

4th edition

Unmet challenges in high risk hematological malignancies: from bedside to clinical practice


Turin, March 26-27, 2026

Starhotels Majestic

Scientific board:

Marco Ladetto (Alessandria)

Umberto Vitolo (Candiolo-TO)



Molecularly driven vs agnostic treatment
strategies in first line DLBCL: **agnostic**

Maria Gomes da Silva

Disclosures of Maria Gomes da Silva

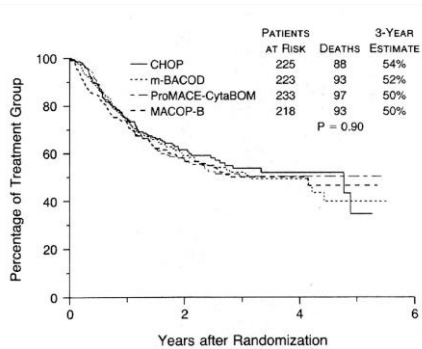
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Travel support
AstraZeneca	X						
Roche						X	X
Johnson & Johnson			X			X	X
Lilly			X			X	
Decera Clinical Education			X				
Gilead	X						X
Abbvie							X
BeOne			X				

Agnostic front line approaches to LBCL: chemoimmunotherapy

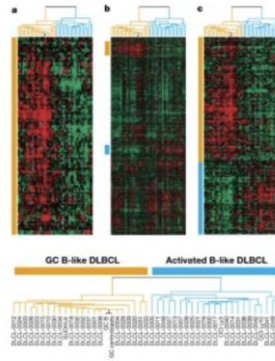
1993

2000

2002

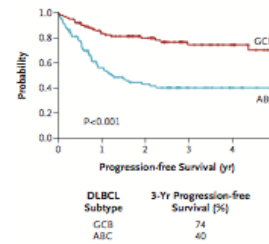
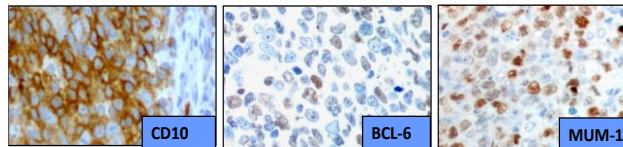


Fisher N Engl J Med 1993;328:1002-1006

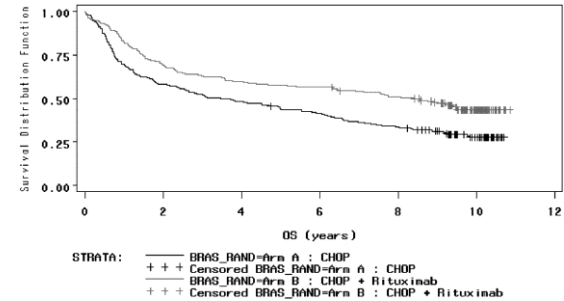


Alizadeh A et al, Nature 2000, **403**:503–511

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



RCHOP: Long term survival ~ 60%



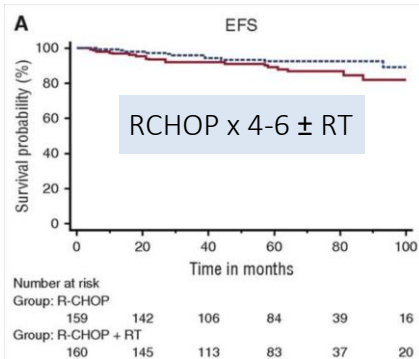
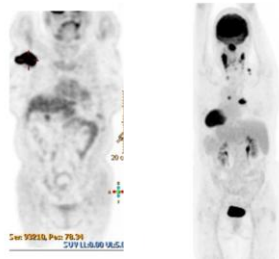
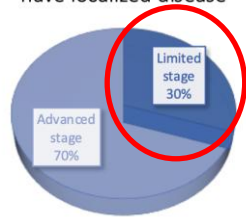
Coiffier B et al *Blood* (2010) 116 (12): 2040–2045

Still 30-40% patients not cured with RCHOP: **what do we need to change and why?**

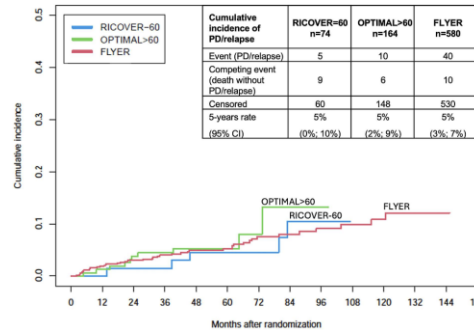
- Outcomes of conventional chemoimmunotherapy are suboptimal for a proportion of patients
 - The first line treatment **for young, clinically high risk** patients requires improvement
 - Biological high risk** groups do poorly with conventional therapy
 - The therapeutic choices for **elderly/frail** are unsatisfactory
 - We increasingly recognize the biological heterogeneity of DLBCL and identify possible vulnerabilities
 - New, mostly immune (**agnostic**) therapies proved effective at relapse and are moving into first line
-
- And what we probably **do not need to change**: the (**agnostic**) approach to low risk patients

R-CHOP is very effective in patients with low risk disease

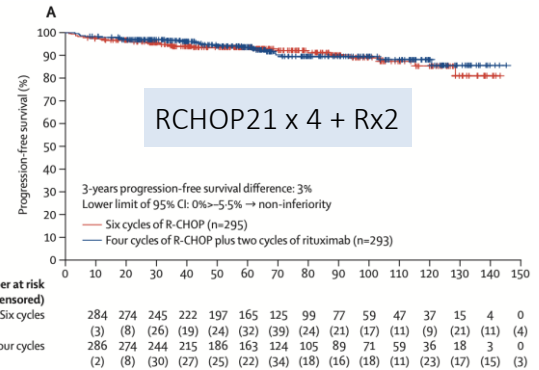
One third of patients have localized disease



Lamy T et al, Blood. 2018; 131:174-181

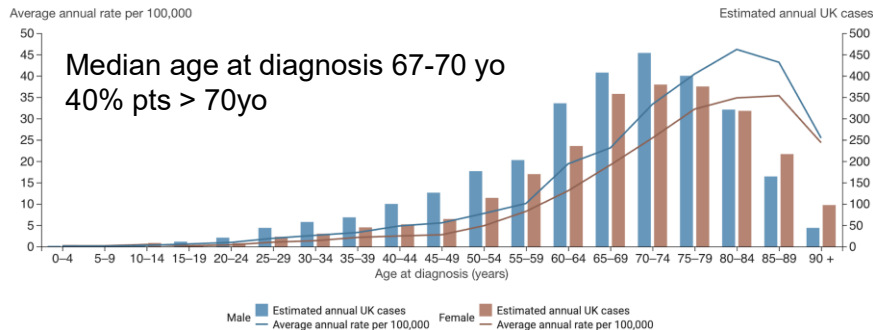


Thurner L et al. Hematological Oncology 2025, pg 202

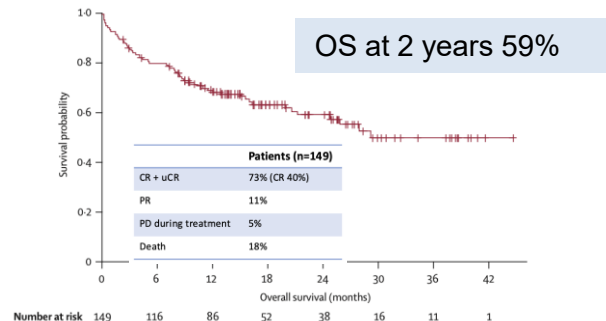


Poeschel V et al, Lancet 2019; 394: 2271-81

What about high risk patients? The case for the elderly/unfit



HMRN. https://hmrn.org/factsheets#large_cell_lymphomas.



Peyrade et al, Lancet Oncol. 2011 May;12(5):460-8.

Improving outcomes:
clinical trials building
on
chemimmunotherapy

R-miniCHOP + 5azacytidine ph2/3
NCT04799275

R-miniCHOP vs Pola R-miniCHOP ph3
POLAR BEAR (NCT04332822)

R-miniCHOP + acalabrutinib
(ARCHED / GLA 2022-1) NCT05820841

ZR2 vs R-miniCHOP (NCT05179733)

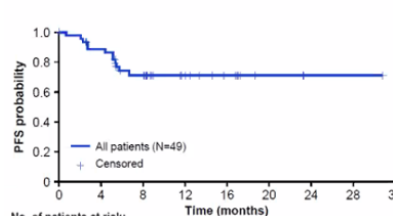
Inclusion criteria:

- Age, stage
- Comorbidities

What about high risk patients? The case for the elderly/unfit

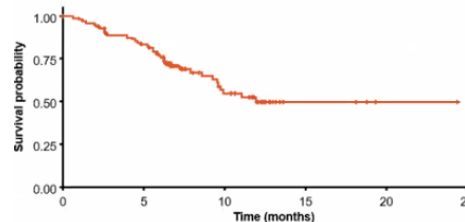
Improving outcomes:
clinical trials with chemo
light/chemo free **agnostic**
strategies

Mosunetuzumab



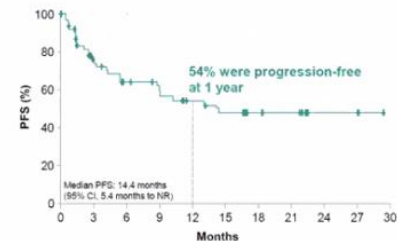
1y-PFS: 71.3%
1y-OS: 74.7%

Mosun-Pola



1y-PFS: 49.7%
1y-OS: NA

Epcoritamab



1y-PFS: 54%
1y-OS: 65%

Sharman J et al. *Blood*. 2025;146:62

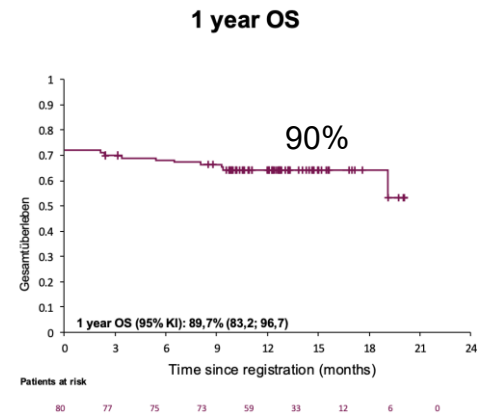
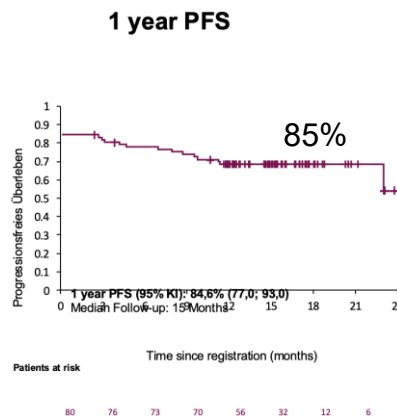
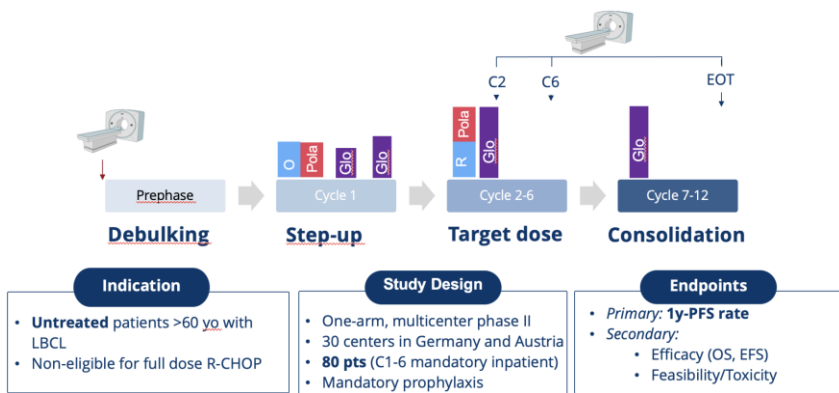
Vitolo U et al. *Blood*. 2025;146:63

Belada D et al. *Hematol Oncol*. 2025;43:205-206

Olszewski A et al. *Blood* (2023) 142 (Supplement 1): 855.

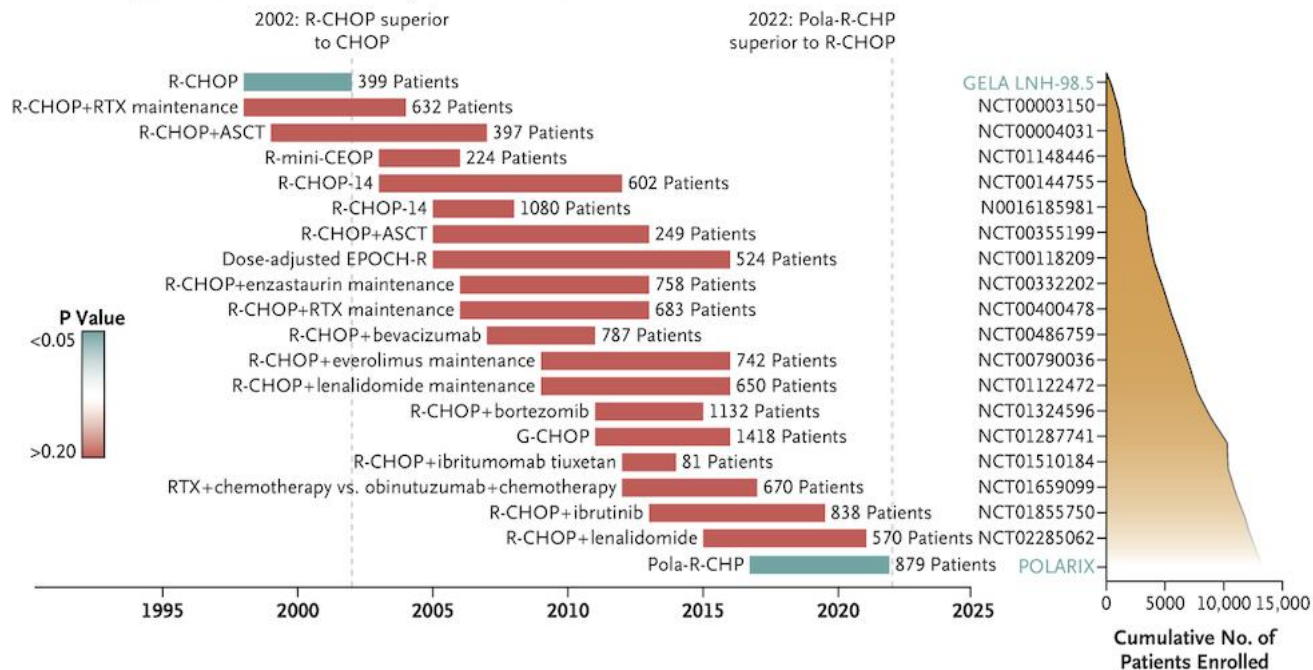
Phase II frontline chemolight R-pola-glo trial induces high and durable response rates in elderly and medically unfit/frail patients with aggressive B-cell lymphoma

Björn Chapuy, ...Georg Lenz... and Richard Greil. *Blood* (2025) 146 (Supplement 1): 61.



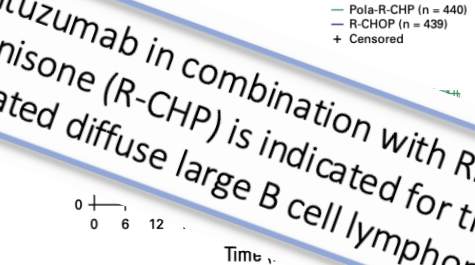
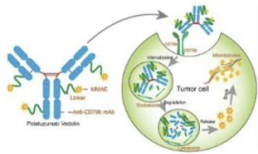
Improving upon R-CHOP: 20 years of unsuccessful trials

A Randomized, Controlled Trials for Previously Untreated DLBCL



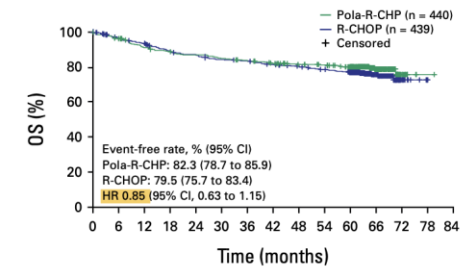
2022: Polatuzumab CHP improved outcomes over RCHOP

Polatuzumab in combination with Rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B cell lymphoma (DLBCL)



Number at risk

Polatuzumab-CHP	440	407	357	335	318	303	292	280	258	211	
R-CHOP	439	391	332	302	287	274	258	251	240	192	95



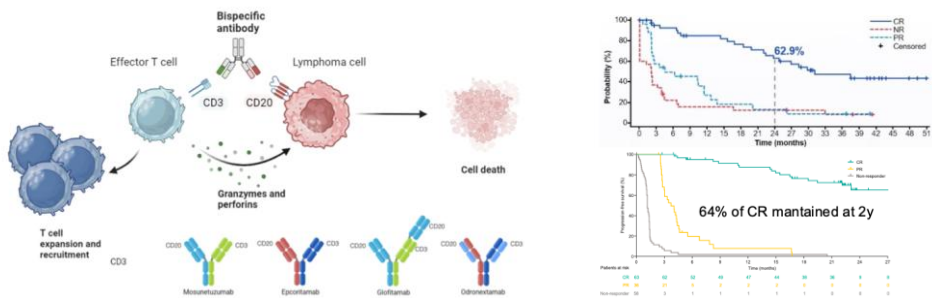
Number at risk

Polatuzumab-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

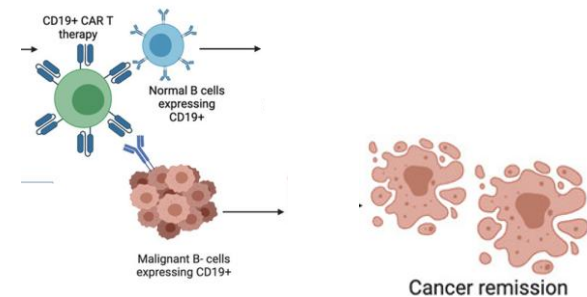
Baseline Risk Factors	PFS				95% Wald CI	Pola-R-CHP Better	R-CHOP Better
	Polatuzumab-CHP (n = 440)	R-CHOP (n = 439)	HR	95% Wald CI			
All patients	440	439	59.1	0.78	0.62 to 0.97		
Age group, years							
≤65	225	219	64.3	0.80	0.57 to 1.11		
>65	215	220	54.5	0.78	0.58 to 1.06		
Age group 2, years							
≤60	140	131	69.2	0.96	0.62 to 1.49		
>60	300	308	55.8	0.72	0.55 to 0.93		
Ann Arbor stage - IPI score							
2	167	167	68.3	0.91	0.61 to 1.36		
3-5	273	272	53.5	0.72	0.55 to 0.94		
Ann Arbor stage - IPI score							
Absent	247	247	60.0	0.61	0.44 to 0.83		
Present	193	192	57.9	1.02	0.73 to 1.41		
Ann Arbor stage - IPI score							
1-2	146	154	64.8	0.83	0.55 to 1.23		
3-5	293	284	55.7	0.77	0.59 to 1.01		
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Ann Arbor stage - IPI score							
1-2	146	154	64.8	0.83	0.55 to 1.23		
3-5	293	284	55.7	0			

Agnostic treatments being tested at first line in DLBCL

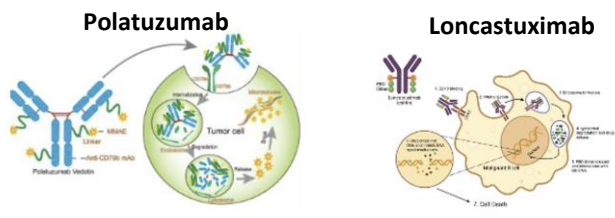
CD3-CD20 bispecific antibodies



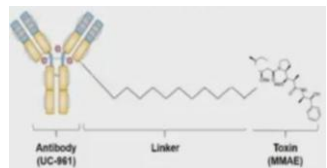
CAR T cells



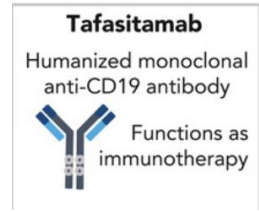
ADCs



Zilovertamab

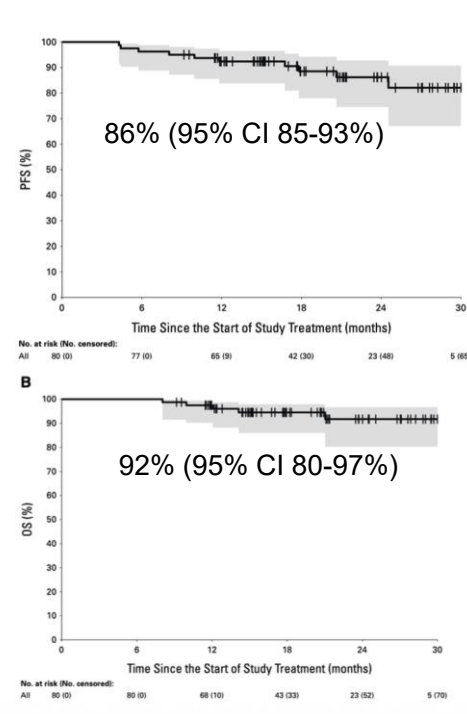


MoAb



Front line trials with bispecific antibody combinations for LBCL

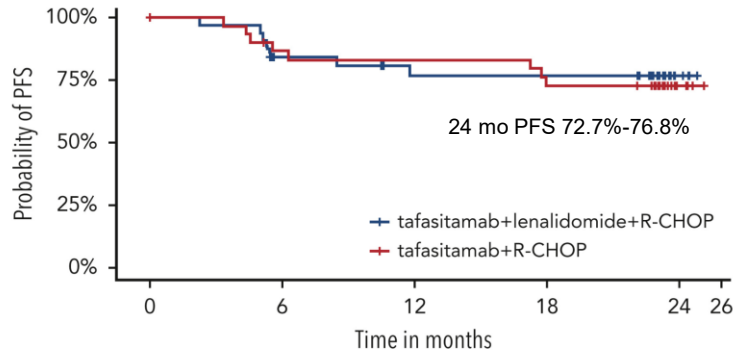
Trial*	Combination	N	ORR CR (%)	PFS
Phase 1/2 trials with chemotherapy				
NCT03677141	Mosun + CHOP	40	85 85	2 years: 65%
NCT03677141	Mosun + Pola- CHP	40	85 73	2 years: 71%
NCT03467373	Glofit + R- CHOP	56	93 86	NR
NCT03467373	Glofit + Pola- R- CHP	24	100 96	NR
NCT04914741	Glofit + R- CHOP	40	100 92	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



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

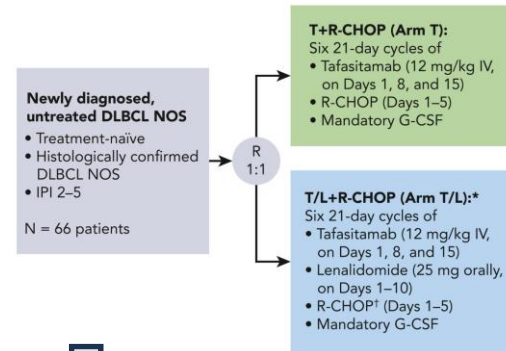
Trial	Patient population	Histologies	Primary outcome
POLARIX (Pola RCHP vs RCHOP)	N=1000 Age 18-80 y IPI 2-5 ECOG 0-2	DLBCL, HGBCL, TCHRLBL, EBV- positive, ALK- positive, HHV8-positive	PFS
FrontMIND RCHOP+Tafa+Len vs RCHOP	N=880 PI 3-5 (if >60 y) aalPI 2-3 (if ≤60 y) Diagnosis to treatment interval <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

Other immunotherapies being tested at front line in high risk patients

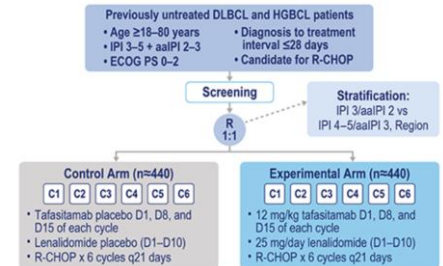


	0	6	12	18	24
Number at risk (number censored)					
Tafasitamab+ lenalidomide+ R-CHOP	33 (0)	23 (5)	20 (6)	20 (6)	4 (22)
Tafasitamab+ R-CHOP	33 (0)	25 (4)	24 (4)	21 (4)	4 (21)

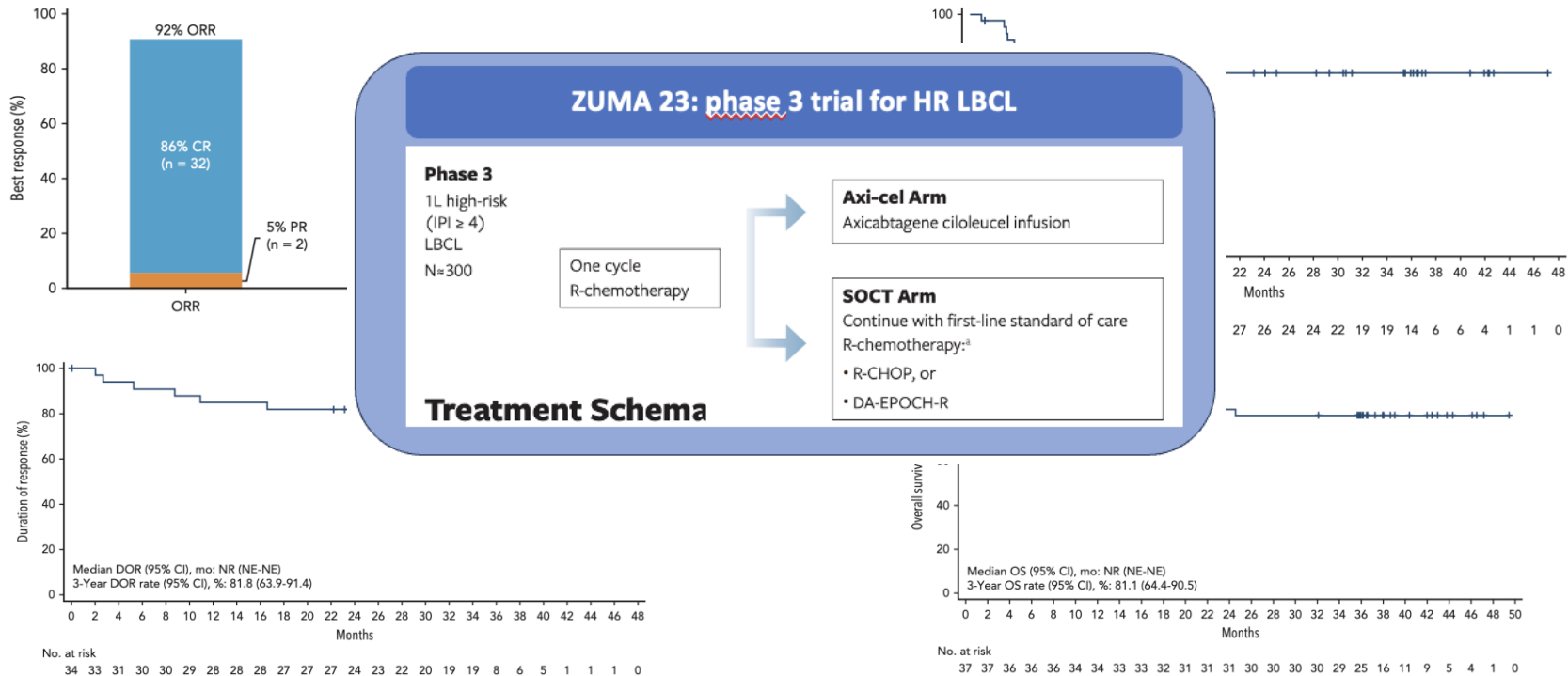
Belada D et al, *Blood* (2023) 142 (16): 1348–1358



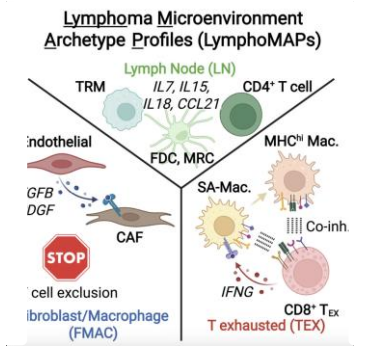
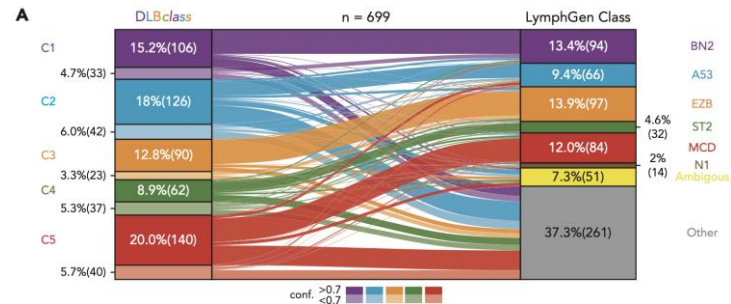
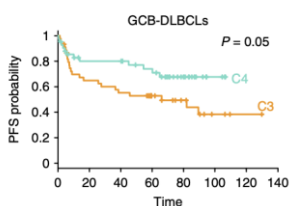
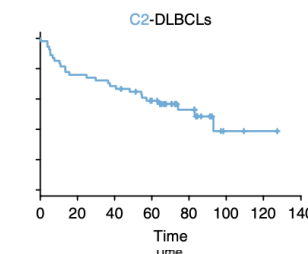
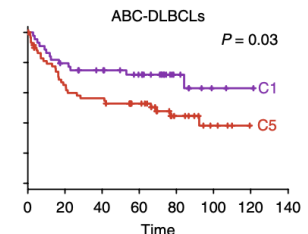
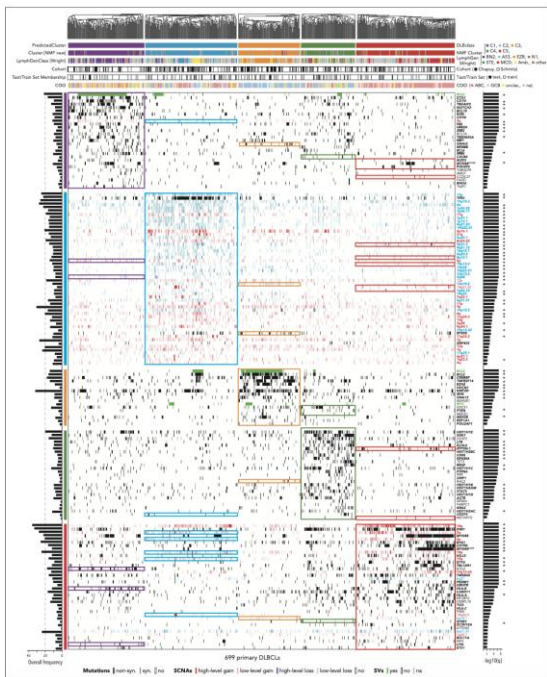
FrontMIND (NCT04824092)



CD19 CAR T as front line treatment for DLBCL: ZUMA 12



LBCL is biologically heterogeneous but... are we ready to apply genomic classification(s)?



Selected front line trials evaluating targeted therapies in LBCL

Drug	Trial	n	Population
R-CHOP±tucidinostat NCT04231448	R-CHOP vs R-CHOP+tucidinostat	423	Age 18-80 IPI 2-4 ECOG 0-2 DLBCL with MYC and BCL2 expression by IHC
ESCALADE (ACE-LY312) NCT 04529772	R-CHOP vs R-CHOP+ acalabrutinib	600	Age 18-75 IPI 1-5 ECOG 0-2 DLBCL non GC by GEP
GUIDANCE 02 NCT 05351346	R-CHOP + X vs R-CHOP	1100	Age 18-80 IPI 2-5 ECOG 0-2 LBCL (subtyping by LymphPlex – 38 gene)
BELIEVE 01 NCT 05234684	R-CHOP + Orelabrutinib vs R-CHOP	150	Age 18-80 IPI 2-5 ECOG 0-2 DLBCL MCD subtype
ENGINE 01 NCT 03263026	R-CHOP + Enzaustaurine vs R-CHOP	256	Age >18 IPI 3-5 ECOG 0-2 DLBCL, HGBCL

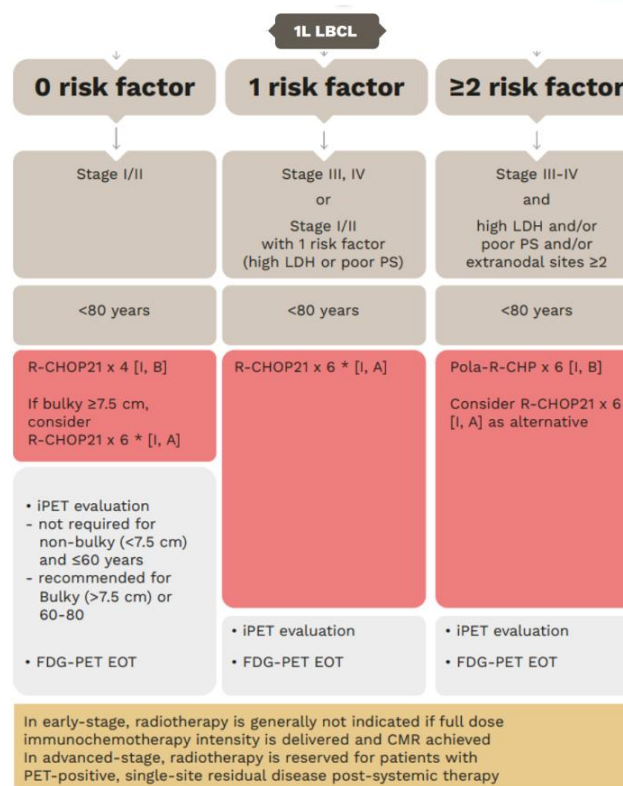
SUBTYPE	COMPOUND
MCD type	ORELABRUTINIB
BN2 type	
N1 type	
EZB type	LENALIDOMIDE
ST2 type	
NOS	
TP53 mut	DECITABINE

Zhao W et al. Hematological Oncology 2025, OT25

EHA Guidelines

Large B-cell lymphomas: first line and beyond

Thieblemont C., Gomes Da Silva M., Leppä S., Lenz G., Cottreau AS., Fox CP., Lopez-Guillermo A., Illidge T., Jurczak W., Eich H., Aurer I., Trneny M., Rosenwald A., Davies A., Zwezerijnen G., Bolanos N., Marković M., Jais JP., Broussais F., Dreyling M., Vitolo, U., Tilly H., Kersten MJ.



Molecularly driven vs agnostic treatment strategies in 1L DLBCL?

Depends...

- On our capacity to identify targets in a standardized, reproducible and timely manner
- On identifying targets in the majority patients
- On the availability of drugs
- On toxicity of those drugs, and combinations
- On costs

As of March 2026...

- No front line regimen improved survival over RCHOP
- ... which is affordable and accessible to most LBCL patients
- Trials adding targeted drugs to RCHOP were negative for many years – exception is now Polatuzumab
- Most promising current trials are using “agnostic” agents: bispecific antibodies, ADC, CAR T, MoAb

4th edition

Unmet challenges in high risk hematological
malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic