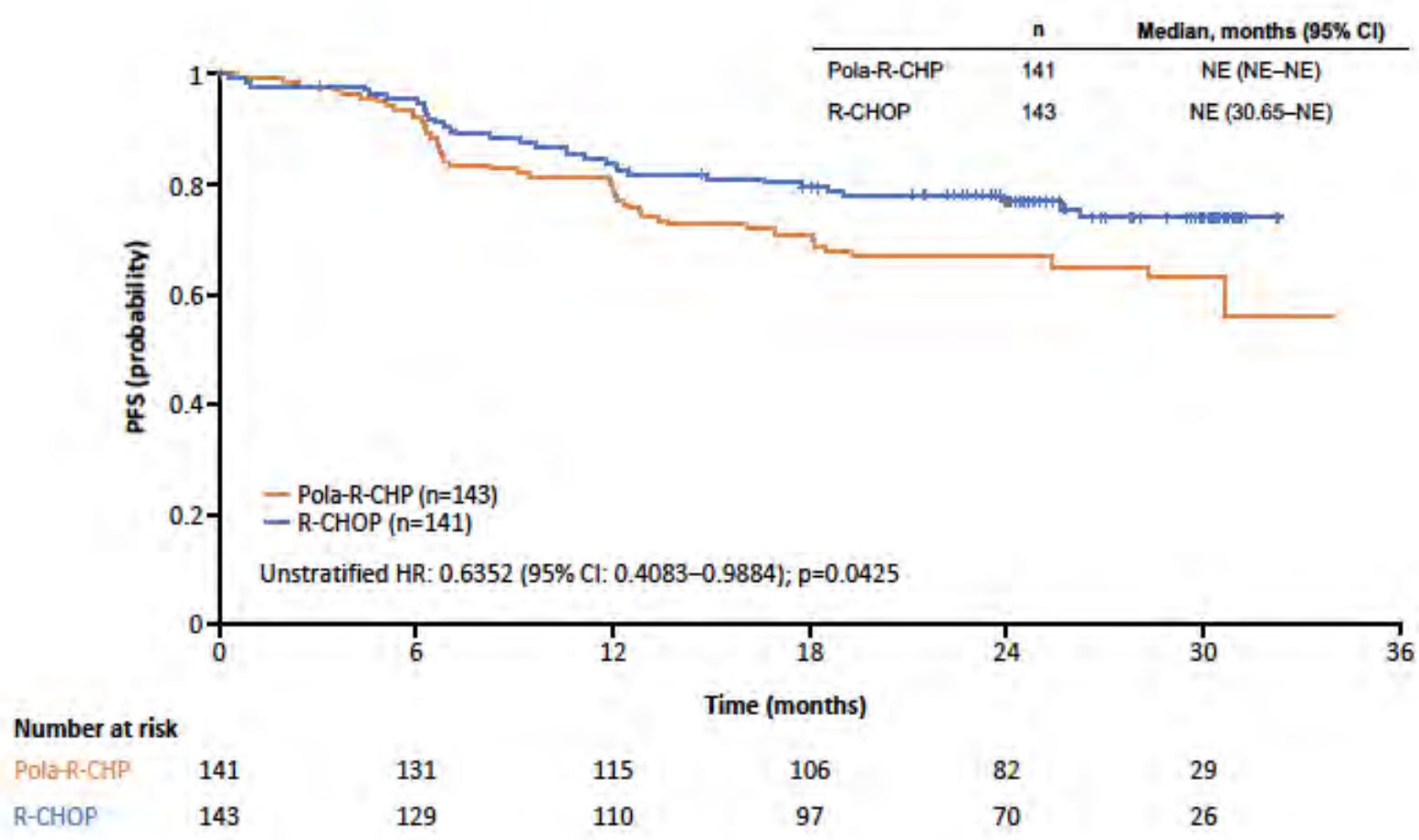
Dark Zone Signature-Positive DLBCL: Trend to Improved PFS





Morschhauser et al, ASH Abstract #3000

POLARIX: PFS in Elderly Patients Aged ≥70 Years



2-year PFS: 77.1% Pola-R-CHP vs 67.0% R-CHOP

Hu et al, ASCO 2023

Phase 3 POLAR BEAR Trial: R-POLA-MINI-CHP vs R-MINI-CHOP in Elderly or Frail Patients with DLBCL

Screening period
≤4 weeks

- Age ≥80 y or frail
  75-80 y
- Stage II-IV
- PS 0 – 3

R
1:1

Arm A

Arm B

Treatment period
18 weeks

R-miniCHOP R-miniCHOP R-miniCHOP R-miniCHOP R-miniCHOP R-miniCHOP

Response after 3 cycles

R-polaminiCHP R-polaminiCHP R-polaminiCHP R-polaminiCHP R-polaminiCHP R-polaminiCHP

Follow up period
36 months

Efficacy assessment:
6 weeks + **3, 6, 12 AND 24 MONTHS**
CT of thorax, abdomen/pelvis and neck *or PET-CT*
HRQOL assessment
Samples for ctDNA

Follow-up visits:
3, 6, 9, 12, 15, 18, 21, 24, 30, and 36 months
after end of treatment

Primary endpoint: PFS
Sample size:
300 patients

Jerkeman et al, EHA 2023

Initial Safety Analysis - Patient Characteristics (n=140)

Characteristic		R-mini-CHOP (n=71)		R-pola-mini-CHP (n=69)	
Sex	male	42	(60.9)	30	(46.2)
	female	27	(39.1)	35	(53.8)
Age group	<80	12	(18.2)	10	(15.9)
	80-85	38	(57.6)	47	(74.6)
	>85	16	(24.2)	6	(9.5)
Stage	2	12	(20.0)	11	(19.6)
	3-4	48	(67.6)	45	(65.2)
IPI	Low (0-1)	12	(16.9)	12	(17.3)
	Low intermediate (2)	12	(17.6)	11	(16.9)
	High intermediate (3)	12	(17.6)	11	(16.9)
	High (4-5)	32	(45.1)	31	(44.9)
WHO Performance Status	0-1	41	(57.7)	40	(57.9)
	2	17	(26.6)	13	(20.6)
	3	6	(9.4)	10	(15.9)
Lymphoma subtype	DLBCL	61	(92.4)	56	(87.5)
	FL grade 3B	1	(1.5)	4	(6.3)
	HGBCL with MYC/BCL2	3	(4.5)	4	(6.3)
	Other	1	(1.5)	0	(0.0)
CIRS-G	< 10	36	(50.7)	46	(66.7)
	>= 10	11	(15.5)	10	(14.5)
	Missing	24	(33.8)	13	(18.8)

Jerkeman et al, EHA 2023

Select Adverse Events

Adverse event		R-mini-CHOP (n=71)		R-pola-mini-CHP (n=69)	
Anemia[1]	Grade 3-5	2	2.8%	10	14%
Neutropenia[1]	Grade 3-5	8	11%	9	13%
Thrombocytopenia[1]	Grade 3-5	0	0	1	1.4%
Infection	Total	32	45%	39	57%
	Grade 3-5	10	14%	11	16%
Gastrointestinal	Total	22	31%	38	55%
	Grade 3-5	12	17%	21	30%
Cardiovascular	Total	21	30%	16	23%
	Grade 3-5	6	8.5%	6	8.7%
Peripheral neuropathy	Grade 1	7	9.9%	9	13%

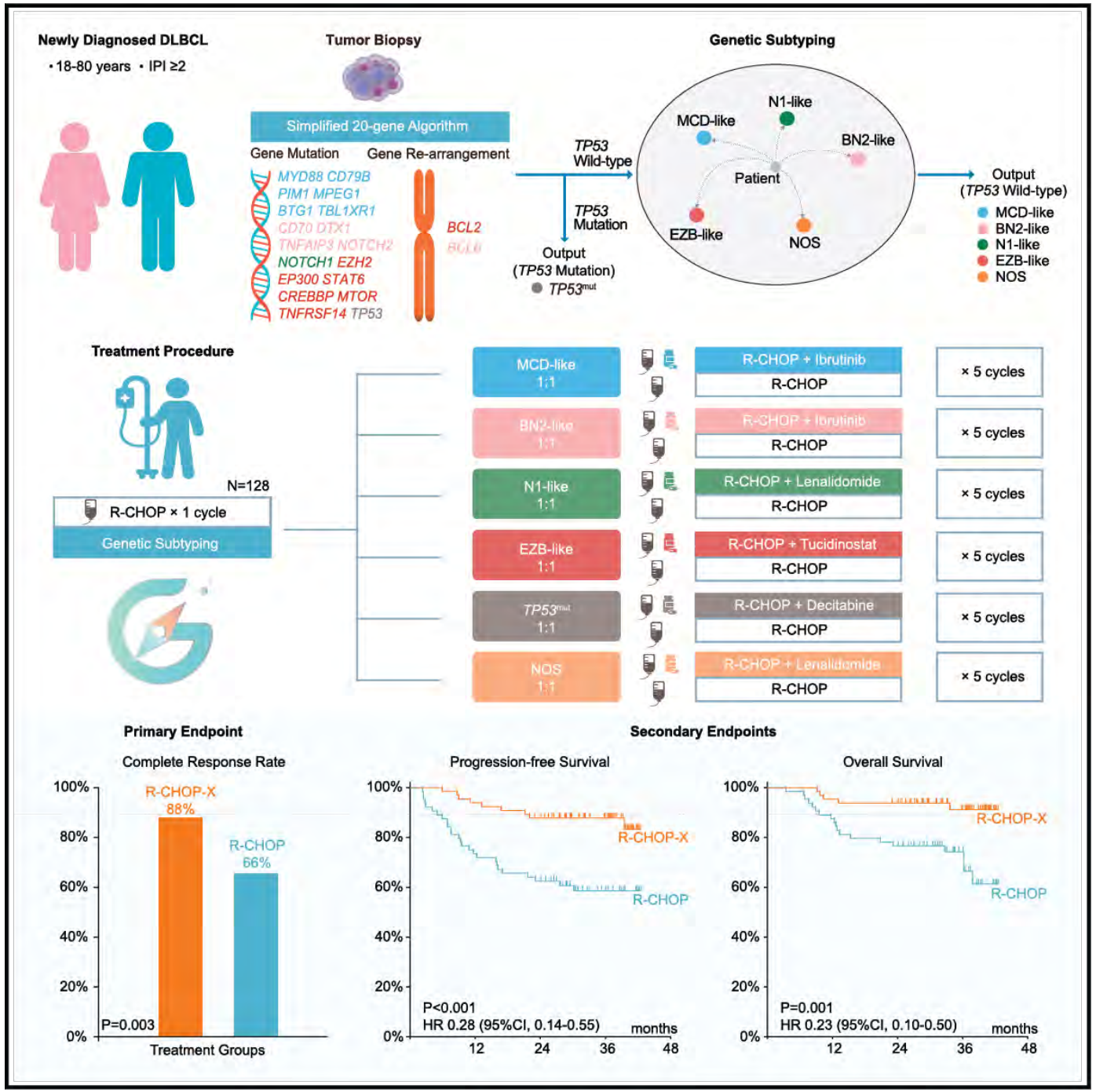
[1]For hematological toxicity, only grade 3-5 was recorded

Jerkeman et al, EHA 2023

Ongoing/Planned Trials in Upfront DLBCL

- **BTK-inhibitor + R-CHOP trials**
  - Acalabrutinib-R-CHOP: ESCALADE (non-GCB); ReMoDL-A (all)
- **First-MIND Trial:** Tafasitamab/Lenalidomide-R-CHOP
- **ZUMA-23:** Axi-cel *v* R-CHOP/DA-EPOCH-R (Stage 3/4, IPI 4-5)
- **CD20/CD3 Bispecific Antibodies + R-CHOP/Pola-R-CHP**
- **Response-adapted trials (ctDNA)**
- **Novel therapy approaches (Smart Stop trial)**
- **Biology-driven trials**

GUIDANCE-01:
a model for trials of precision medicine based on genetics-based subtypes



Zhang et al *Cancer Cell* 2023

Faculty Case Presentations

Case Presentation: Dr Flowers

Initially admitted with epidural DLBCL with compression fracture

- IR Biopsy showed ABC subtype
- PET/CT Stage IV disease with BM involvement by PET
- LDH > ULN
- LP negative
- Initiated on pola-R-CHP

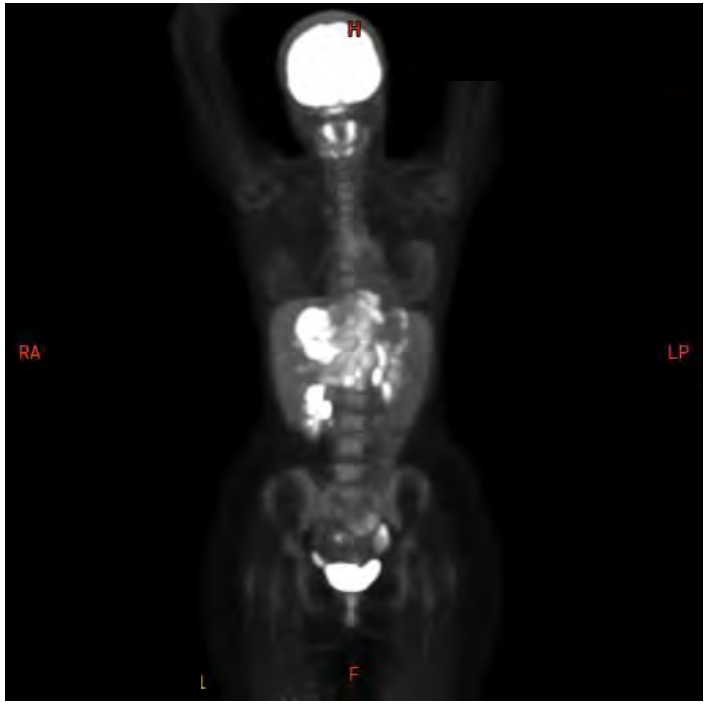
QUESTIONS FOR THE FACULTY

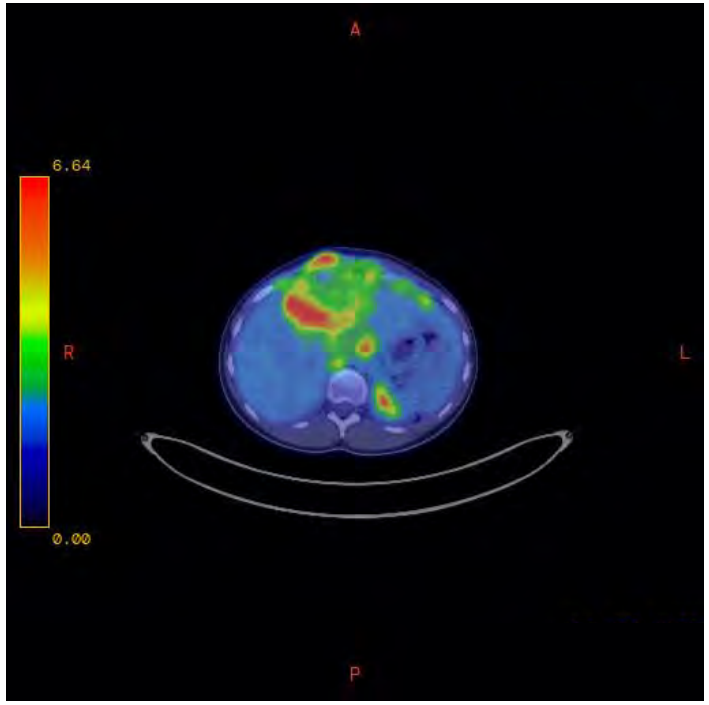
In general, how do you choose between polatuzumab vedotin/R-CHP and R-CHOP as first-line treatment for DLBCL?

Do you believe that cell of origin assay results available to community-based oncologists are reliable enough to guide treatment decision-making?

Case Presentation: Dr Nowakowski

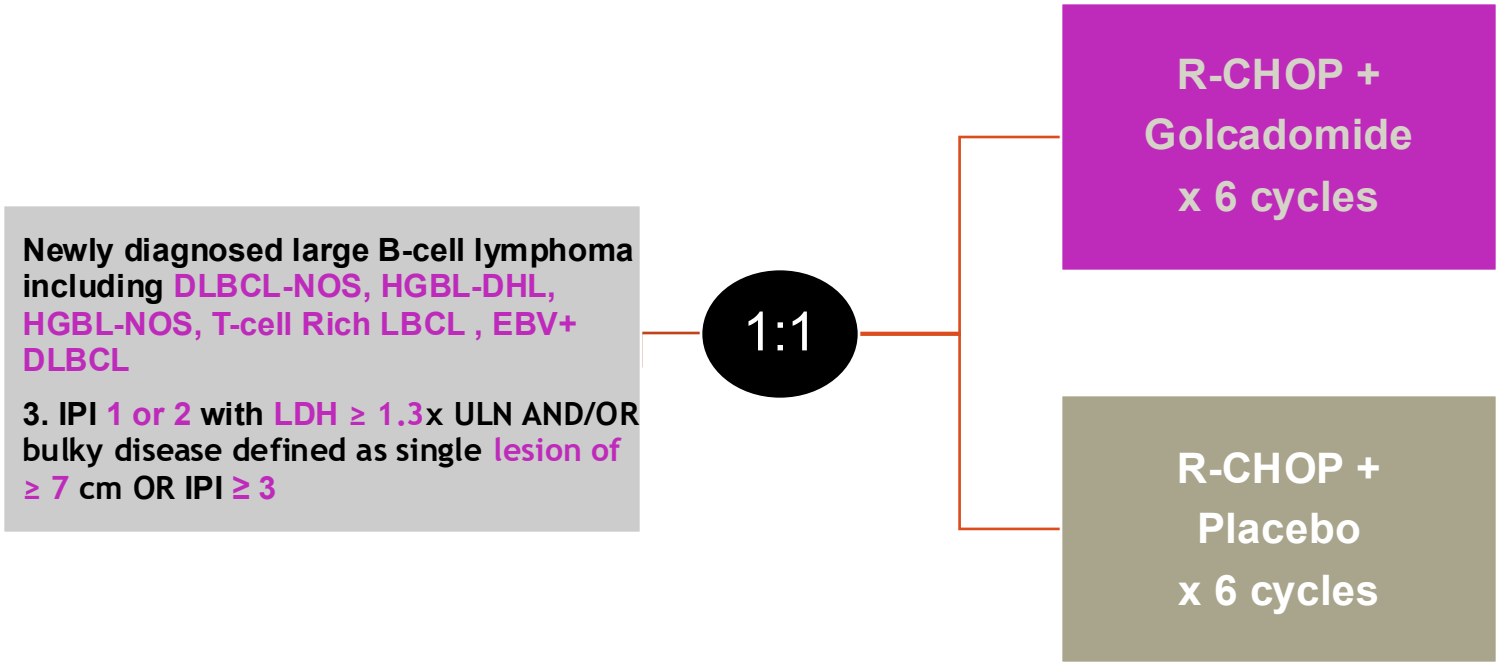
- 19-year-old female presented with couple of weeks history of anterior abdominal wall mass
- CT showed mass involving chest wall but also liver lesions
- CT-guided biopsy of chest lesion showed diffuse large B-cell lymphoma, GCB phenotype without myc translocation and without double expression of myc or BCL2, Lymph3Cx – GCB, non PMLBCL
- PET scan showed conglomerate/multifocal anterior abdominal wall and hepatic lesions
- Paraesophageal, upper abdominal, and gastrohepatic metastatic FDG avid lymphadenopathy





Case Presentation: Dr Nowakowski (cont.)

- GCB DLBCL, Stage 4, IPI 3 (stage, elevated LDH, >1 extra nodal site)
- Pt entered study R-CHOP+Golcadomide vs. R-CHOP+Placebo (Double Blind Placebo Controlled)



QUESTIONS FOR THE FACULTY

What do you think the results of the first-line R-CHOP with or without golcadomide trial are going to show?

What other ongoing clinical trials evaluating first-line treatment for DLBCL are you most excited about?

In general, what is your usual up-front treatment for double-hit DLBCL?

Agenda

Module 1: Front-Line Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Sehn

Module 2: Integration of Novel Agents into the Care of Patients with Relapsed/Refractory DLBCL — Dr Flowers

Module 3: Bispecific Antibody Therapy for DLBCL — Dr Nowakowski

Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Christopher Flowers, MD, MS, FASCO

Division Head
Chair, Professor

Division of Cancer Medicine
Department of Lymphoma/Myeloma

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Dr Flowers — Disclosures

Consulting Agreements	AbbVie Inc, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Celgene Corporation, Denovo Biopharma, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Karyopharm Therapeutics
Contracted Research	4D Pharma PLC, AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Alaunos Therapeutics, Allogene Therapeutics, Amgen Inc, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Cellectis, EMD Serono Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, Iovance Biotherapeutics, Janssen Biotech Inc, Kite, A Gilead Company, MorphoSys, Nektar Therapeutics, Novartis, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Sanofi, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc, Xencor
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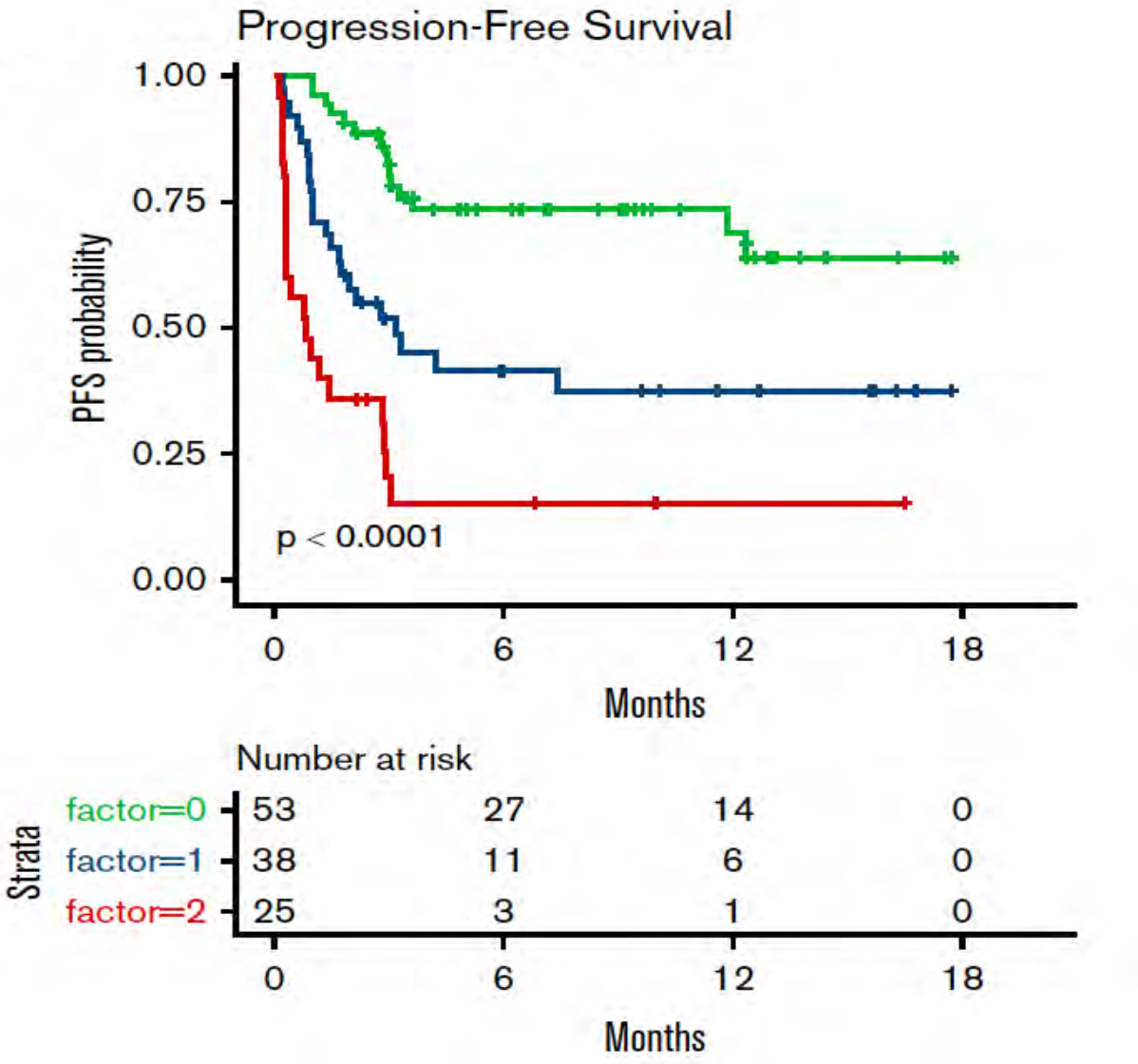
Not Everyone Will Benefit from CAR-T



Predictive factors associated with poor outcome following CAR T-cell therapy:

- ≥ 2 extranodal sites
- TMTV > 80 mL
- Elevated LDH

Vercellino L et al. *Blood Adv*. 2020;4(22):5607-5615.

Selected Therapies Approved in R/R DLBCL

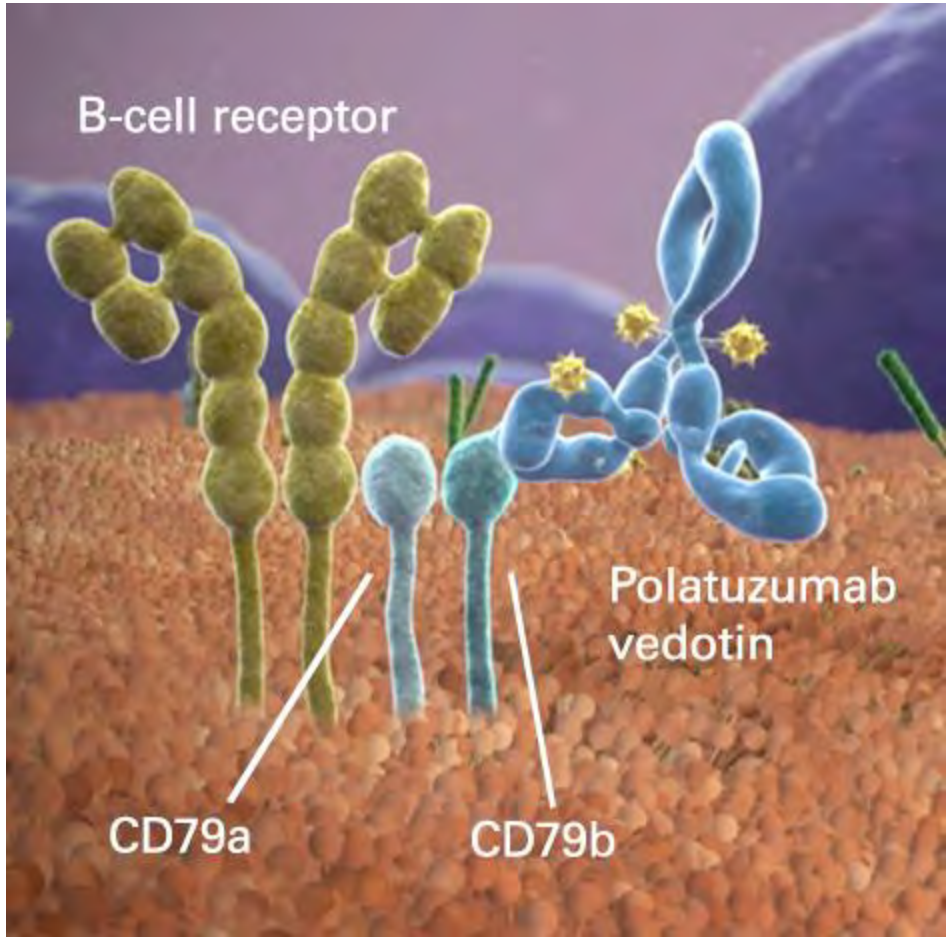
	Pola-BR	Selinexor	Tafasitamab/Lenalidomide	Loncastuximab Tesirine
MOA	Anti-CD79b ADC	XPO-1 inhibitor	Anti-CD19 mAb/Immunomodulator	Anti-CD19 ADC
ORR	45%	28%	58%	48%
CR rate	40%	10%	40%	24%
PFS	9.2 m	2.6 m	11.6 m	4.9 m
DOR	12.6 m	9.3 m	43.9 m	10.3 m
OS	12.4 m	NR	33.5 m	9.9 m

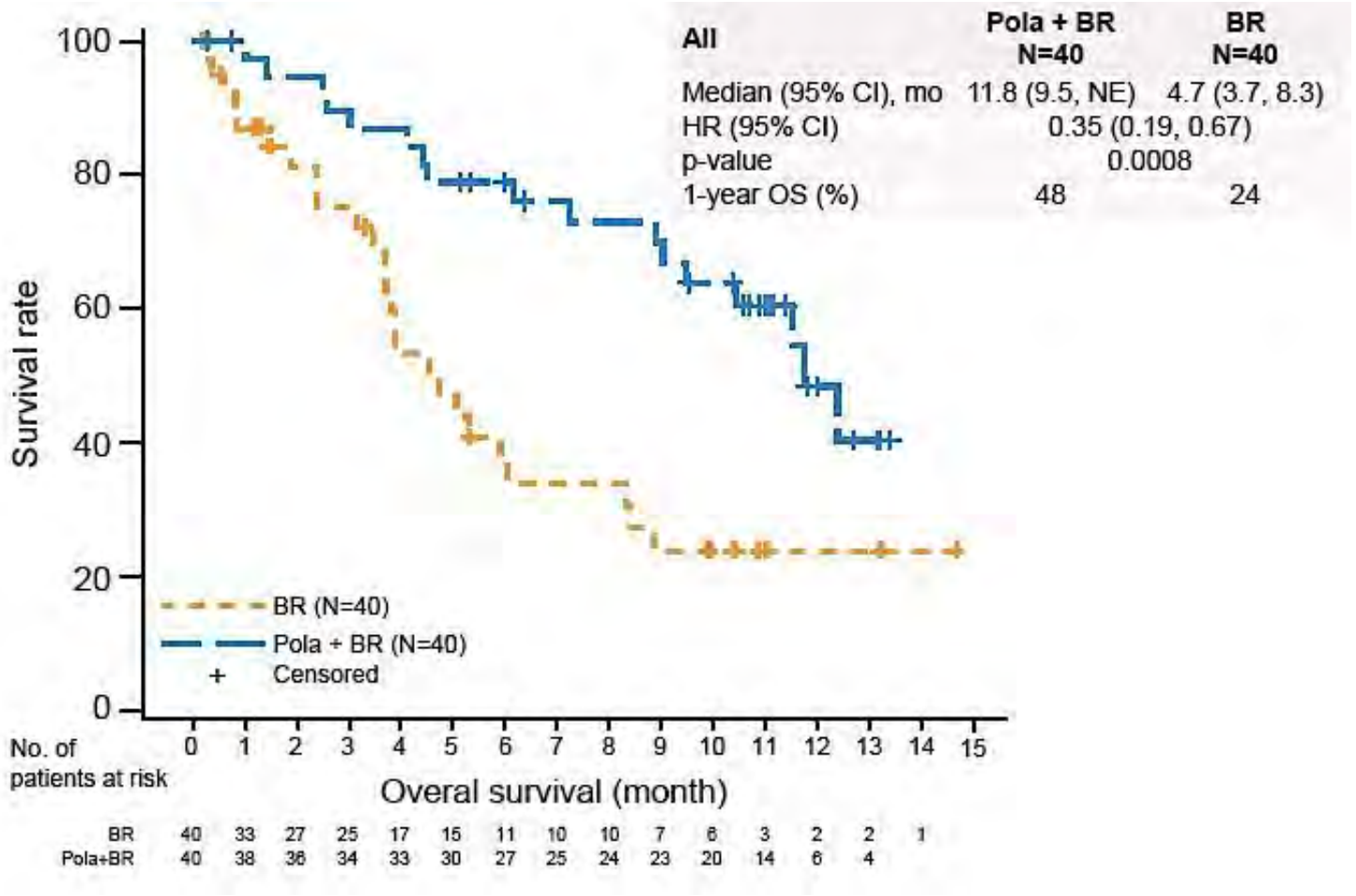
Novel salvage regimens may improve outcomes with ASCT

Sehn LH et al. *Blood Adv*. 2022;6(2):533-543.
Kalakonda N et al. *Lancet Haematol.* 2020;7(7):e511-e522.
Duell J et al. *Haematologica*. 2021;106(9):2417-2426.
Caimi PF et al. *Lancet Oncol.* 2021;22(6):790-800.

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma *J Clin Oncol.* 2020

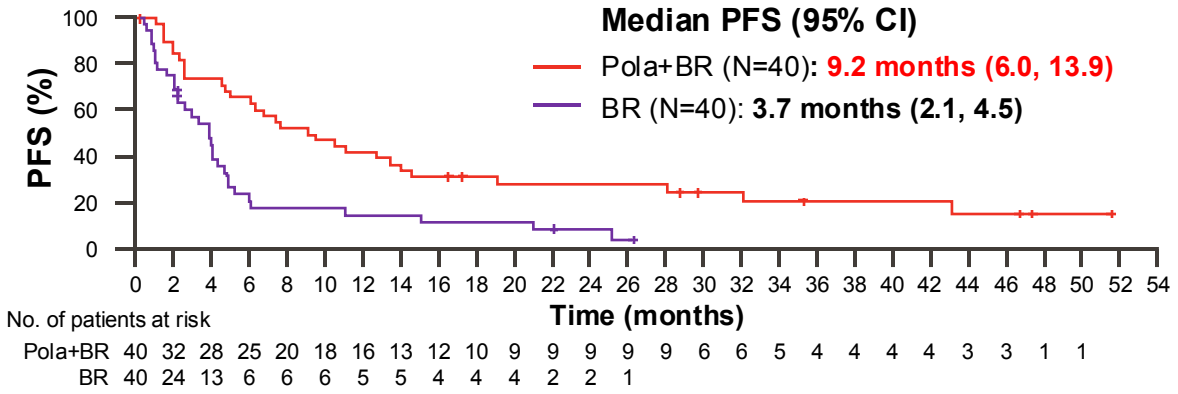
Laurie H Sehn, Alex F Herrera, Christopher R Flowers, Manali Kamdar, Andrew McMillan, Mark Hertzberg, Sarit Assouline, Tae Min Kim, Won Seog Kim, Muhit Ozcan, Jamie Hirata, Elicia Penuel, Elicia Penuel, Ji Cheng, Joseph N. Paulson, Grace Ku, Matthew Matasar

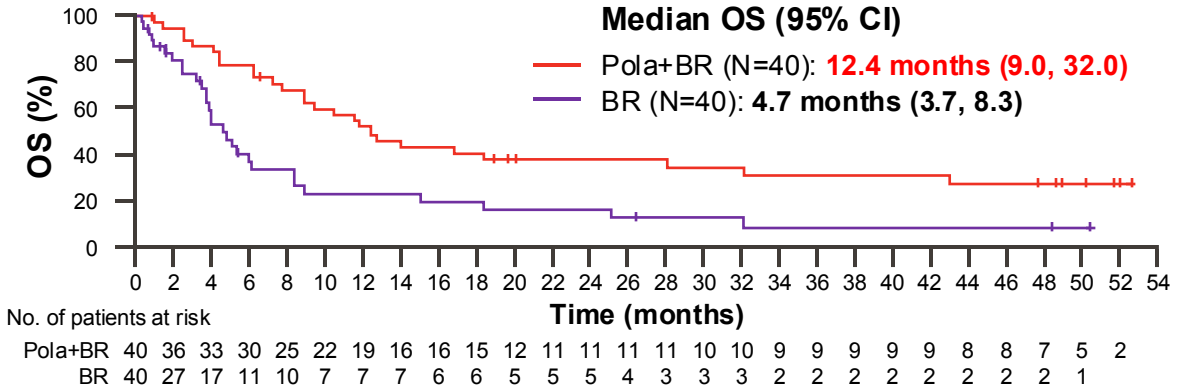




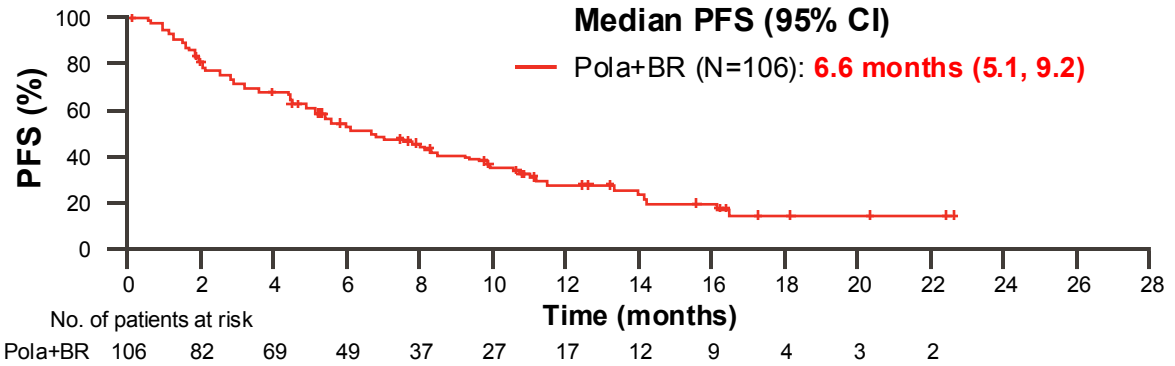
Pola-BR PFS and OS

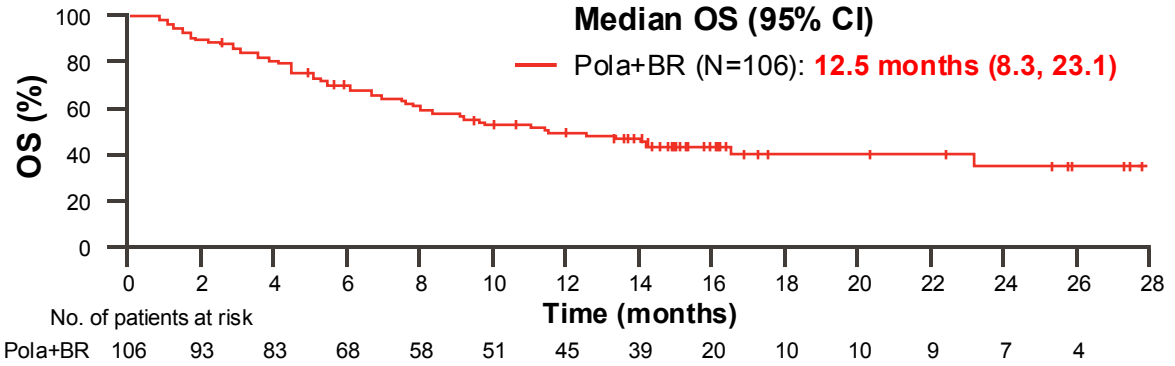
Randomized





Extension cohort





Sehn LH et al. ASH 2020. Abstract 3020; Sehn LH et al. *Blood Adv*. 2022;6(2):533-543.

- The significant survival benefit with Pola+BR persists with longer follow-up
- Response rates in the extension cohort consistent with the randomized Pola+BR arm
- The 2-year PFS 28.4% and the 2-year OS 38.2% for patients in the randomized Pola+BR cohort

BR, bendamustine plus rituximab; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; pola, polatuzumab.

Pola-BR Safety Summary

AE summary, n (%)	Randomized		Extension Cohort Pola+BR (N=106)	Pooled Pola+BR (N=151)
	BR (N=39)	Pola+BR (N=39)		
Any Grade AEs	38 (97.4)	39 (100)	105 (99.1)	150 (99.3)
Grade 3–4 AEs	28 (71.8)	34 (87.2)	83 (78.3)	122 (80.8)
SAEs	24 (61.5)	26 (66.7)	56 (52.8)	86 (57.0)
Grade 5 AEs	10 (25.6)	11 (28.2)	6 (5.7)	17 (11.3)

No new safety signals identified with longer follow-up in randomized arms + patients in the extension cohort

Sehn LH et al. ASH 2020. Abstract 3020.

Common AEs, n (%)	Pooled Pola+BR (N=151)	
	Any grade	Grade 3–4
Hematological AEs		
Neutropenia	**71 (47.0)**	**49 (32.5)**
Thrombocytopenia	49 (32.5)	31 (20.5)
Anemia	49 (32.5)	19 (12.6)
Non-hematological AEs		
Infections and infestations	**74 (49.0)**	**33 (21.9)**
Diarrhea	54 (35.8)	6 (4.0)
Nausea	50 (33.1)	1 (0.7)
Pyrexia	44 (29.1)	2 (1.3)
Fatigue	40 (26.5)	3 (2.0)
Decreased appetite	39 (25.8)	4 (2.6)
AEs of special interest		
Peripheral neuropathy	**47 (31.1)**	**3 (2.0)**

Sehn LH et al. ASH 2022. Final Analysis Abstract 4260

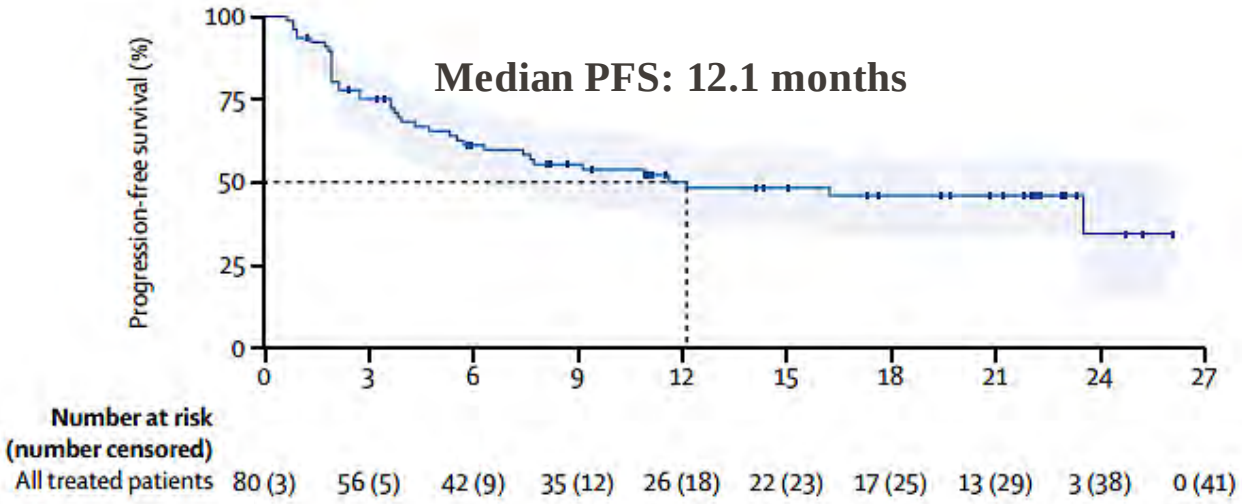
Tafasitamab + Lenalidomide: Outcomes

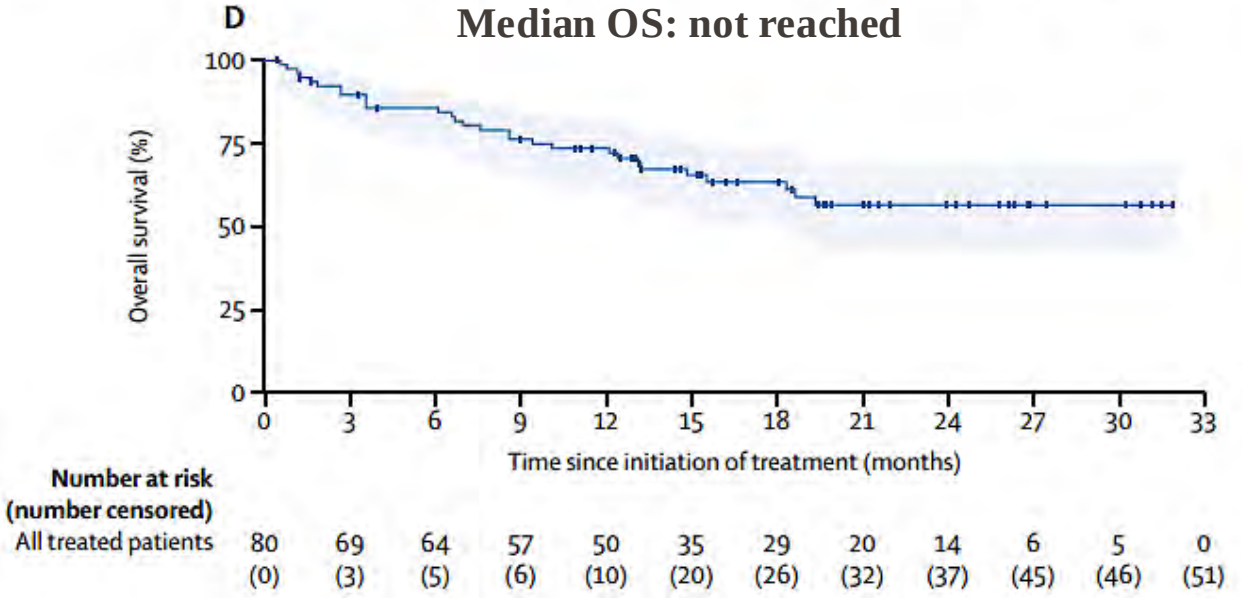
	N= 80 (%)
Objective Response Rate	48 (60)
Complete Response	34 (43)
Partial Response	14 (17)

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

Final 5-Year Efficacy Analysis:
Objective response rate 57.5%
Median PFS 11.6 months
Median OS 33.5 months

Duell J et al. *Haematologica* 2024;109(2):553-66.

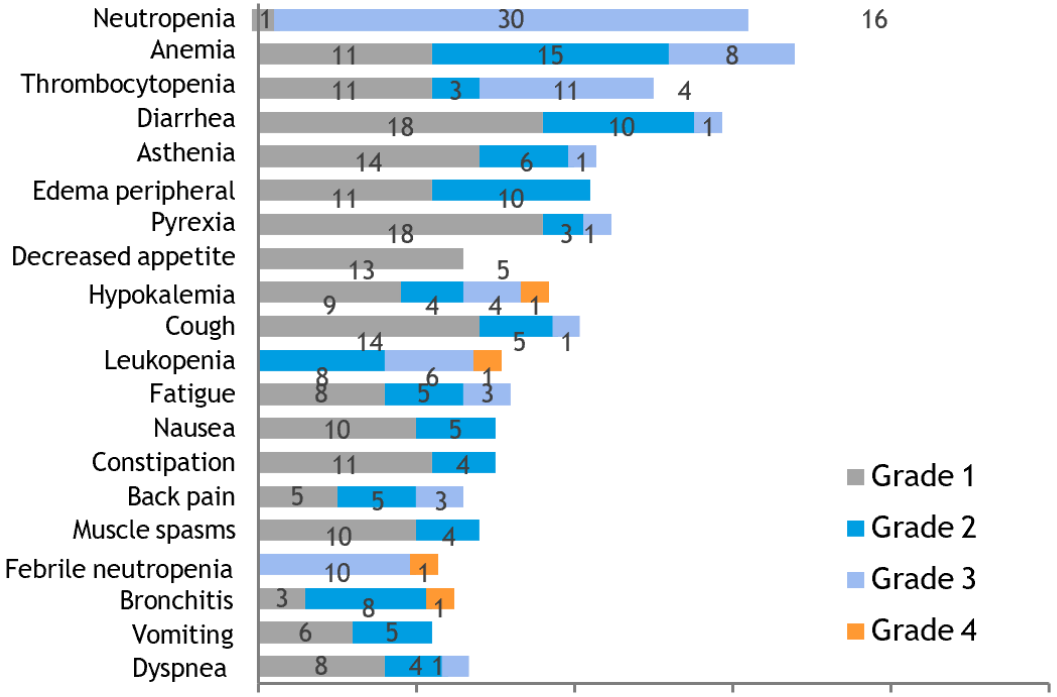




Salles G et al. *Lancet Oncol.* 2020;21(7):978-988.

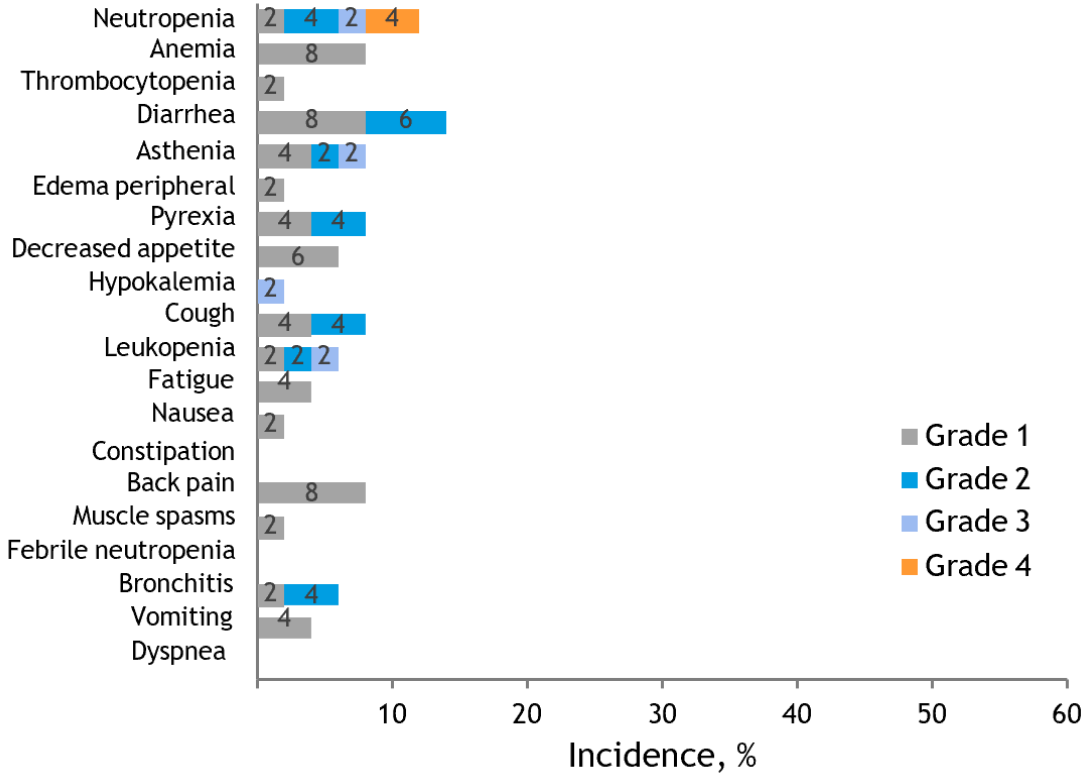
Tafasitamab + Lenalidomide: Safety

Tafasitamab + LEN Combination (Up to 12 Cycles) N=80, Median Exposure 6.2 Months[a]



- 37 patients (43%) required lenalidomide dose reduction
- 62/80 patients (78%) were able to stay at dose ≥ 20mg/d

Tafasitamab Monotherapy (Cycle 13 Onward or After LEN Discontinuation) N=51, Median Exposure 4.1 Months[a]



- Incidence and severity of TEAEs are lower during the tafasitamab monotherapy phase
- Ten patients (12%) discontinued tafasitamab + LEN because of AEs

[a]AE collection period included 30 days after end of treatment

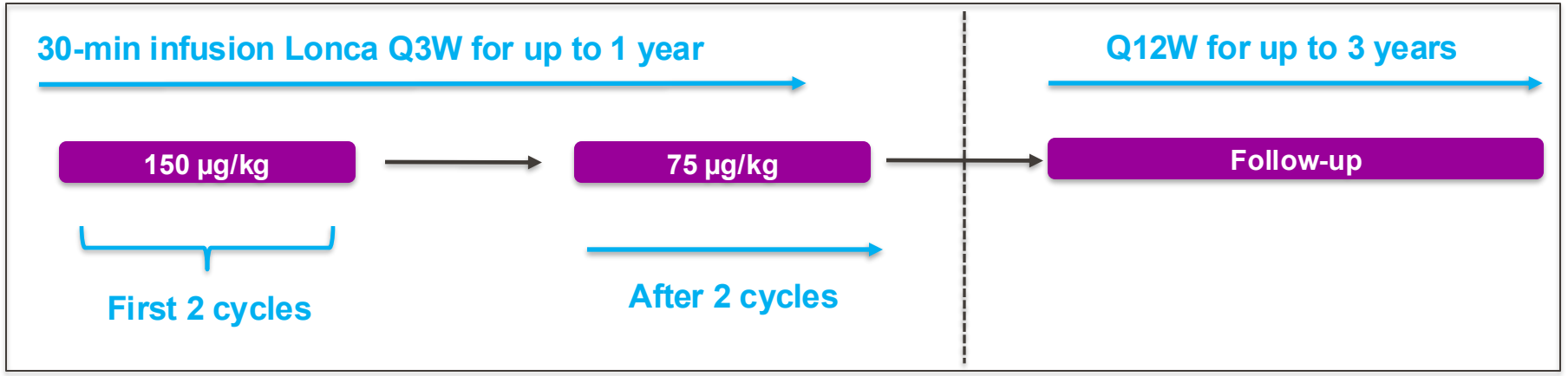
AEs, adverse events; LEN, lenalidomide; TEAEs, treatment-emergent AEs .

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

Loncastuximab Tesirine: LOTIS-2 Trial
Single Arm Open Label Phase 2 Study in DLBCL

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

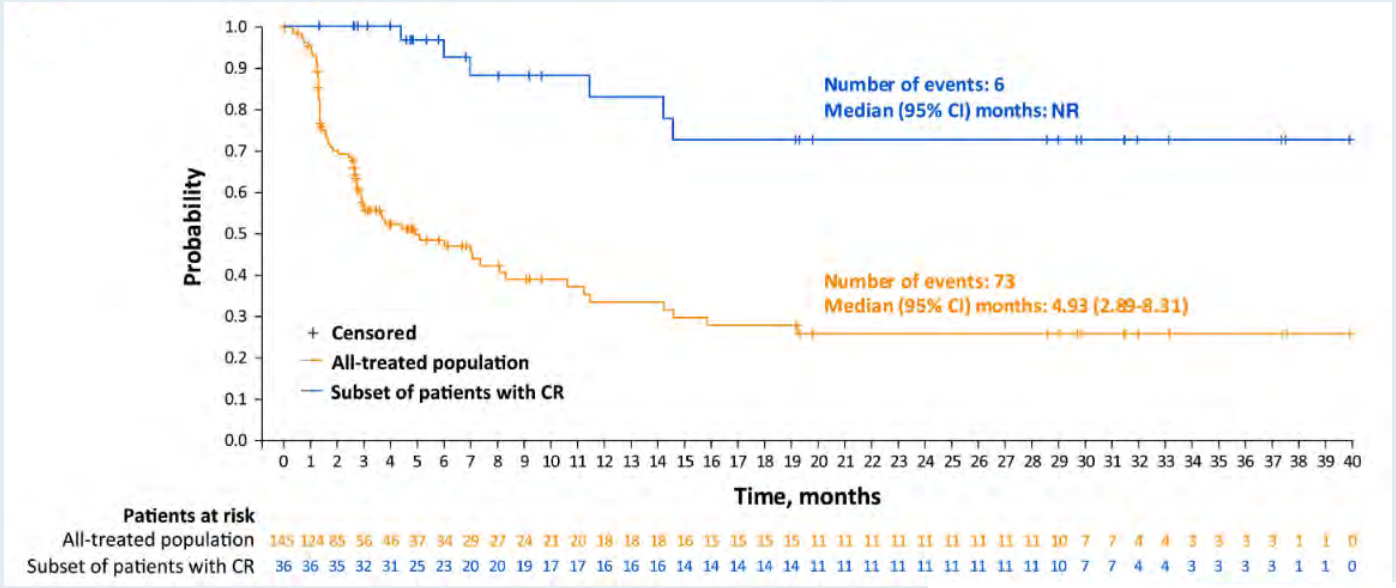
Primary objective:
Evaluate efficacy, **using ORR** (central review), and **safety** of the full Phase 2 study population



Lonca, loncastuximab tesirine; ORR, overall response rate; Q3W, every 3 weeks; Q12W, every 12 weeks; R/R, relapsed/refractory.

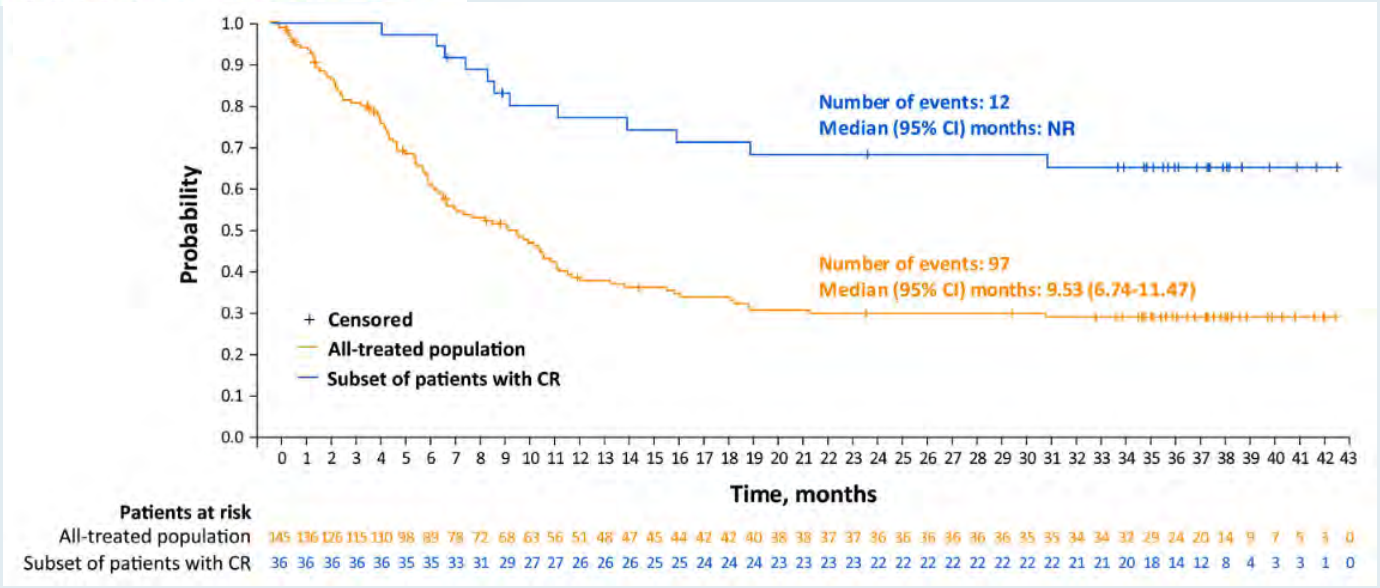
Caimi PF et al. *Lancet Oncol.* 2021

LOTIS-2 Trial: Long-Term Efficacy with Loncastuximab Tesirine for R/R DLBCL



PFS

OS



Caimi PF et al. *Haematologica* 2024;109(4):1184-93.

Loncastuximab Tesirine: Adverse Events

Adverse Event (AE)	Patients n (%)
Any Treatment Emergent AE	143 (98.6)
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral Edema	29 (20.0)

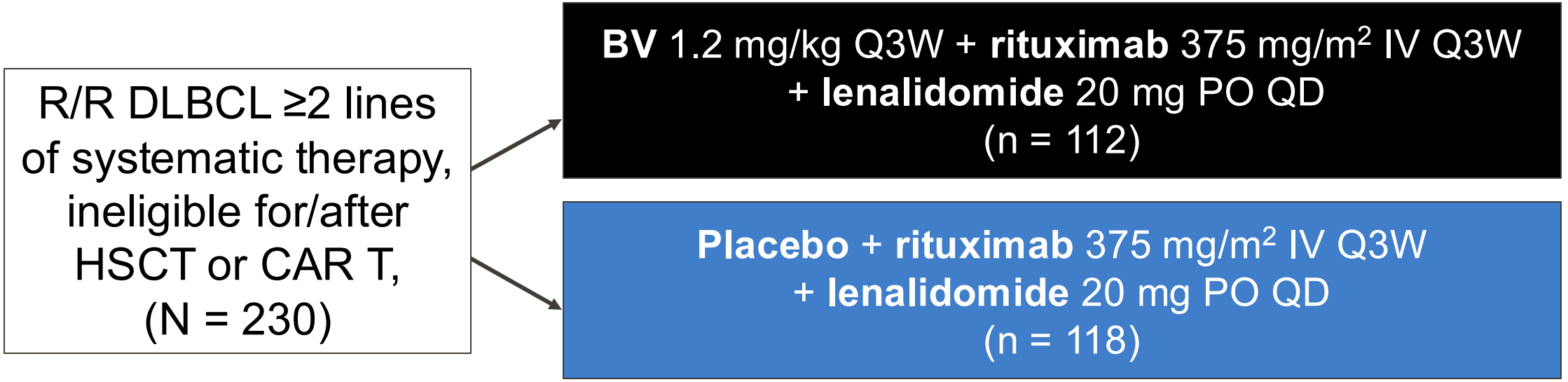
GGT, gamma glutamyltransferase ; SAEs, serious adverse events; TEAE, treatment-emergent adverse event..

TEAE leading to treatment discontinuation: 26 (17.9%)

Caimi PF et al. *Lancet Oncol.* 2021

ECHELON-3: Study Design

- Multicenter, double-blind, placebo-controlled, randomized phase 3 trial
- **Primary endpoint**: OS in ITT population



Stratification:

- CD30 status (≥1% vs <1%)
- Cell of origin (GCB vs non-GCB)
- Prior CAR T-cell therapy (yes vs no)
- Prior SCT (yes vs no)

Kim. ASCO 2024. Abstract LBA7005

ECHELON-3: Outcomes - Response

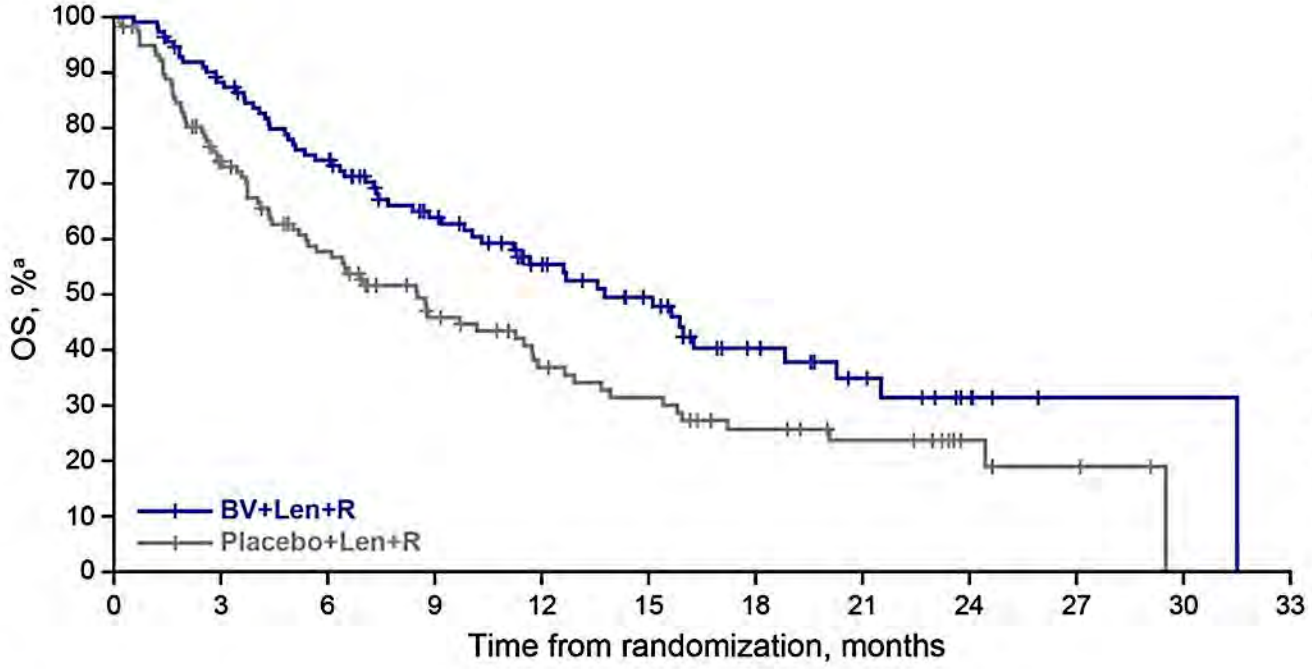
All patients	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
ORR, % ▪ CR	64.3 40.2	41.5 18.6
With CD30-negative disease (<1%)	**n = 76**	**n = 80**
ORR, % ▪ CR	60.5 40.8	37.5 15.0
With CD30-positive disease (≥1%)	**n = 36**	**n = 38**
ORR, % ▪ CR	72.2 38.9	50.0 26.3

Kim. ASCO 2024. Abstract LBA7005

ECHELON-3: Outcomes-PFS

PFS	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
Median PFS, mo	4.2	2.6
HR (95% CI)	0.527 (0.380-0.729)	

ECHELON-3: Outcomes



	BV+Len+R (n=112)	Placebo+Len+R (n=118)
OS, median (95% CI), months	**13.8** (10.3-18.8)	**8.5** (5.4-11.7)
Hazard ratio (95% CI)[b]	0.629 (0.445-0.891)	
Log-rank *P* value[c]	.0085	
Events (deaths)	58	76
Follow-up, median (95% CI), months	15.5 (12.2-18.1)	18.9 (12.2-23.2)

ECHELON-3: Adverse Events

TEAEs, %	BV + Len + R (n = 112)	Placebo + Len + R (n = 116)
Any grade	97	97
Peripheral neuropathy	31	24
Grade ≥3	88	77
▪ Febrile neutropenia	9	9
Grade 5	12	8

Kim. ASCO 2024. Abstract LBA7005

Faculty Case Presentations

Case Presentation: Dr Nowakowski

- 76-year-old gentleman who was diagnosed with DLBCL, GCB phenotype, no myc rearrangement in March of 2019
- Therapy with R-CHOP and radiation therapy to mesenteric mass to total of 30 Gy completed in October of 2019 with CR
- July 2021, recurrent disease – initiated on RICE salvage chemotherapy which was associated with significant toxicity, SD as best response
- Lenalidomide and tafasitamab with CR – continued for 12 cycles of combination and then tafasitamab single for 2 years
- Feb 2024, retro esophageal mass, bx revealed DLBCL: CD19 expression was negative per immunohistochemistry, rapid progression required pola-v rituximab bridging
- March, CART – lisocabtagene maraleucel – in CR day 30 and PET 7/17/24 showing ongoing CR

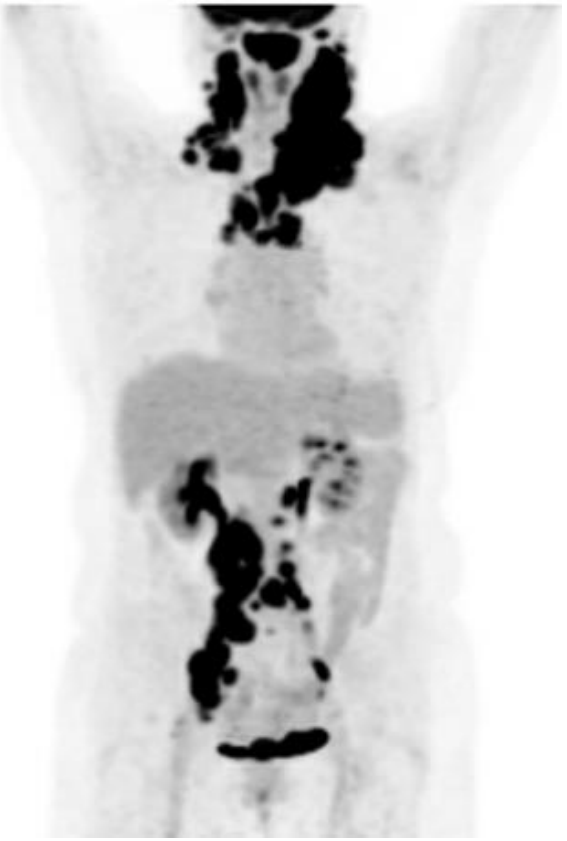
QUESTIONS FOR THE FACULTY

In general, what has been your clinical experience in terms of efficacy and tolerability with tafasitamab/lenalidomide for patients with DLBCL?

For patients with relapsed DLBCL, how do you generally sequence bispecific antibodies, CAR T-cell therapy and tafasitamab/lenalidomide?

Case Presentation: Dr Sehn

- 75 yo female with hypertension, type 2 diabetes and osteoarthritis
- Presented with fatigue, night sweats and bilateral neck fullness, ECOG PS 2
- Labs: mild anemia 9.4 g/dL, LDH 420 U/L (ULN 240)
- PET/CT: lymphadenopathy above and below diaphragm (maximum 14 cm)
- Biopsy of cervical LN: DLBCL, ABC subtype



- ➢ Treated with 6 cycles of dose-reduced R-CHOP (with 1 delay due to infection)
- ➢ CR on post-treatment PET/CT

Case Presentation: Dr Sehn (cont'd)

- 20 months later, she developed enlarged cervical nodes, PET/CT and biopsy confirmed recurrent DLBCL

- Not considered to be a transplant candidate
- CAR T-cell therapy not available second-line
- Treated with Pola-BR for 6 cycles, achieved a CR, and remains in remission 2 years later

QUESTIONS FOR THE FACULTY

What treatment options would you discuss with a patient with DLBCL who is not eligible for or whose disease has progressed on bispecific antibodies, CAR T-cell therapy and tafasitamab/ lenalidomide?

Would you ever attempt to rechallenge with polatuzumab vedotin later in the treatment course for a patient who received it up front and experienced subsequent disease progression?

In general, what has been your clinical experience in terms of efficacy and tolerability with loncastuximab tesirine for patients with DLBCL?

Agenda

Module 1: Front-Line Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Sehn

Module 2: Integration of Novel Agents into the Care of Patients with Relapsed/Refractory DLBCL — Dr Flowers

Module 3: Bispecific Antibody Therapy for DLBCL — Dr Nowakowski

MAYO CLINIC

Bispecific Antibody Therapy for DLBCL

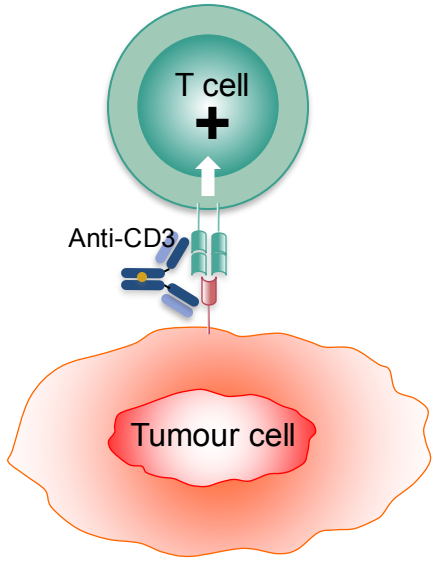
Grzegorz (Greg) S. Nowakowski MD, FASCO
Professor of Medicine and Oncology
Chair, Lymphoid Malignancy Group
Deputy Director Mayo Clinic Comprehensive Cancer Center
Mayo Clinic

Dr Nowakowski — Disclosures

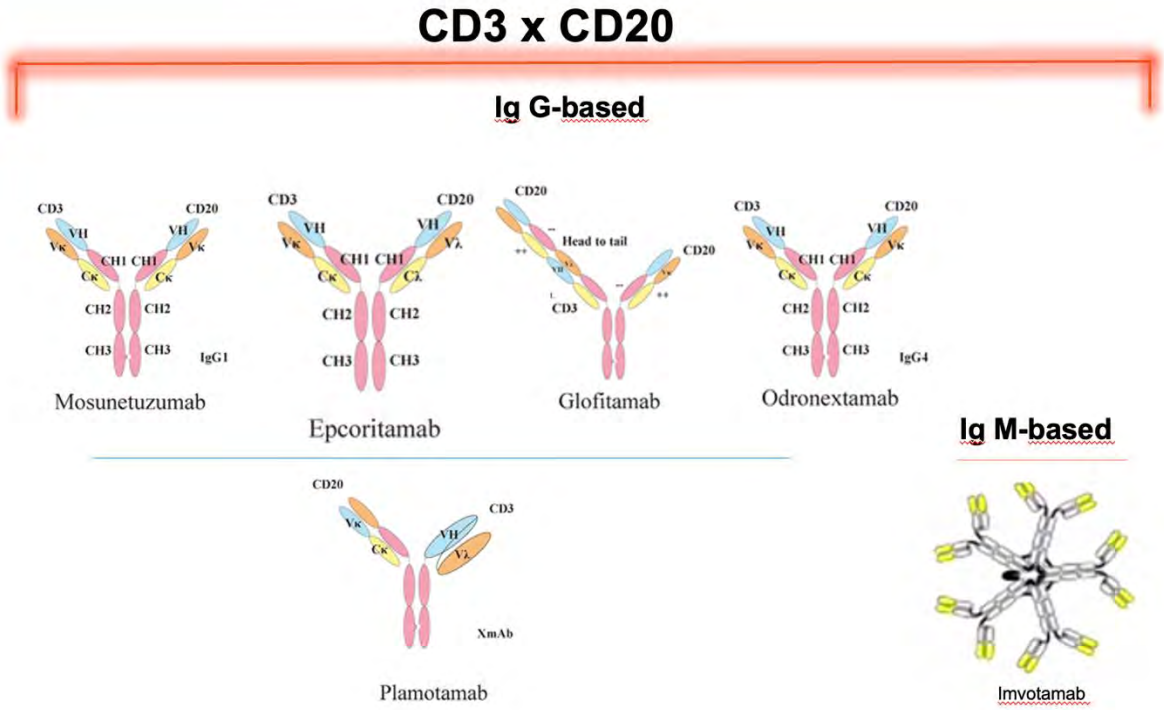
Consulting Agreements	AbbVie Inc, ADC Therapeutics, Bantam Pharmaceutical, Blueprint Medicines, Bristol Myers Squibb, Celgene Corporation, Curis Inc, Daiichi Sankyo Inc, Debiopharm, F Hoffmann-La Roche Ltd, Fate Therapeutics, Genentech, a member of the Roche Group, Incyte Corporation, Karyopharm Therapeutics, Kite, A Gilead Company, Kymera Therapeutics, MEI Pharma Inc, MorphoSys, Ryvu Therapeutics, Seagen Inc, Selvita, TG Therapeutics Inc, Zai Lab

How do they work — T-Cell Engagers Revolution

T-cell bispecifics



T Cell Engagers



Adapted Ma et al. *Frontiers in Immunology* 2021

Glofitamab Activity in Aggressive B-Cell Lymphoma

Pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (NP30179)

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

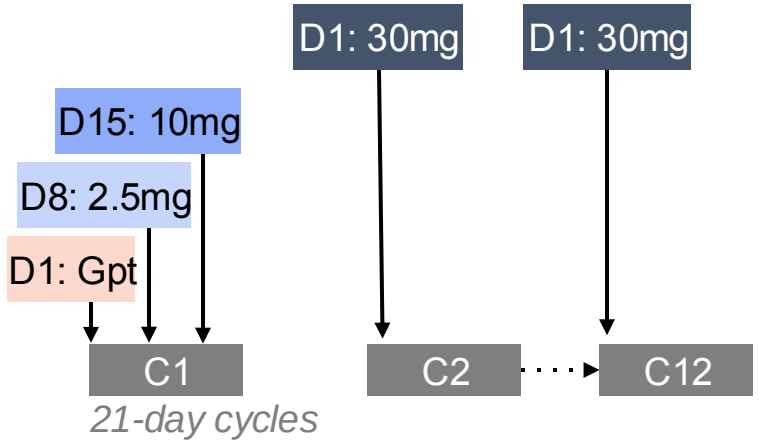
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles (fixed duration)

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



- **Primary: CR (best response) rate by IRC**
- **Key secondary:** ORR rate, DoR, DoCR, PFS, and OS

Michael Dickinson, et al. *NEJM* 2022 & EHA 2022
Falchi L, et al. ASCO 2023 Abstract P7550

Glofitamab – expansion cohort
Response and duration of response

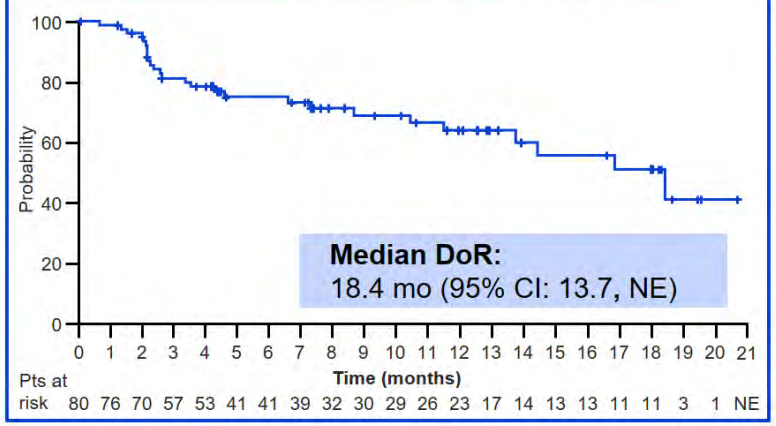
	IRC (N=155)*
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median follow-up, months (range)	18.2 (0–33)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, months (95% CI)	26.9 (18.4–NE)

*Intent-to-treat population; CI, confidence interval; NE, not estimable.

Extended follow-up of 18 months.
Median time on study was 21.2 months

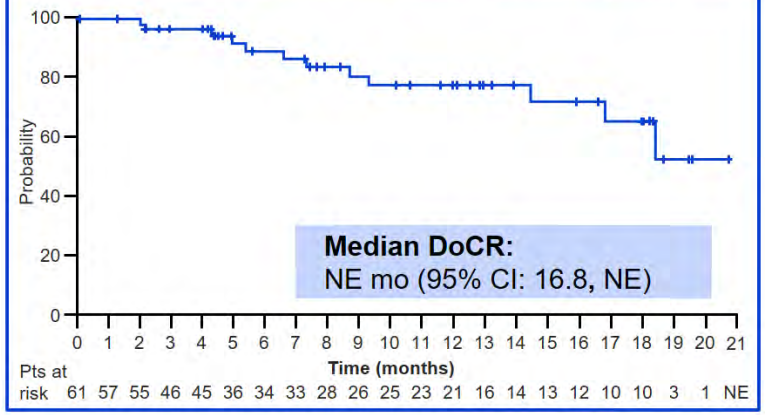
Prior CART: 34%

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)

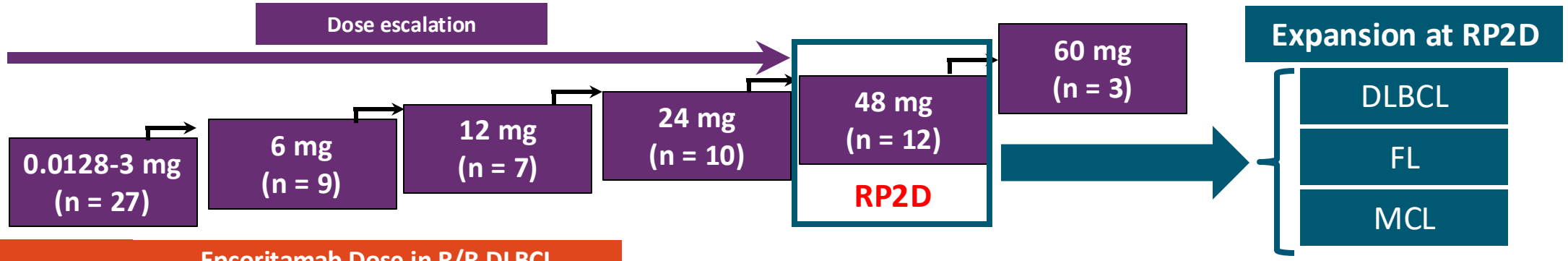
Duration of complete response by IRC



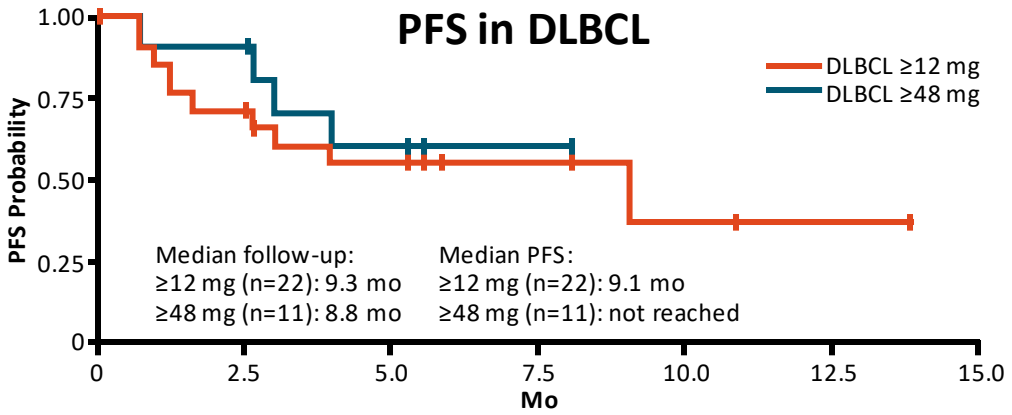
	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

Michael Dickinson, et al. *NEJM* 2022 & EHA 2022 oral presentation
Falchi L, et al. ASCO 2023 Abstract P7550

Phase I/II Study of Subcutaneous Epcoritamab in R/R B-Cell NHL



Response, n (%)	Epcoritamab Dose in R/R DLBCL		
	12-60 mg (n = 22)	48 mg (n = 8)	60 mg (n = 3)
ORR	15 (68)	7 (88)	3 (100)
▪ CR	10 (45)	3 (38)	3 (100)



AE of special interest, n (%)	Total (n = 68)	Epcoritamab dose		
		≤24 mg (n = 53)	48 mg (n = 12)	60 mg (n = 3)
Cytokine release syndrome				
All grade	40 (59)	30 (57)	8 (67)	2 (67)
▪ Grade 1	20 (29)	15 (28)	4 (33)	1 (33)
▪ Grade 2	20 (29)	15 (28)	4 (33)	1 (33)
Neurologic symptoms				
All grade	4 (6)	4 (8)	0	0
▪ Grade 1	2 (3)	2 (4)	0	0
▪ Grade 3	2 (3)	2 (4)	0	0

Hutchings. *Lancet* 2021;398:1157.

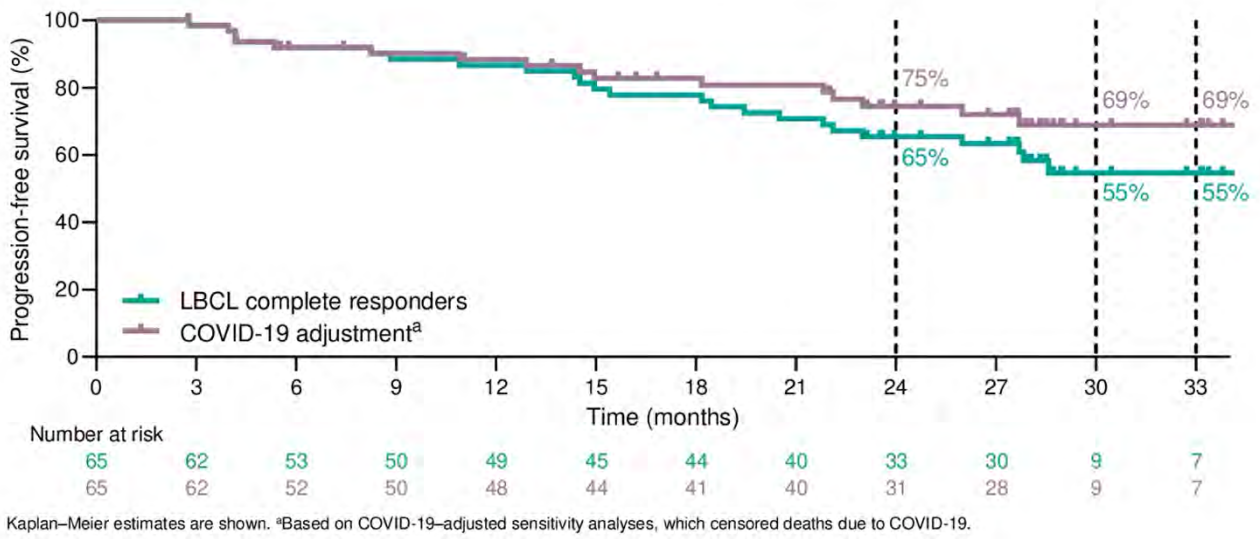
Epcoritamab – expansion cohort
Response rate

Responses assessed by investigator	LBCL N=157[a]
ORR, n (%)	92 (59)
CR	65 (41)
PR	27 (17)
DOCR, median, mo	NR
24-mo KM estimate, %	62
30-mo KM estimate, %	54
Follow-up, median, mo	26.4

Extended follow-up beyond 2.5 years

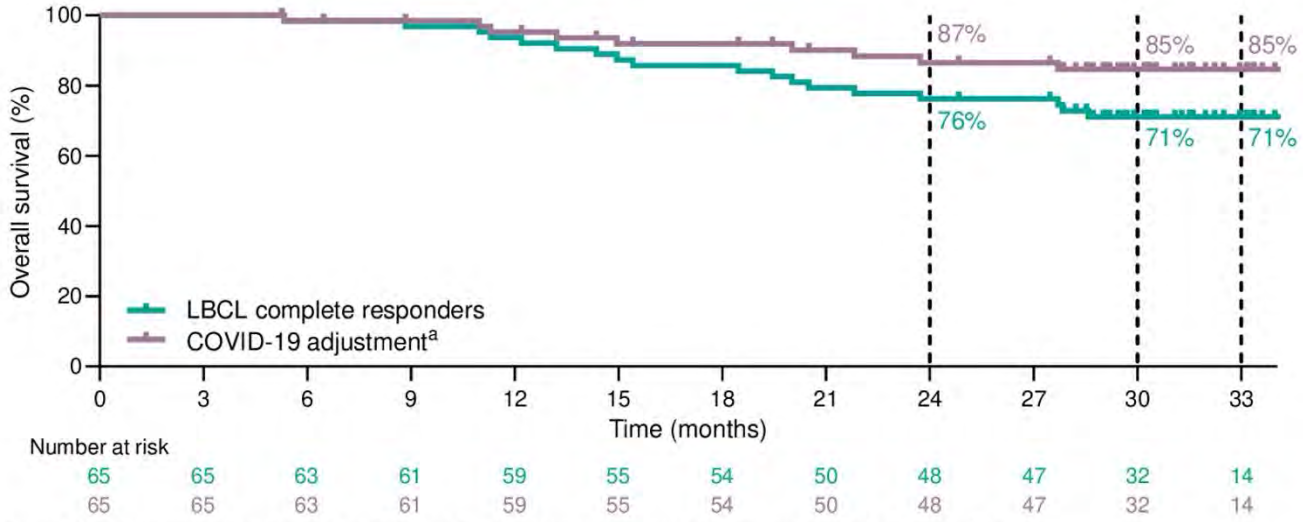
Prior CART: 39%

PFS among complete responders



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.

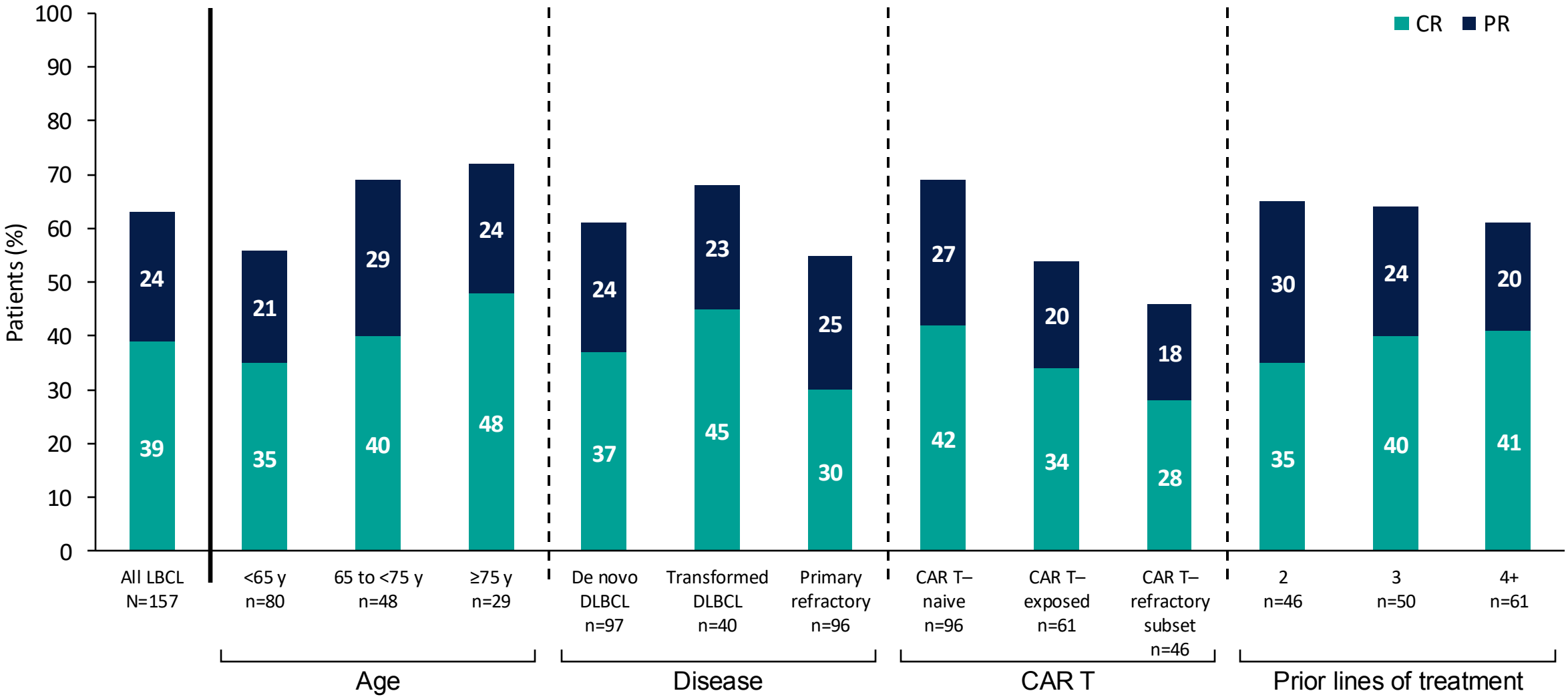
OS among complete responders



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.

Catherine Thieblemont, et al. *J Clin Oncol* 2022
Karimi YH, et al. ASCO 2024 Abstract 7039

Deep Responses Consistent Across Key Subgroups



Based on IRC assessment and Lugano criteria.

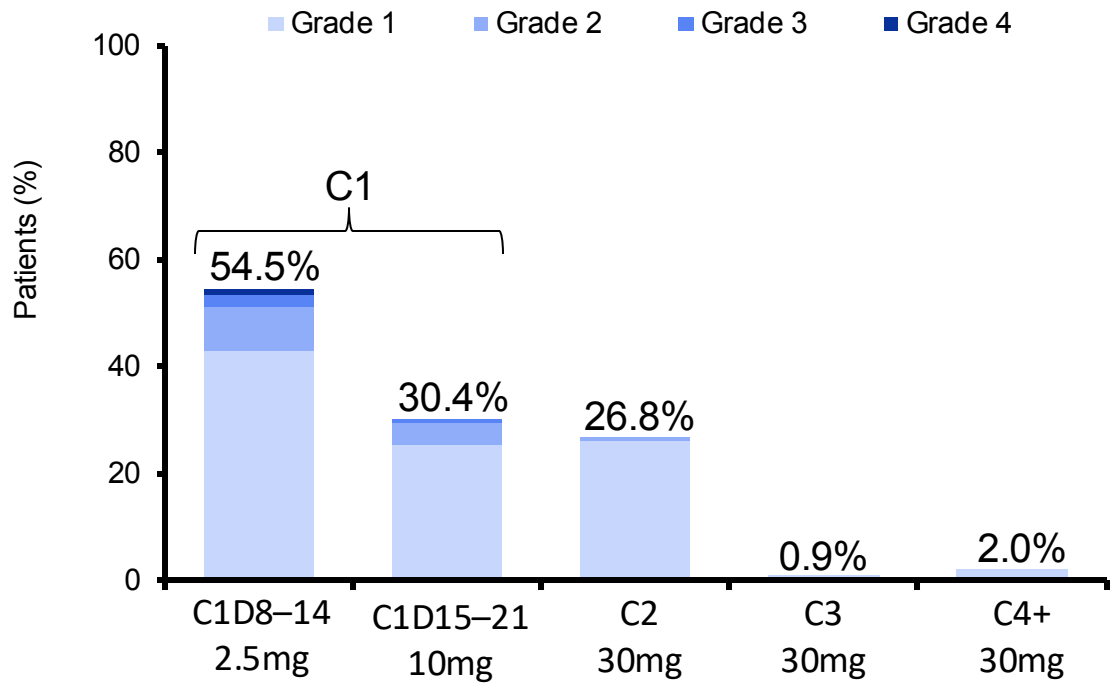
Thieblemont C, et al. *J Clin Oncol* 2022

Cytokine release syndrome — Glofitamab

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

*After 18 months of follow-up CRS remained the most common AE, occurring in 64% of patients. CRS events were mostly grade 1 (48%), grade 2 (12%) grade 3 (3%) and grade 4 (1%) events were uncommon.

CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

Falchi L, et al. ASCO 2023 Abstract P7550

Dickinson M, et al. NEJM 2022 & EHA 2022 oral presentation

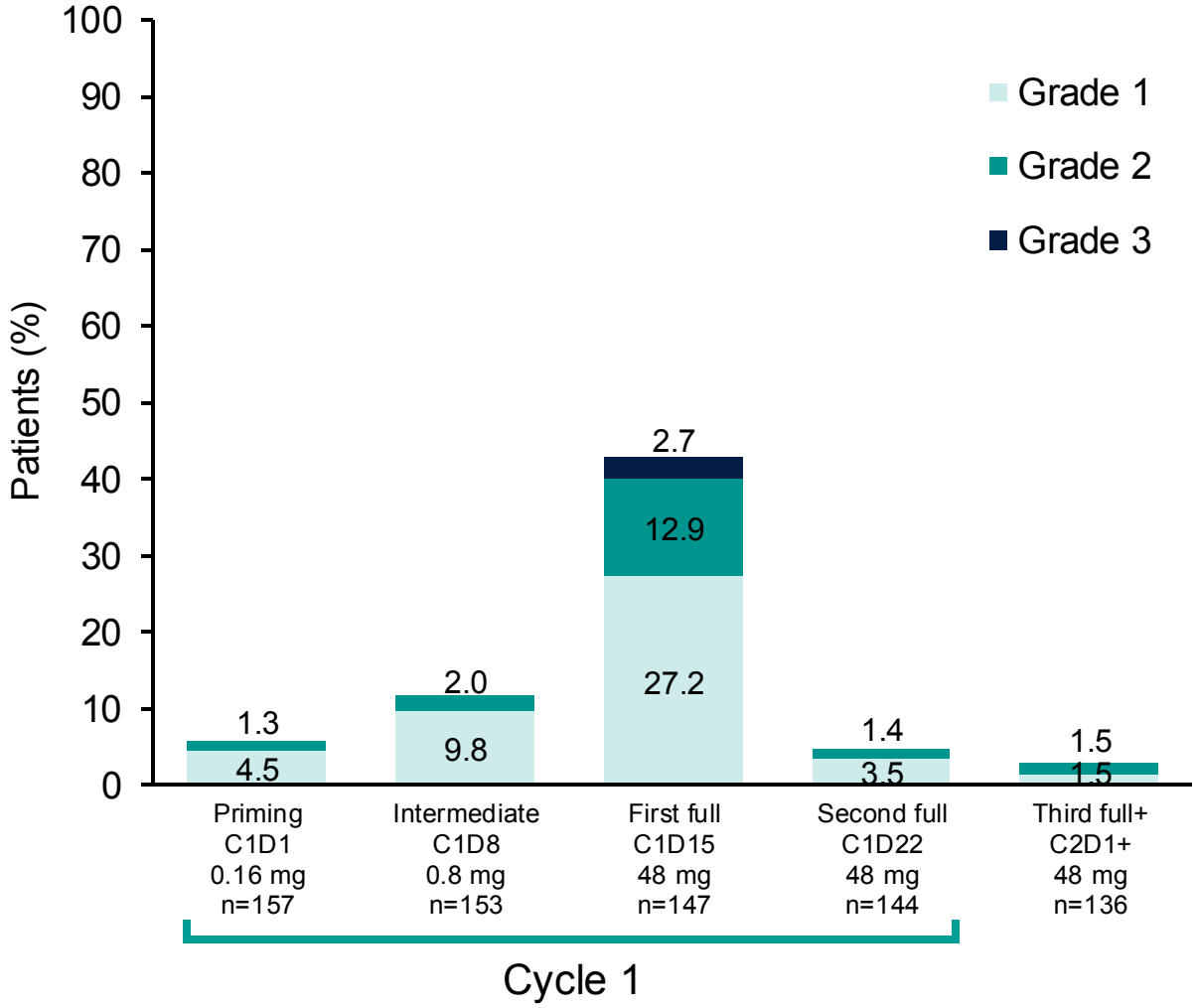
Cytokine release syndrome — Epcoritamab

	Expansion N=157	C1 Optimization N=81
CRS, n (%)[a]	80 (51)	30 (37)
G1	50 (32)	21 (26)
G2	25 (16)	8 (10)
G3	5 (3)	1 (1)
Treated with tocilizumab, n/n (%)[b]	23/80 (29)	13/30 (43)
Treated with corticosteroid, n/n (%)[b]	17/80 (21)	6/30 (20)
Leading to treatment discontinuation, n (%)	1 (1)	0
CRS resolution, n/n (%)[b]	78/80 (98)	30/30 (100)
Median time to resolution (range),[b] d	2 (1–27)	2 (1–15)

[a]Graded by Lee et al 2019 criteria.[9] [b]Among patients with CRS.

CRS was primarily low grade and predictable: most events occurred following the first full dose. C1 optimization reduced the incidence and severity of CRS.

CRS Events by Dosing Period

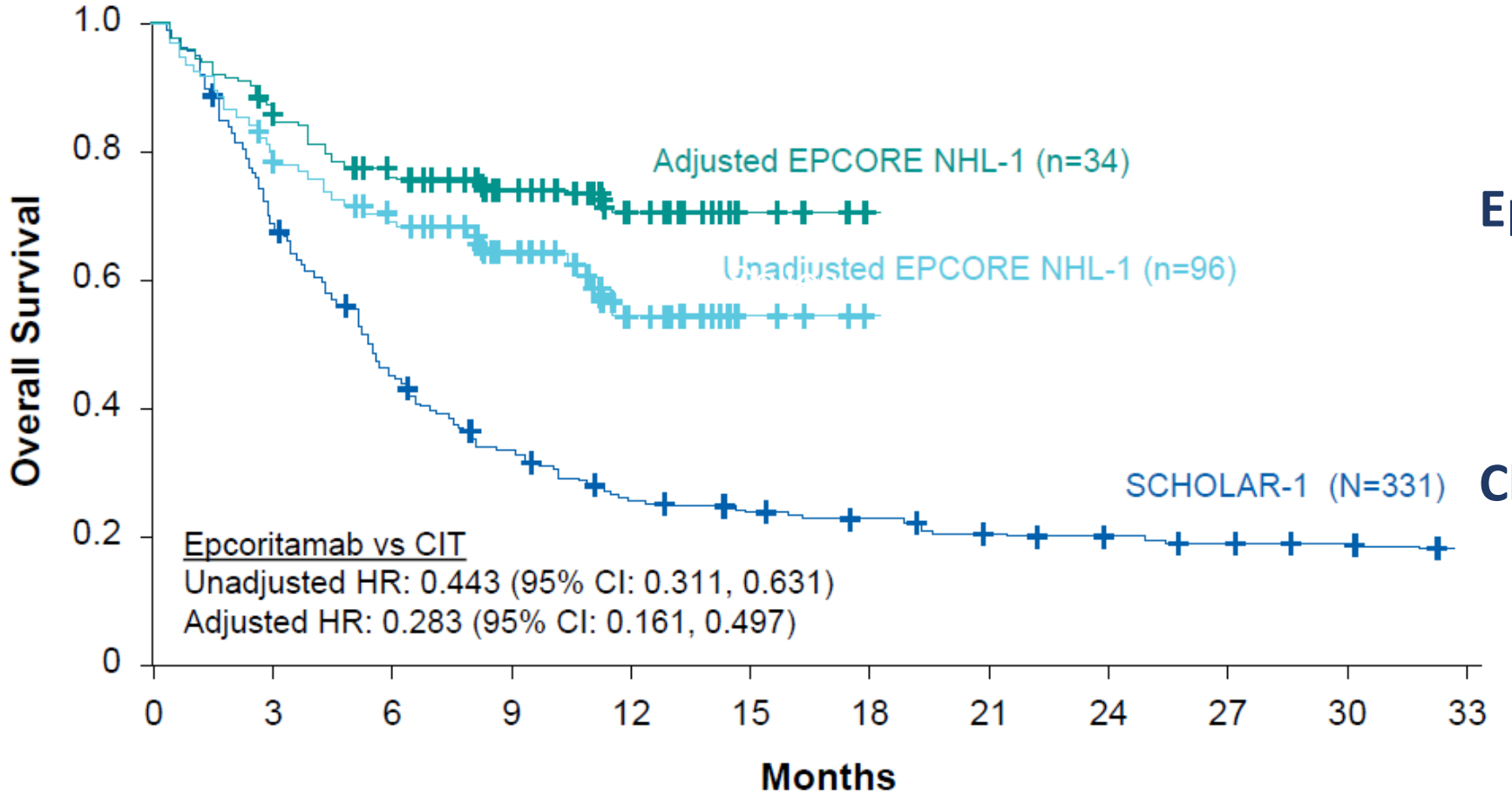


Karimi YH, et al. ASCO 2024 Abstract 7039

Thieblemont C, et al. J Clin Oncol 2022 and EHA oral presentation

OS: Epcoritamab vs Chemotherapy (historical comparison)

Figure 3. Comparison of OS vs SCHOLAR-1



Epcoritamab

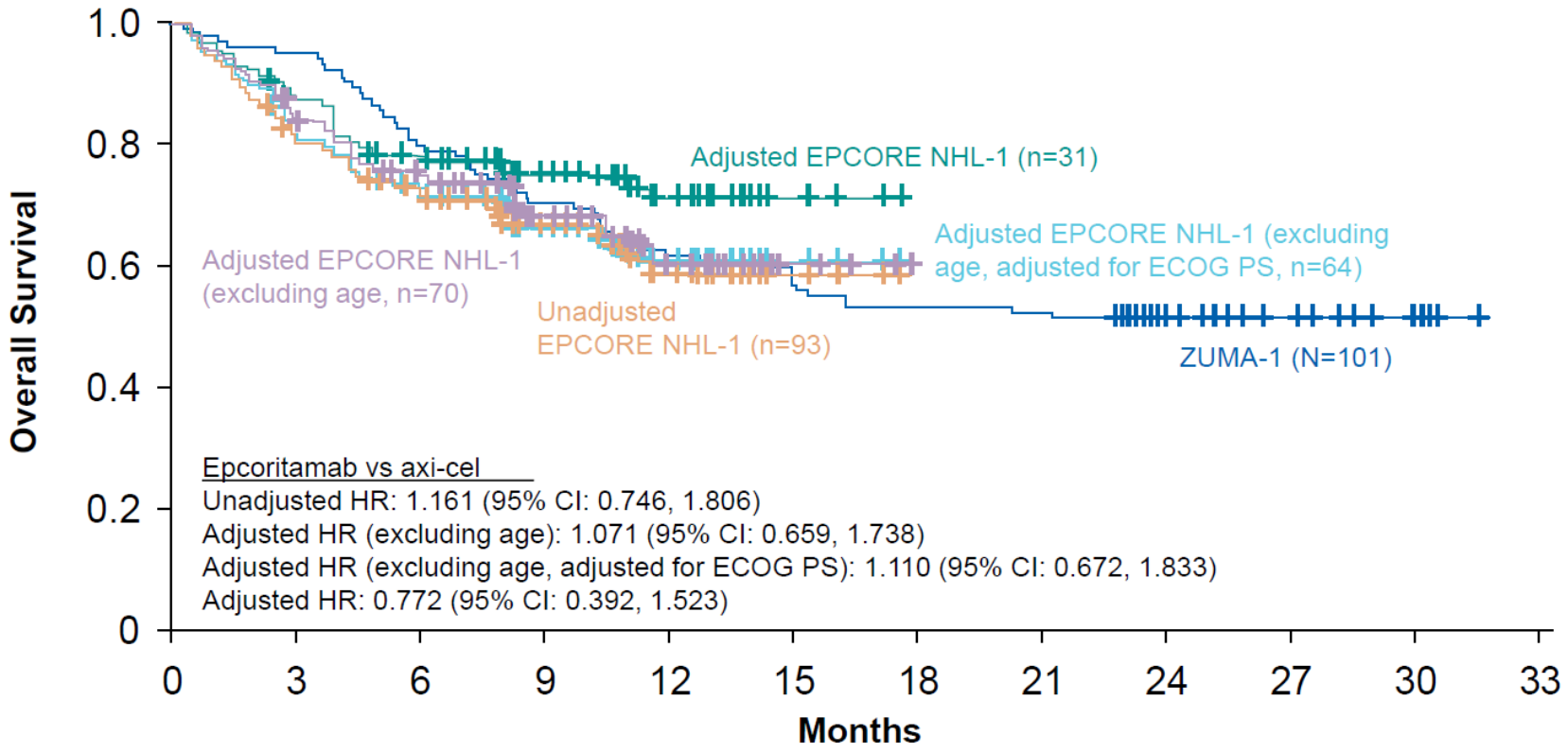
Chemotherapy

CIT, chemoimmunotherapy; HR, hazard ratio; OS, overall survival.

Salles G et al., ASH 2022, Abstr 4912

OS: Epco vs CAR-T (historical comparison)

Figure 4. Comparison of OS vs non-ITT ZUMA-1 Study Population



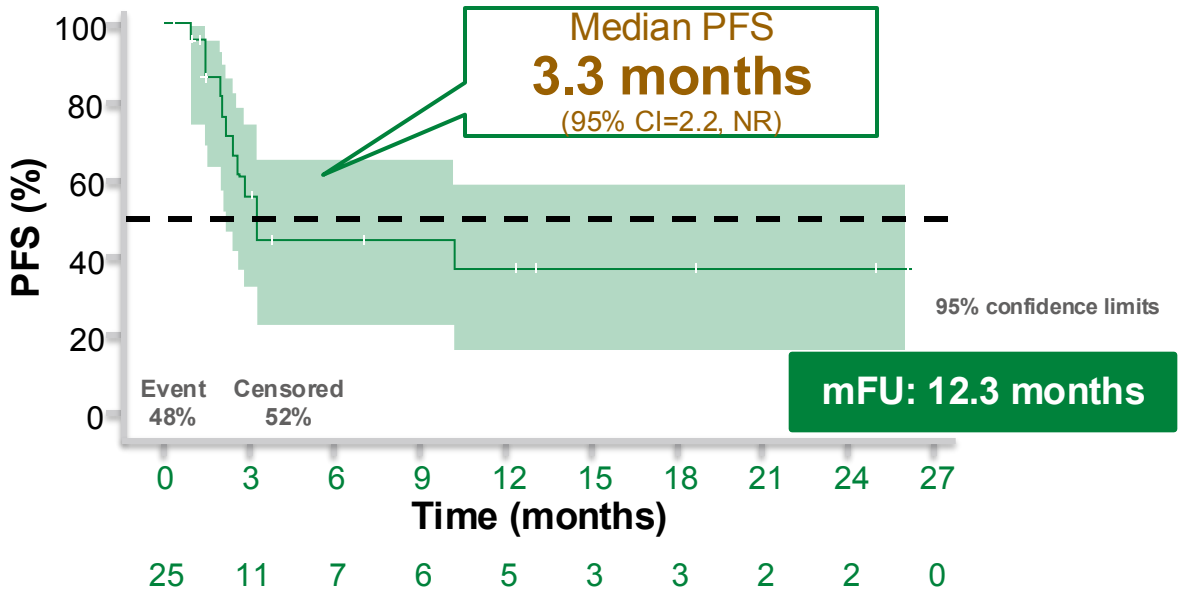
Number at risk												
EPCORE NHL-1	93	74	61	41	21	4	0					
ZUMA-1	101	96	80	70	61	56	53	52	50	25	7	0

Salles G et al., ASH 2022, Abstr 4912

CAR T-cells after BsAb treatment

Patients with aggressive LBCL
n=28

Outcomes post-CAR T	R/R LBCL subgroup (n=23)
CAR T received, % Axi-cel Tisa-cel	 72 28
ORR, % **CR** **PR**	**91.6** **45.8** **45.8**
Median PFS, mo (95% CI) 6-mo PFS, % (95% CI) 1-year PFS, % (95% CI)	3.3 (2.2, NR) 44.6 (22.4, 64.7) 37.2 (15.9, 58.7)
Median DOR, mo (95% CI) 1-year DOR, % (95% CI)	2.4 (1.4, NR) 40.7 (17.4, 63.1)



Initial results suggest CAR T may be effective as post-BsAb salvage therapy; however, longer follow-up in larger cohorts is needed

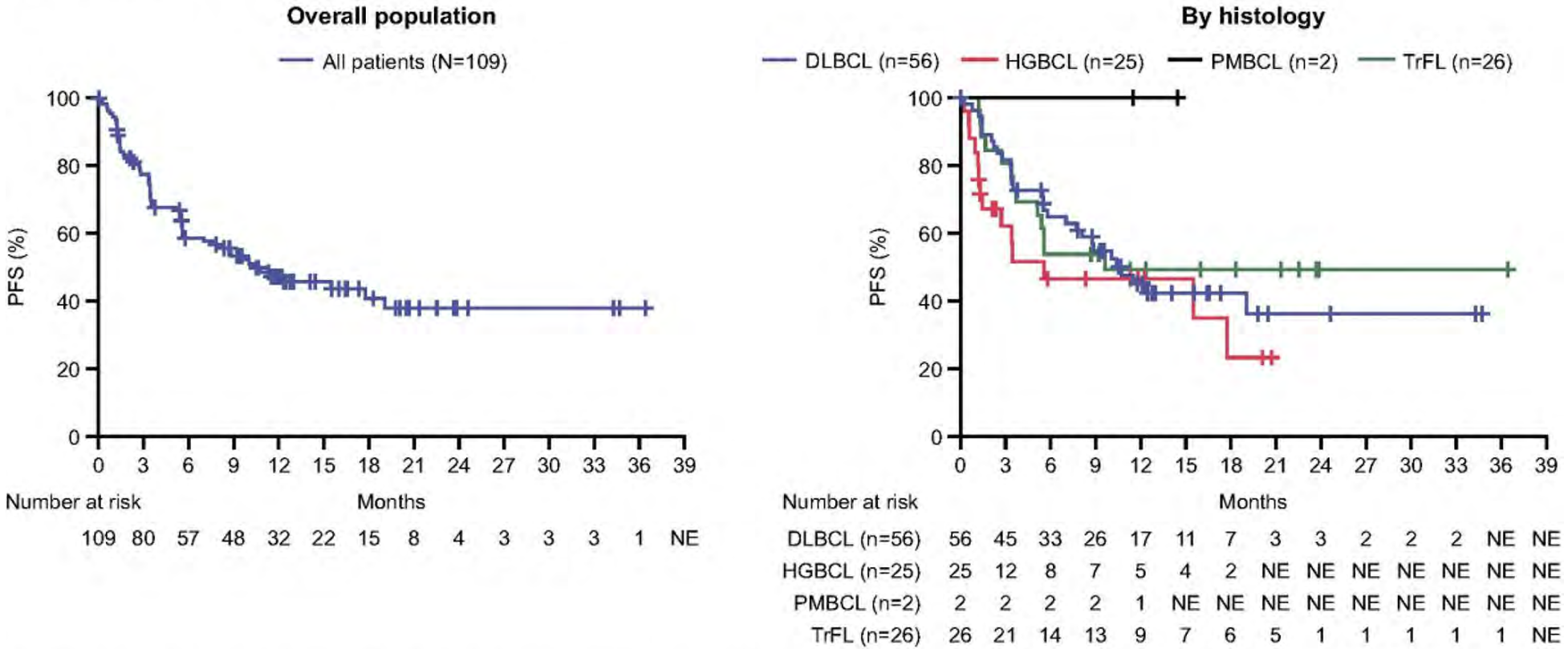
[a] n=20 DLBCL, n=2 FL, n=1 Grade 3b FL, n=3 MCL, n=2 other LBCL

axi-cel: axicabtagene ciloleucel; BsAb: bispecific antibody; CAR: chimeric antigen receptor; CD: cluster of differentiation; CI: confidence interval; CL: confidence limit; CR: complete response; DOR: duration of response; NR: not reached; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; tisa-cel: tisagenlecleucel

Crochet G, *et al.* ASH 2022 (Abstract 2026; poster)

TCE can be combined…

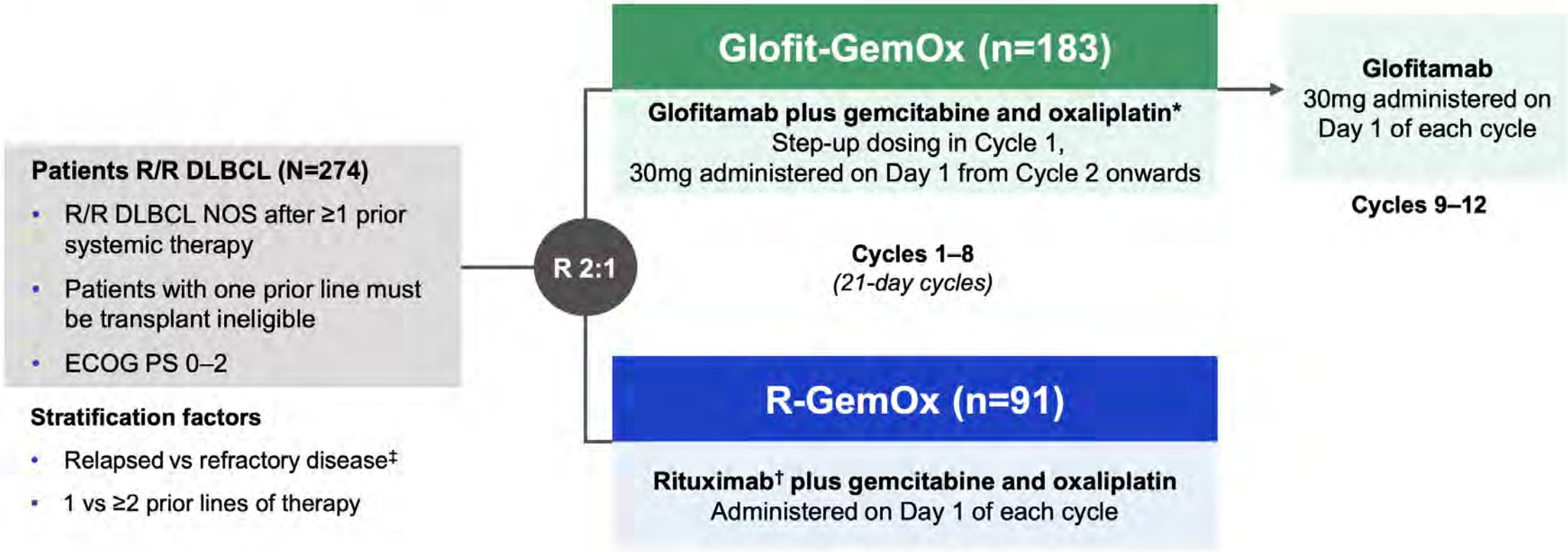
Figure. PFS with Glofit+Pola



DLBCL, diffuse large B-cell lymphoma; Glofit+Pola, glofitamab plus polatuzumab vedotin; HGBCL, high-grade B-cell lymphoma; NE, not estimable; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; TrFL, transformed follicular lymphoma

Hutchings M. ASH 2023

STARGLO: randomized Phase III trial in ASCT-ineligible patients with R/R DLBCL

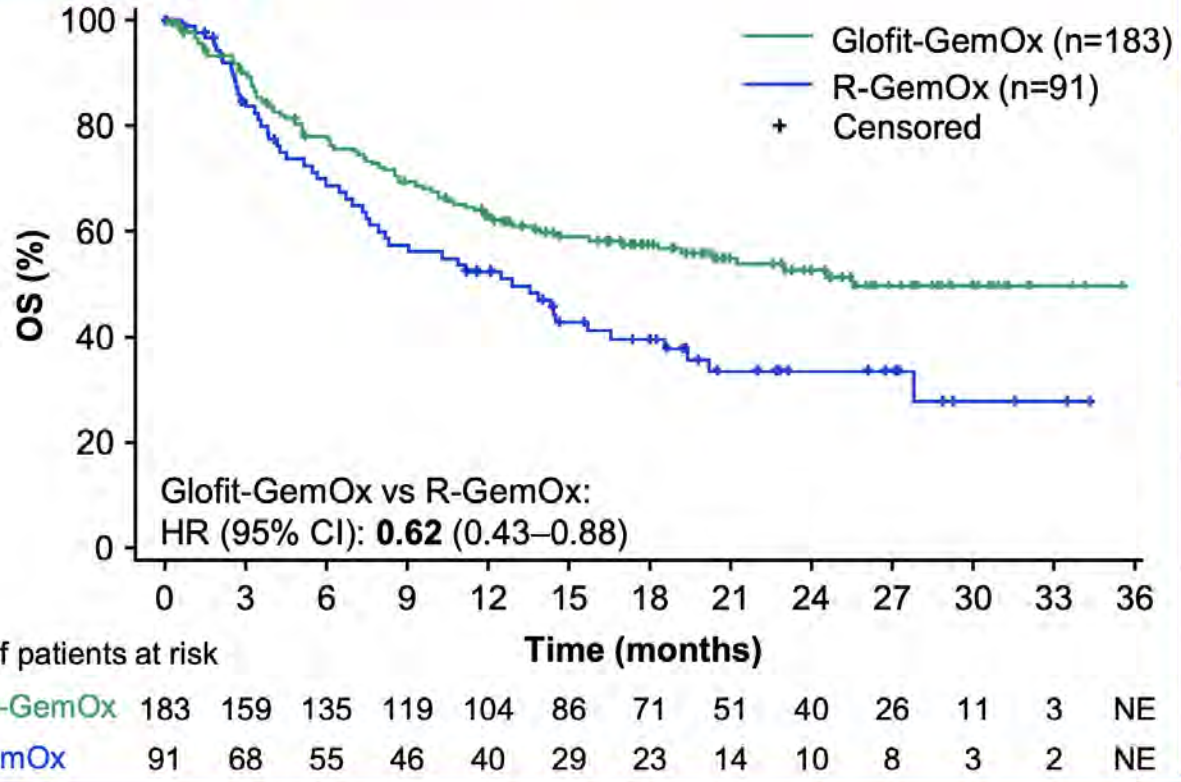


*Gemcitabine 1000mg/m² and oxaliplatin 100mg/m². In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m². ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. ASCT, autologous stem cell transplant; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; NOS, not otherwise specified; R 2:1, patients randomized in a 2:1 ratio.

Abramson J. EHA 2024

Primary endpoint: overall survival

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

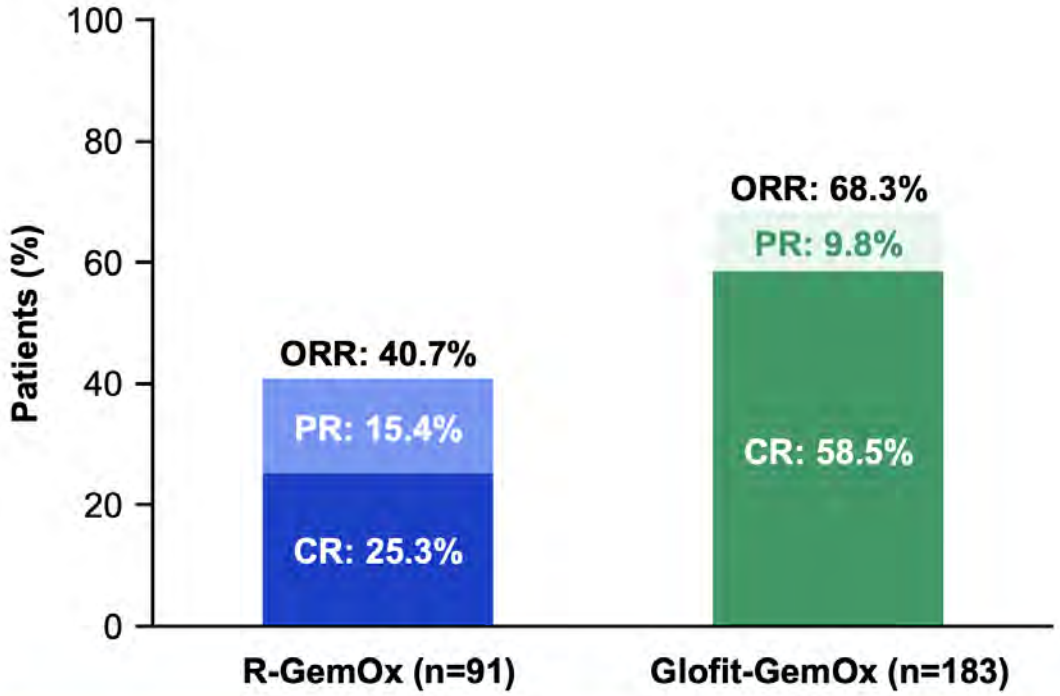
Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** vs R-GemOx

24-month OS not reported at the primary analysis as data were not sufficiently mature.
*p-value is alpha controlled at the primary analysis and descriptive at updated analysis. CI, confidence interval; HR, hazard ratio; NE, not evaluable.

Abramson J. EHA 2024

Response rates by IRC assessment

Response rates at the updated analysis



- **33.2%** difference in CR rate between treatment arms (95% CI: 19.7–44.5)
- CR rate significantly better with Glofit-GemOx vs R-GemOx (descriptive p-value **<0.0001***)

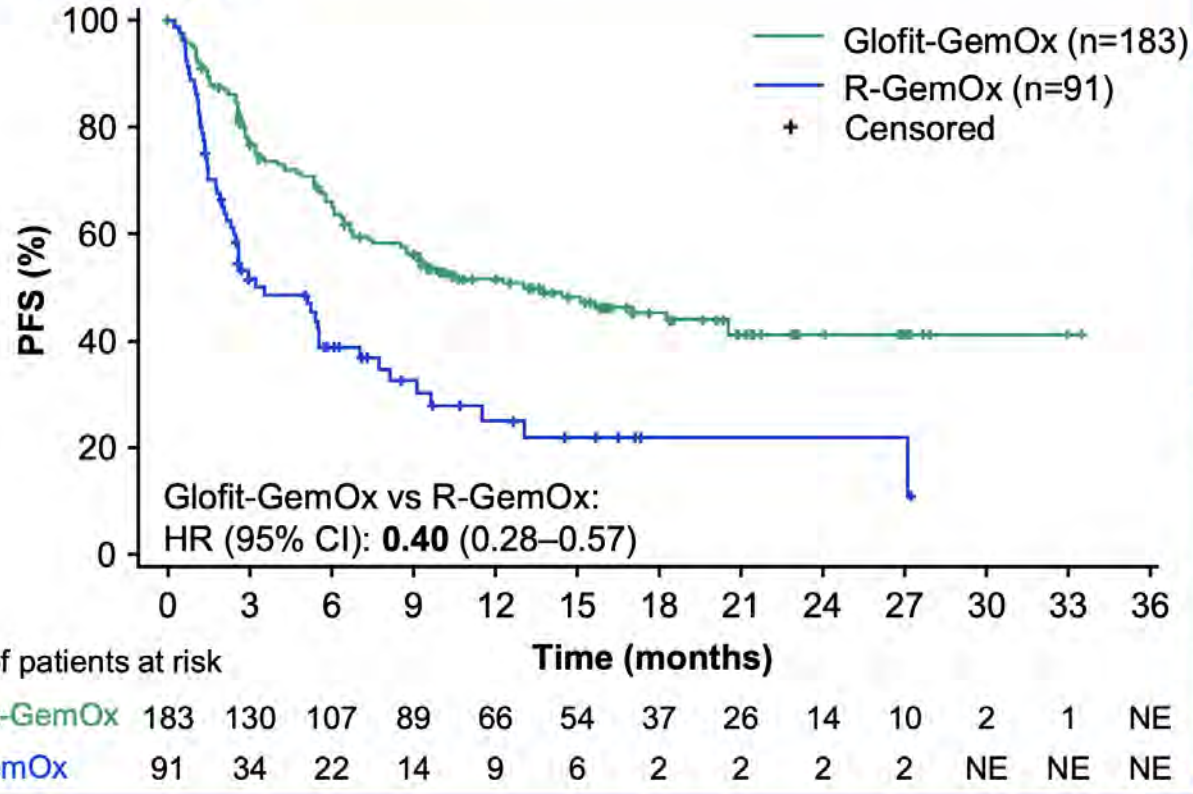
CR rate was statistically significant at primary analysis, with increased difference between treatment arms at the updated analysis

Difference in duration of CR between treatment arms had not reached statistical significance at the time of analysis.
*p-value based on Cochran-Mantel-Haenszel method. ORR, overall response rate; PR, partial response.

Abramson J. EHA 2024

Progression-free survival by IRC assessment

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 9.6 months)		
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)
HR (95% CI)	**0.37** (0.25–0.55)	
p-value*	<0.000001	
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.40** (0.28–0.57)	
p-value*	<0.000001*	
12-month PFS (95% CI)	25.2% (13.6–36.9)	51.7% (44.0–59.4)

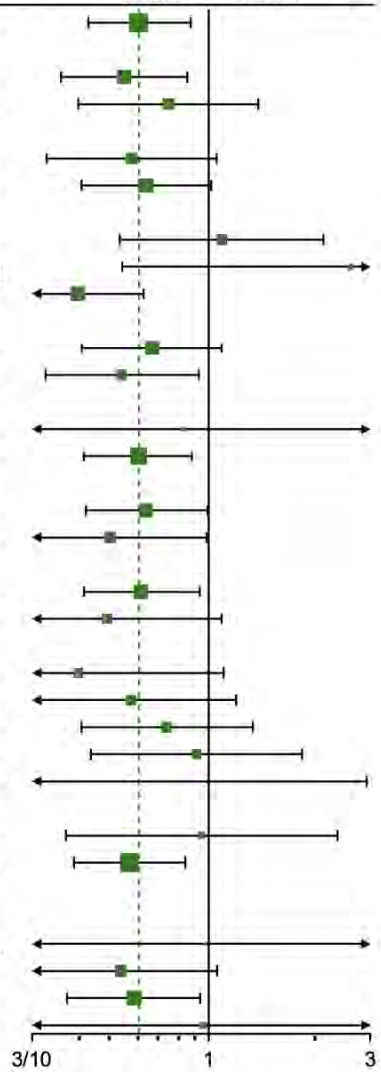
Statistically significant and clinically meaningful **PFS benefit for Glofit-GemOx** vs R-GemOx

12-month PFS not reported at the primary analysis as data were not sufficiently mature. Three patients proceeded to ASCT after study treatment, all three patients are alive as of today.
*p-value is alpha controlled at the primary analysis and descriptive at updated analysis. PFS, progression-free survival.

Abramson J. EHA 2024

OS in prespecified subgroups

Baseline Risk Factors	Total n	R-GemOx (n=91) n	Events	Median (Months)	Glofit-GemOx (n=183) n	Events	Median (Months)	HR	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Sex									
Male	158	53	36	10.3	105	51	20.4	0.56	(0.37, 0.86)
Female	116	38	16	20.2	78	29	NE	0.76	(0.41, 1.40)
Age group									
<65	102	35	19	9.0	67	29	NE	0.59	(0.33, 1.06)
≥65	172	56	33	14.3	116	51	22.9	0.65	(0.42, 1.01)
Enrollment by geographic region									
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Rest of the World	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
No. of previous lines of systemic therapy for DLBCL									
1	172	57	28	15.7	115	44	NE	0.68	(0.42, 1.09)
≥2	102	34	24	6.7	68	36	18.3	0.55	(0.33, 0.93)
Prior CAR T-cell therapy									
Yes	21	8	4	27.8	13	6	13.7	0.84	(0.23, 3.01)
No	253	83	48	12.9	170	74	NE	0.62	(0.43, 0.89)
Relapse or refractory to last line of therapy									
Refractory	166	54	36	7.5	112	61	11.9	0.65	(0.43, 0.99)
Relapsed	108	37	16	27.8	71	19	NE	0.51	(0.26, 0.98)
Refractory to first line of therapy									
Yes	153	47	34	7.3	106	59	10.2	0.60	(0.40, 0.92)
No	121	44	18	27.8	77	21	NE	0.54	(0.29, 1.01)
Total number of risk factors for IPI (Derived)									
Low (0–1)	61	13	6	NE	48	12	NE	0.41	(0.15, 1.10)
Low–intermediate (2)	70	28	14	18.5	42	16	NE	0.59	(0.28, 1.20)
High–intermediate (3)	79	30	20	14.3	49	26	21.2	0.75	(0.42, 1.35)
High (4–5)	55	17	11	8.3	38	24	8.5	0.92	(0.45, 1.88)
Unknown	9	3	1	0.6	6	2	NE	0.18	(0.01, 2.93)
Bulky disease ≥10cm									
Yes	37	14	7	11.1	23	13	12.0	0.95	(0.38, 2.40)
No	236	76	45	13.5	160	67	NE	0.58	(0.40, 0.85)
Unknown	1	1	0	NE	-	-	-	NE	NE
Cell of origin									
ABC	6	2	1	NE	4	2	NE	0.97	(0.09, 10.98)
GCB	89	29	15	11.1	60	25	NE	0.55	(0.29, 1.06)
Non-GCB (by IHC + non-GCB unclassified)	147	48	32	10.9	99	45	25.5	0.60	(0.38, 0.94)
Unknown	32	12	4	20.2	20	8	NE	0.96	(0.28, 3.21)



Abramson J. EHA 2024

Conclusions

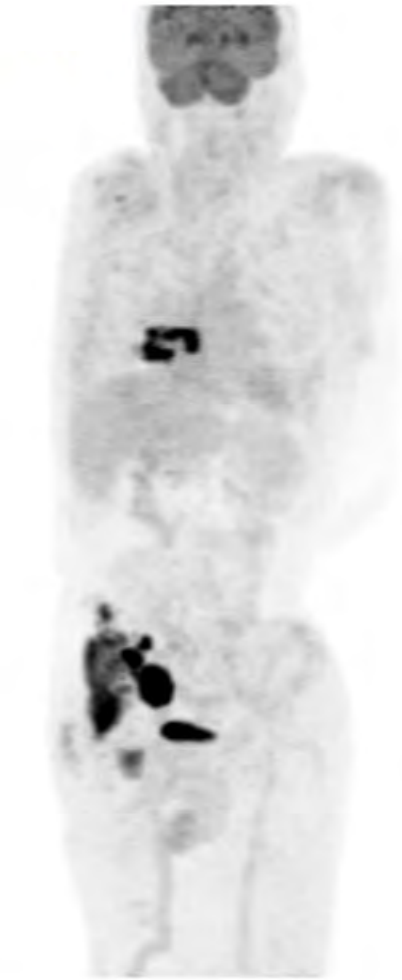
- **The CD3/CD20 bispecific antibodies work – and work very well**
  - **Glofitamab: ORR 52%, CRR 40%**
  - **Epcoritamab: ORR 59%, CRR 41%**
  - ***Regardless of prior therapy or molecular subtype***
- **The toxicity profile is favorable:**
  - **Very little CRS > grade 2**

- **Bispecific antibodies can be combined and sequenced**
- **Addition of bispecific antibodies can revive salvage chemoimmunotherapy**

Faculty Case Presentations

Case Presentation: Dr Sehn

- 58 yo male, no comorbidities
- Presented with abdominal discomfort, ECOG PS 1
- Labs: LDH 350 U/L (ULN 240)
- PET/CT: paravertebral soft tissue mass at T7 with extension into RLL, right pelvic sidewall mass (maximum 6 cm)
- Core biopsy of abdominal mass: DLBCL, GCB subtype, no *MYC* rearrangement



- ➢ Treated with 6 cycles of R-CHOP
- ➢ CR on post-treatment PET/CT

Case Presentation: Dr Sehn (cont'd)

- 14 months later, he developed recurrent abdominal pain, PET/CT and biopsy confirmed recurrent DLBCL

- Planned for salvage and ASCT, but had progression after 2 cycles R-GDP
- 1 cycle Pola-R bridging followed axicabtagene ciloleucel
- CR on PET/CT at 3 months, but progression on PET/CT at 6 months post CAR T-cell therapy
- Recently completed 12 cycles of glofitamab, achieved a CR

QUESTIONS FOR THE FACULTY

For a patient with DLBCL to whom you've decided to administer a bispecific antibody, how to you determine which one to use? How do efficacy, convenience and tolerability factor into the decision?

In what line of therapy do you generally offer a bispecific antibody to patients with DLBCL? Regulatory and reimbursement aside, in what line of therapy would you like to administer bispecific antibodies?

Outside of a clinical trial, are there currently any situations in which you would combine a bispecific antibody with chemotherapy (eg, GemOx) for a patient with relapsed/refractory DLBCL?

Case Presentation: Dr Flowers

- Initially diagnosed with DLBCL at age 56 with extensive retroperitoneal disease and treated on protocol with R-CHOP + X. Tolerated therapy well with the exception of being admitted twice for neutropenic fever. Improved on empiric antibiotics, Cultures negative.
- Experienced relapse at 18 months and received CAR T-cell therapy
- Now returns with a new inguinal LN biopsy proven to be relapsed DLBCL with ABC subtype and here for initiation of next line of therapy

QUESTIONS FOR THE FACULTY

For a patient who is not tolerating your first-choice bispecific antibody, would you switch to another?

In general, how do you sequence bispecific antibodies and CAR T-cell therapy for a patient with DLBCL who is eligible to receive both?

Thank you for joining us!
Your feedback is very important to us.

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