con il patrocinio di

AIL Caserta Valentina Picazio

SIE Società Italiana di Ematologia

La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Hotel Royal Contintental • 14–15 Maggio 2026

Strategie terapeutiche consolidate e future nel trattamento dei pazienti con Large B-Cell Lymphoma

Annarosa Cuccaro

Hematology-Oncology & Stem Cell Transplantation Unit National Cancer Institute, IRCCS Fondazione 'G. Pascale' Naples, Italy

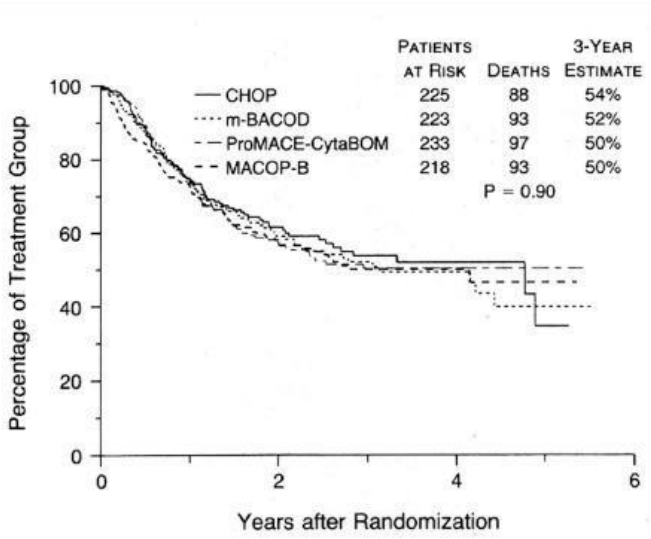
Istituto Nazionale Tumori IRCCS - Fondazione Pascale

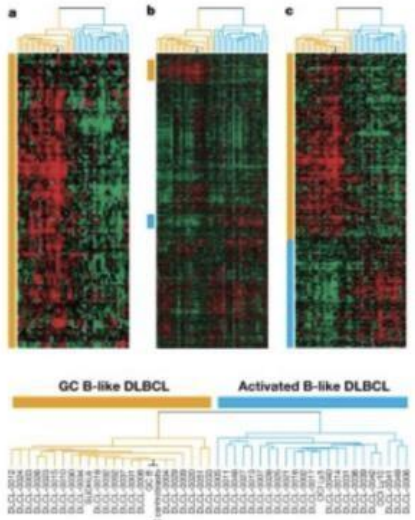
Disclosures of Annarosa Cuccaro

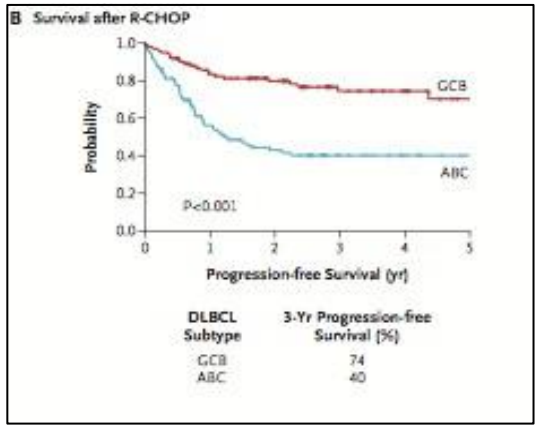
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosures							

DLBCL is a curable disease…but many patients are failed by our current therapies

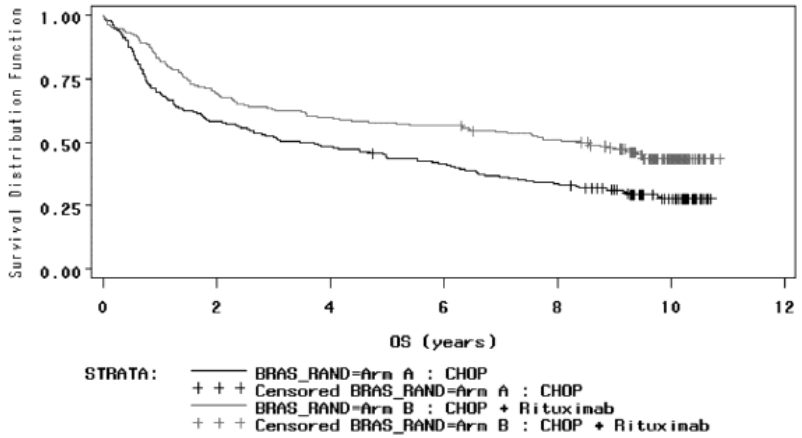
1993 — 2000 — 2002

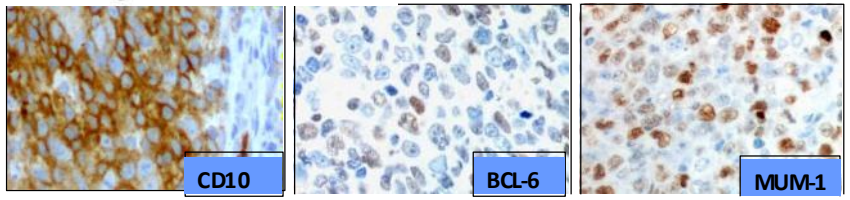






RCHOP: Long term survival ~ 60%





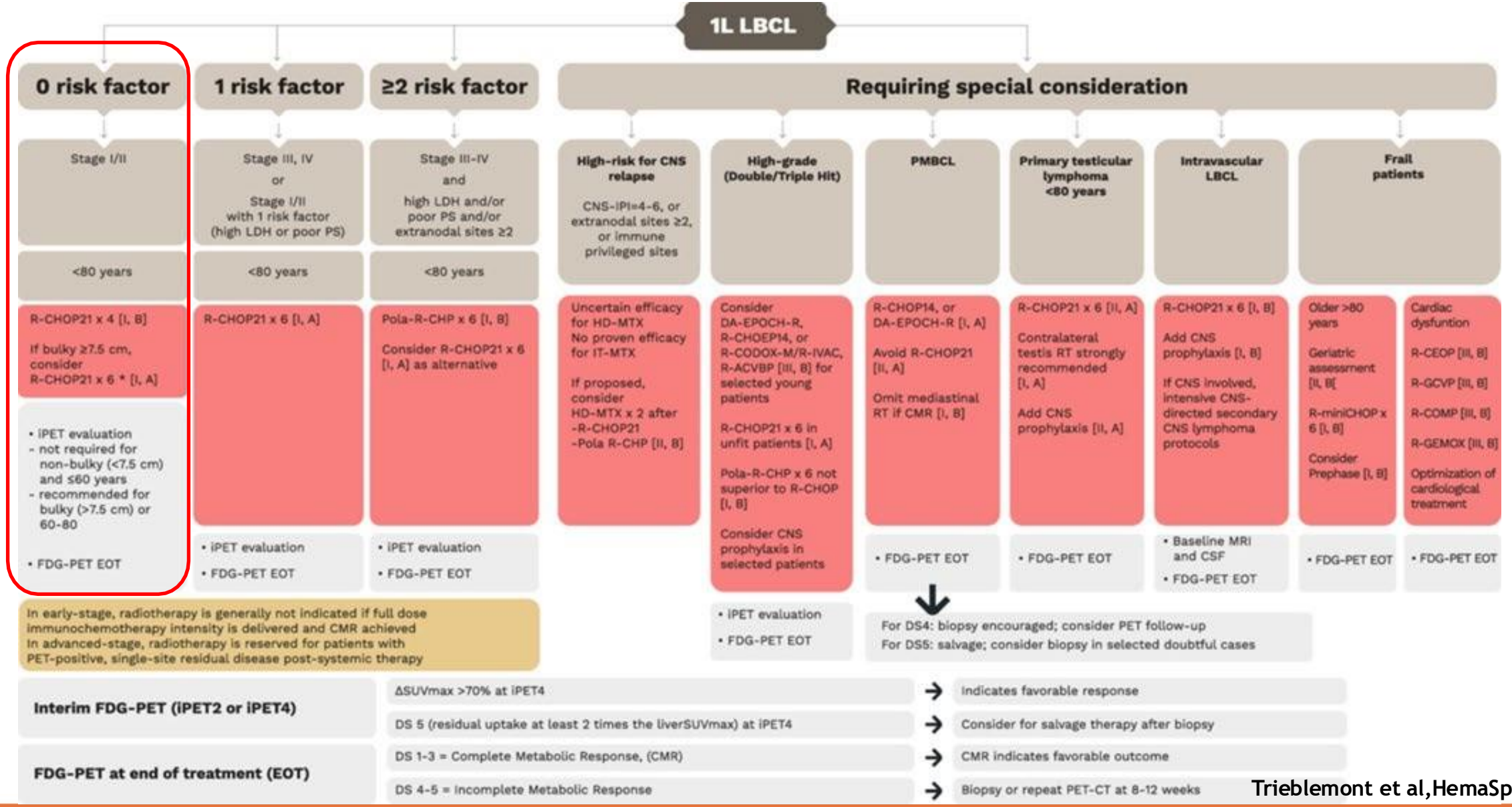
Fisher et al, N Engl J Med 1993

Alizadeh A et al, Nature 2000, 403:503-511

Lenz G and Staudt L, N Engl J Med 2010;362:1417-29

Coiffier et al, Blood 2010

LBCL: EHA Clinical Practice Guidelines



Trieblemont et al,HemaSphere 2025

Limited stage DLBCL

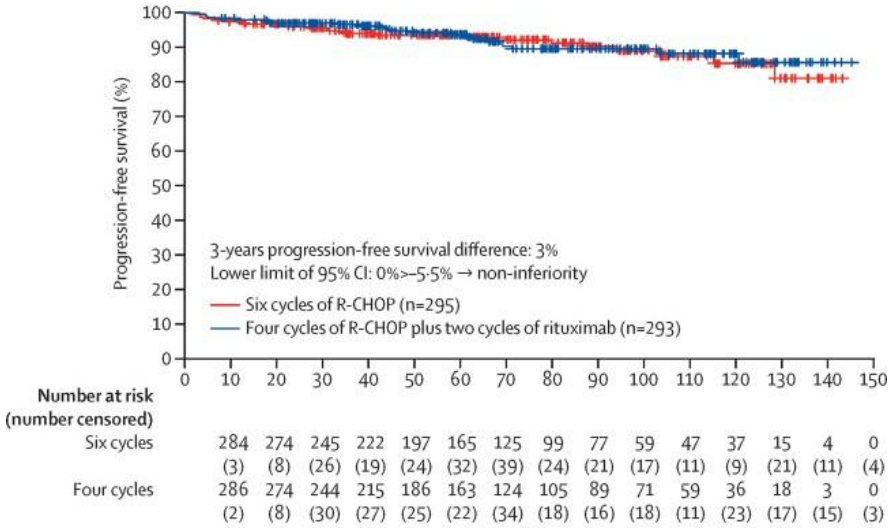
The FLYER study Poeschel *et al* Lancet 2019; 394: 2271-81

- Phase 3 non-inferiority (margin −5·5%) RCT in ≤60 years with no IPI risk factors or bulk
  - **RCHOPx4 (+2R) *versus* RCHOPx6**
  - 33% of patients had extra-nodal disease
  - No RT planned (except for testicular)

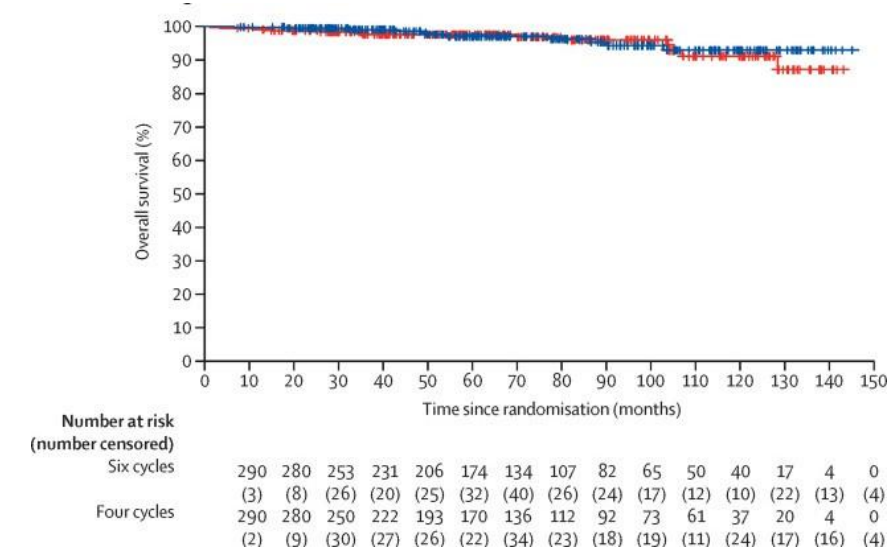
- n=588 patients in the intention-to-treat analysis.
- 3-year PFS with R-CHOPx4 (+2R) = 96% (95% CI 94–99)

RCHOPx4 (+2R) is non-inferior to RCHOPx6 for IPI 0, non-bulky DLBCL

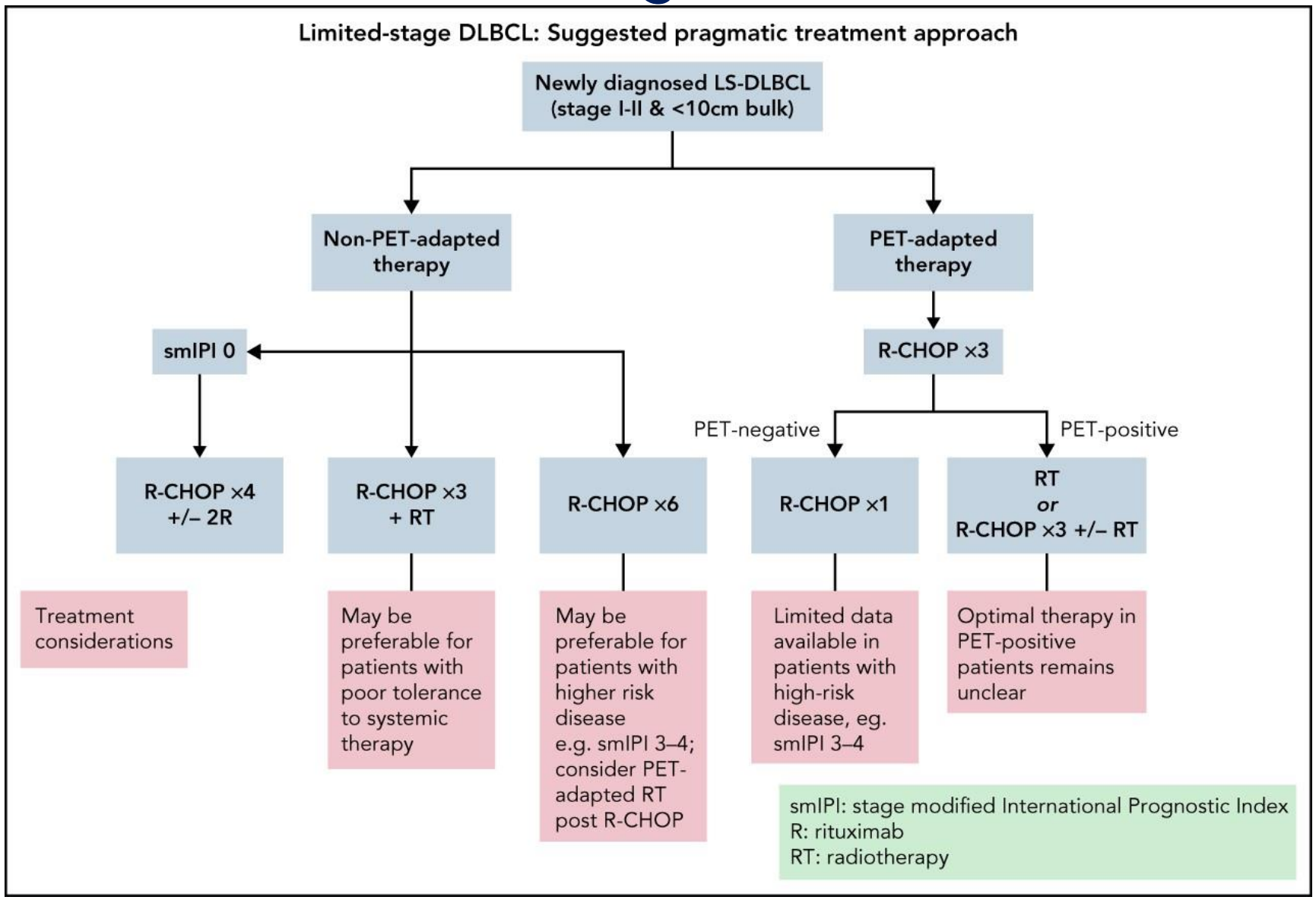
Progression-free survival



Overall survival

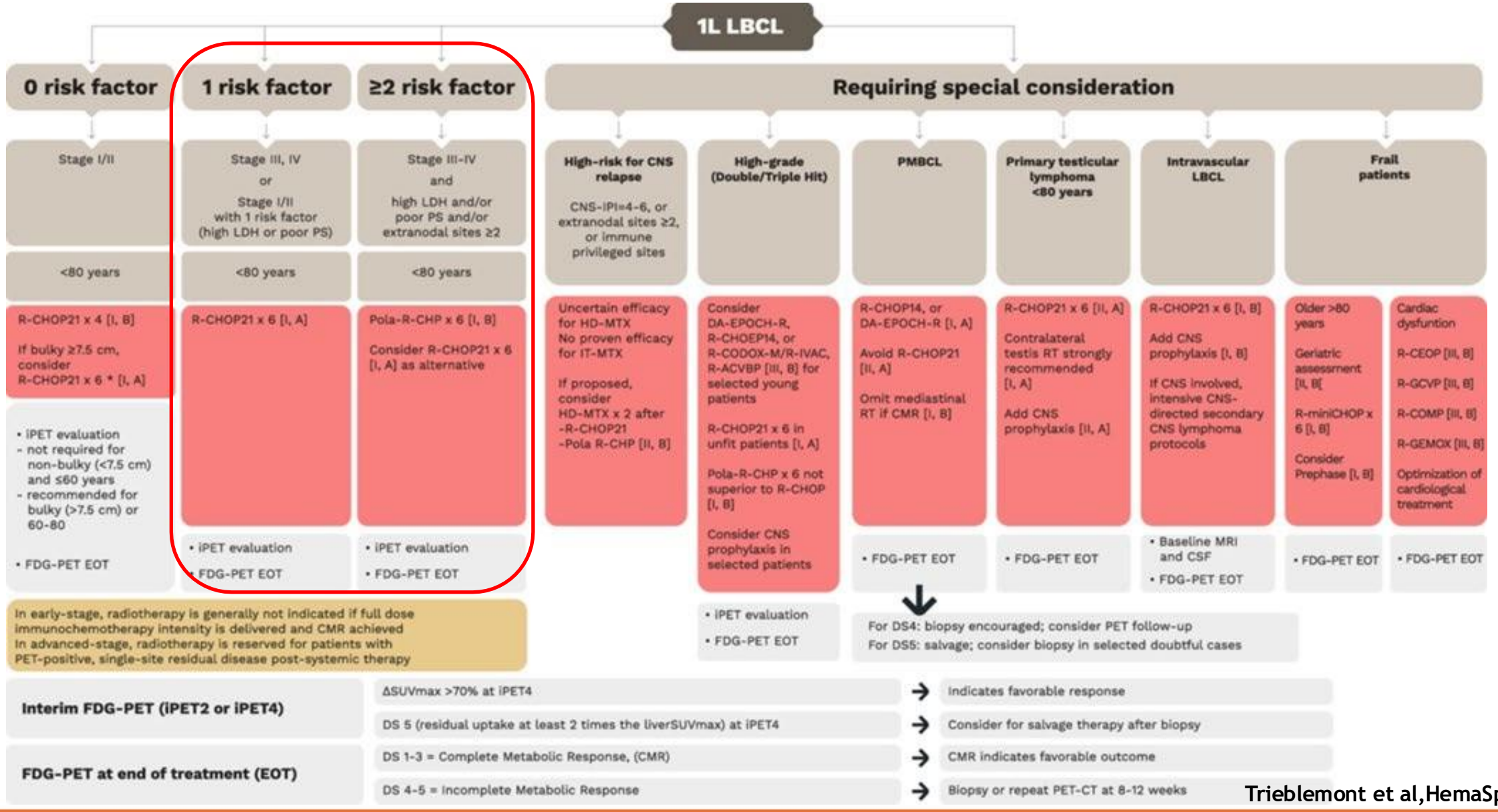


Limited stage DLBCL



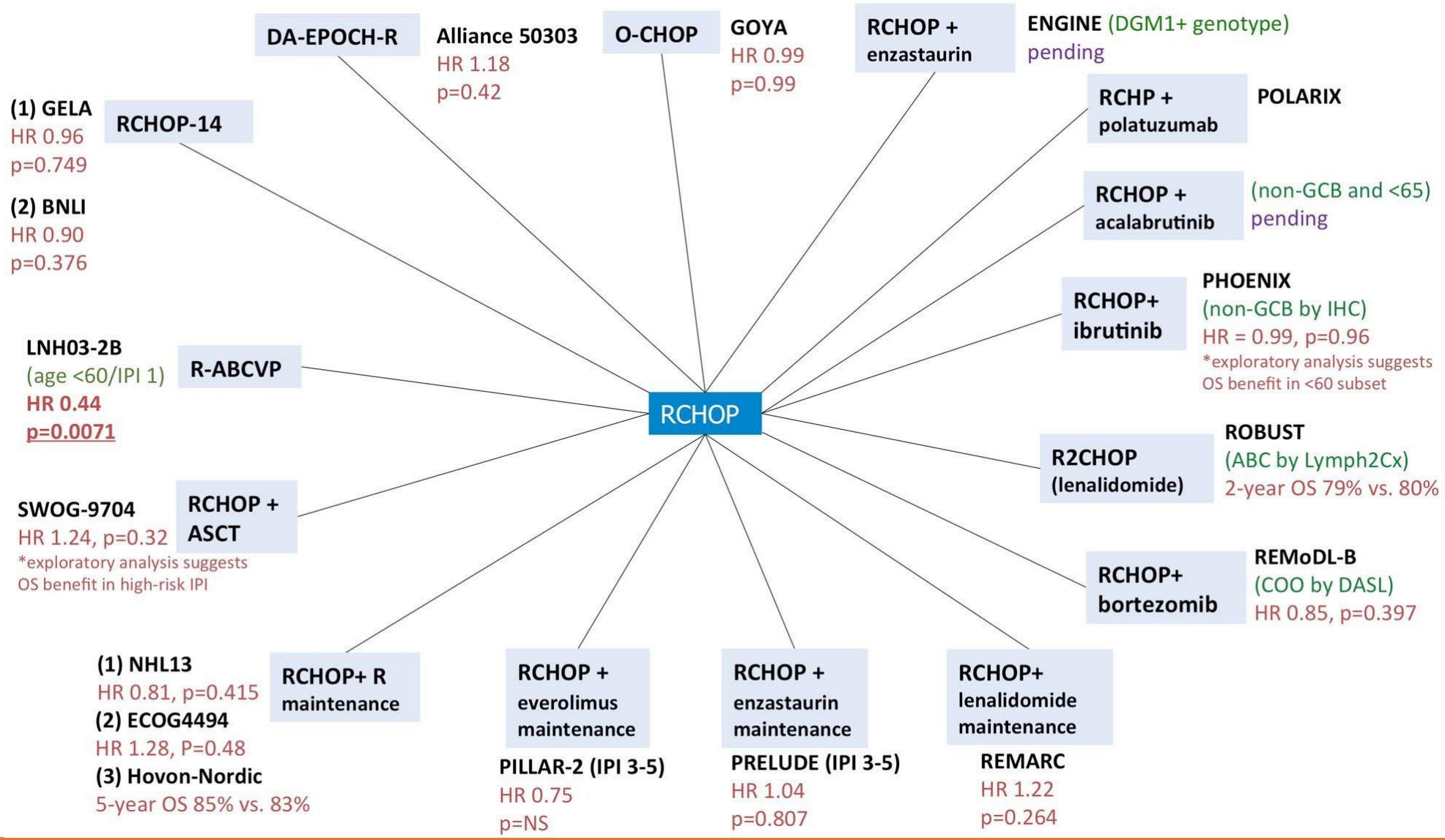
E. A. Hawkes et al, Blood 2022

LBCL: EHA Clinical Practice Guidelines



Trieblemont et al,HemaSphere 2025

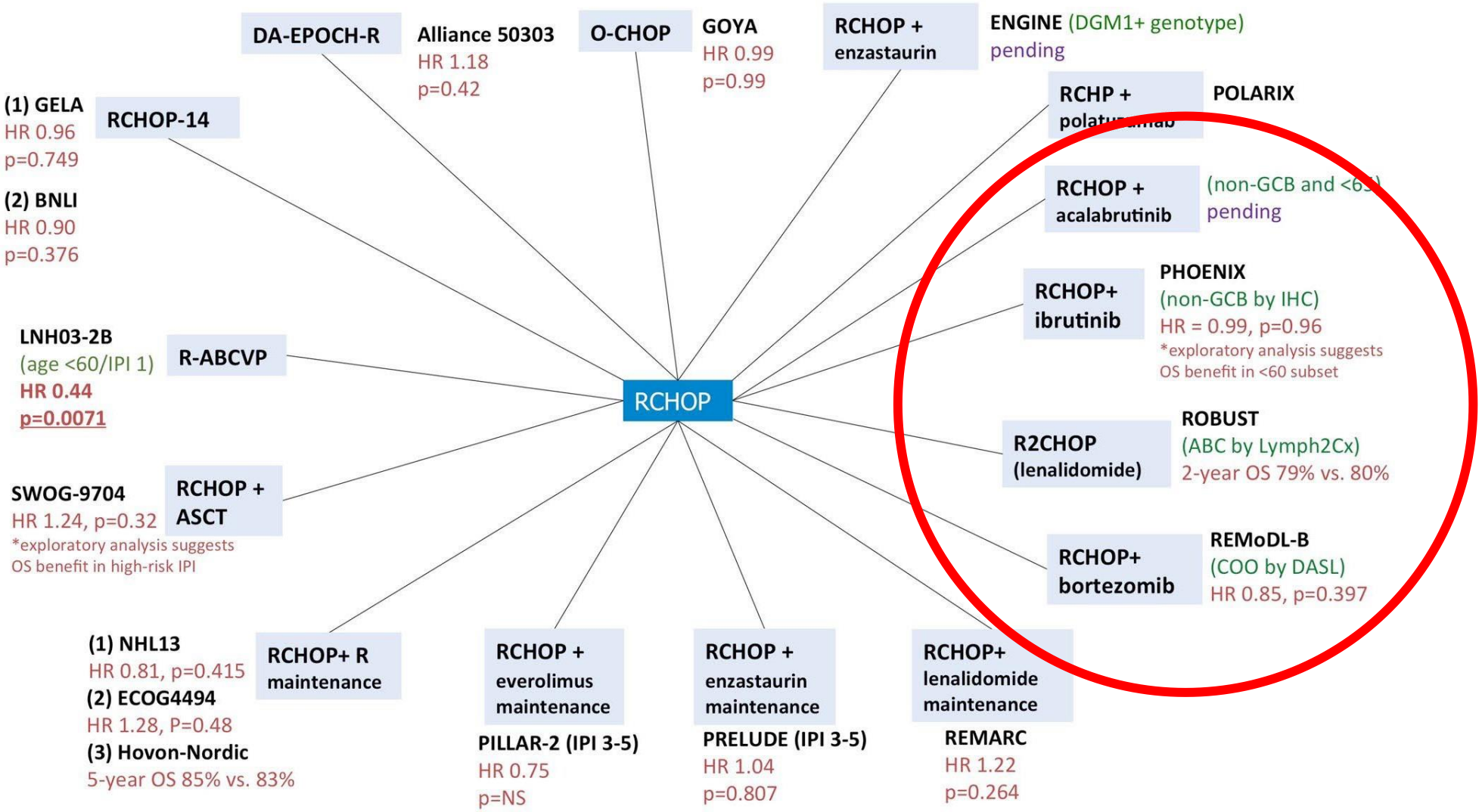
Some great trials….apart from the results



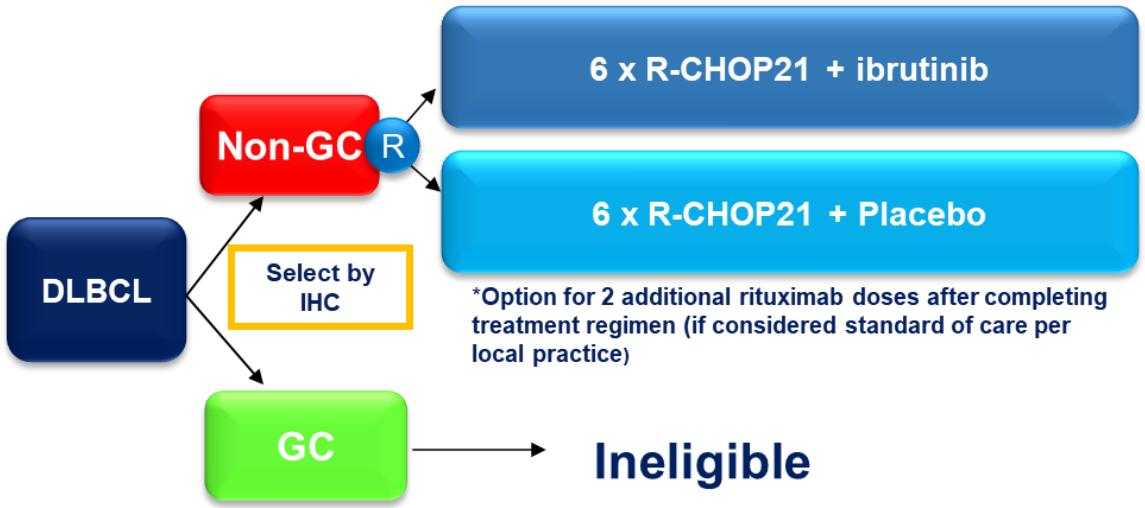
Competing schools of thought:

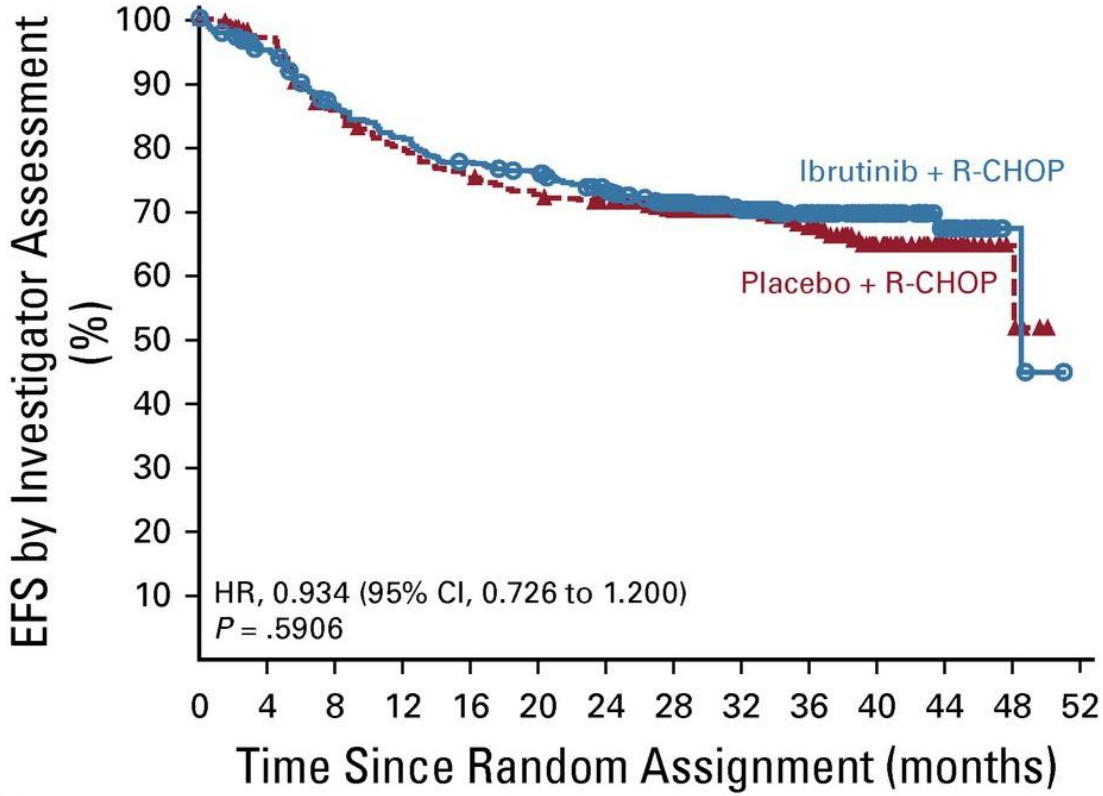
- Targeted therapy based on molecular phenotype
  - Gene expression/genomic typing
  - Small molecule inhibitors
- Better ways to use the cell surface markers
  - Antibodies with benefits
  - T-cell recruitment/expansion

Strategies to capitalise on the biology?



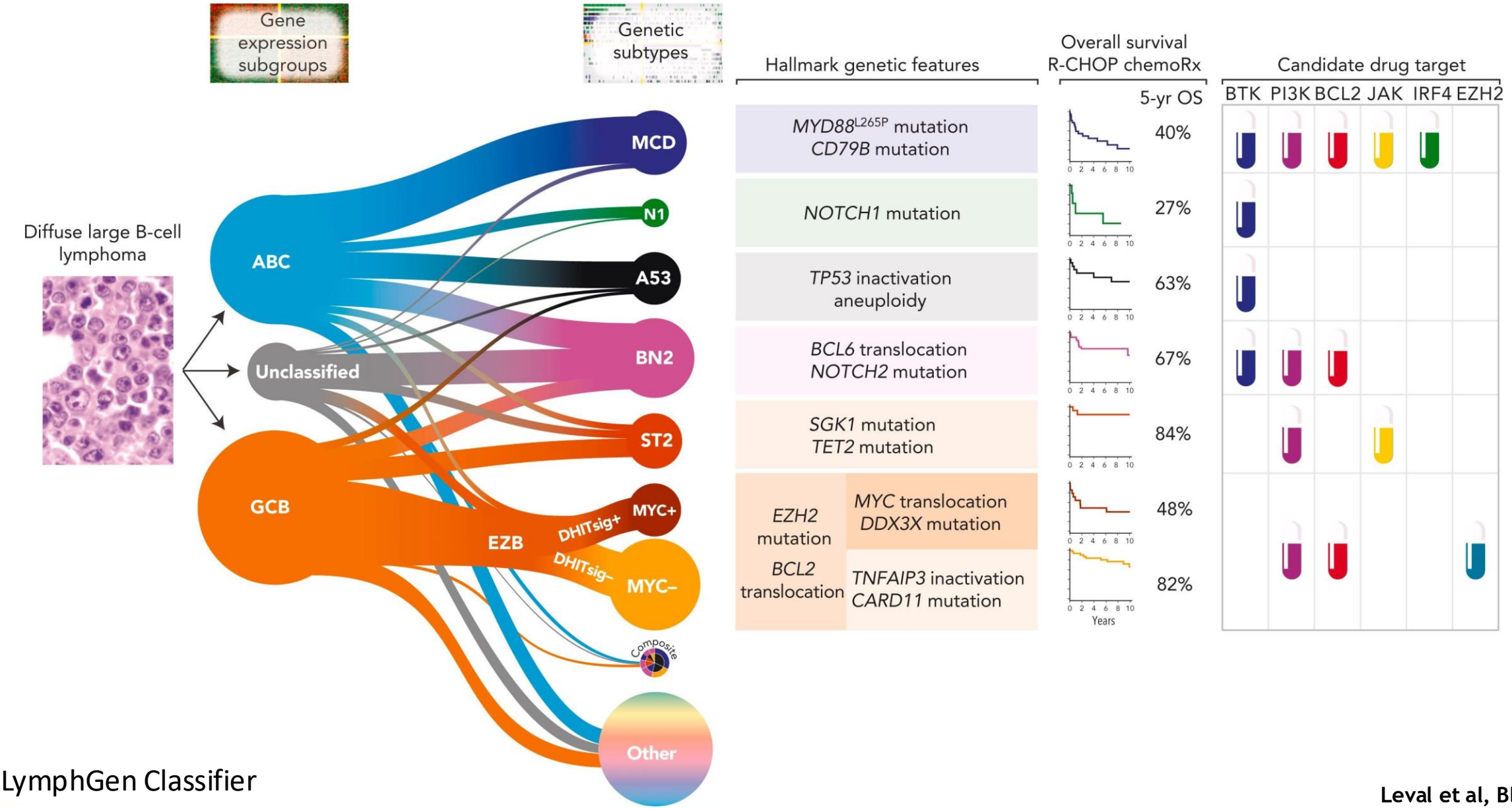
PHOENIX: Phase III double blind study of ibrutinib





- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18-80
- Primary Endpoint = EFS
- N = 800

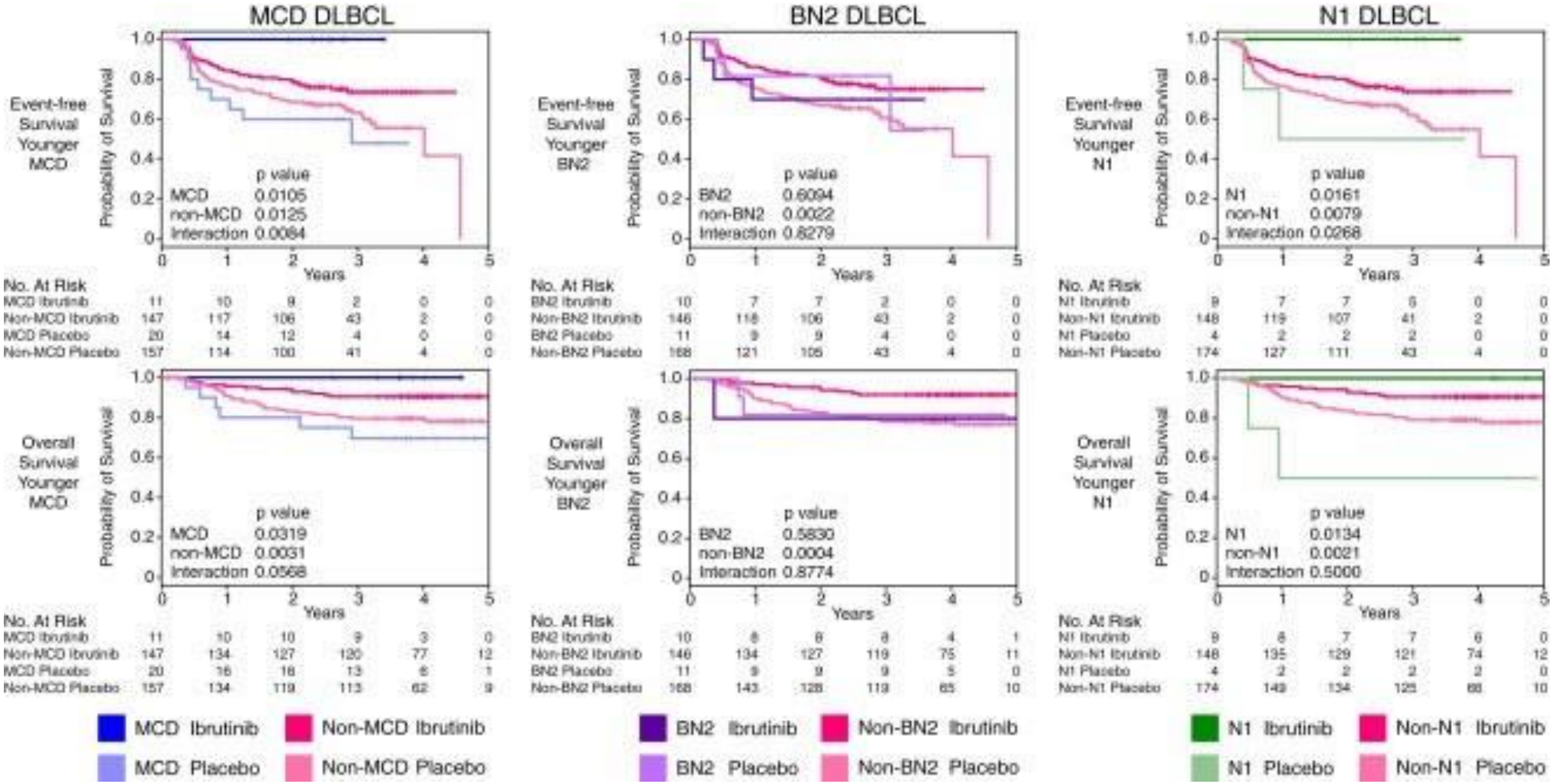
A Younes et al, J Clin Oncol 2019



LymphGen Classifier

Leval et al, Blood 2022

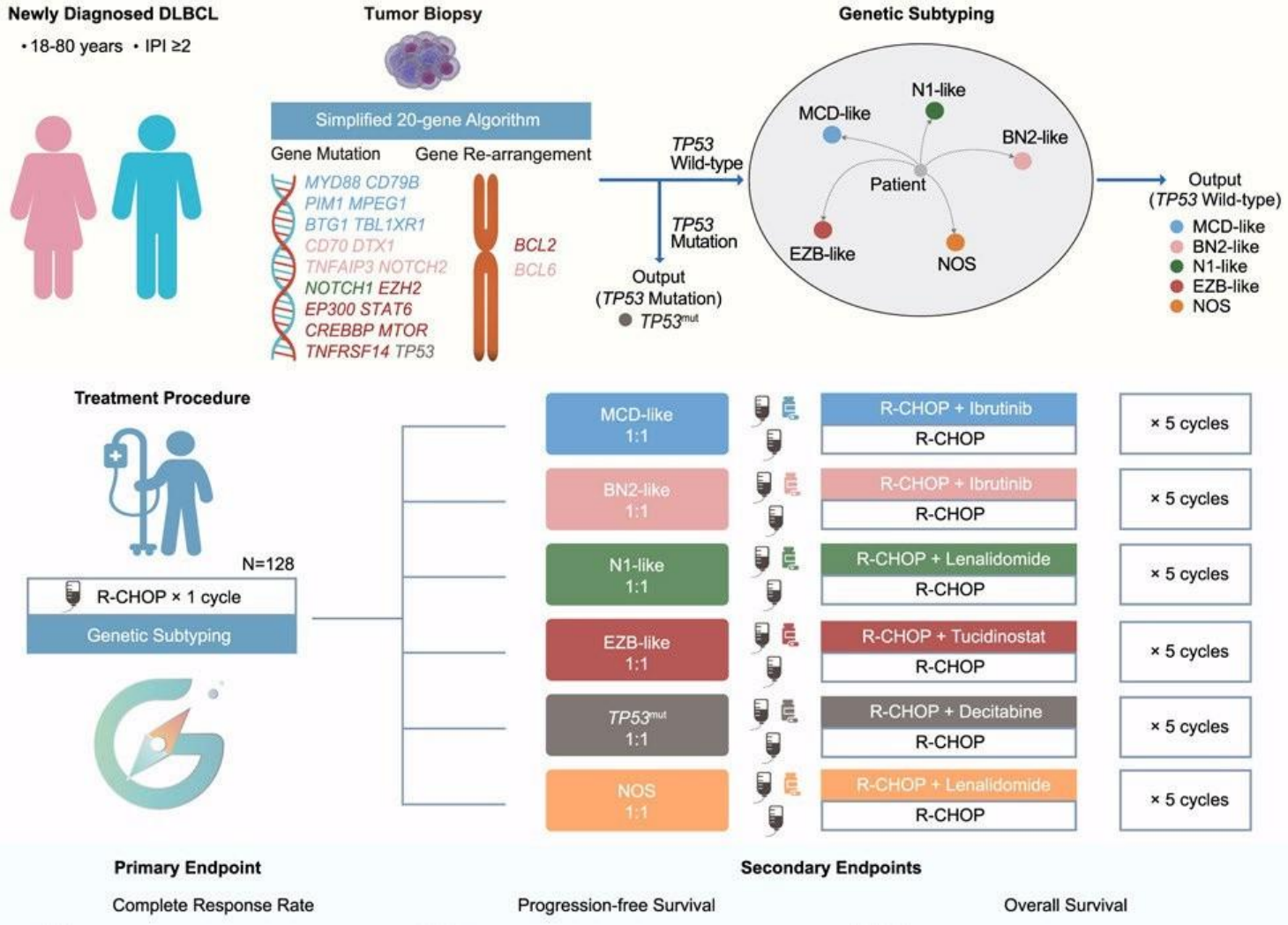
Perhaps outcomes to target therapies by genomic class

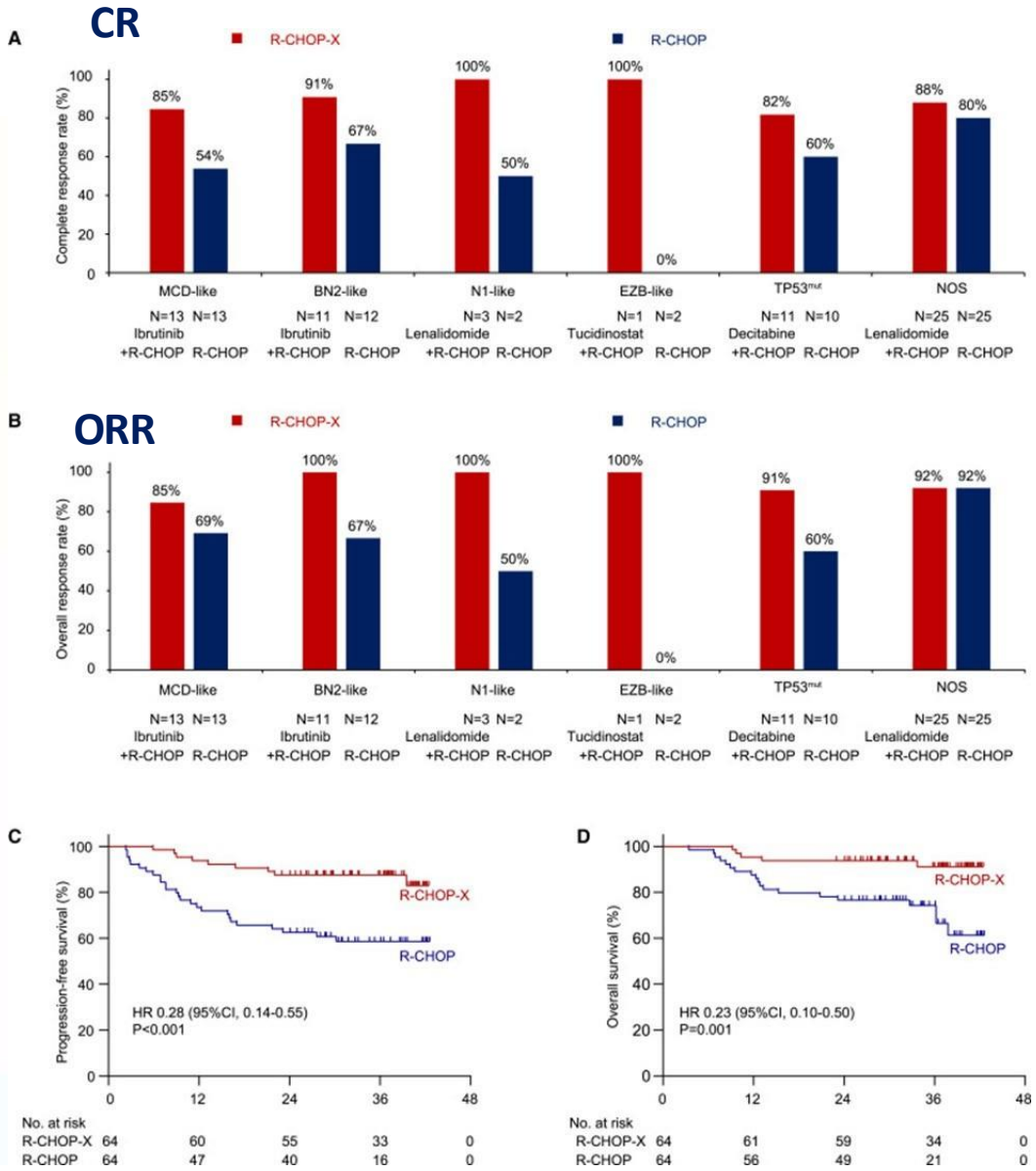


Wilson et al, 2021 Cancer Cell

GUIDANCE-01

n=128





Zhang et al, Cancer Cell 2023

The agnostic approach

Better ways of exploiting widely expressed cell surface antigens

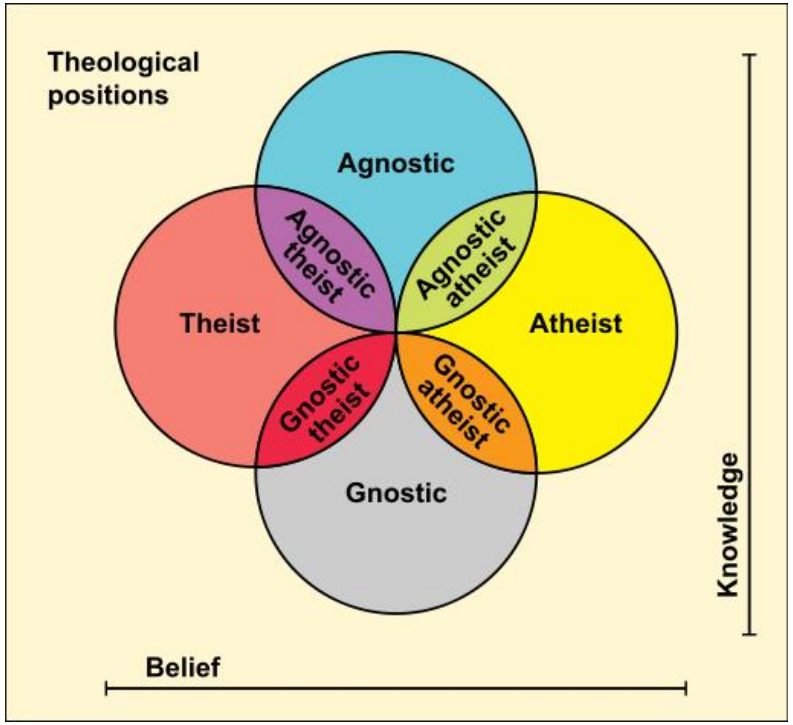
Antibody drug conjugates

? New antibodies

? Bispecifics

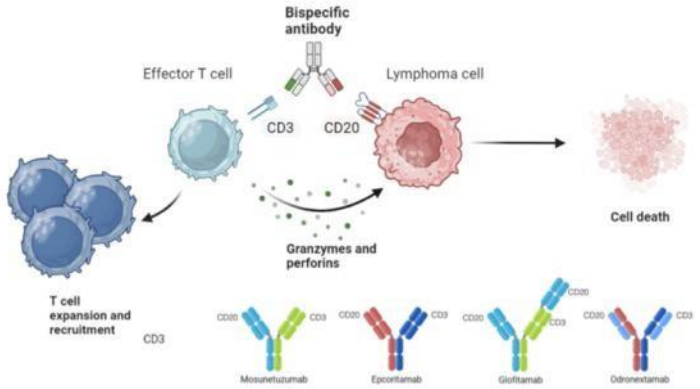
? CAR-T

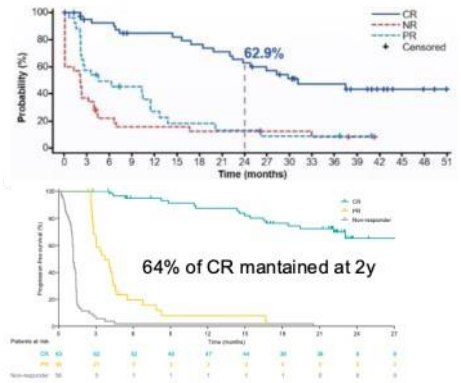
? New ADCs



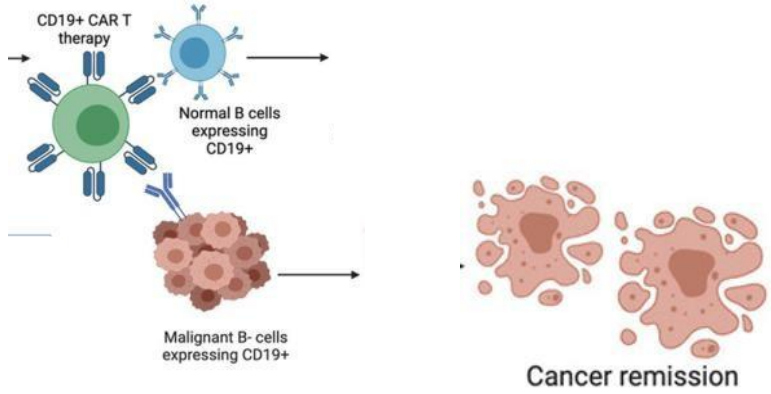
Agnostic treatments

CD3-CD20 bispecific antibodies



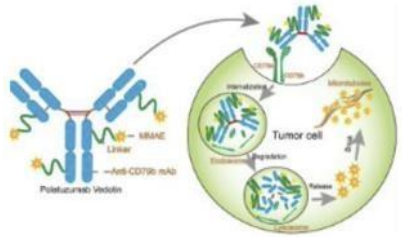


CAR T cells

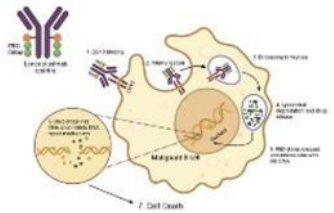


ADCs

Polatuzumab



Loncastuximab



MoAb

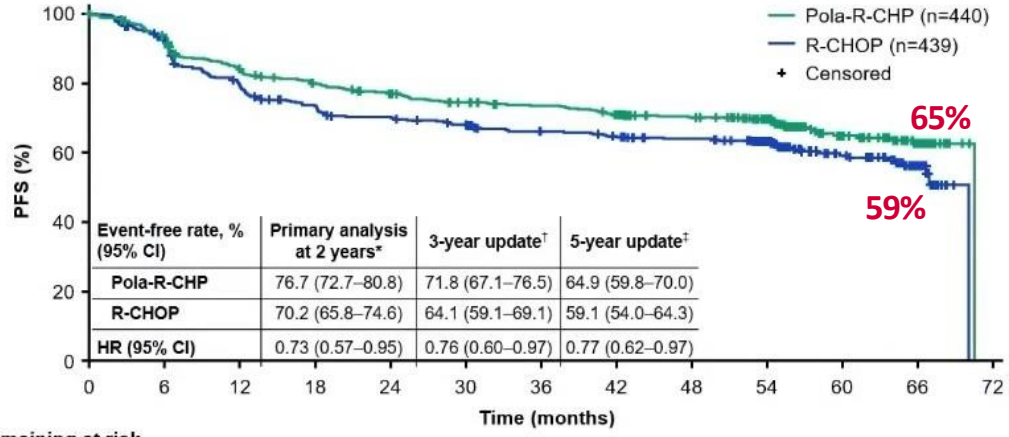
Tafasitamab

Humanized monoclonal anti-CD19 antibody

Functions as immunotherapy

Dickinson M et al, Blood 2024 ,Thieblemont C et al, Leukemia 2024

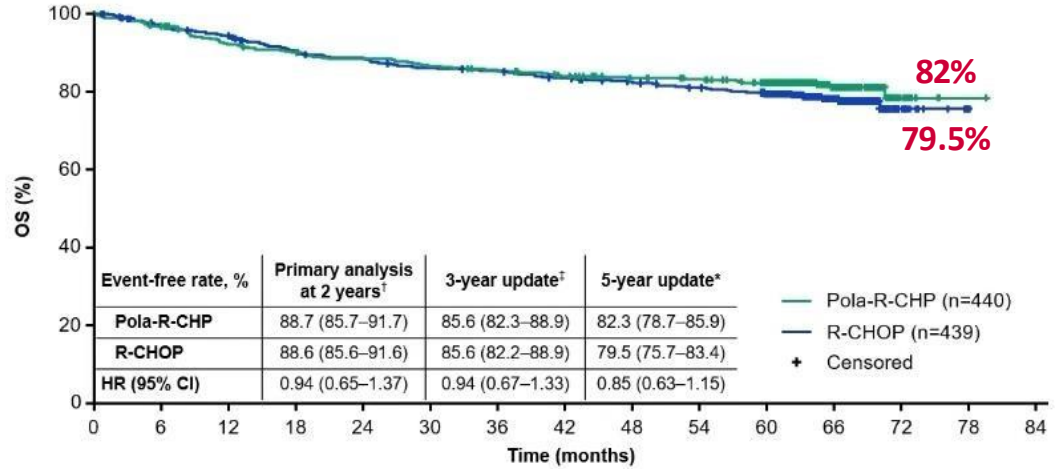
Pola-R-CHP significantly improved PFS versus R-CHOP



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

Patients remaining at risk

Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

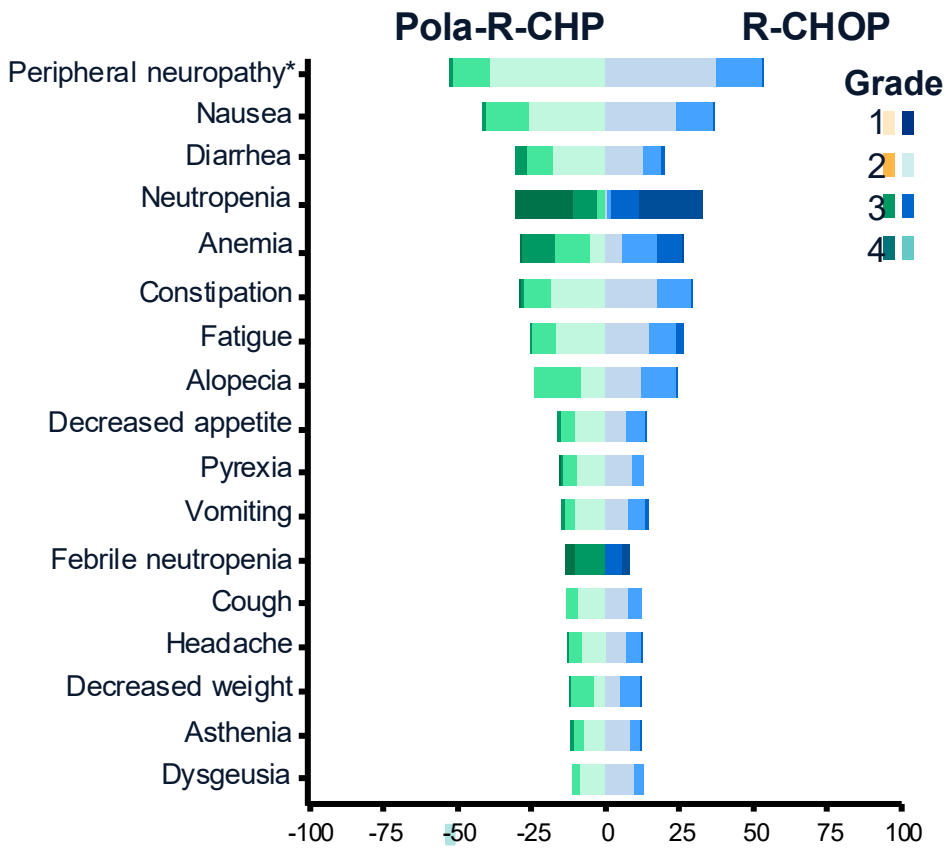


Event-free rate, %	Primary analysis at 2 years†	3-year update‡	5-year update*
Pola-R-CHP	88.7 (85.7–91.7)	85.6 (82.3–88.9)	82.3 (78.7–85.9)
R-CHOP	88.6 (85.6–91.6)	85.6 (82.2–88.9)	79.5 (75.7–83.4)
HR (95% CI)	0.94 (0.65–1.37)	0.94 (0.67–1.33)	0.85 (0.63–1.15)

Patients remaining at risk

Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

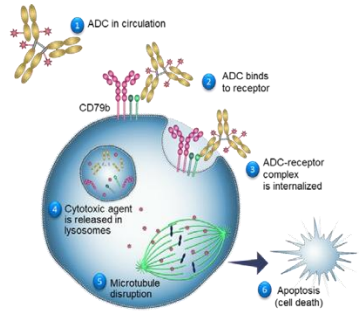
No significant increase in toxicity



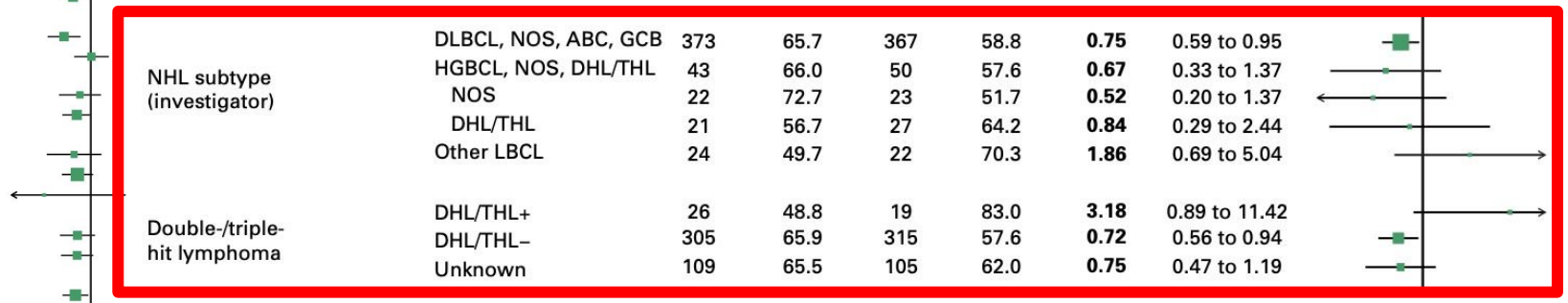
***predominant benefit seen ABC, non-bulky and IPI 3-5 patients**

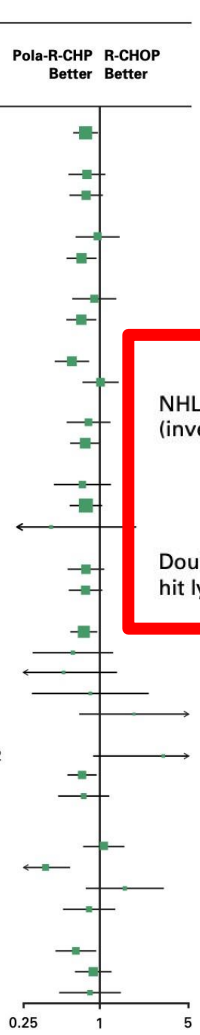
Tilly, et al. NEJM 2021; Morschhauser, et al. JCO 2025

POLARIX: PFS subset analysis (exploratory)



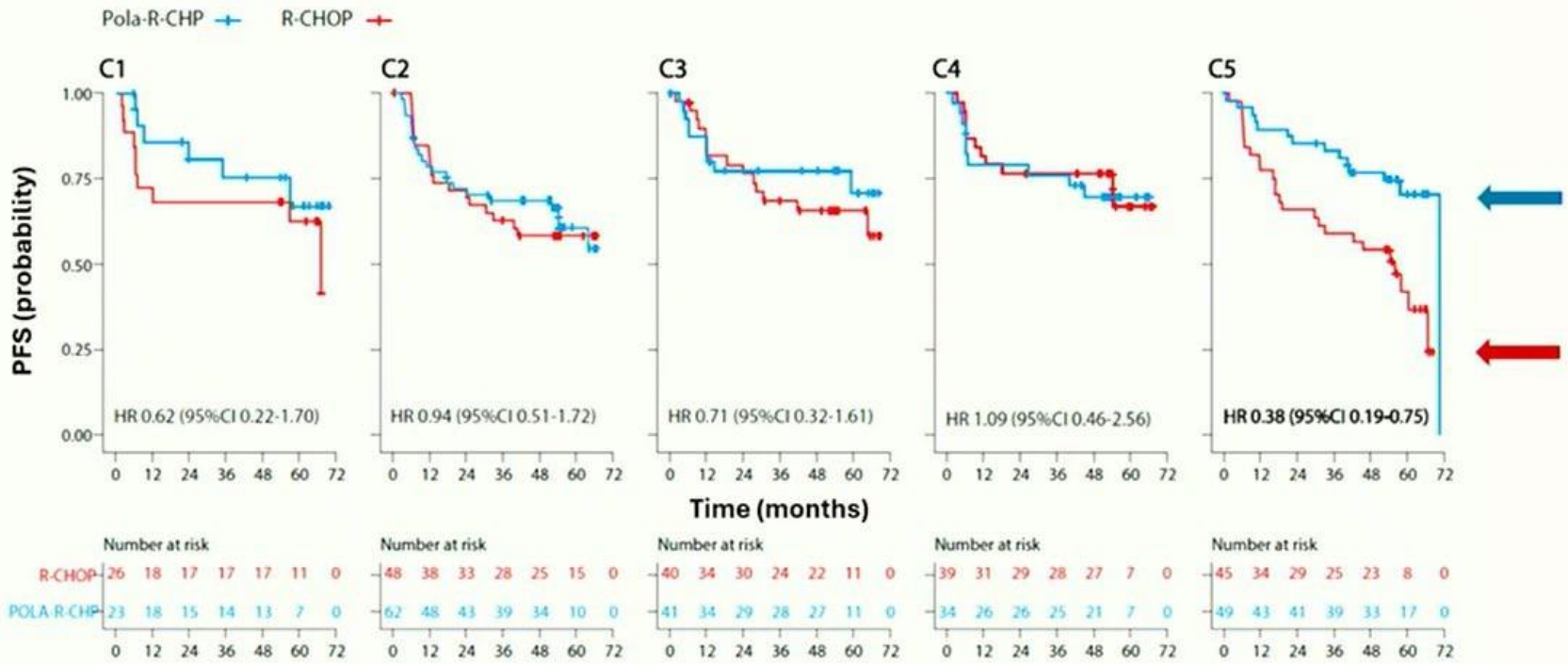
Baseline Risk Factor		Pola-R-CHP (n = 440) No.	Pola-R-CHP (n = 440) 60-Month, %	R-CHOP (n = 439) No.	R-CHOP (n = 439) 60-Month, %	PFS HR	PFS 95% Wald CI
All patients		440	64.9	439	59.1	**0.78**	0.62 to 0.97
Age group, years	≤65	225	69.6	219	64.3	**0.80**	0.57 to 1.11
	>65	215	60.0	220	54.5	**0.78**	0.58 to 1.06
Age group 2, years	≤60	140	67.6	131	69.2	**0.96**	0.62 to 1.49
	>60	300	63.6	308	55.8	**0.72**	0.55 to 0.93
Stratification – IPI score	2	167	67.2	167	68.3	**0.91**	0.61 to 1.36
	3-5	273	63.2	272	53.5	**0.72**	0.55 to 0.94
Stratification – bulky disease (≥7cm)	Absent	247	69.9	247	60.0	**0.61**	0.44 to 0.83
	Present	193	58.5	192	57.9	**1.02**	0.73 to 1.41
Baseline LDH	≤1×ULN	146	65.3	154	64.8	**0.83**	0.55 to 1.23
	>1×ULN	291	64.3	284	55.7	**0.77**	0.59 to 1.01
Bone marrow involvement	Yes	76	53.3	72	44.2	**0.75**	0.47 to 1.20
	No	342	67.3	349	63.2	**0.80**	0.61 to 1.04
	Indeterminate	11	70.0	11	51.9	**0.44**	0.10 to 1.85
No. of extranodal sites	0-1	227	68.1	226	64.2	**0.78**	0.56 to 1.09
	≥2	213	61.2	213	53.8	**0.78**	0.58 to 1.06
NHL subtype (investigator)	DLBCL, NOS, ABC, GCB	373	65.7	367	58.8	**0.75**	0.59 to 0.95
	HGBCL, NOS, DHL/THL	43	66.0	50	57.6	**0.67**	0.33 to 1.37
	NOS	22	72.7	23	51.7	**0.52**	0.20 to 1.37
	DHL/THL	21	56.7	27	64.2	**0.84**	0.29 to 2.44
	Other LBCL	24	49.7	22	70.3	**1.86**	0.69 to 5.04
Double-/triple-hit lymphoma	DHL/THL+	26	48.8	19	83.0	**3.18**	0.89 to 11.42
	DHL/THL–	305	65.9	315	57.6	**0.72**	0.56 to 0.94
	Unknown	109	65.5	105	62.0	**0.75**	0.47 to 1.19
NanoString COO	GCB	187	65.9	170	65.8	**1.07**	0.74 to 1.56
	ABC	106	72.5	129	45.8	**0.38**	0.24 to 0.59
	UNC	44	55.2	53	70.8	**1.60**	0.79 to 3.25
	Unknown	103	60.2	87	59.7	**0.83**	0.51 to 1.33
Double expressor by IHC	DEL	139	63.1	151	50.0	**0.65**	0.45 to 0.94
	Non-DEL	223	66.6	215	64.7	**0.89**	0.64 to 1.24
	Unknown	78	63.7	73	63.5	**0.84**	0.48 to 1.47





Morschhauser, et al. JCO 2025

Benefit of Polatuzumab is restricted to C5

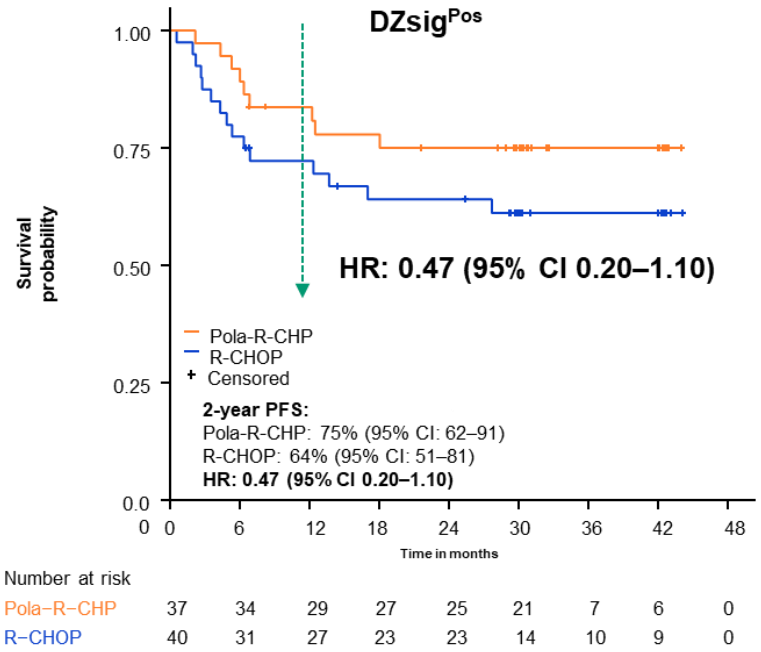


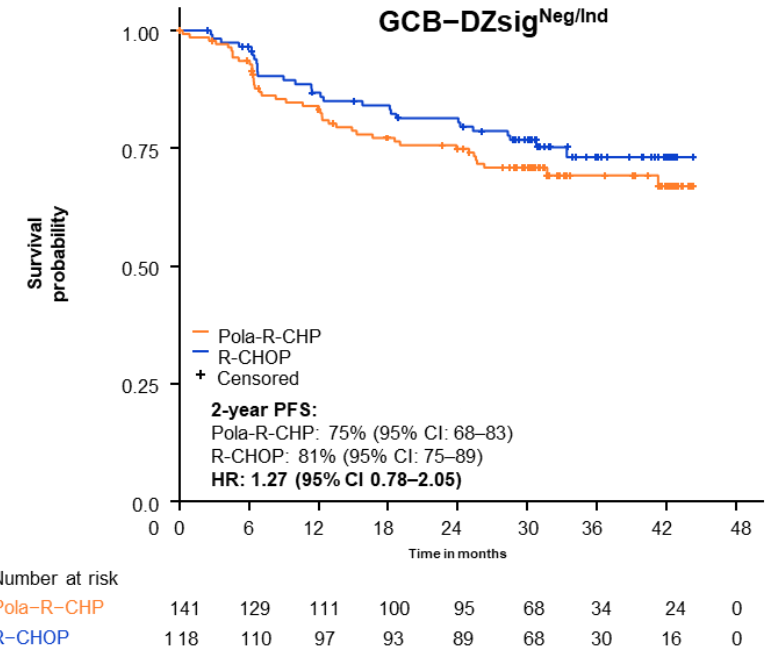
- Patients with C5 DLBCLs – 5-yr PFS higher in Pola-R-CHP versus R-CHOP treatment arm
  - Pola-R-CHP **70.4%** (95%CI 57.6-86.1)
  - R-CHOP **42.0%** (95% CI 28.0-63.0)
- Hazard ratio (HR) for Pola-R-CHP vs R-CHOP **0.38** (95% CI 0.19-0.75, **p=0.005**) in patients with C5 DLBCLs
- Pola-containing regimen abrogated the predicted poor outcome in C5 tumors.
- In contrast, 5-yr PFSs and HRs comparable for patients with C1-C4 DLBCLs in the two treatment arms

Calabretta et al, ICML 2025

Investigator-Assessed PFS* by DZsig subtype (GCB group)

COO ABC vs. GC (…only informative… but…)



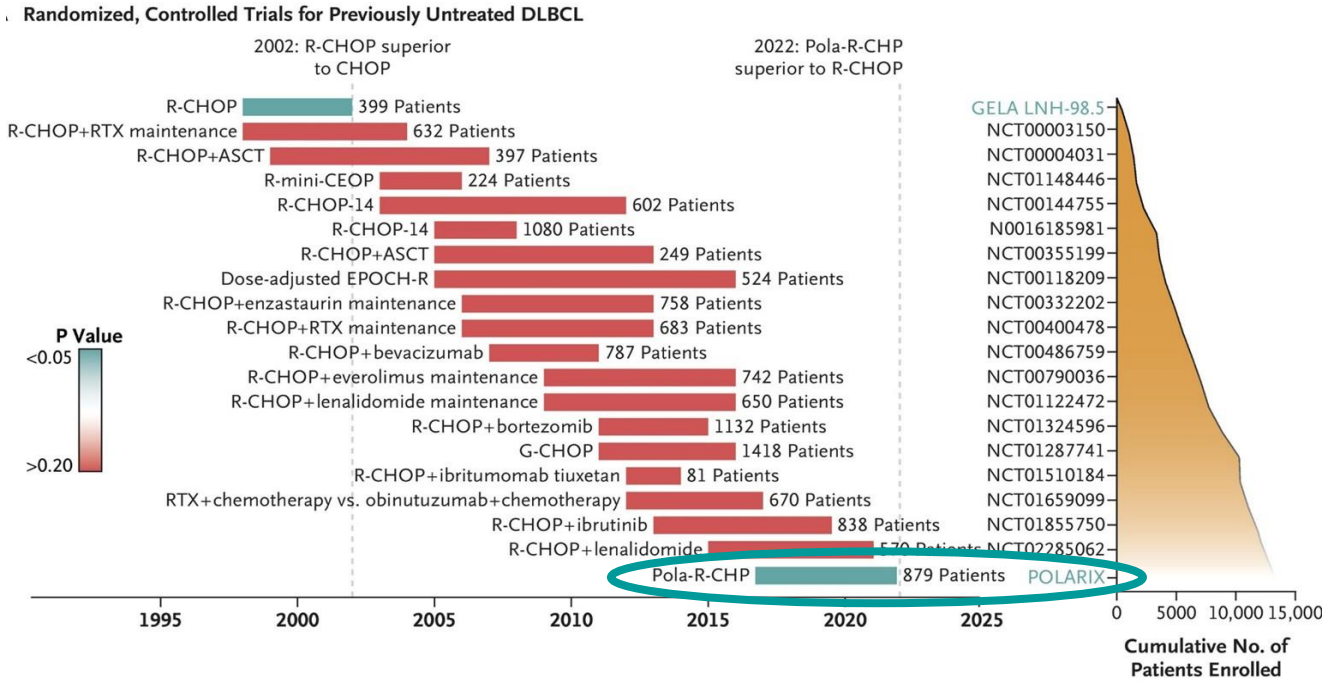


- In the R-CHOP arm, patients with DZsig^{Pos} DLBCL experienced poorer PFS vs those with DZsig$^{Neg/Ind}$ GCB-DLBCL (HR 2.04 [95% CI: 1.08–3.86]; 2-year PFS, 64% [95% CI: 51–81] vs 81% [95% CI: 75–89])
- The 2-year PFS trended in favour of patients with DZsig^{Pos} DLBCL treated with Pola-R-CHP vs R-CHOP, but not in those with DZsig$^{Neg/Ind}$ GCB-DLBCL

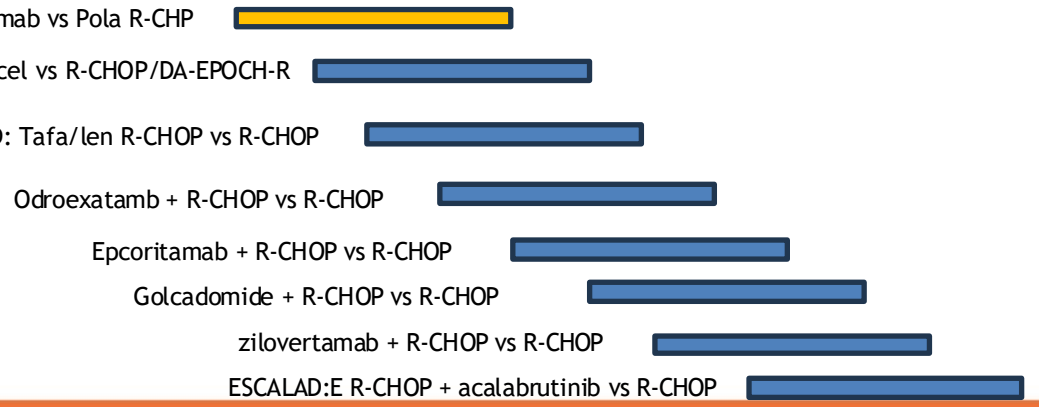
Morschhauser F, et al *Blood* 2023; 142 (Supplement 1): 3000. doi: https://doi.org/10.1182/blood-2023-178623.

*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data. DZsig$^{Neg/Ind}$, dark zone signature negative/indeterminate

Improving upon R-CHOP: 20 years of unsuccessful trials



How are we going to make sense of the future landscape….

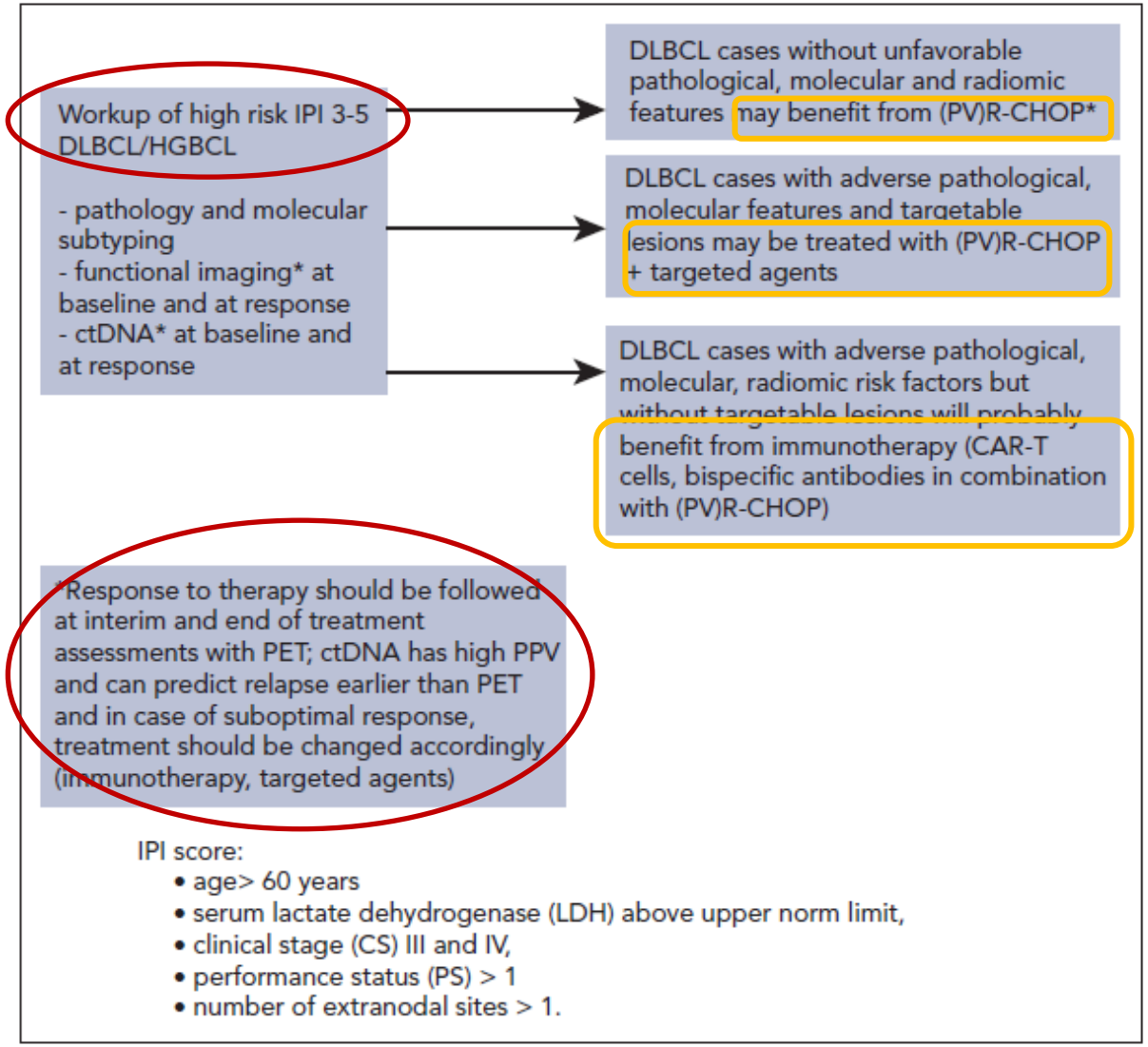


Some of these trials will be positive as these drugs are effective

Palmer et al, NEJM 2023

Who is @ High-Risk ?

Risk factors	High-risk features	Survival
Clinical factors	IPI = 3; high-intermediate	5-y OS (43%-67%)
	IPI = 4, 5; high risk	5-y OS (26%-53.9%)
	R-IPI = 3 (3-5 risk factors)	4-y OS (55%-60.9%)
	NCCN-IPI = 6-8; high risk	5-y OS (33%-49%)
Biological factors	COO = ABC subtype	5-y OS (35%-56%)
	COO = type 3 unclassifiable	5-y OS (39%-62%)
	DEL	5-y OS (30%-40%)
	DHL/THL	2-y OS (38%-82%)
	DHTsig$^+$ DZsig	5-y TTP 57%
Biological factors: molecular taxonomy	MCD/C5/MYD88	5-y OS (26%-60%)
	N1	5-y OS (27%-40%)
	A53/C2	5-y OS 63% (33%-100%)
	BN2/C1/NOTCH2	5-y OS 67% (38%-100%)
	EZB DHTsig$^+$ MYC$^+$	5-y OS (40%-48%)
Radiomics prognostic factors: baseline and dynamic	ΔSUVmax < 66% at iPET2	2-y OS 54.2%
	High TMTV > 328 cm^3 and ΔSUVmax < 66% at iPET2	2-y OS 37.1%
	ECOG-PS ≥ 2 and TMTV > 220 cm^3	4-y OS (41%-61%)
	High-risk IMIPI	3-y OS 51.5%
	High-risk clinical PET model	2-y PFS 48.6%
ctDNA: baseline and dynamic	No EMR	2-y EFS 50%
	No MMR	2-y EFS 46%



Dabrowska-Iwanicka A & Nowakowski GS *Blood*. 2024

Selected phase 3 front line trials in young, high risk patients

Trial	Patient population	Histologies	Primary outcome
POLARIX (Pola RCHP vs RCHOP)	N=1000 Age 18-80 y IPI 2-5 ECOG 0-2	DLBCL, HGBCL, TCHRLBL, EBV- positive, ALK-positive, HHV8-positive	PFS
FrontMIND RCHOP+Tafa+Len vs RCHOP	N=880 PI 3-5 (if >60 y) aaIPI 2-3 (if ≤60 y) Diagnosis to treatment interval <28 d Age 18-80 y ECOG 0-2	DLBCL, HGBCL, t-iNHL, FL3B, TCHRLBL, EBV-positive, ALK-positive, HHV8-positive	PFS
SKYGLO **Pola-R-CHP + glofitamab vs Pola-R-CHP**	**N=1130** **PI 2-5 (IPI 2 capped at 35%) Age 18-80 y** **ECOG 0-2**	LBCL (further detail not specified)	PFS
OLYMPIA-3 **CHOP + Odronextamab vs R-CHOP**	**N=904** **Age ≤75 y** **IPI 2-5 (part 2)**	LBCL (further detail not specified)	PFS
EPCORE DLBCL-2 **R-CHOP + epcoritamab vs R-CHOP**	**N=900** **IPI 2-5 (IPI 2 capped at 35%) Age 18-79 y** **ECOG 0-2**	DLBCL, HGBCL (DH/TH) TCHRLBCL, EBV-positive, FL3B, tFL	PFS in IPI 3-5
GOLSEEK-1 R-CHOP + golcadomide vs R-CHOP	N=850 Age 18-80 y ≥1.3 × ULN, or single lesion IPI 3-5 (or IPI 1-2 + LDH ≥7 cm)	DLBCL, HGBCL, TCHRLBCL, EBV positive	PFS
waveLINE 010 R-CHOP + Zilovertamab vs RCHP	R-CHOP + Zilovertamab vs RCHOP	DLBCL NOS, TCHRLBCL, EBV positive	PFS

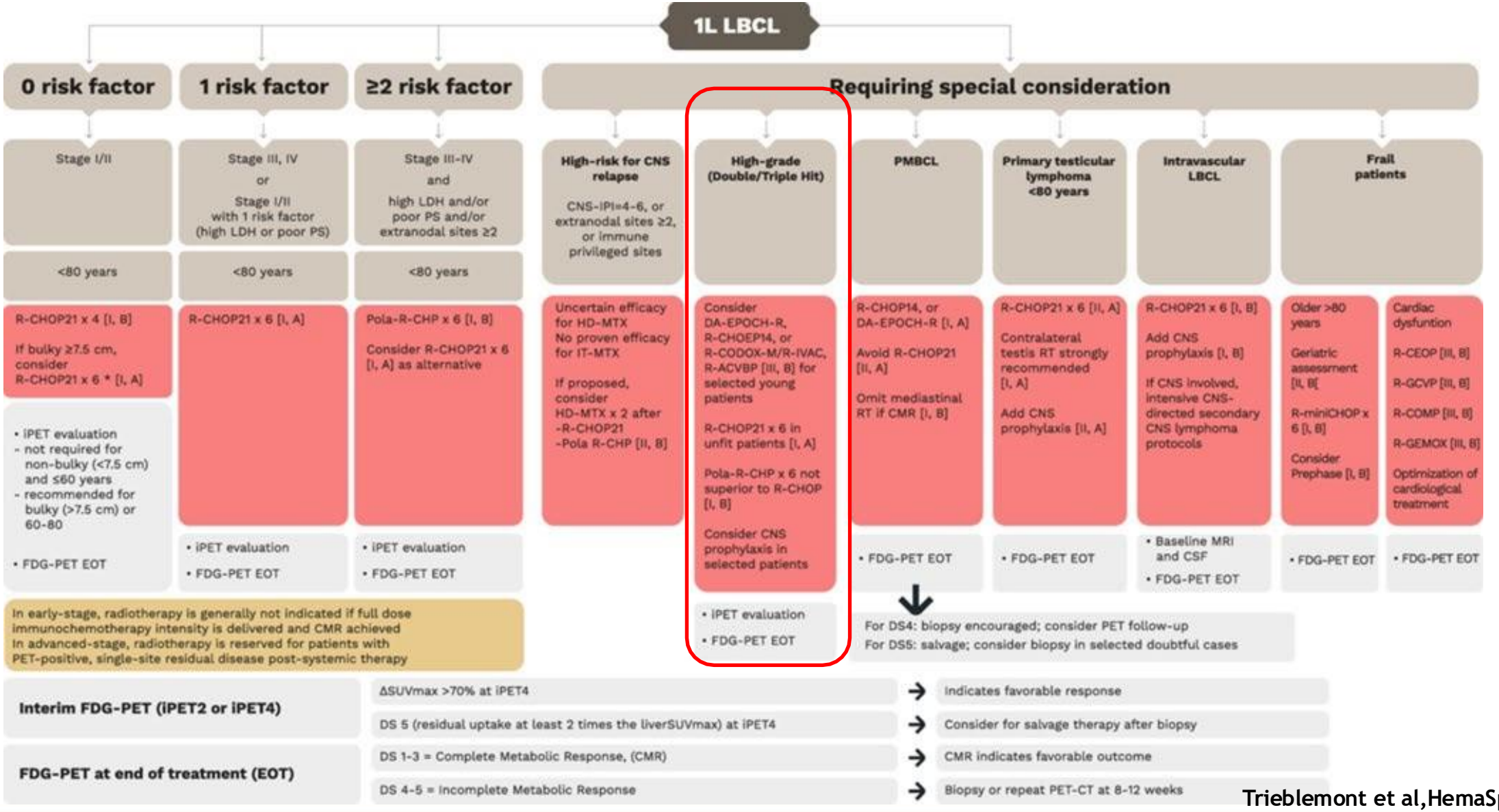
Adapted from Qualls D et al. Blood 2025

Front line trials with bispecific antibody combinations for LBCL

Trial*	Combination	N	ORR | CR (%)	PFS
Phase 1/2 trials with chemotherapy				
NCT03677141	Mosun + CHOP	40	85 | 85	2 years: 65%
NCT03677141	Mosun + Pola- CHP	40	85 | 73	2 years: 71%
NCT03467373	Glofit + R- CHOP	56	93 | 86	NR
NCT03467373	Glofit + Pola- R- CHP	24	100 | 96	NR
NCT04914741	Glofit + R- CHOP	40	100 |92	12 mo: 90%
NCT04914741	Glofit + Pola- R- CHP	40	100 | 92	12 mo: 95%
NCT04663347	Epcor + R- CHOP	47	100 | 87	2 years 74%
NCT05283720	Epcor + Pola + R- CHP	37	100 | 87	NR
NCT04663347	Epcor +R- miniCHOP	28	89 | 82	12 mo: 88%
Phase 1/2 chemo free or chemo light combinations				
NCT03677154	Mosun + Pola	108	55 | 45	NR
2022–003398- 51	R Ploa Glofit	80	90 | 82	NR
NCT05660967	Epcor + Lena	NR	NR	NR

Dickinson M et al, Br J Haematol 2026; Minson A et al, J Clin Oncol 2025

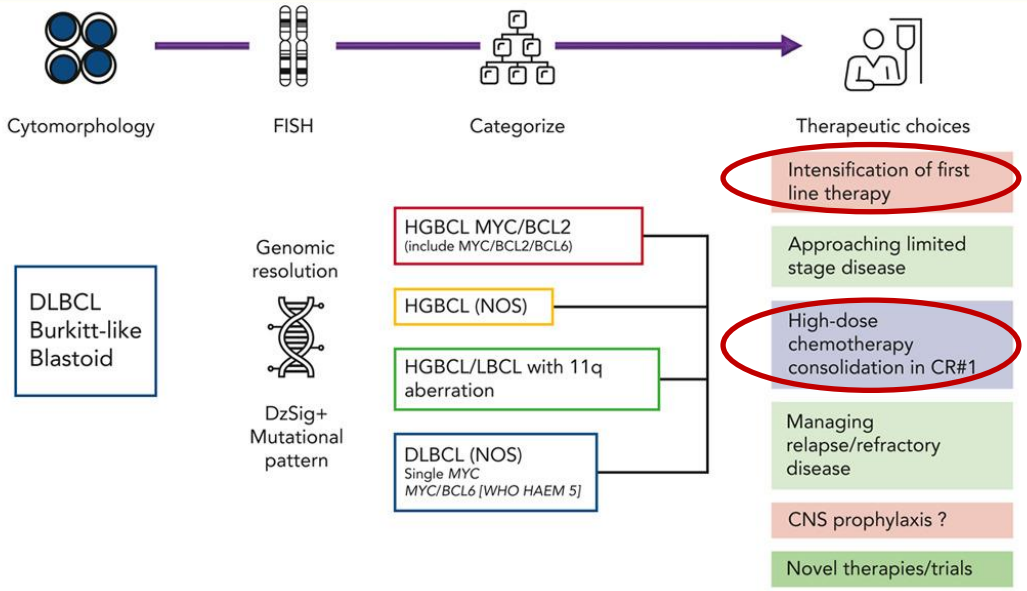
LBCL: EHA Clinical Practice Guidelines



Trieblemont et al, HemaSphere 2025

R-CHOP performs poorly in Hi-Risk LBCLs…

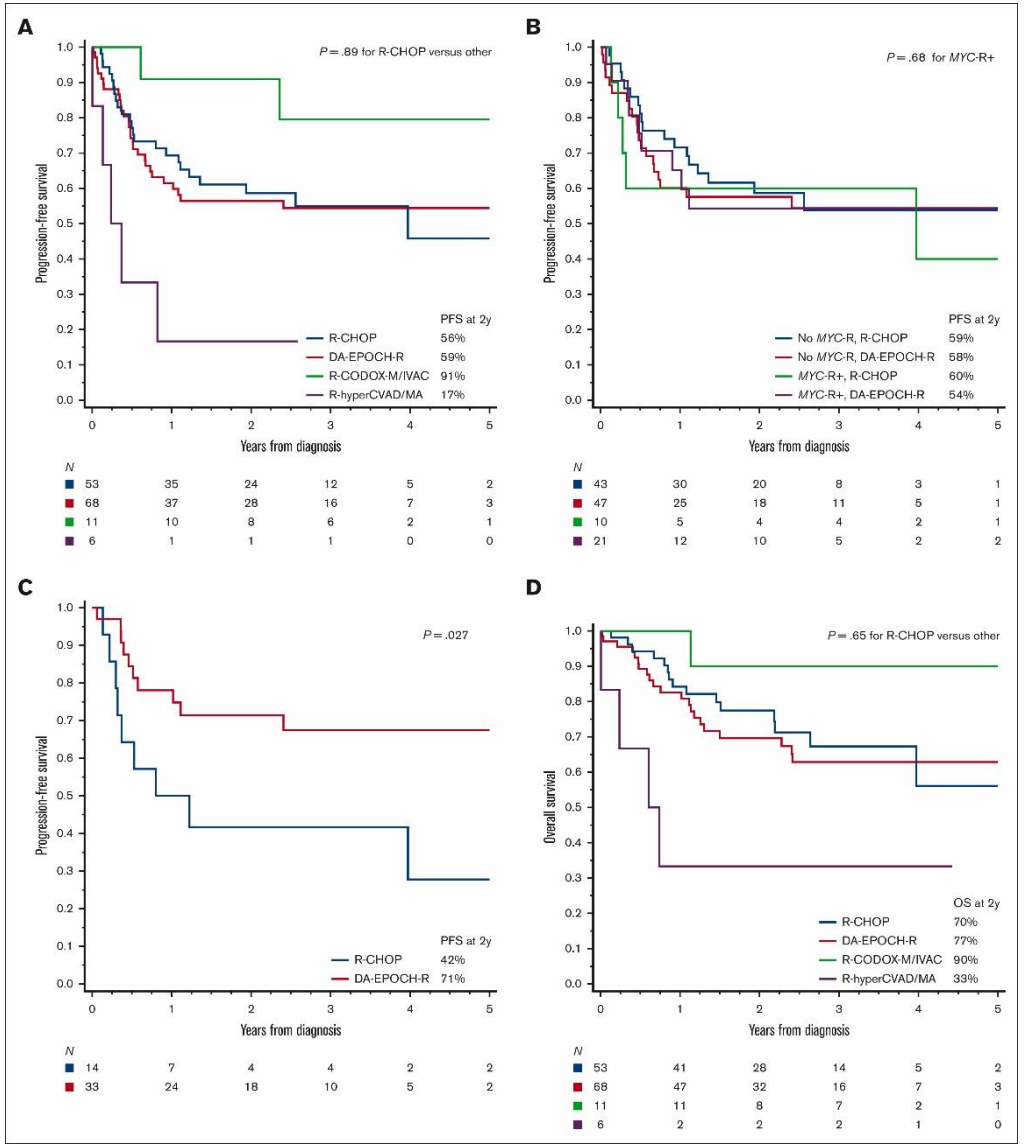
The High-Grade B-Cell Lymphomas (HGBCL): Double Hit and More



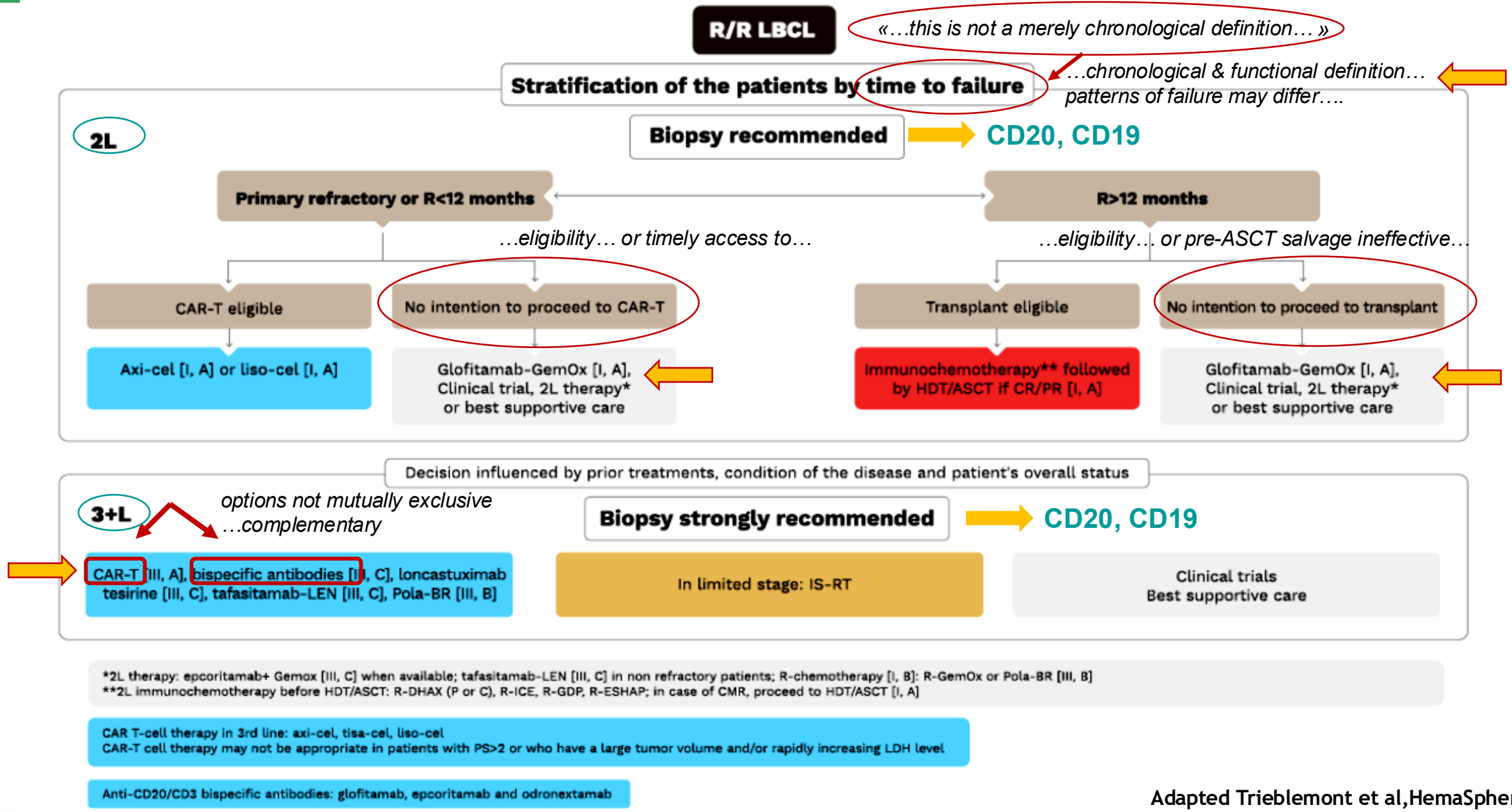
Conclusions: **The categorization of high-grade B-cell lymphomas is based on the aggregate of various morphological characteristics, cytogenetic rearrangements, and molecular signatures. Optimal treatment regimens are selected based on this classification.**

*Davies. DOI: 10.1182/**blood**.2023020780*

blood Visual Abstract



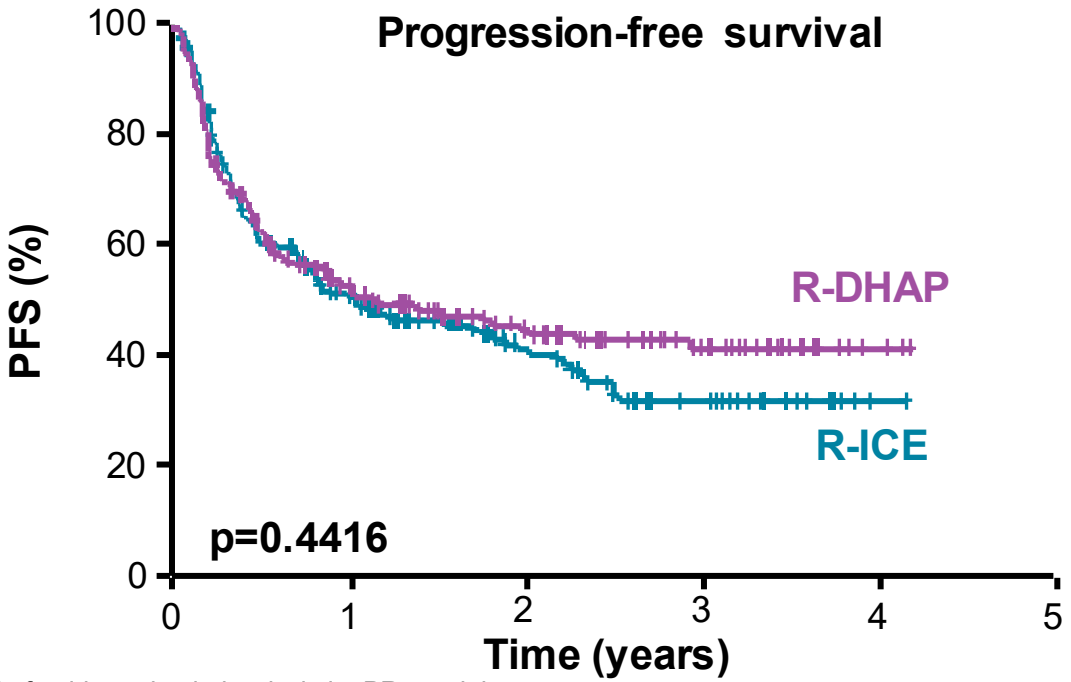
Zayac AS et al, Blood Adv 2023

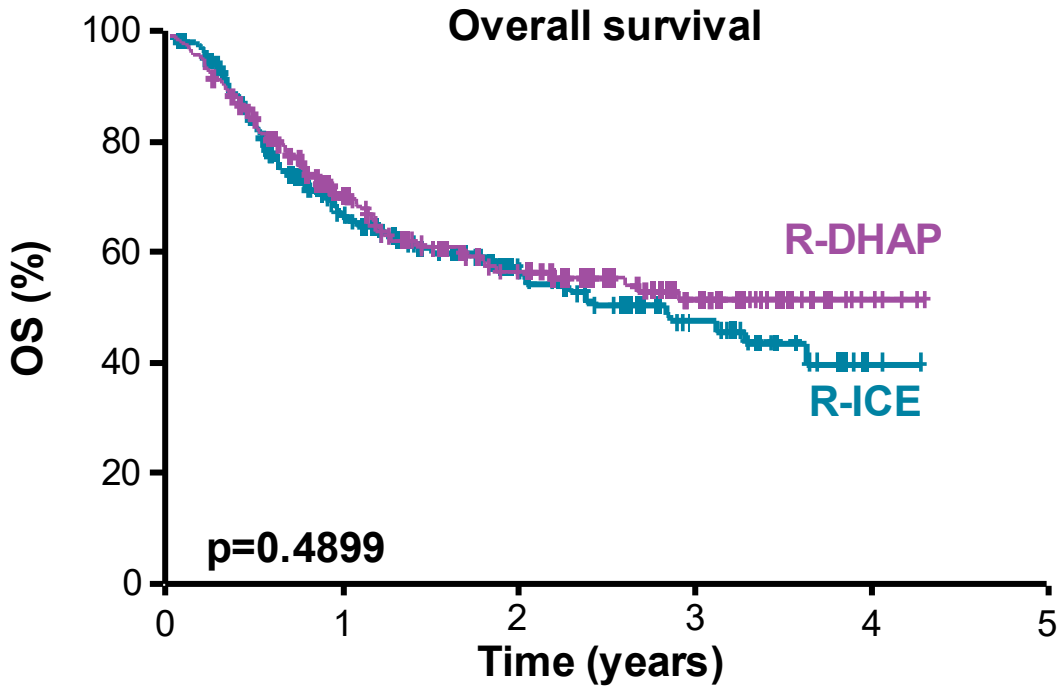


Adapted Trieblemont et al,HemaSphere 2025

Is there a better second line regimen?

CORAL: Randomised study of R-ICE vs. R-DHAP in patients with R/R DLBCL after 1L R-CHOP (N=396)



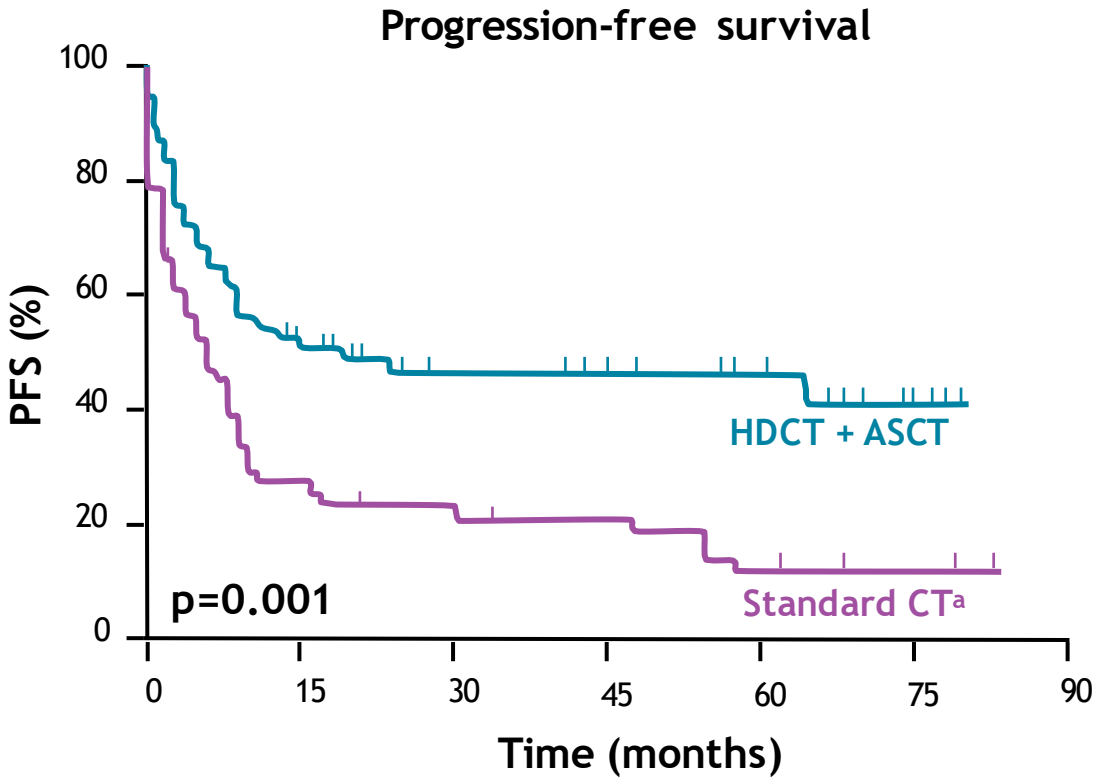


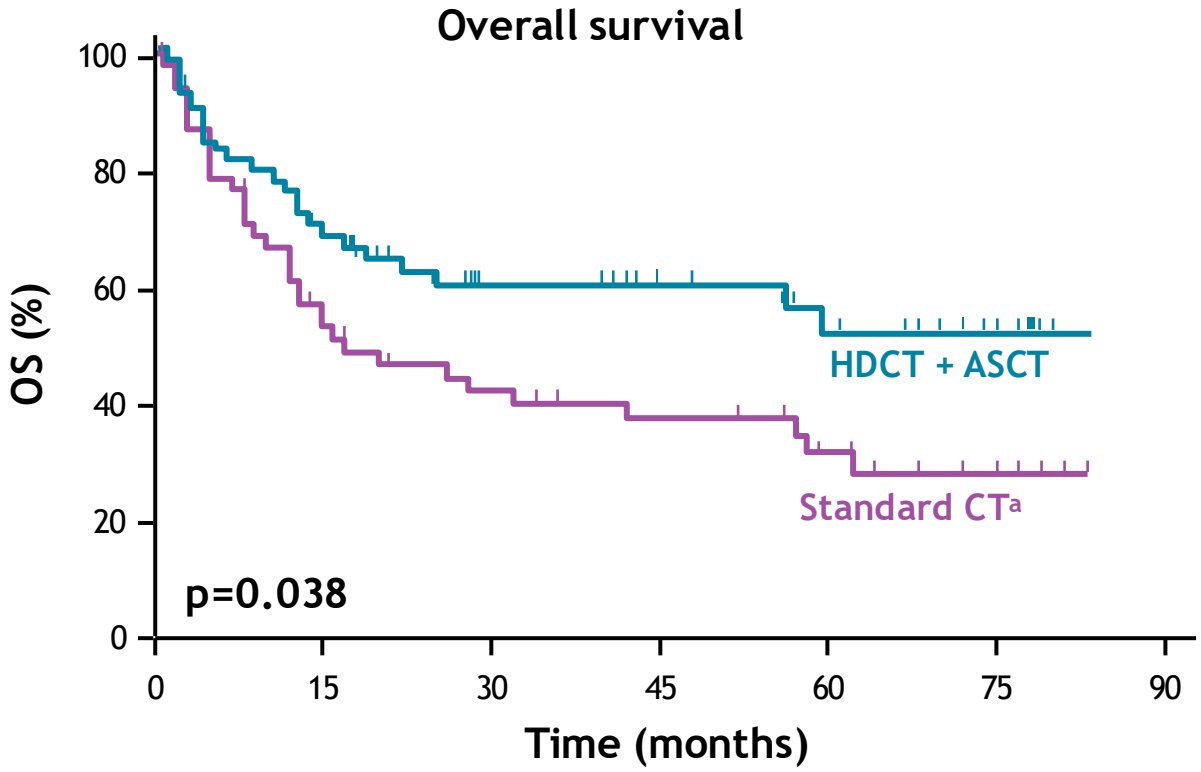
ICE: ifosfamide, carboplatin, cisplatin; PR: partial response

Gisselbrecht C, et al. J Clin Oncol 2010

The Parma trial for relapsed aggressive NHL: HDCT + ASCT better than standard chemotherapy

Randomised study of HDCT + ASCT vs. standard chemotherapy in patients with relapsed chemo-sensitive aNHL (N=109)





[a] Four courses of DHAP every 3–4 weeks followed, if no progression, by radiotherapy of the involved field
aNHL: aggressive non-Hodgkin lymphoma; CT: chemotherapy; DHAP: dexamethasone, cytarabine, cisplatin

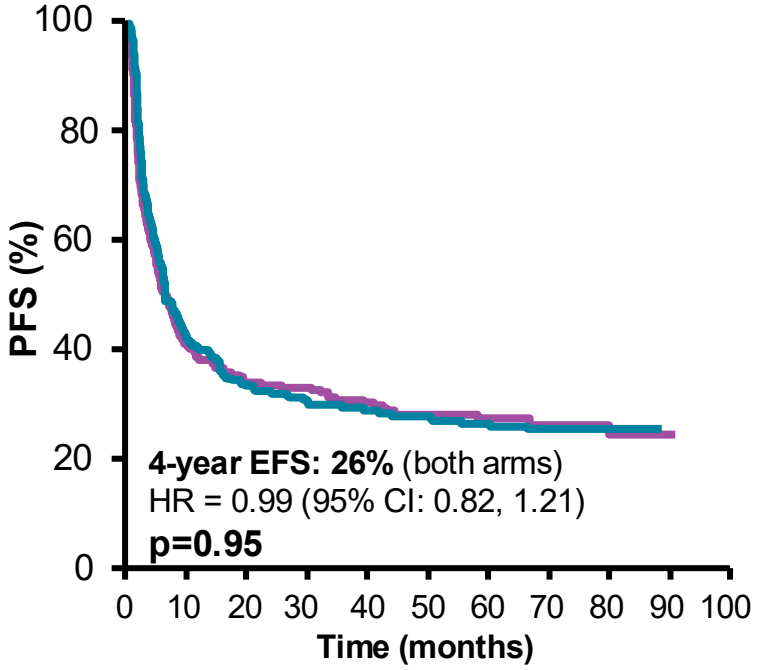
Philip T, et al. N Engl J Med 1995

Canadian study: GDP vs. DHAP therapy

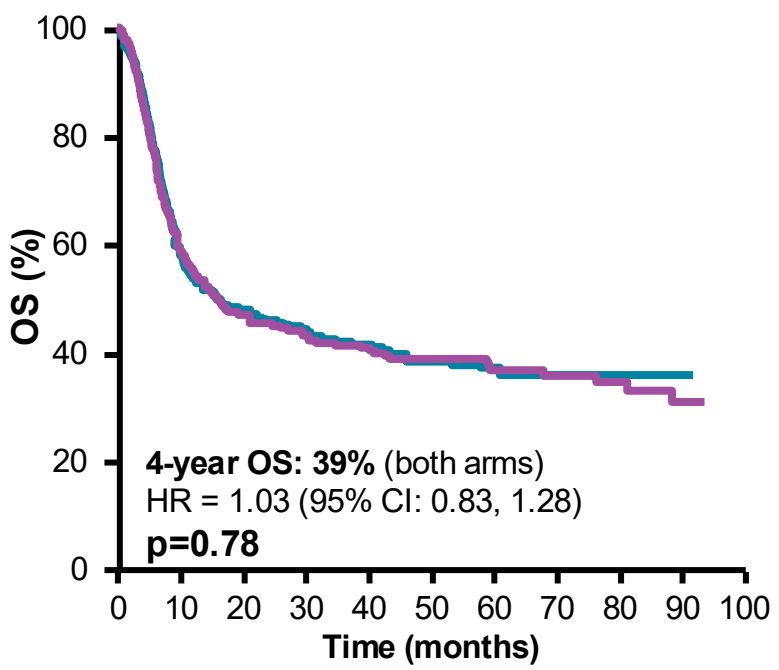
NCIC-CTG LY.12: Randomised Phase III study of outpatient GDP vs. standard DHAP[a] prior to ASCT in R/R aNHL (N=619)

(R[a])-DHAP (R[a])-GDP

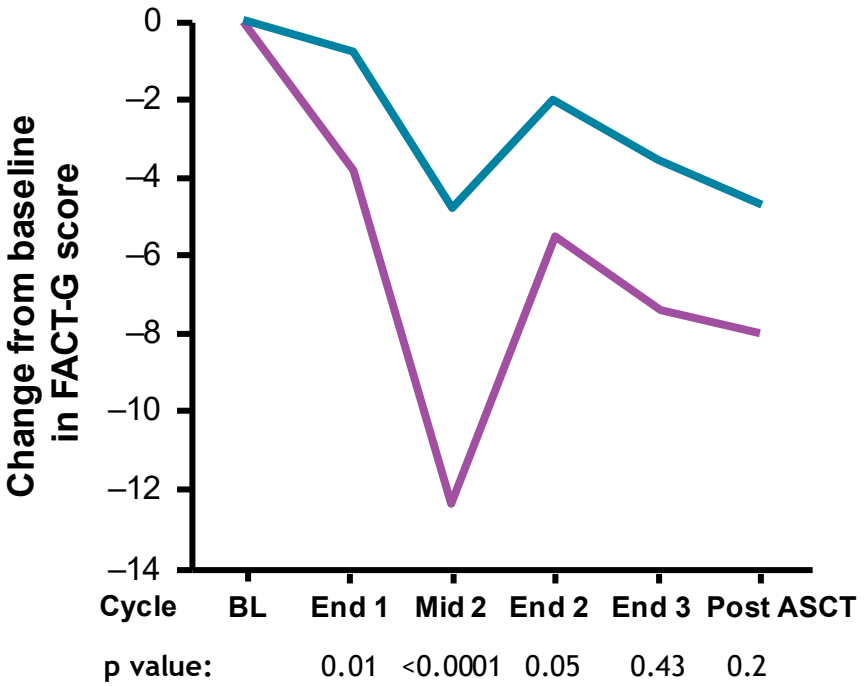
Progression-free survival



Overall survival



Change in quality of life

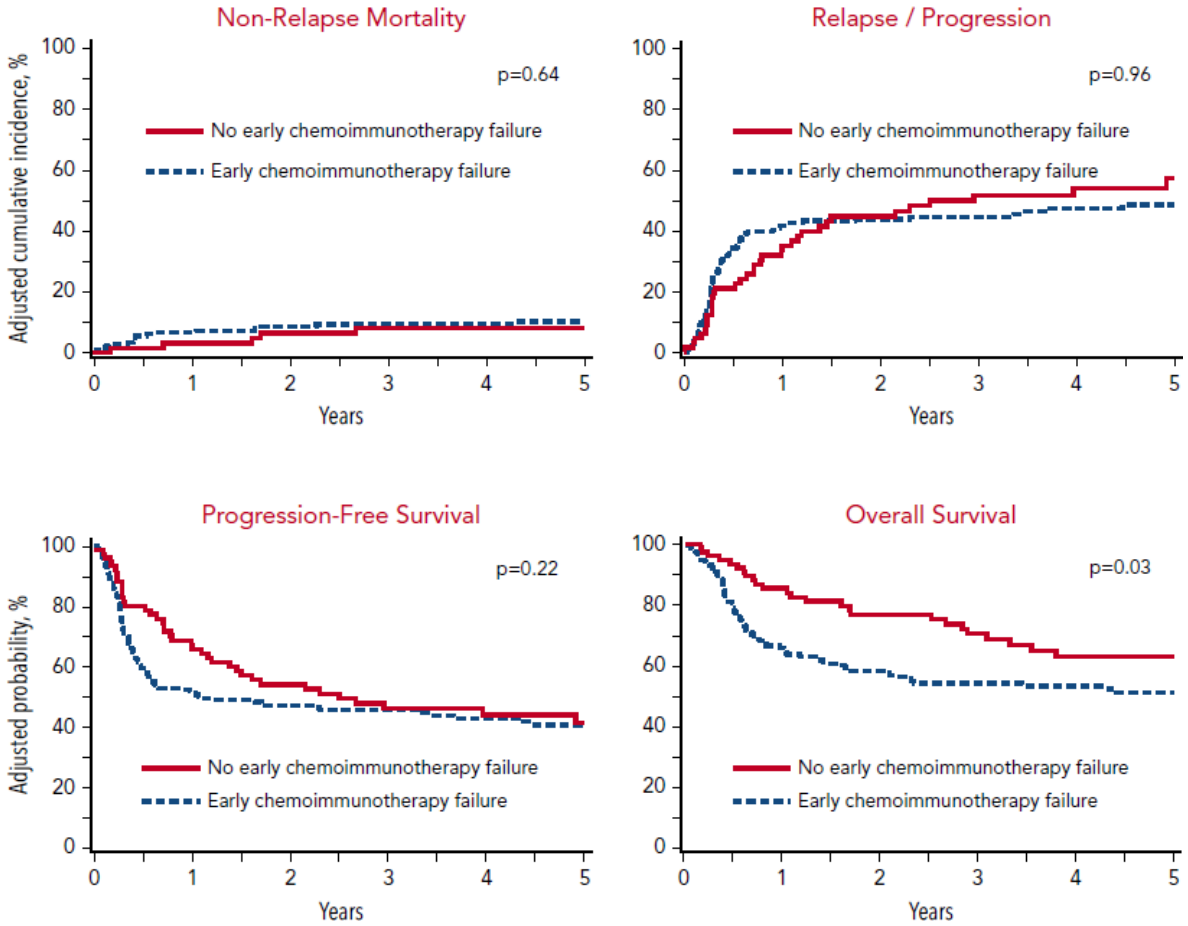


GDP RESULTED IN SIMILAR RATES OF TRANSPLANTATION, EFS AND OS TO STANDARD DHAP, WITH LESS TOXICITY, IMPAIRMENT OF QOL AND NEED FOR HOSPITALISATION

[a] Study regimens amended to include rituximab for pts with CD20+ disease from November 2005

Crump M, et al. J Clin Oncol 2014

Should ASCT be offered to patients in PET+ PR?



- CIBMTR (n = 249) relapsed DLBCL PET+ PR
- Included early chemotherapy failures (relapse within 12 months; n = 182)
  - 79% were primary refractory

	5-year
PFS	41%
OS	51%

- Cures with low NRM/modest cost

ASCT, autologous stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; DLBCL, diffuse large B-cell lymphoma; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease.

Shah N, et al. *Blood*. 2021, *Oncologist*. 2020

Polatuzumab plus rituximab and bendamustine

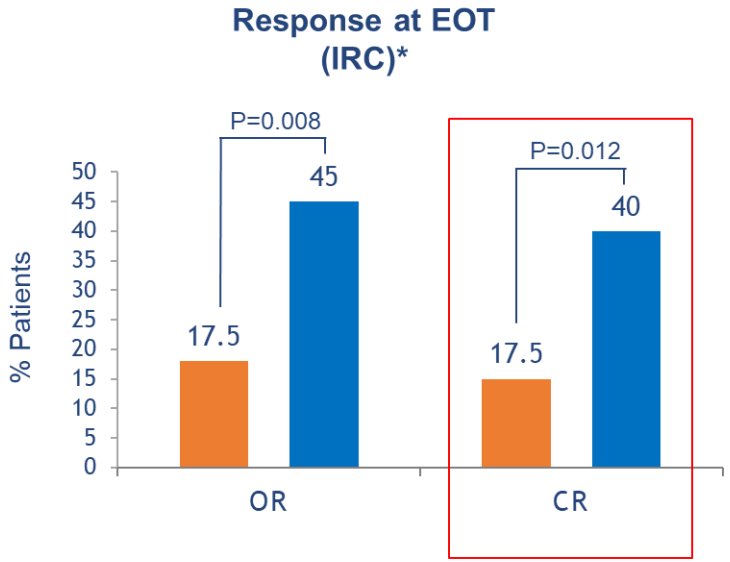
- Transplant ineligible R/R DLBCL
- ECOG 0-2
- Grade >1 peripheral neuropathy excluded

R 1:1

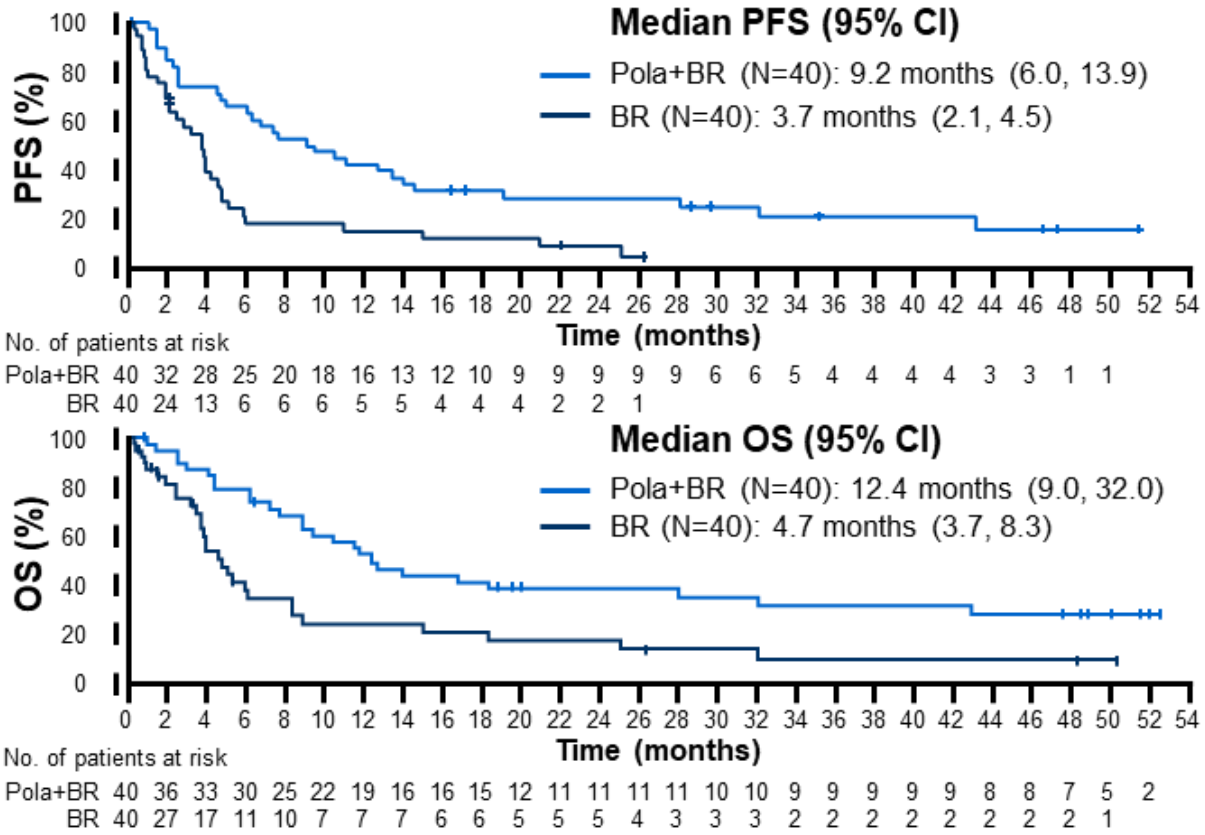
BR
x 6 cycles
(N=40)

Stratification
DOR ≤12 vs >12 months to last prior treatment

pola 1.8mg/kg + BR
x 6 cycles
(N=40)



*Primary endpoint



- Caution with bendamustine if CAR T-cell therapy is an option

Sehn LH et al, ASH; Dec 2020

Addition of bispecifics

STARGLO[1]

A Phase 3, open-label, randomized study of glofitamab + GemOx in R/R DLBCL

Patients (estimated enrollment N=270)

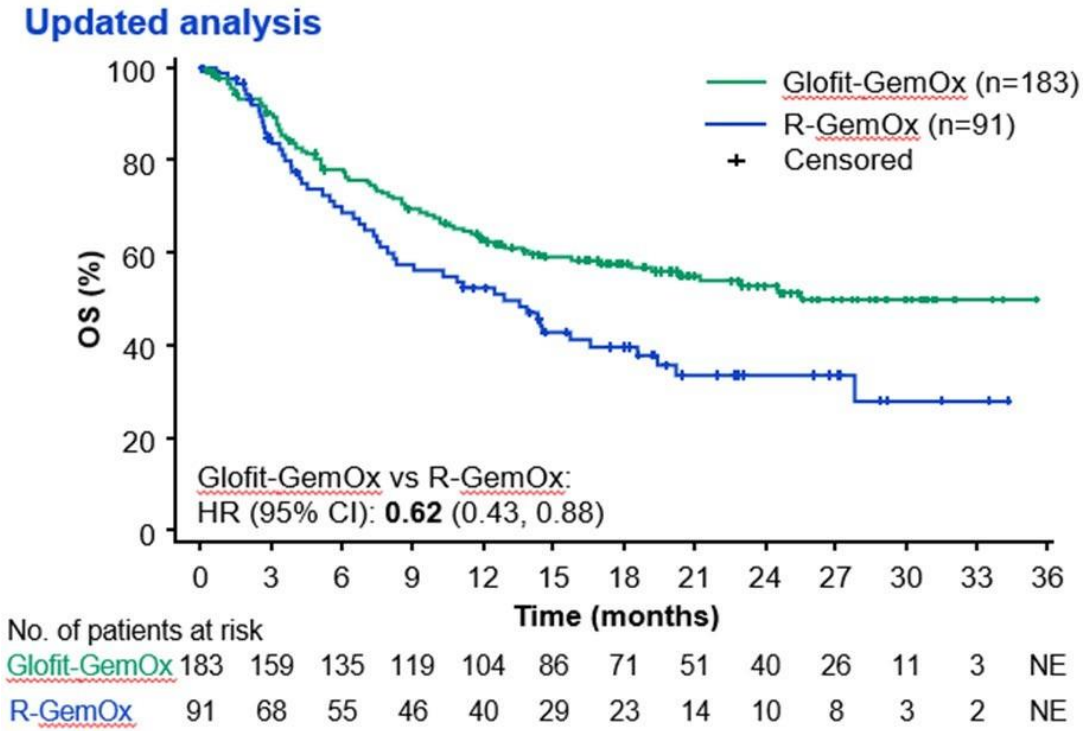
- ✓ R/R DLBCL after ≥1 prior therapy
- ✓ Age ≥18 years
- ✓ ECOG PS 0–2
- ✓ Ineligible for ASCT

R 2:1

- Glofitamab + GemOx
- R-GemOx
- Glofitamab monotherapy

Primary endpoint: OS

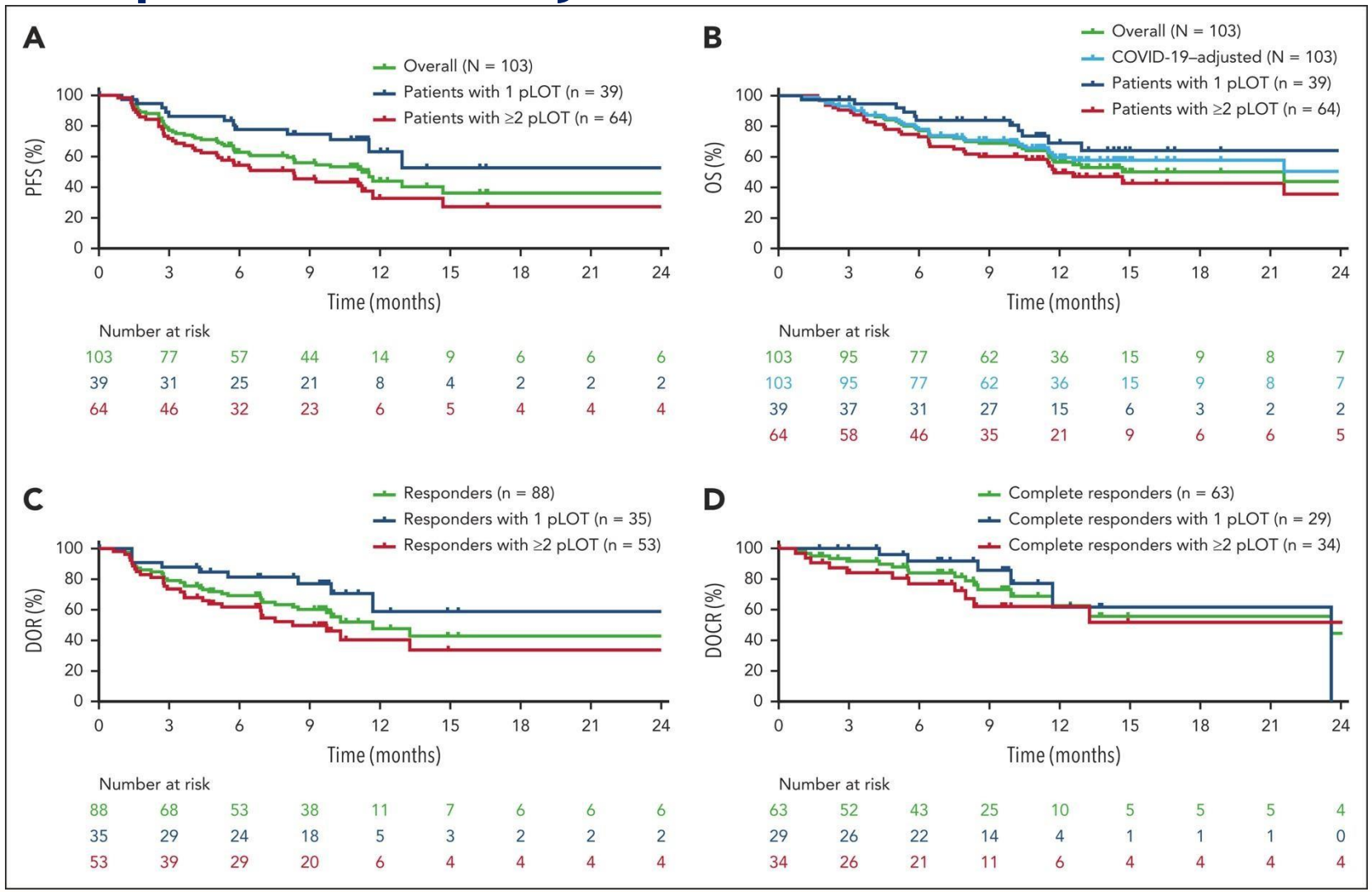
Secondary endpoints: PFS, CR, ORR, DoR, safety, tolerability



Hertzberg M et al, J Clin Oncol 2021
Abramson J, et al., EHA 2024

- First line studies (eg SKYGLO, EPCORE DLBCL-2, EPCORE NHL-5 (pola R-CHP + epcor), OLYMPIA 3
- For older patients ?chemotherapy free approaches with bispecific backbone

Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: EPCORE NHL-2 trial

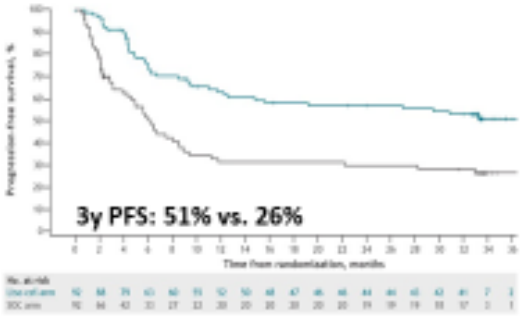


Brody et al, Blood 2025

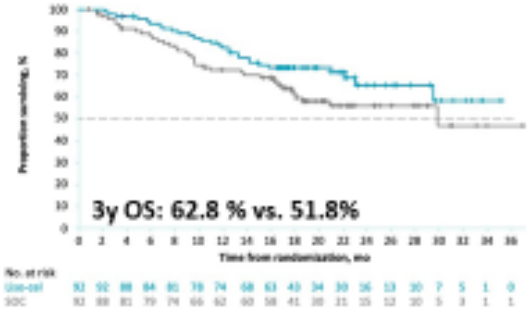
Liso-cel and Axi-cel are superior to chemotherapy as 2nd line therapy in primary refractory or early relapsed LBCL

Liso-cel vs. SOC in 2nd line

Median PFS NR vs. 6.2 mos
HR 0.422 (0.279—0.639)



Median OS NR vs. NR
HR 0.757 (0.481—1.191)



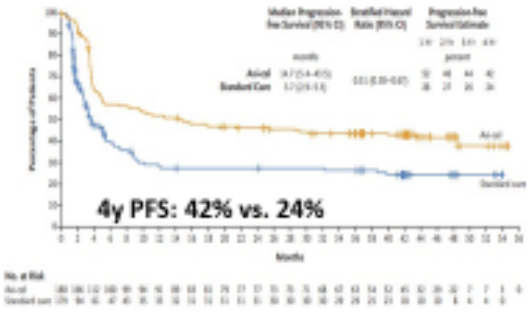
Improved QOL for Liso-cel over SOC by PRO

Toxicity	%
CRS	
Any grade	49
Grade 3	1
Neurotoxicity	
Any grade	11
Grade 3	4

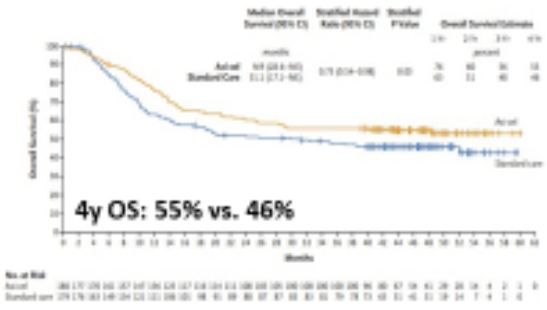
Abramson, et al. Proc EHA 2024

Axi-cel vs. SOC in 2nd line

Median PFS 14.7 vs. 3.7 mos
HR 0.51 (0.38-0.67)



Median OS NR vs. 31.1 mos
HR 0.73 (0.54-0.98)

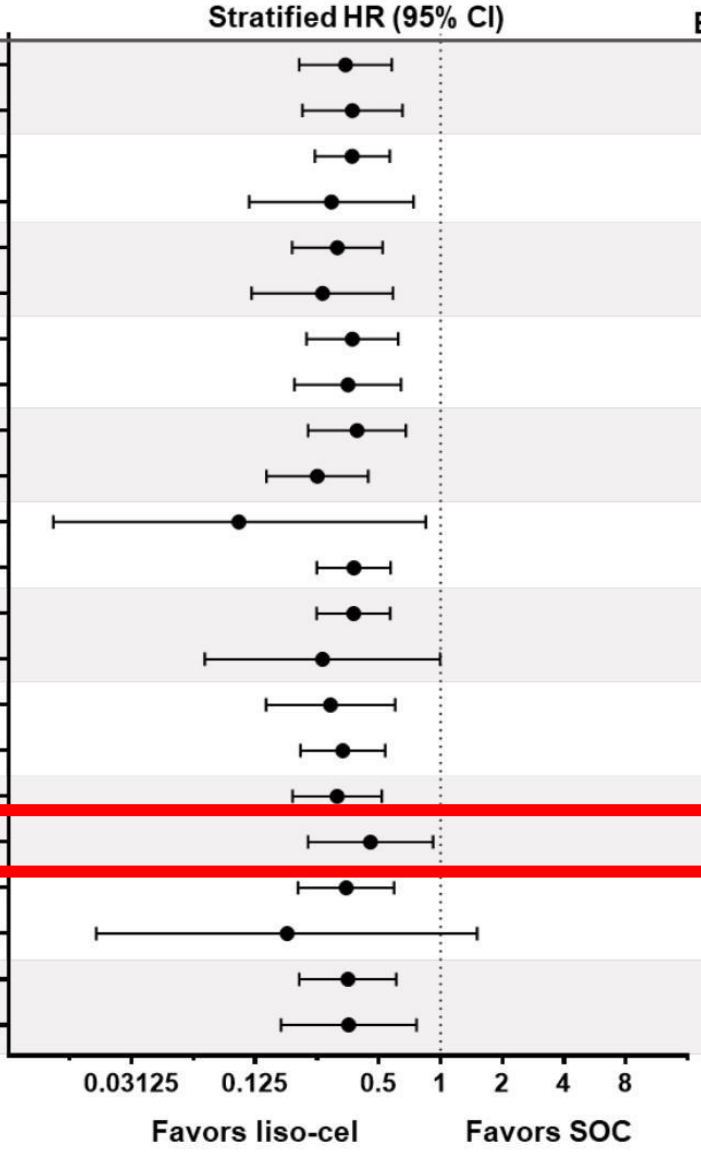


Improved QOL for Axi-cel over SOC by PRO

Toxicity	%
CRS	
Any grade	92
Grade ≥3	6
Neurotoxicity	
Any grade	60
Grade ≥3	21

Westin, et al. NEJM 2023

TRANSFORM Subset Analysis for EFS (ITT population)



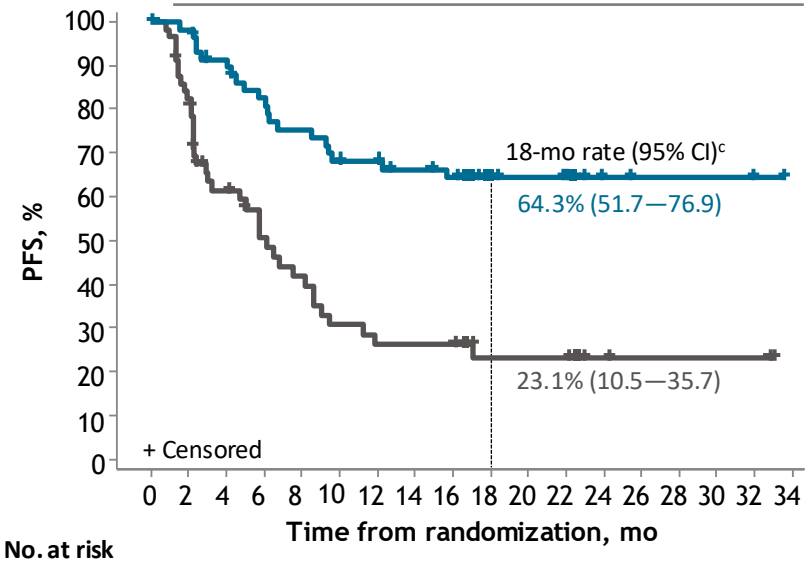
Subgroup	Events/patients (%)	Events/patients (%)	Stratified HR (95% CI)
sAAIPI: 0 or 1	23/56 (41)	39/55 (71)	0.344 (0.205–0.579)
sAAIPI: 2 or 3	21/36 (58)	32/37 (86)	0.372 (0.212–0.653)
Prior response status: refractory	37/67 (55)	57/70 (81)	0.371 (0.244–0.565)
Prior response status: relapse to last prior therapy	7/25 (28)	14/22 (64)	0.294 (0.117–0.739)
Age group, years: <65	23/56 (41)	51/67 (76)	0.314 (0.189–0.523)
Age group, years: ≥65 to <75	21/36 (58)	18/23 (78)	0.266 (0.120–0.586)
Sex: male	23/44 (52)	47/61 (77)	0.372 (0.222–0.622)
Sex: female	21/48 (44)	24/31 (77)	0.354 (0.194–0.643)
ECOG PS (at screening): 0	20/48 (42)	40/57 (70)	0.392 (0.226–0.678)
ECOG PS (at screening): 1	24/44 (55)	31/35 (89)	0.251 (0.142–0.444)
SPD: >50 cm^2	3/10 (30)	9/10 (90)	0.104 (0.013–0.848)
SPD: ≤50 cm^2	38/77 (49)	59/76 (78)	0.378 (0.250–0.572)
Lactate dehydrogenase: <500 unit/L	38/79 (48)	60/81 (74)	0.377 (0.249–0.569)
Lactate dehydrogenase: ≥500 unit/L	5/10 (50)	11/11 (100)	0.266 (0.071–0.995)
Prior CT response status: chemorefractory (PD, SD)	18/26 (69)	17/18 (94)	0.291 (0.141–0.602)
Prior CT response status: chemosensitive (PR, CR)	26/66 (39)	54/74 (73)	0.334 (0.208–0.537)
NHL type: DLBCL	[illegible]	[illegible]	[illegible]
NHL type: HGBCL	18/22 (82)	18/21 (86)	0.456 (0.226–0.921)
DLBCL subtype: DLBCL NOS de novo	23/53 (43)	39/50 (78)	0.347 (0.202–0.594)
DLBCL subtype: DLBCL transformed from indolent NHL	2/7 (29)	7/8 (87.5)	0.179 (0.021–1.507)
DLBCL subtype based on cell of origin: GCB	27/45 (60)	32/40 (80)	0.354 (0.205–0.609)
DLBCL subtype based on cell of origin: ABC, non-GCB	10/21 (48)	26/29 (90)	0.357 (0.167–0.764)

Abramson, et al. Blood 2023

TRANSFORM PFS by LBCL type (ITT set)

DLBCL

	Liso-cel arm (n = 60)	SOC arm (n = 58)
Median (95% CI)[a] PFS, mo	**NR** (NR—NR)	**6.0** (2.9—8.6)
HR (95% CI)[b]	0.306 (0.175—0.537)	

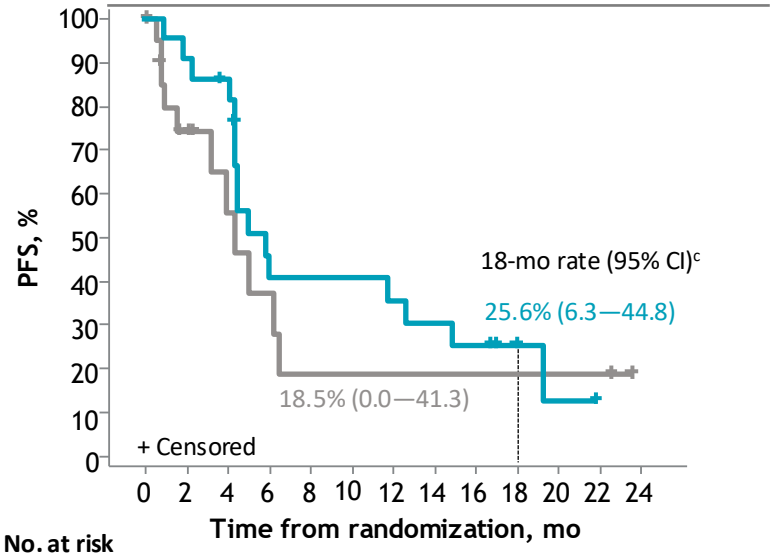


No. at risk

Liso-cel	60	58	51	45	42	38	37	34	32	17	15	13	4	2	2	2	2	0
SOC	58	44	30	23	19	14	12	12	12	7	7	7	3	2	2	2	2	0

HGBCL

	Liso-cel arm (n = 22)	SOC arm (n = 21)
Median (95% CI)[a] PFS, mo	**5.8** (4.3—14.8)	**4.3** (1.4—6.5)
HR (95% CI)[b]	0.659 (0.293—1.485)	

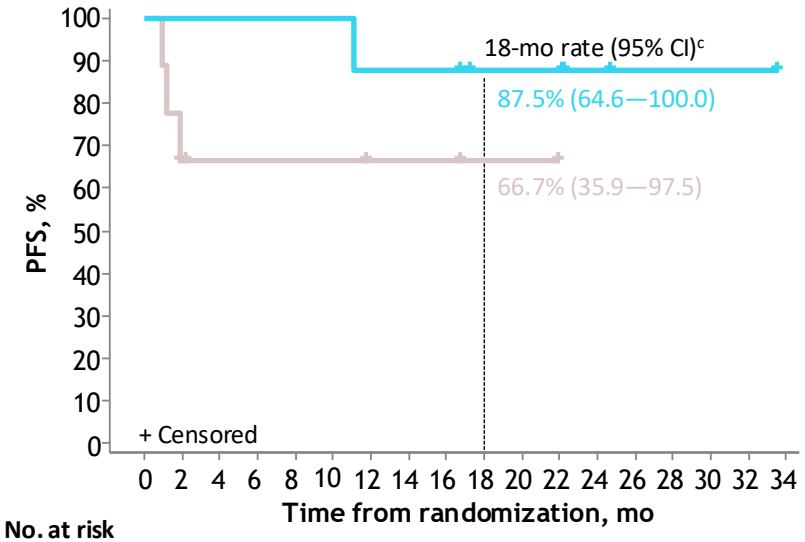


No. at risk

Liso-cel	22	20	18	8	8	8	7	6	5	3	1	0	
SOC	21	13	6	4	2	2	2	2	2	2	2	2	0

PMBCL

	Liso-cel arm (n = 8)	SOC arm (n = 9)
Median (95% CI)[a] PFS, mo	**NR** (11.0—NR)	**NR** (1.0—NR)
HR (95% CI)[b]	0.311 (0.031—3.165)	



No. at risk

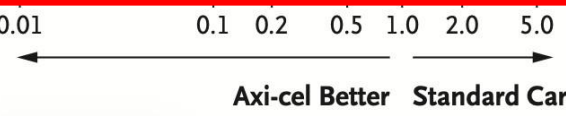
Liso-cel	8	8	8	8	8	8	7	7	7	4	4	4	2	1	1	1	1	0
SOC	9	5	3	3	3	3	2	2	2	1	1	0						

- Many patients were censored for PFS, and analyses were limited by small numbers in the HGBCL and PMBCL subgroups

Makita S, et al, JSH 2023

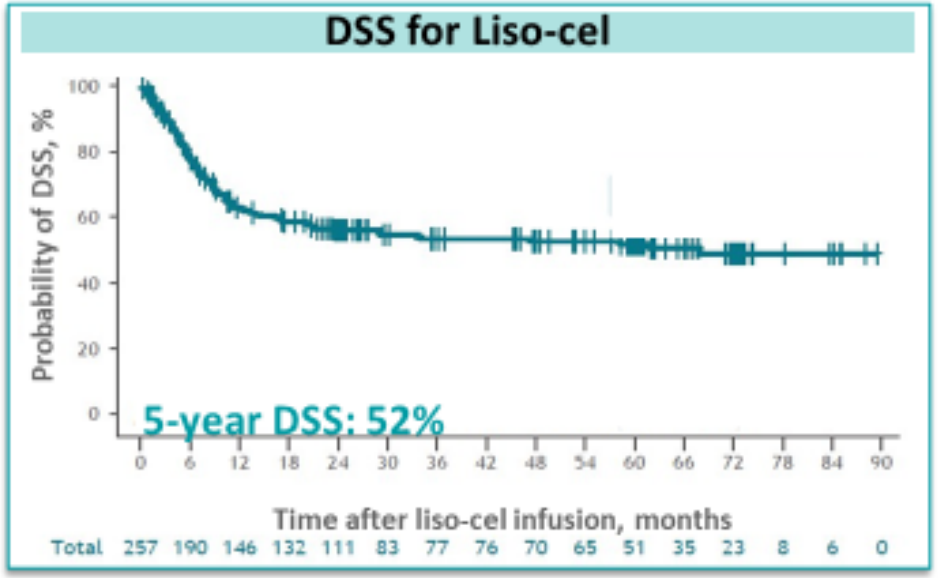
ZUMA-7 Subset Analysis for EFS

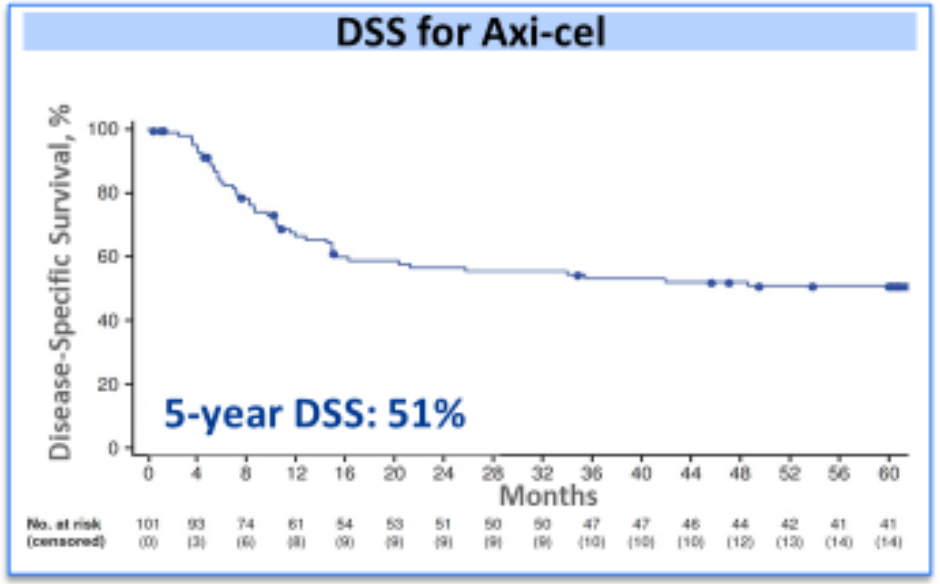
Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



Locke et al, NEJM 2021

CAR T-cells can CURE Large B-cell Lymphomas as 3rd line or later therapy: 5-year Follow up From ZUMA-1 and TRANSCEND





Liso-cel durable efficacy	
Overall response	73%
Complete response	53%
Median DOCR	NR at 5y
Median PFS	7 m
Median OS	28 m

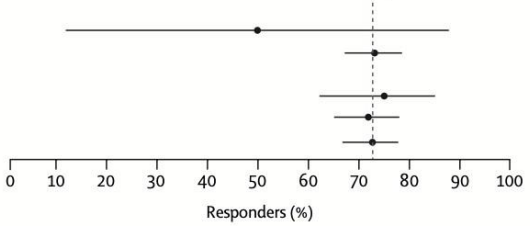
Axi-cel durable efficacy	
Overall response	74%
Complete response	54%
Median DOCR	62 m
Median PFS	6 m
Median OS	26 m

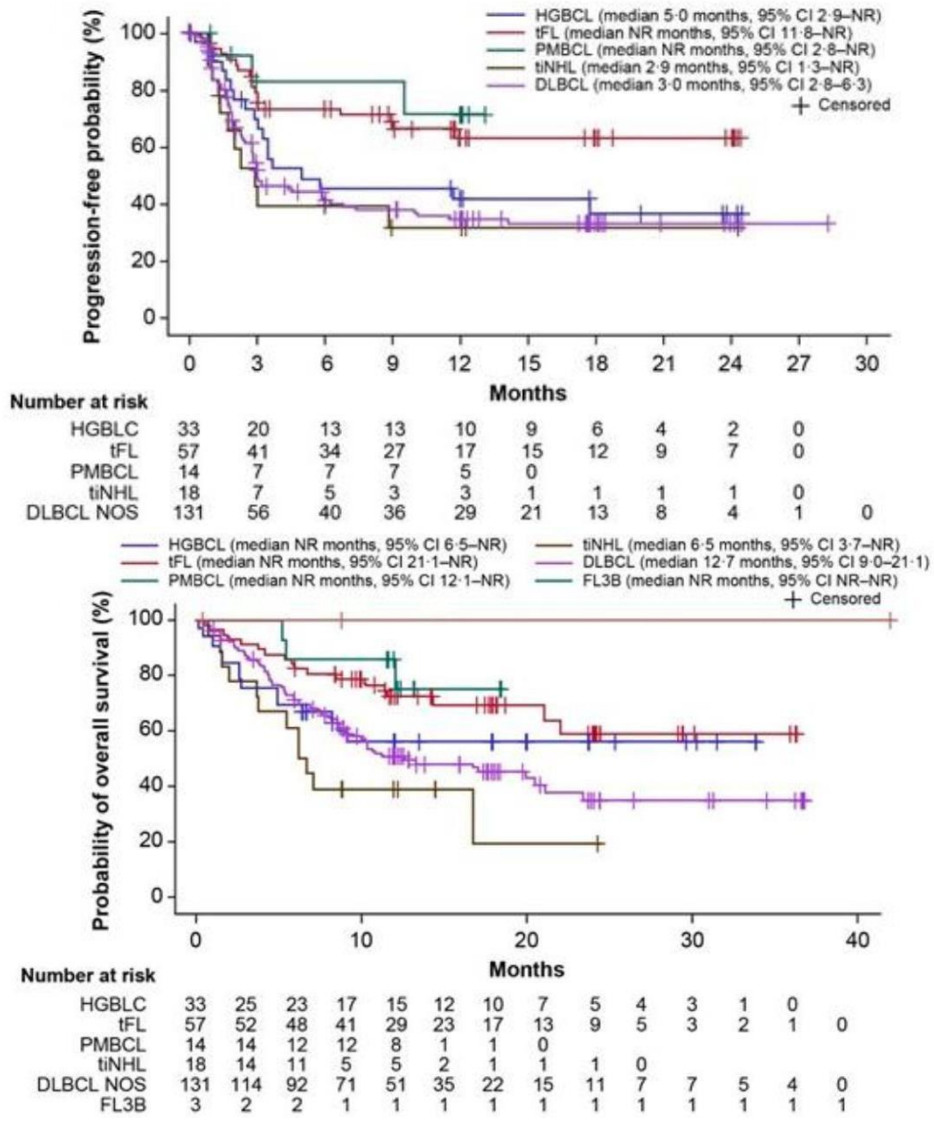
Abramson JS, et al. Proc ASH 2024.; Neelapu, et al. Blood 2023.

Direct comparison is not possible as these are clinical trials with different backgrounds

TRANSCEND: No difference between HGBCL and DLBCL

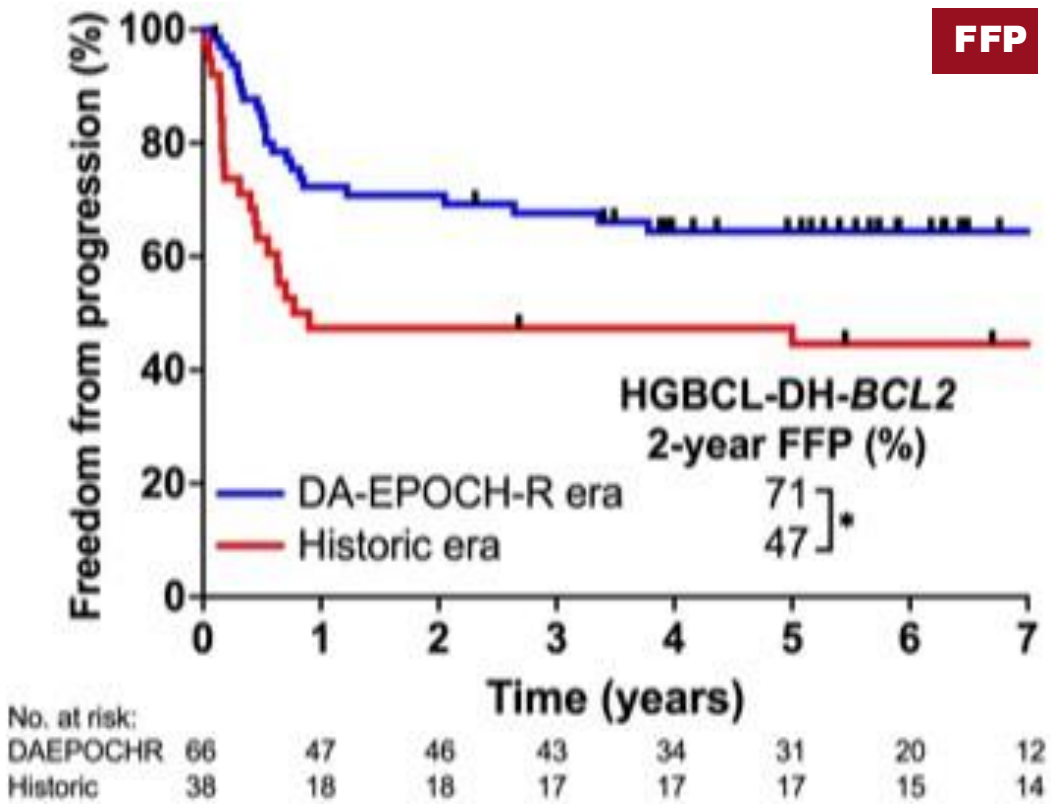
Objective response	Evaluable patients (n)	Patients with objective response (n)	Objective response rate (95% CI)
Dose level			
DL1	40	27	67·5 (50·9–81·4)
DL2	169	125	74·0 (66·7–80·4)
DL3	41	30	73·2 (57·1–85·8)
Age, years			
≥65	108	82	75·9 (66·7–83·6)
<65	148	104	70·3 (62·2–77·5)
Sex			
Male	169	125	74·0 (66·7–80·4)
NHL histology			
DLBCL NOS	131	89	67·9 (59·2–75·8)
HGBCL	33	25	75·8 (57·7–88·9)
Transformed iNHL	18	11	61·1 (35·7–82·7)
PMBCL	14	11	78·6 (49·2–95·3)
Bridging therapy			
Yes	150	101	67·3 (59·2–74·8)
No	106	85	80·2 (71·3–87·3)
SPD*			
≥50 cm²	70	43	61·4 (49·0–72·8)
<50 cm²	177	136	76·8 (69·9–82·8)
C-reactive protein†			
≥20 mg/L	146	101	69·2 (61·0–76·5)
<20 mg/L	109	84	77·1 (68·0–84·6)
Response to last therapy‡			
Refractory	203	141	69·5 (62·6–75·7)
Relapsed	53	45	84·9 (72·4–93·3)
Chemotherapy response			
Refractory	171	120	70·2 (62·7–76·9)
Sensitive	85	66	77·6 (67·3–86·0)
HSCT			
Yes	87	68	78·2 (68·0–86·3)
No	169	118	69·8 (62·3–76·6)
Lactate dehydrogenase			
≥500 U/L	57	36	63·2 (49·3–75·6)
<500 U/L	199	150	75·4 (68·8–81·2)
Secondary CNS lymphoma			
Yes	6	3	50·0 (11·8–88·2)
No	250	183	73·2 (67·3–78·6)
Comorbidities§			
Yes	60	45	75·0 (62·1–85·3)
No	196	141	71·9 (65·1–78·1)
Overall	**256**	**186**	**72·7 (66·8–78·0)**

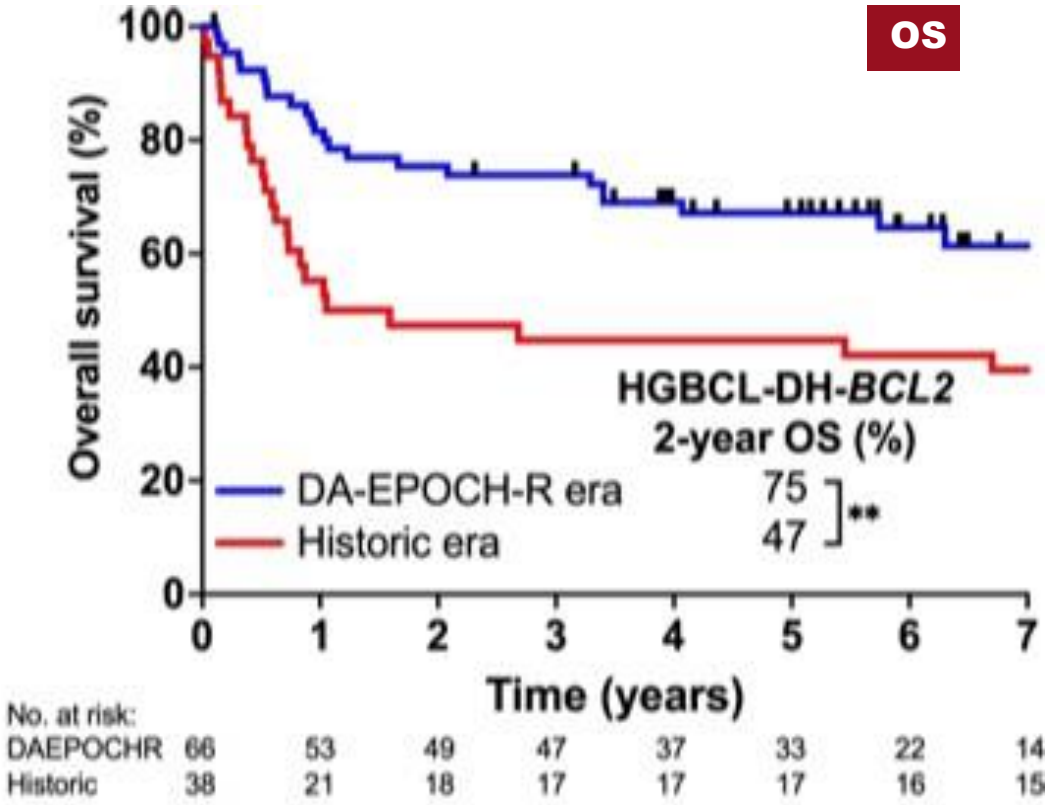




Abramson JS, et al. Lancet 2000

British Columbia Experience





No significant improvement with FFP and OS in DLBCL (NOS) patients across eras

Alduaij et al, Blood Advances 2025

Anti-CD20/CD3 Bispecific antibodies for 3rd line+ LBCL

Glofitamab

Fixed duration IV therapy for 12 cycles

Baseline Characteristics	N=154
Median age (range)	66 (21-90)
Median prior tx (range)	3 (2-7)
Prior ASCT	28 (18%)
Prior CAR	51 (33%)
Refractory to last tx	132 (86%)

Best response
ORR: 52%
CRR: 39%
Median DoR: 18.4 mo
Median PFS: 4.9 mo
CRS 63% (gr≥3, 4%)

11 HGBCL
2 PR, no CR

Epcoritamab

Continuous SC therapy

Baseline Characteristics	N=157
Median age (range)	64 (20-83)
Median prior tx (range)	3 (2-11)
Prior ASCT	31 (20%)
Prior CAR	61 (39%)
Refractory to last tx	130 (83%)

Best response
ORR: 63%
CRR: 39%
Median DoR: 12.0 mo
Median PFS: 4.4 mo
CRS 50% (gr≥3, 2.5%)

9 HGBCL, 13 DHL
"consistent with DLBCL"

Odronextamab

Continuous IV therapy

Baseline Characteristics	N=127
Median age (range)	67 (24-88)
Median prior tx (range)	2 (2-8)
Prior ASCT	16%
Double/triple hit	20%
Refractory to last tx	86%

Best response
ORR: 52%
CRR: 32%
Median DoR: 10.0 mo
Median PFS: 4.4 mo
CRS 55% (gr≥3, 4%)

11 DHL
Response NR

Dickinson, et al. NEJM 2022; Thieblemont, et al.,JCO 2023

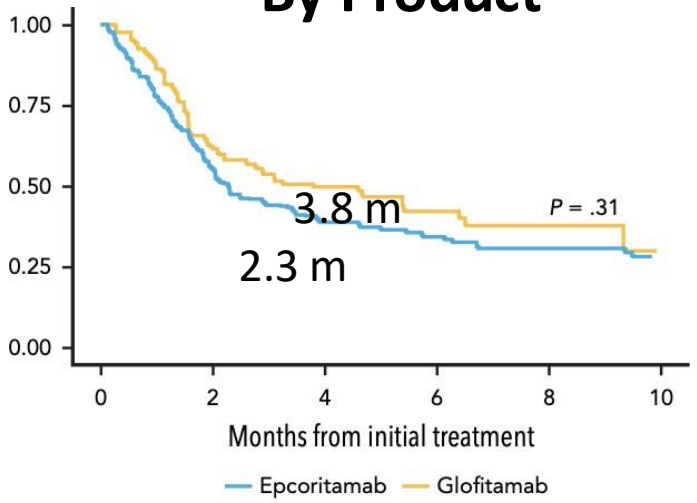
Bispecifics in LBCL: Real World Data

By Product

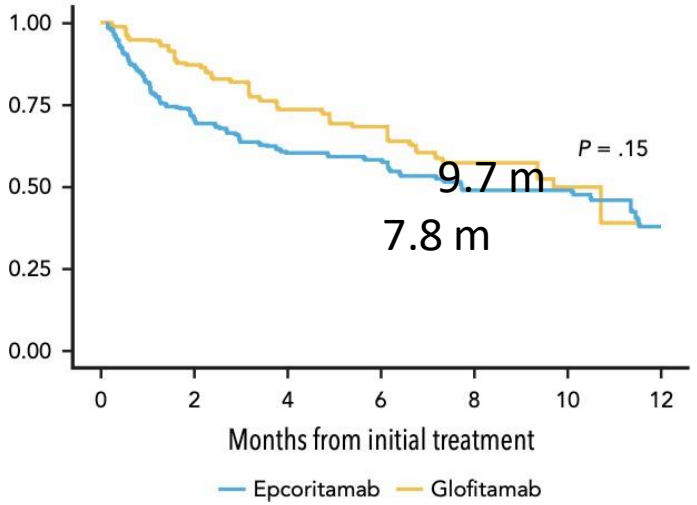
CR rate

Glofit 30%
Epco 23%

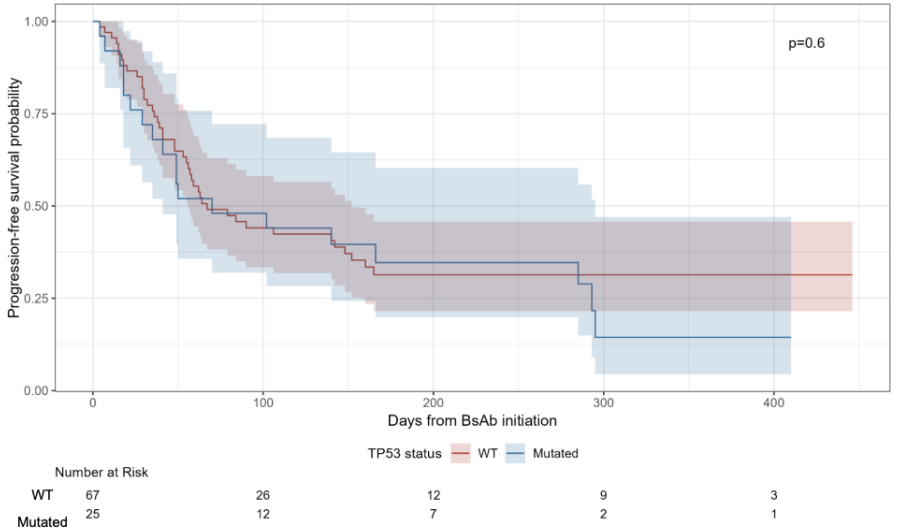
PFS

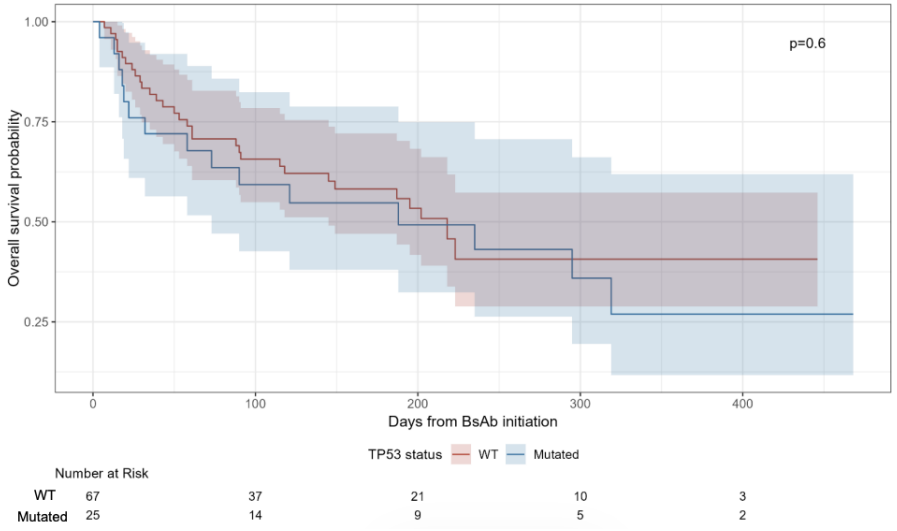


OS



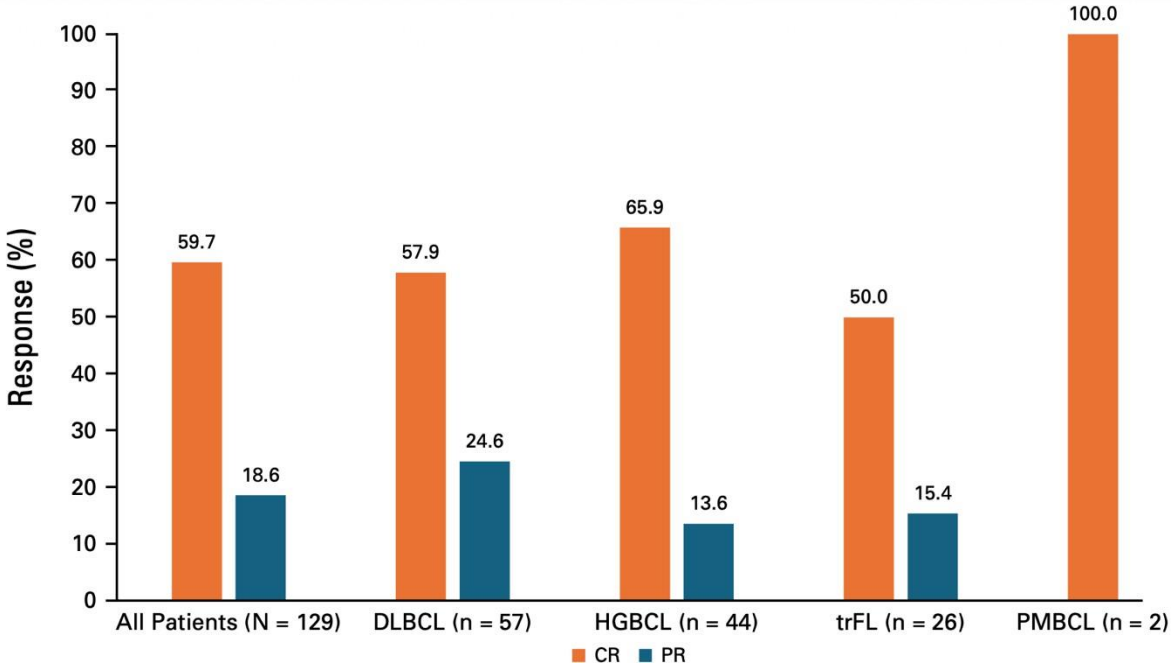
By TP53 mut

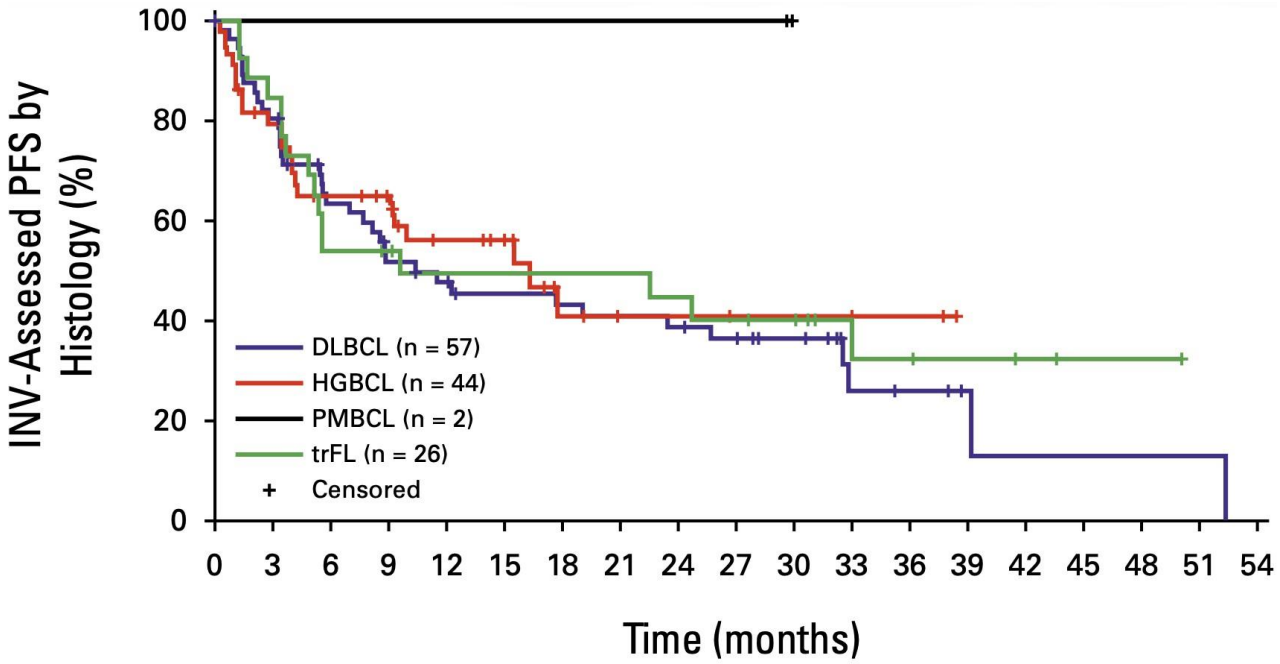




Brooks, et al. Blood 2025

Glofitamab-Polatuzumab in Relapsed/Refractory LBCL subsets



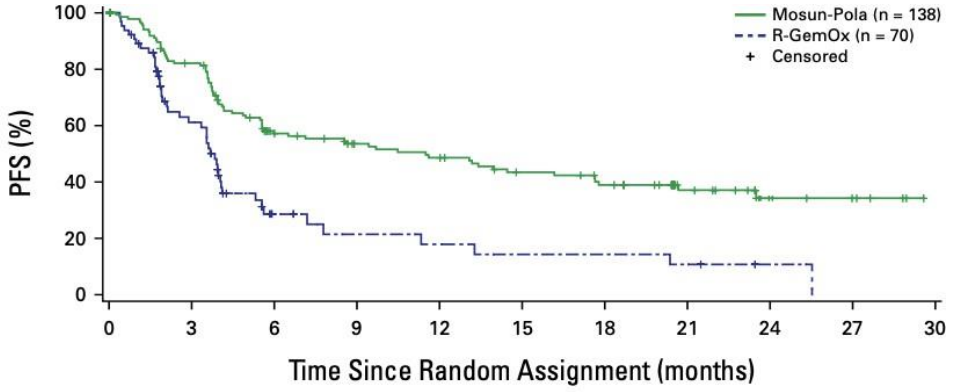


Number at risk

DLBCL	57	45	33	26	23	20	19	18	17	15	12	5	4	2	1	1	1	1	NE
HGBCL	44	33	26	23	17	14	7	4	4	3	3	2	2	NE	NE	NE	NE	NE	NE
PMBCL	2	2	2	2	2	2	2	2	2	2	NE	NE	NE	NE	NE	NE	NE	NE	NE
trFL	26	22	14	13	11	11	11	11	10	9	8	5	4	3	2	1	1	NE	NE

Hutchings, et al. JCO 2025

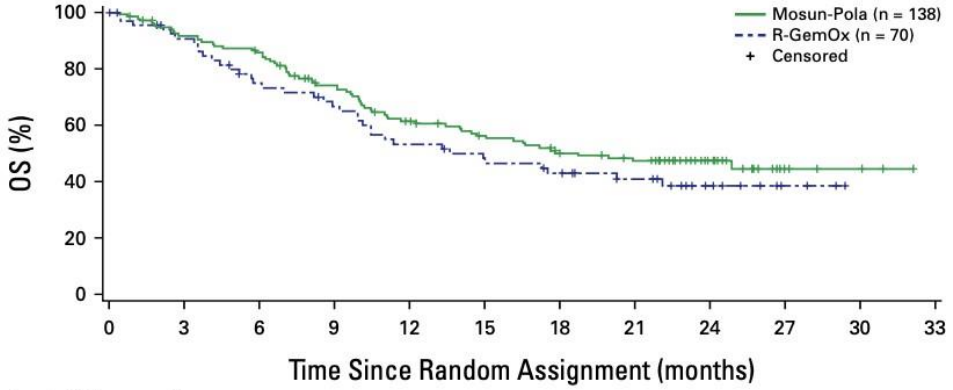
Mosun-Pola in LBCL: SUNMO trial



Number at risk (censored)

Mosun-Pola	138 (0)	108 (6)	65 (17)	54 (24)	49 (24)	40 (28)	34 (30)	20 (43)	8 (54)	5 (57)	NE
R-GemOx	70 (0)	33 (14)	9 (22)	6 (23)	5 (23)	4 (23)	4 (23)	3 (23)	1 (25)	NE	NE

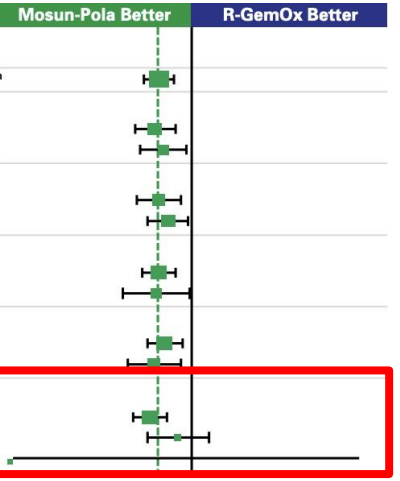
C



Number at risk (censored)

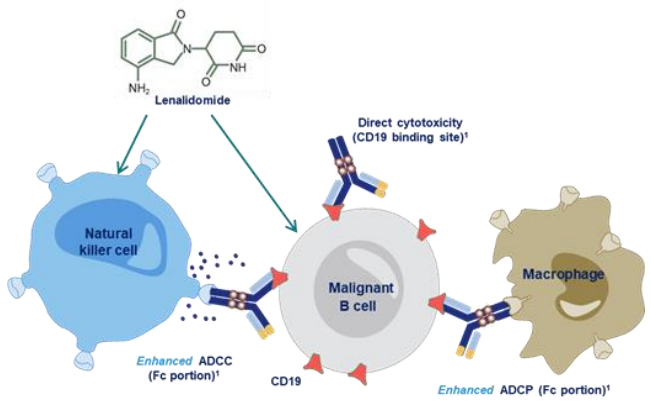
Mosun-Pola	138 (0)	122 (5)	113 (6)	93 (11)	75 (13)	65 (17)	55 (20)	50 (22)	24 (48)	5 (66)	3 (68)	NE
R-GemOx	70 (0)	58 (6)	46 (8)	40 (9)	32 (9)	27 (10)	24 (11)	19 (15)	11 (22)	3 (30)	NE	NE

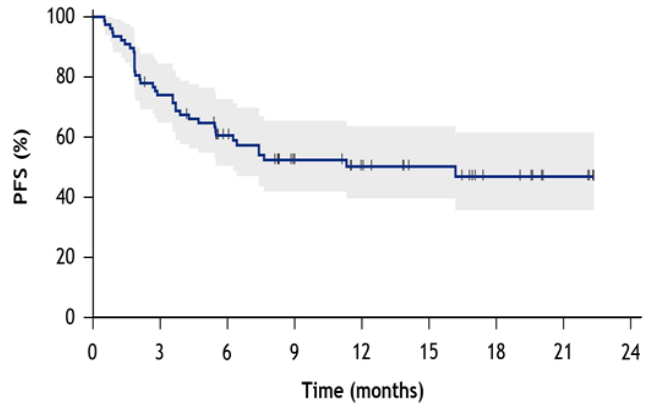
		Mosun-Pola (n = 138)			R-GemOx (n = 70)				
Baseline risk factors	Total No.	No.	Events	Median (months)	No.	Events	Median (months)	HR	95% CI
All patients	208	138	76	11.5	70	45	3.8	0.41	(0.28 to 0.61)[a]
Age group (years)									
<65	122	84	46	11.5	38	25	3.5	0.39	(0.23 to 0.64)
≥65	86	54	30	13.1	32	20	4.0	0.47	(0.27 to 0.84)
No. of previous lines of therapy									
1	91	61	32	14.5	30	22	3.6	0.38	(0.22 to 0.67)
≥2	117	77	44	8.6	40	23	3.9	0.49	(0.29 to 0.82)
Status of last previous therapy									
Refractory	145	97	63	5.5	48	36	2.6	0.39	(0.26 to 0.60)
Relapse	63	41	13	NE	22	9	11.3	0.37	(0.16 to 0.88)
Status of first previous therapy									
Refractory	121	79	54	4.2	42	31	2.6	0.46	(0.29 to 0.72)
Relapse	87	59	22	23.5	28	14	5.6	0.35	(0.18 to 0.70)
NHL subtype									
DLBCL	163	109	58	11.5	54	34	3.5	0.38	(0.24 to 0.59)
HGBCL	40	26	18	9.7	14	9	4.0	0.78	(0.35 to 1.77)
FL3b	5	3	0	NE	2	2	12.0	<0.01	(0.00 to NE)



Budde, et al. JCO 2025

Tafasitamab (MOR208) and lenalidomide





Number of patients at risk

PFS	81	56	38	26	20	15	9	4

ORR was 58% (ITT analysis)
CR rate was 33% (investigator-assessed)

Median follow-up duration of 12 months

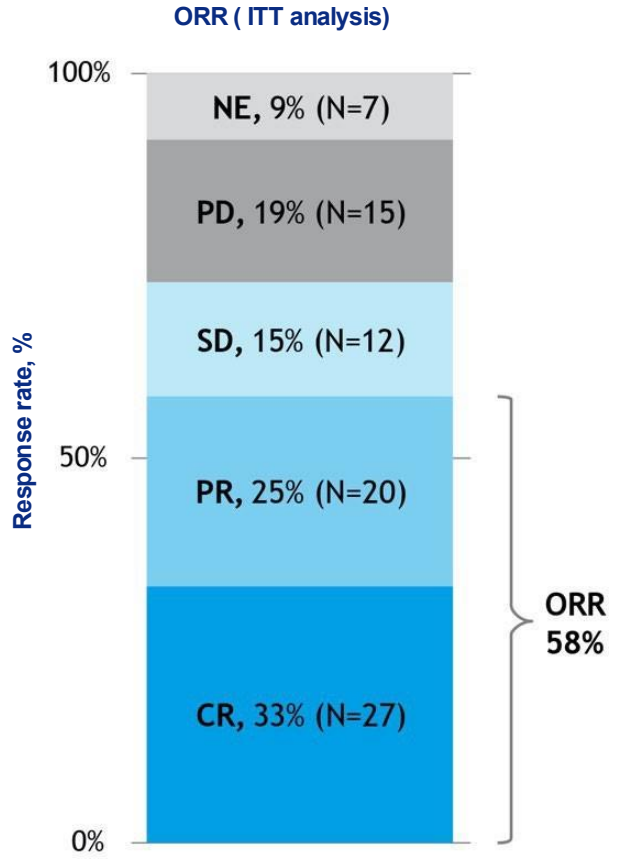
Median duration of response

was not reached

n=81 Demographics

Important: no PD within 6/12, no DHL/THL

	PFS
Median	16.2 mo.
12 month PFS rate	50.1% (39.5–63.6)

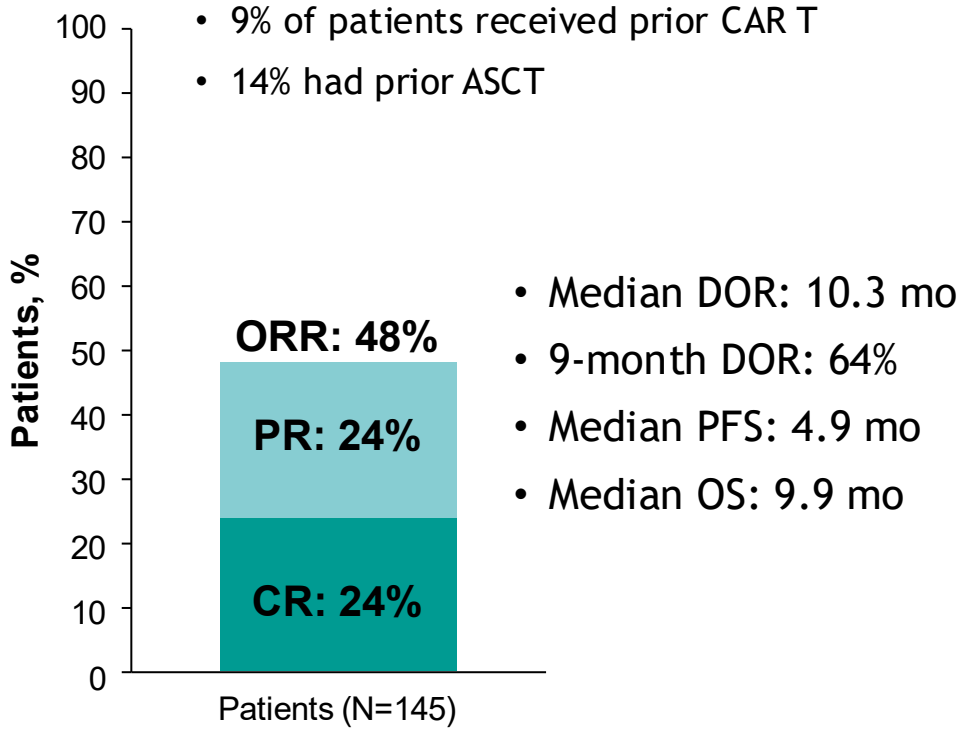


Salles G, et al. Blood 2018

LOTIS-2 Phase 2 Trial
Loncastuximab Teserine in 3L+ DLBCL

Eligibility
- Aged ≥18 years
- R/R DLBCL
- ≥2 prior regimens
- Prior CAR T permitted (persistent CD19 expression required)

Lonca IV as 30-min infusion
In 21-d cycles
C1-2: 150 µg/kg Q3W
C3+: 75 µg/kg Q3W for up to 1 year or PD/unacceptable toxicity



- 9% of patients received prior CAR T
- 14% had prior ASCT

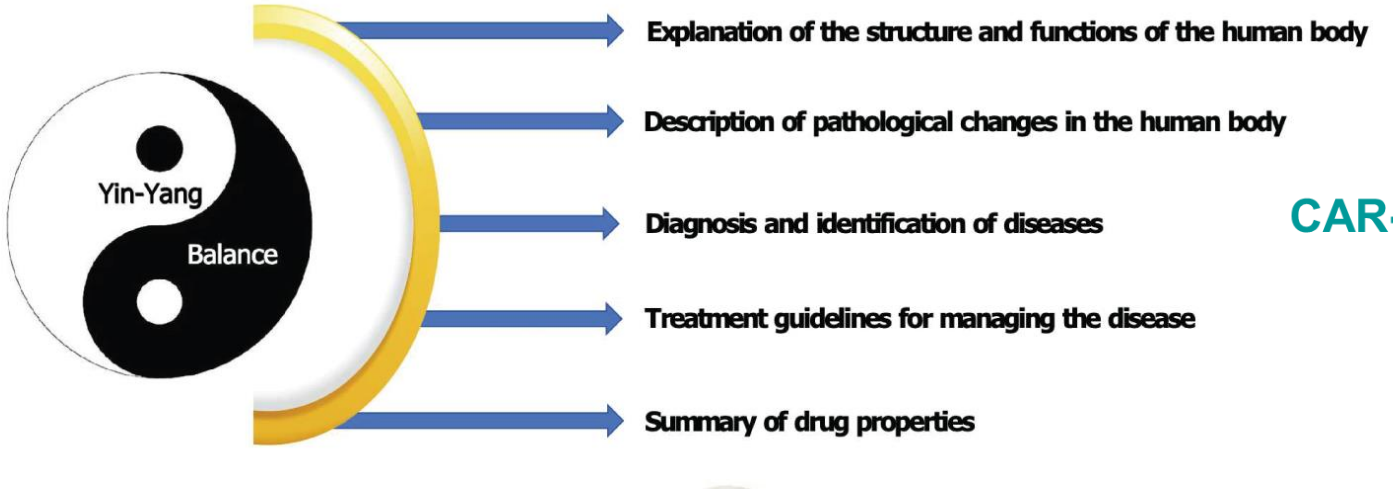
- Median DOR: 10.3 mo
- 9-month DOR: 64%
- Median PFS: 4.9 mo
- Median OS: 9.9 mo

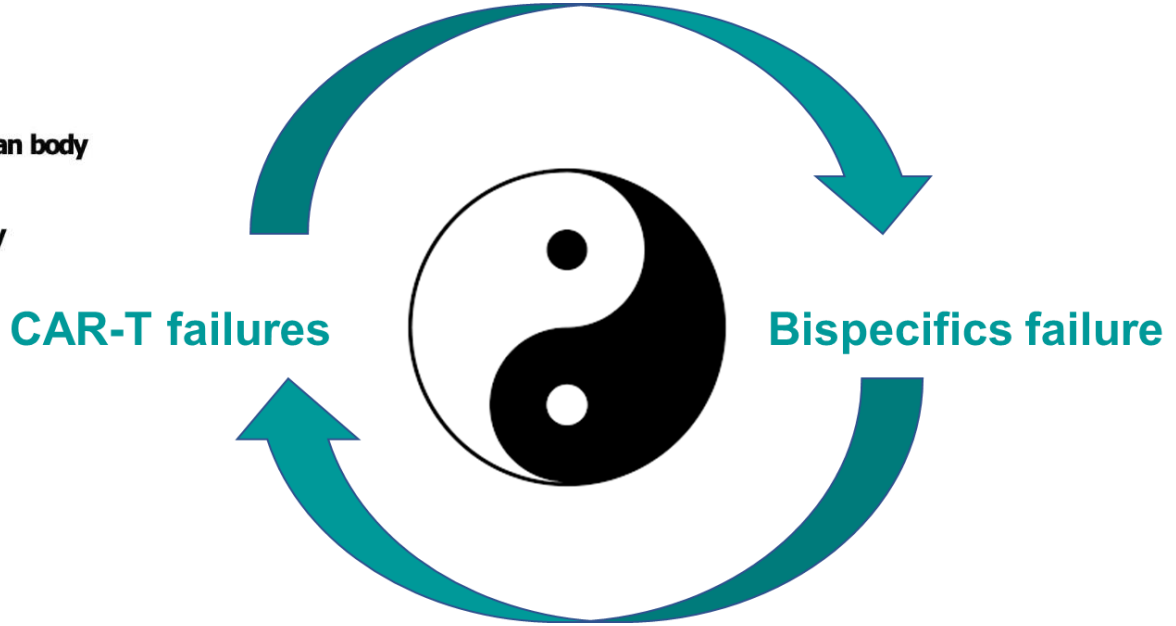
Most Common TEAEs (≥20% Any Grade or ≥5% Grade ≥3)

Patients, %	Patients (N=145)	
	Grade 1-2	Grade 3-4
Neutropenia	14	26
GGT increased	24	16
Thrombocytopenia	15	18
Anemia	16	10
Fatigue	26	1
Nausea	23	0
Cough	21	1
Peripheral edema	19	1
Blood alkaline phosphatase increased	19	1
Hypophosphatemia	10	6
Leukopenia	6	9
Lymphopenia	2	6

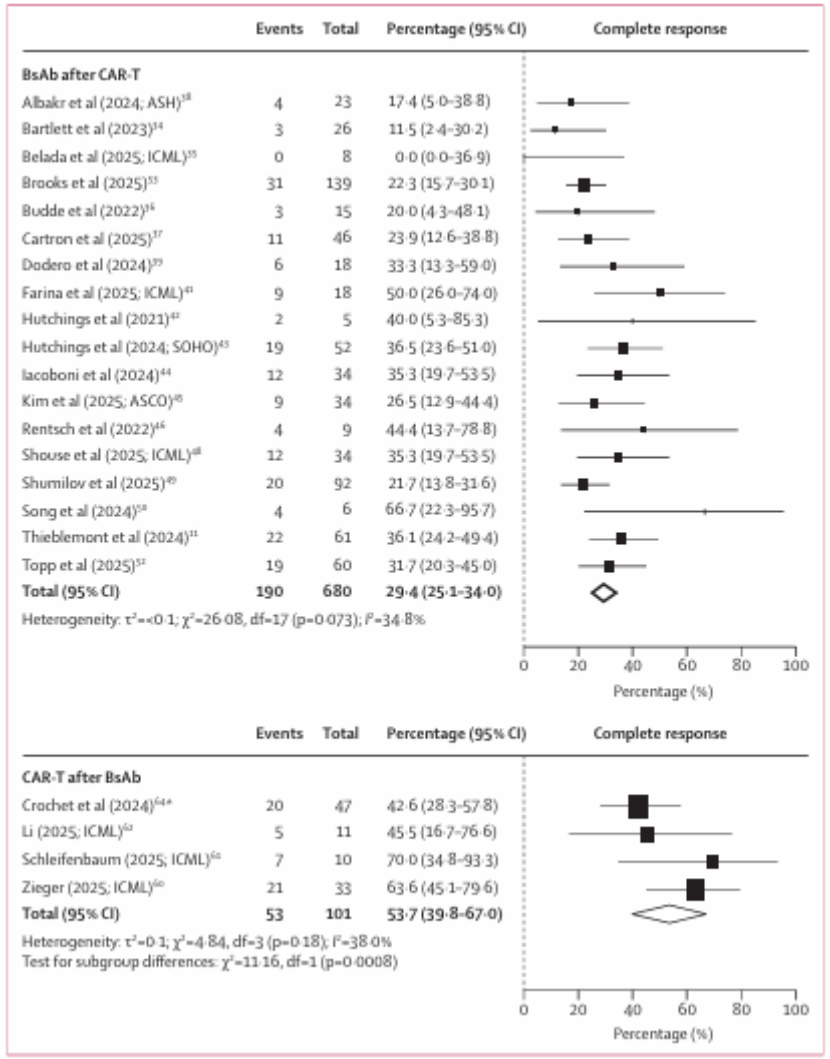
Caimi P et al, *Lancet Oncol* 2021

T-Cell Redirection: a "*yin and yang problem*" to optimize ≥3L treatments in RR-LBCL





Sequencing BsAb ⟺ CAR-T



	Events	Total	Percentage (95% CI)
BsAb after CAR-T			
Albakr et al (2024; ASH)[38]	4	23	17·4 (5·0–38·8)
Bartlett et al (2023)[34]	3	26	11·5 (2·4–30·2)
Belada et al (2025; ICML)[35]	0	8	0·0 (0·0–36·9)
Brooks et al (2025)[55]	31	139	22·3 (15·7–30·1)
Budde et al (2022)[36]	3	15	20·0 (4·3–48·1)
Cartron et al (2025)[37]	11	46	23·9 (12·6–38·8)
Dodero et al (2024)[39]	6	18	33·3 (13·3–59·0)
Farina et al (2025; ICML)[41]	9	18	50·0 (26·0–74·0)
Hutchings et al (2021)[42]	2	5	40·0 (5·3–85·3)
Hutchings et al (2024; SOHO)[43]	19	52	36·5 (23·6–51·0)
Iacoboni et al (2024)[44]	12	34	35·3 (19·7–53·5)
Kim et al (2025; ASCO)[45]	9	34	26·5 (12·9–44·4)
Rentsch et al (2022)[46]	4	9	44·4 (13·7–78·8)
Shouse et al (2025; ICML)[48]	12	34	35·3 (19·7–53·5)
Shumilov et al (2025)[49]	20	92	21·7 (13·8–31·6)
Song et al (2024)[58]	4	6	66·7 (22·3–95·7)
Thieblemont et al (2024)[51]	22	61	36·1 (24·2–49·4)
Topp et al (2025)[52]	19	60	31·7 (20·3–45·0)
Total (95% CI)	**190**	**680**	**29·4 (25·1–34·0)**

Heterogeneity: τ^2=<0·1; χ^2=26·08, df=17 (p=0·073); I^2=34·8%

Complete response

0 20 40 60 80 100

Percentage (%)

	Events	Total	Percentage (95% CI)
CAR-T after BsAb			
Crochet et al (2024)[64a]	20	47	42·6 (28·3–57·8)
Li (2025; ICML)[62]	5	11	45·5 (16·7–76·6)
Schleifenbaum (2025; ICML)[61]	7	10	70·0 (34·8–93·3)
Zieger (2025; ICML)[60]	21	33	63·6 (45·1–79·6)
Total (95% CI)	**53**	**101**	**53·7 (39·8–67·0)**

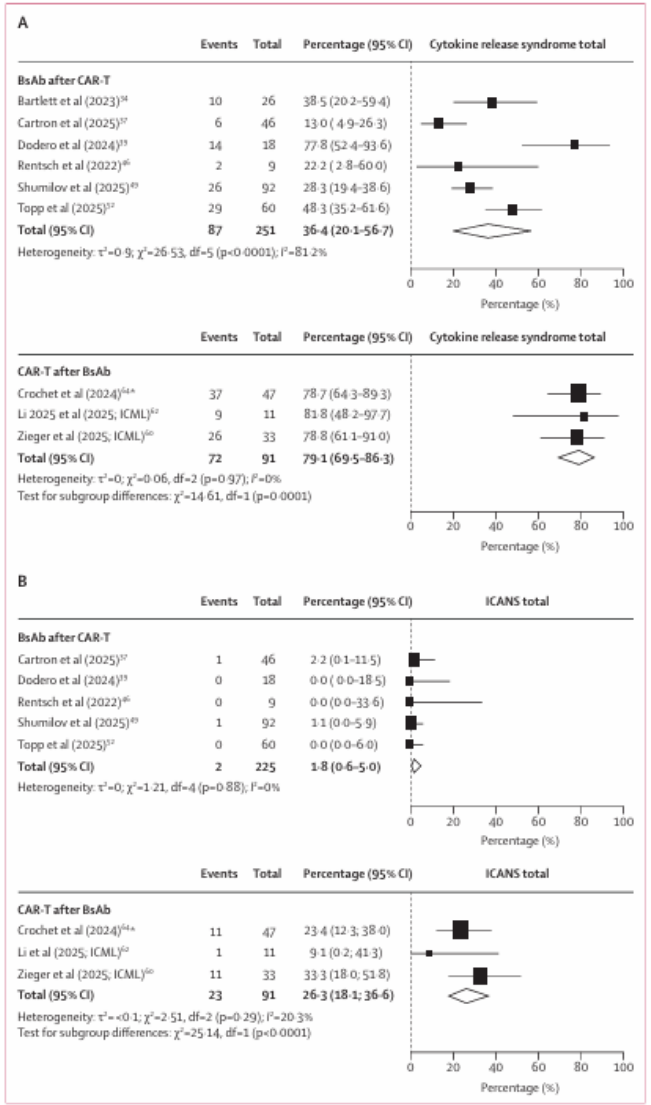
Heterogeneity: τ^2=0·1; χ^2=4·84, df=3 (p=0·18); I^2=38·0%
Test for subgroup differences: χ^2=11·16, df=1 (p=0·0008)

Complete response

0 20 40 60 80 100

Percentage (%)

Pooled complete response rates for patients treated with BsAb monotherapy after CAR-T and CAR-T after BsAb monotherapy



A

	Events	Total	Percentage (95% CI)
BsAb after CAR-T			
Bartlett et al (2023)[34]	10	26	38·5 (20·2–59·4)
Cartron et al (2025)[37]	6	46	13·0 (4·9–26·3)
Dodero et al (2024)[39]	14	18	77·8 (52·4–93·6)
Rentsch et al (2022)[46]	2	9	22·2 (2·8–60·0)
Shumilov et al (2025)[49]	26	92	28·3 (19·4–38·6)
Topp et al (2025)[52]	29	60	48·3 (35·2–61·6)
Total (95% CI)	**87**	**251**	**36·4 (20·1–56·7)**

Heterogeneity: τ^2=0·9; χ^2=26·53, df=5 (p<0·0001); I^2=81·2%

Cytokine release syndrome total

0 20 40 60 80 100

Percentage (%)

	Events	Total	Percentage (95% CI)
CAR-T after BsAb			
Crochet et al (2024)[64a]	37	47	78·7 (64·3–89·3)
Li 2025 et al (2025; ICML)[62]	9	11	81·8 (48·2–97·7)
Zieger et al (2025; ICML)[60]	26	33	78·8 (61·1–91·0)
Total (95% CI)	**72**	**91**	**79·1 (69·5–86·3)**

Heterogeneity: τ^2=0; χ^2=0·06, df=2 (p=0·97); I^2=0%
Test for subgroup differences: χ^2=14·61, df=1 (p=0·0001)

Cytokine release syndrome total

0 20 40 60 80 100

Percentage (%)

B

	Events	Total	Percentage (95% CI)
BsAb after CAR-T			
Cartron et al (2025)[37]	1	46	2·2 (0·1–11·5)
Dodero et al (2024)[39]	0	18	0·0 (0·0–18·5)
Rentsch et al (2022)[46]	0	9	0·0 (0·0–33·6)
Shumilov et al (2025)[49]	1	92	1·1 (0·0–5·9)
Topp et al (2025)[52]	0	60	0·0 (0·0–6·0)
Total (95% CI)	**2**	**225**	**1·8 (0·6–5·0)**

Heterogeneity: τ^2=0; χ^2=1·21, df=4 (p=0·88); I^2=0%

ICANS total

0 20 40 60 80 100

Percentage (%)

	Events	Total	Percentage (95% CI)
CAR-T after BsAb			
Crochet et al (2024)[64a]	11	47	23·4 (12·3–38·0)
Li et al (2025; ICML)[62]	1	11	9·1 (0·2–41·3)
Zieger et al (2025; ICML)[60]	11	33	33·3 (18·0–51·8)
Total (95% CI)	**23**	**91**	**26·3 (18·1–36·6)**

Heterogeneity: τ^2=<0·1; χ^2=2·51, df=2 (p=0·29); I^2=20·3%
Test for subgroup differences: χ^2=25·14, df=1 (p<0·0001)

ICANS total

0 20 40 60 80 100

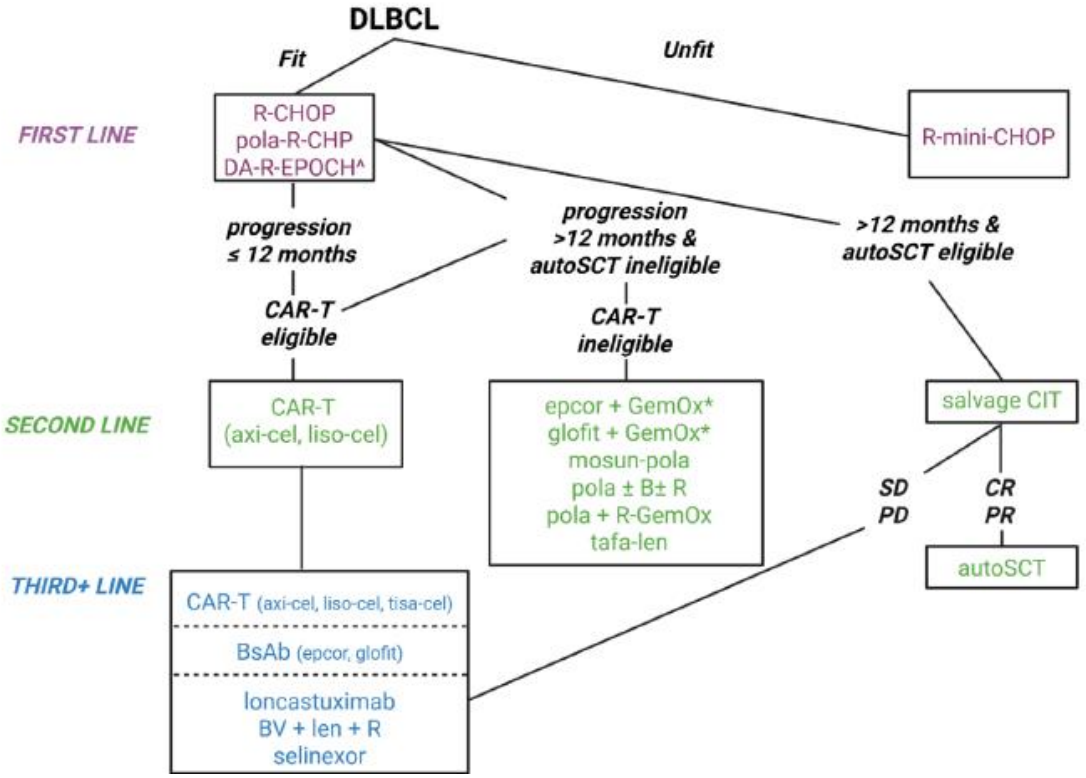
Percentage (%)

Pooled adverse events for patients treated with BsAb monotherapy after CAR-T and CAR-T after BsAb monotherapy for CRS (A) and ICANS (B)

Sorin, Lancet Hematology 2026

2026 Update on the Management of Diffuse Large B-Cell Lymphoma

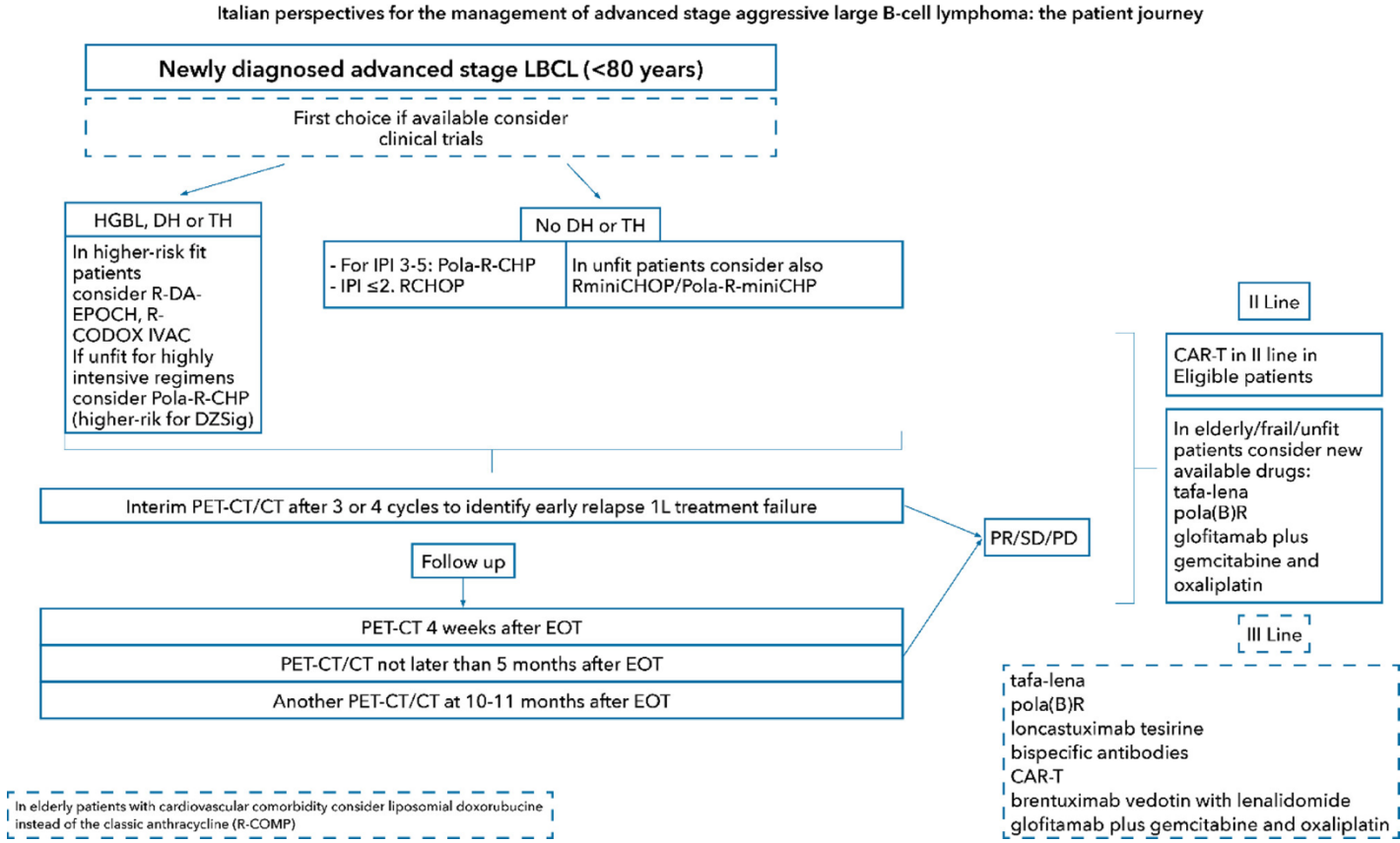
Elise A. Chong[1,2] | Emily B. Tomasulo[1,2] | Stefan K. Barta[1,2]



American Journal of Hematology, 2026; 101:832–863
https://doi.org/10.1002/ajh.70229

Defining and Addressing the Current Unmet Medical Needs for the Frontline Treatment of Advanced Stage Aggressive Large B-Cell Lymphoma: A Perspective From an Ad Hoc Panel of Italian Experts

Antonio Pinto[1] | Carmelo Carlo-Stella[2,3] | Monia Marchetti[4] | Caterina Patti[5] | Annalisa Arcari[6] | Nicola Di Renzo[7] | Marco Laddetto[8] | Maurizio Martelli[9] | Pier Luigi Zinzani[10,11]



Hematological Oncology, 2025; 43:e70152
https://doi.org/10.1002/hon.70152

The Most Important slide....

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