

Immunochemotherapy in the first line for DLBCL: what changes and what doesn't? How to anticipate the risk?

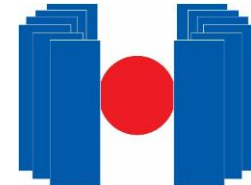
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ONCOLOGIA *DOR*

10/05/25, São Paulo



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Conflicts of interest

Financial support for medical conferences/events : **Jansen, Novartis, Takeda, Kite, Roche, Abbvie**

Sponsored Classes/Speaker : **Jansen, Bristol-Myers Squibb, AstraZeneca, MSD, Takeda, Novartis, Kite, Abbvie, Roche**

Production of scientific material : **Takeda, Jansen, MSD, Kite**

Advisory Board: **Bristol-Myers Squibb, Jansen, MSD, AstraZeneca, Abbvie, Kite**

AGENDA

- Concepts and prognostic factors
- RCHOP as standard therapy for over 20 years
- Pola-R-CHP (Polarix)
- Conclusions

CONCEPTS

- **DLBCL is the main type of lymphoma**, accounting for about 30% of cases.
- **The IPI is the most commonly used prognostic index**, both in daily practice and in clinical studies.
- **R-CHOP is considered the standard first-line protocol**. Despite high response rates, approximately 40% of patients will be refractory or experience a future relapse of their disease.
- Achieving a **complete response (CR) lasting at least 2 years** is associated with a better prognosis.
- Certain subgroups may benefit from a change in therapy. The main ones are defined by **cell-of-origin (COO) and MYC and BCL2 translocations**.
- The **Polarix** study was the first randomized phase 3 trial to demonstrate a progression-free survival (PFS) benefit versus R-CHOP.

Sehn LH and Salles G. N Engl J Med 2021.

Crump M, et al. Blood. 2017.

Maurer MJ, et al. J Clin Oncol 2014

Wright GW, et al. Cancer Cell 2020.

Tilly H, et al. N Engl J Med 2022

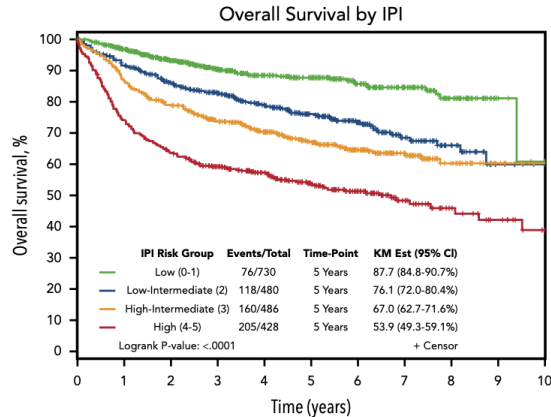
PROGNOSTIC FACTORS

- Clinical aspects (IPI, R-IPI, NCCN-IPI)
- Cell-of-origin (GCB, ABC, unclassified)
- MYC/BCL2 translocations, DHIT-signature and MHG
- Genetic subtypes
- Lymphoma microenvironment (LME)
- ctDNA

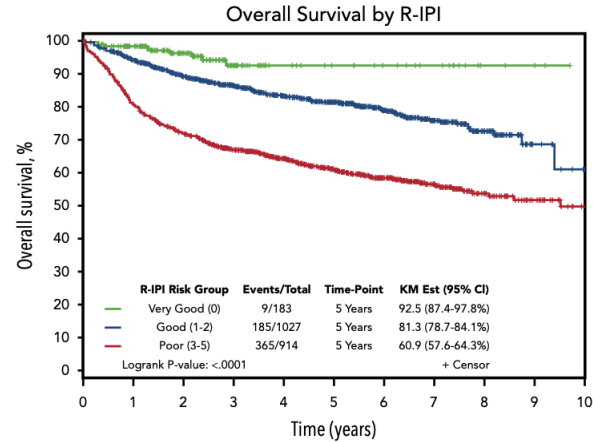
Ruppert AS, et al. Blood. 2020.
Alizadeh AA, et al. Nature 2000
Rosenwald, et al. N Eng J Med 2002
Ennishi D, et al. J Clin Oncol. 2019.
Sha C, et al. J Clin Oncol. 2019.
Wright GW, et al. Cancer Cell 2020.
Zhang, et al. Cancer Cell 2023.
Kotlov N, et al. Cancer Discov. 2021.

Clinical aspects - IPI

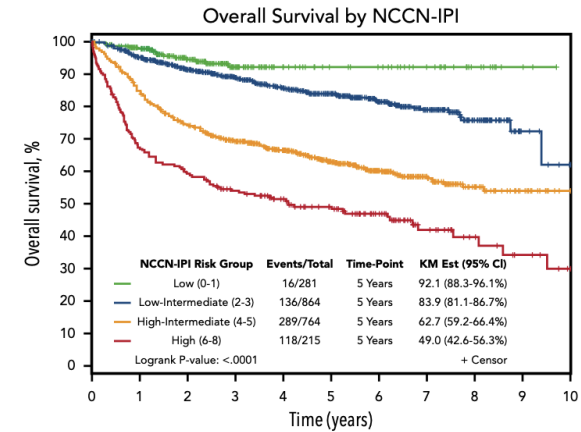
A



B



C



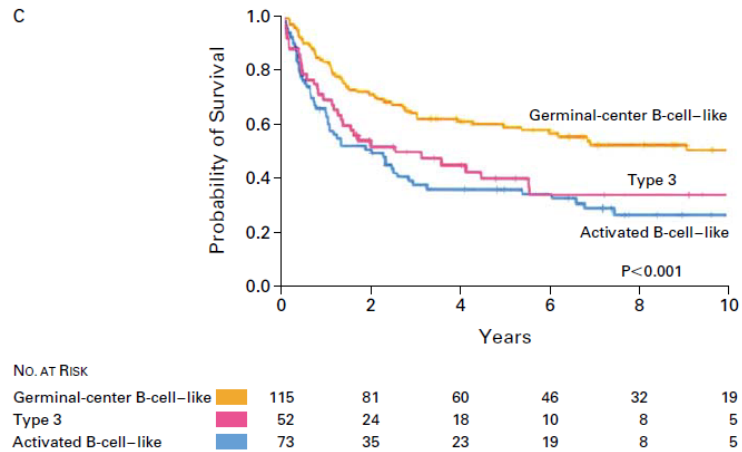
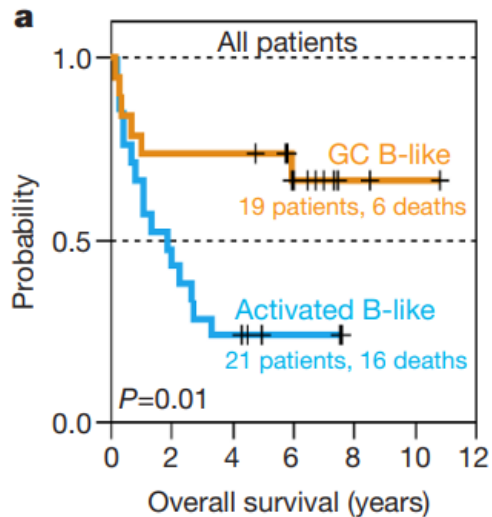
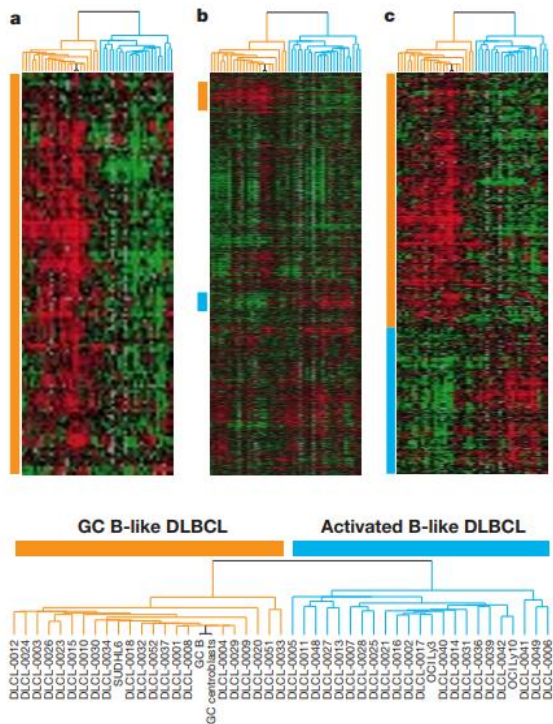
	0	1	2	3	4	5	6	7	8	9	10
Low (0-1) 730	650	493	344	267	227	159	102	46	6	1	
Low-Intermediate (2) 480	431	370	315	260	194	133	69	36	9	4	
High-Intermediate (3) 486	418	368	315	260	201	135	83	38	19	9	
High (4-5) 428	315	268	227	184	136	92	50	27	18	9	

	0	1	2	3	4	5	6	7	8	9	10
Very Good (0) 183	162	104	49	26	21	17	13	4	3	0	
Good (1-2) 1027	919	759	610	501	400	275	158	78	12	5	
Poor (3-5) 914	733	636	542	444	337	227	133	65	37	18	

	0	1	2	3	4	5	6	7	8	9	10
Low (0-1) 281	246	162	80	46	37	32	23	10	3	0	
Low-Intermediate (2-3) 864	786	662	541	452	360	244	146	69	9	3	
High-Intermediate (4-5) 764	640	550	473	383	289	193	109	52	30	15	
High (6-8) 215	142	125	107	90	72	50	26	16	10	5	

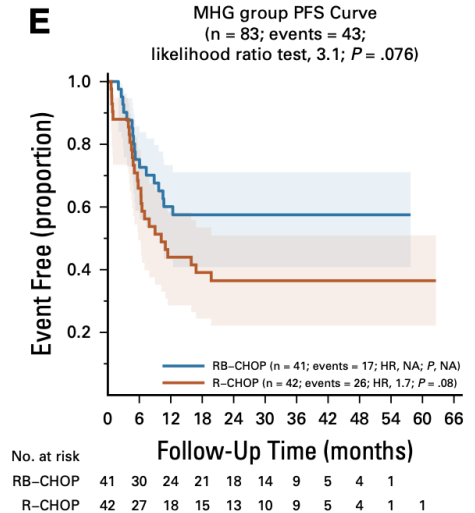
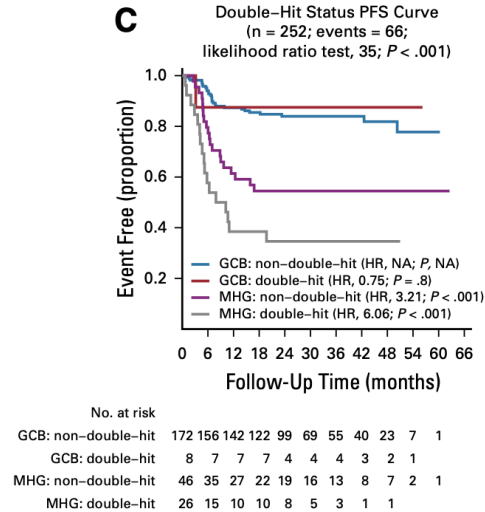
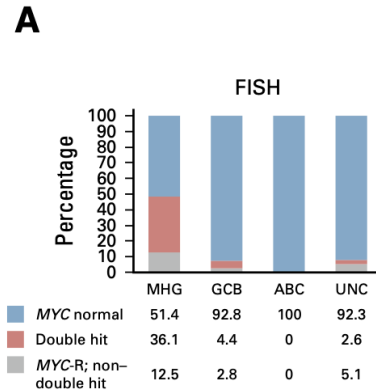
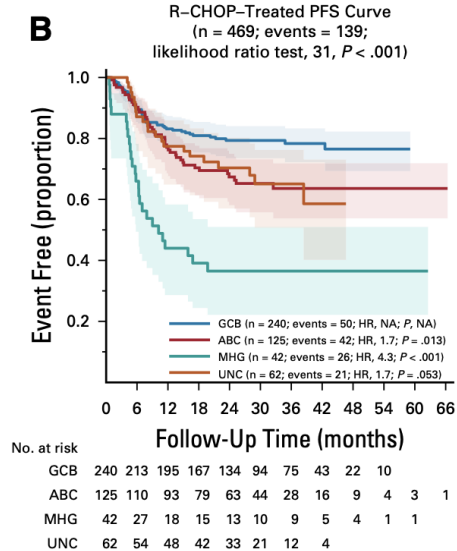
Factors: **Age, PS (>2), LDH, >1 EN sites, CS III/IV**

COO: GCB vs ABC



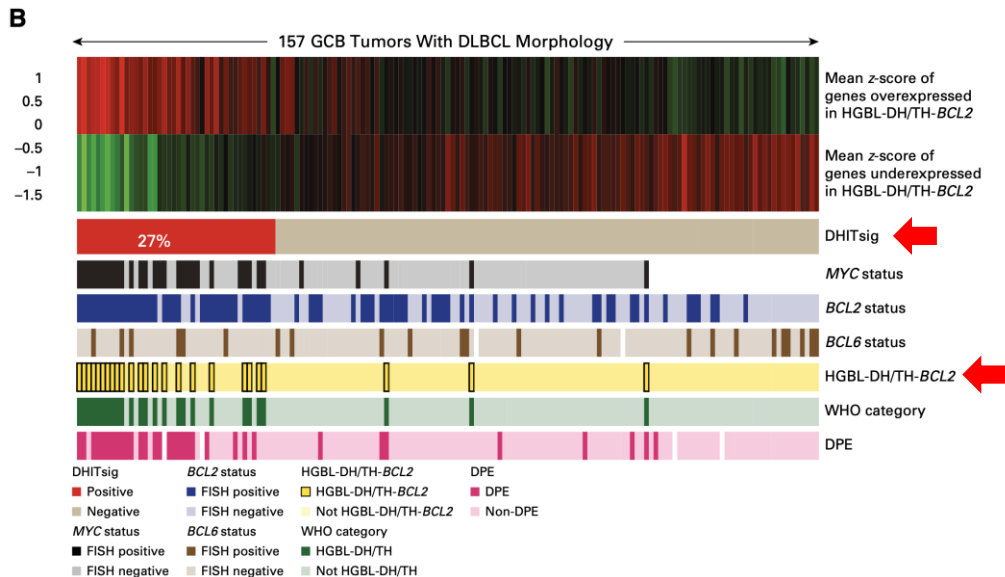
Alizadeh AA, et al. Nature 2000
Rosenwald et al, N Eng J Med 2002

Molecular high-grade (MHG) and double-hit lymphomas



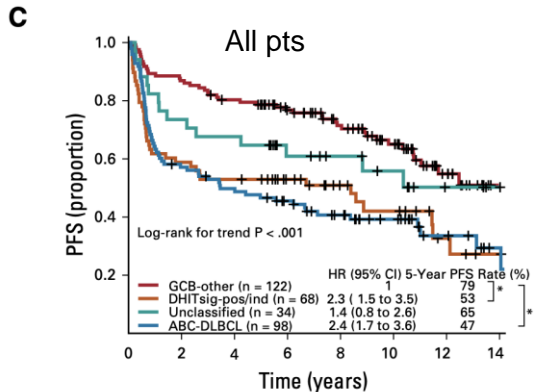
928 pts from the REMoDL-B clinical trial, with whole-genome expression profiling.
400 patients with analysis for somatic mutations with a targeted 70-gene panel.
360 patients tested for MYC, BCL2, and BCL6 rearrangements by FISH.

Double-hit signature



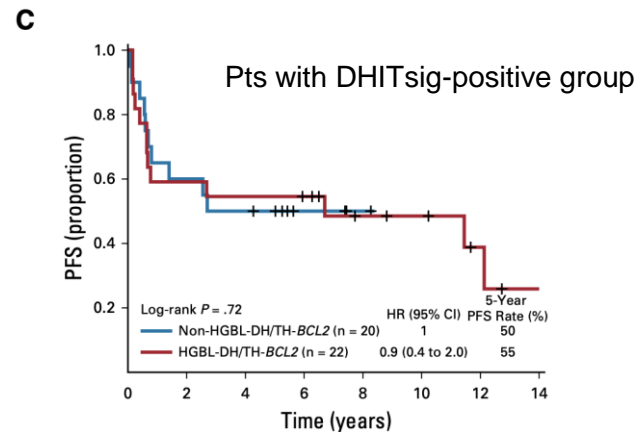
RNAseq (tissue – fresh frozen) from 157 de novo GCB DLBCLs cases (25 HGBL-DH/TH). 104-gene double-hit signature (DHITsig) that assigned 27% of GCB-DLBCLs to the DHITsig-positive group. Changed to 30-gene module (DLBCL90, Nanostring-based). 50% of DHITsig-positive group harbor MYC and BCL2 rearrangements (HGBL-DH/TH-BCL2).

All patients treated with RCHOP.



No. at risk

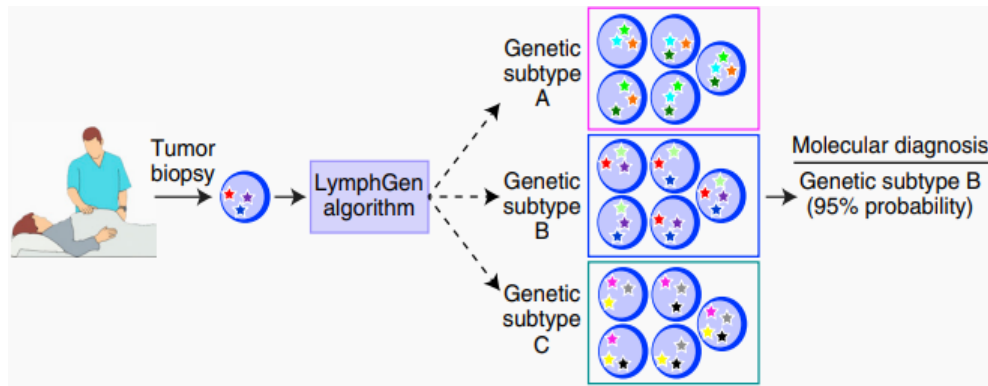
	0	2	4	6	8	10	12	14
GCB-other	122	106	96	80	64	45	19	3
DHITsig-pos/ind	68	40	36	28	19	13	6	3
Unclassified	34	25	23	16	13	10	5	3
ABC-DLBCL	98	55	47	39	30	21	10	4



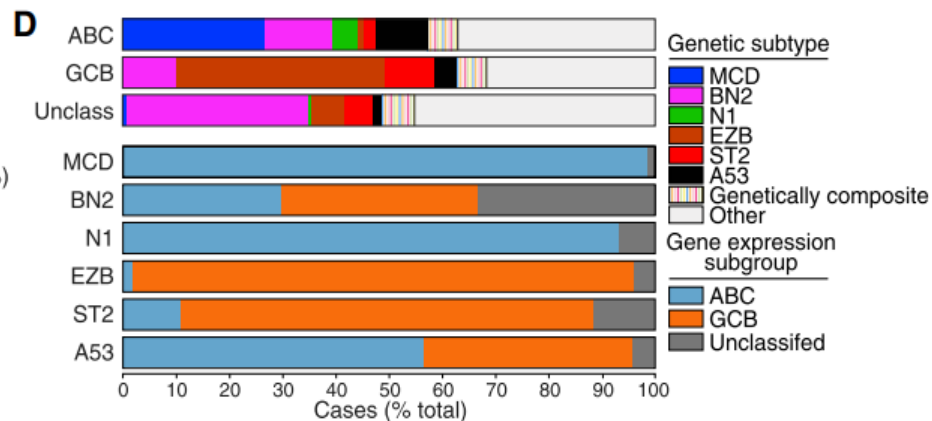
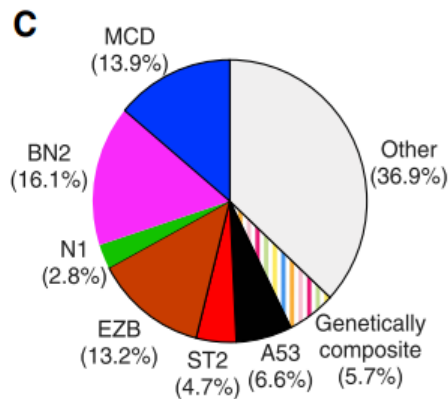
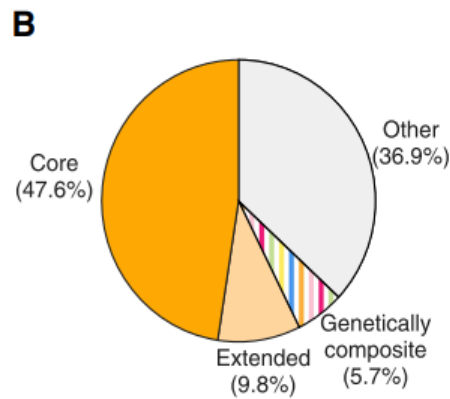
No. at risk

	0	2	4	6	8	10	12	14
Non-HGBL-DH/TH-BCL2	20	12	10	5	2	0	0	0
HGBL-DH/TH-BCL2	22	13	12	11	7	6	3	1

LymphGen: a probabilistic classification algorithm

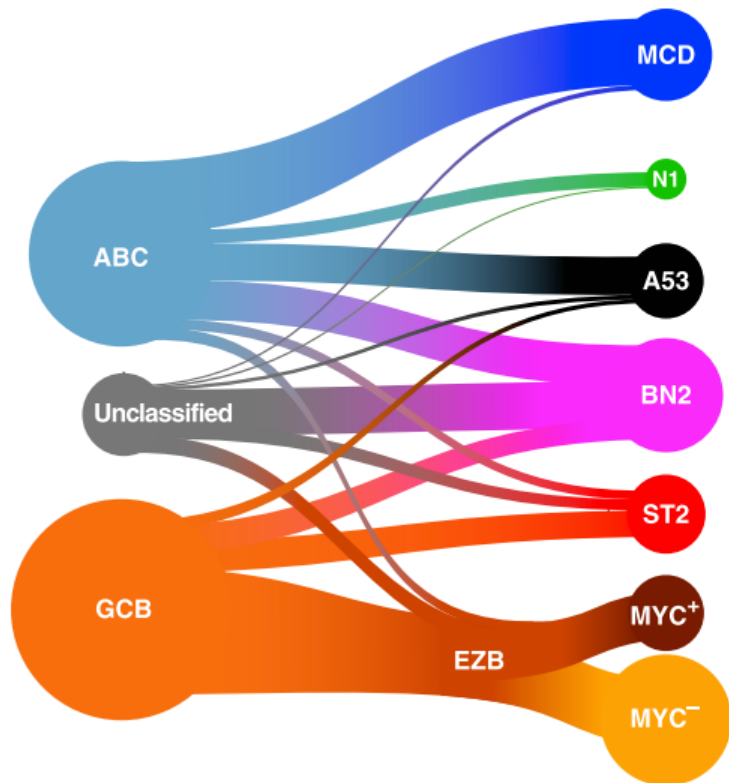


- Using the premise that the tumor may acquire more than one genetic program in its evolution, an algorithm was developed to classify an individual's lymphoma based on the probability of belonging to a specific genetic subtype.



Genetic subgroups classification

A

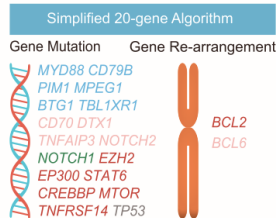


Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF- κ B Immune evasion-MHC class I Cell survival - <i>BCL2</i> expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; IgV $_{\mu}$ 4-34 ⁺⁺	Primary extranodal DLBCL Transformed WM	B cell activation NF- κ B IRF4 Myc Proliferation	BCR-dep. NF- κ B PI3 kinase mTORC1 BCL2-BCLX $_{\lambda}$ -MCL1 JAK1 IRAK4 IRF4
1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
5.8%	63% (All) 33% (ABC) 100% (GCB)	<i>TP53</i> inactivation/DNA damage Aneuploidy Immune evasion - <i>B2M</i> loss BCR: IgM >> IgG; IgV $_{\mu}$ 4-34 ⁺⁺	-	p53 Immune low	BCR-dep. NF- κ B
13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF- κ B Immune evasion - <i>CD70</i> loss Proliferation - Cyclin D3 BCR: IgM >> IgG; IgV $_{\mu}$ 4-34 ⁺⁺	MZL Transformed MZL	B cell activation NF- κ B NOTCH Proliferation	BCR-dep. NF- κ B PI3 kinase mTORC1 BCL2 NOTCH2
6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF- κ B activation <i>P2RY8</i> - <i>GNA13</i> inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
5.9% (MYC ⁺) 17.6% (MYC ⁻)	48% (MYC ⁺) 82% (MYC ⁻)	Chromatin modification Anti-apoptosis PI3 kinase signaling <i>STPR2</i> - <i>GNA13</i> inactivation Altered T _{H1} interactions MYC (EZB-MYC ⁺) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC ⁺)	GC LZ (MYC ⁻) GC IZ (MYC ⁺) BCL6 (MYC ⁺) TCF3 (both) T _{H1} cells (MYC ⁻) Stromal (MYC ⁻) Immune low (MYC ⁺)	PI3 kinase mTORC1 EZB2 BCL2-MCL1

Newly Diagnosed DLBCL

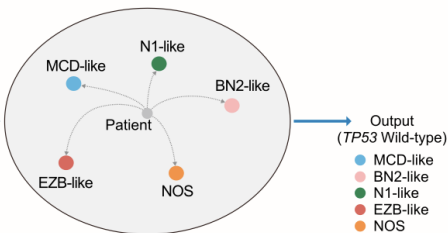
• 18-80 years • IPI ≥ 2

Tumor Biopsy

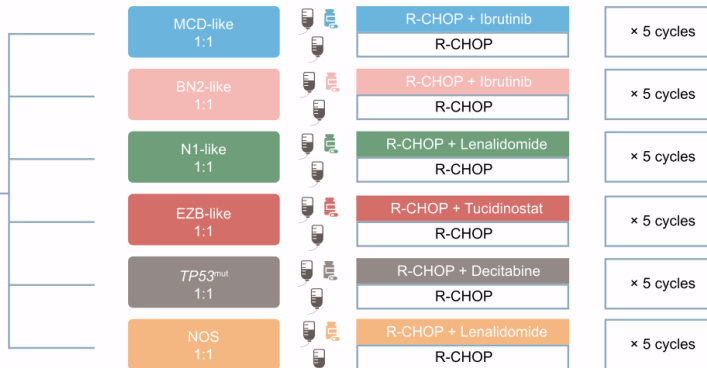
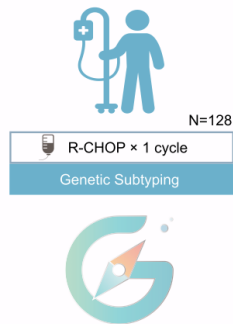


TP53 Wild-type
TP53 Mutation
Output (TP53 Mutation)
● TP53^{mut}

Genetic Subtyping

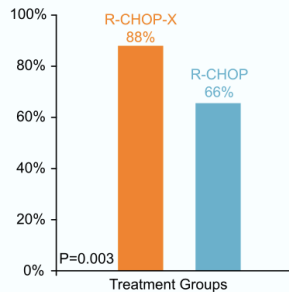


Treatment Procedure



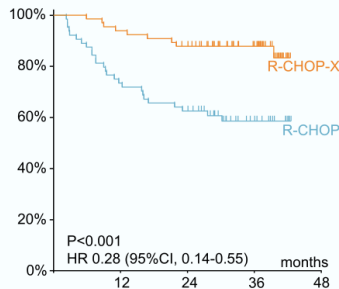
Primary Endpoint

Complete Response Rate

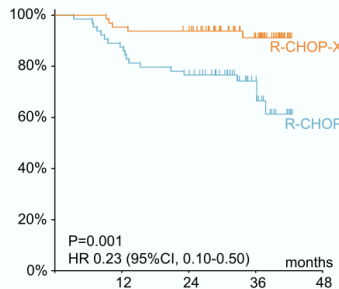


Secondary Endpoints

Progression-free Survival



Overall Survival



GUIDANCE-01

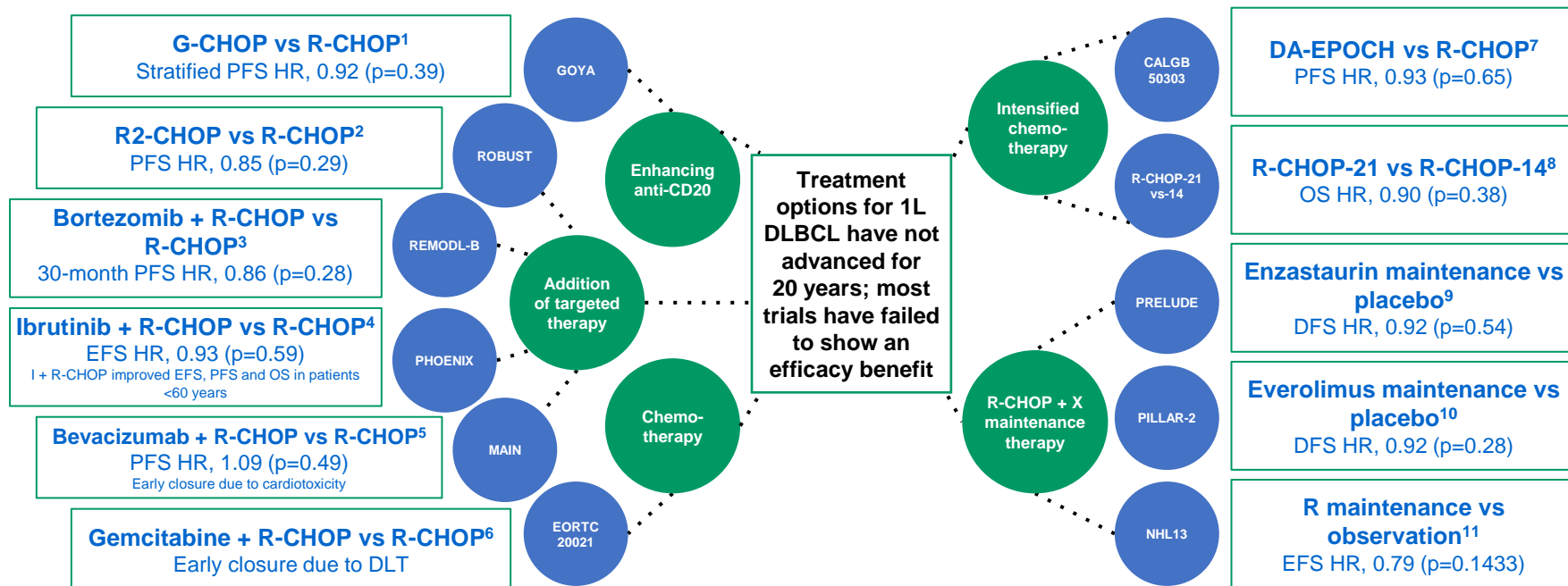
Ph2 study, randomized (1:1)
N = 128 pts. Single institution.
Primary end point CR
- 88% vs. 66%, $p = 0.003$

The median time from diagnosis to treatment was 18 days.

The median time from enrollment to response to classifying patients according to genetic subtypes was 14 days.

Simplified 20-gene algorithm on tissue (targeted sequencing and FISH).

RCHOP: standard therapy for over 20 years



1. Vitolo U, et al. J Clin Oncol 2017;35:3529–37; 2. Vitolo U, et al. Hematol Oncol 2019;37:36–37; 3. Davies A, et al. Lancet Oncol 2019;20:649–62; 4. Younes A, et al. J Clin Oncol 2019;37:1285–95; 5. Seymour JF, et al. Haematologica 2014;99:1343–49; 6. Aurer I, et al. Eur J Haematol 2011;86:111–16; 7. Bartlett NL, et al. J Clin Oncol 2019;37:1790–99; 8. Cunningham D, et al. Lancet 2013;381:1817–26; 9. Crump M, et al. J Clin Oncol 2016;34:2484–92; 10. Witzig TE, et al. Ann Oncol 2018;29:707–14; 11. Jaeger U, et al. Haematologica 2015;100:955–63.

POLARIX (GO39942)

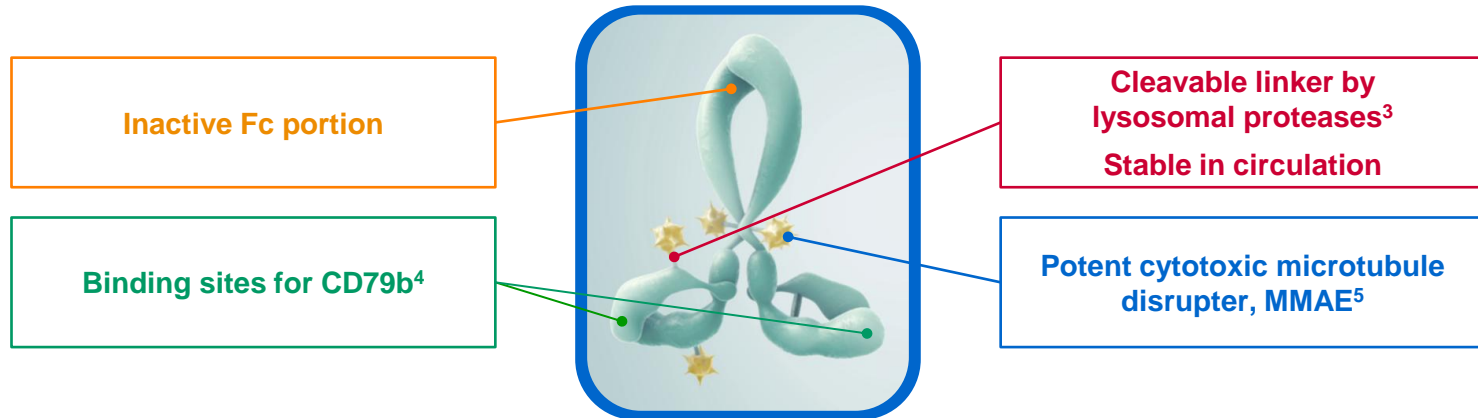
Primary analysis – global population

A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP vs R-CHOP in previously untreated patients with DLBCL

Polatuzumab

POLIVY: ADC with proven effective MOA

- CD79b-targeted ADC that specifically delivers a potent anti-mitotic agent (MMAE) to targeted B cells
- Proven safety and efficacy in R/R DLBCL and in Ph Ib/II study in 1L DLBCL^{1, 2}



1. Sehn LH, et al. J Clin Oncol 2020;38:155–65; 2. Tilly H, et al. Lancet Oncol 2019;20:998–1010;
3. Dornan D, et al. Blood 2009;114:2721–29; 4. Polson A, et al. Expert Opin Invest Drug 2011;20:75–85;
5. Doronina SO, et al. Nat Biotechnol 2003;21:778–84.

Study design overview

- **Double-blind, randomized controlled**
- Collaboration with LYSA
- NCT03274492

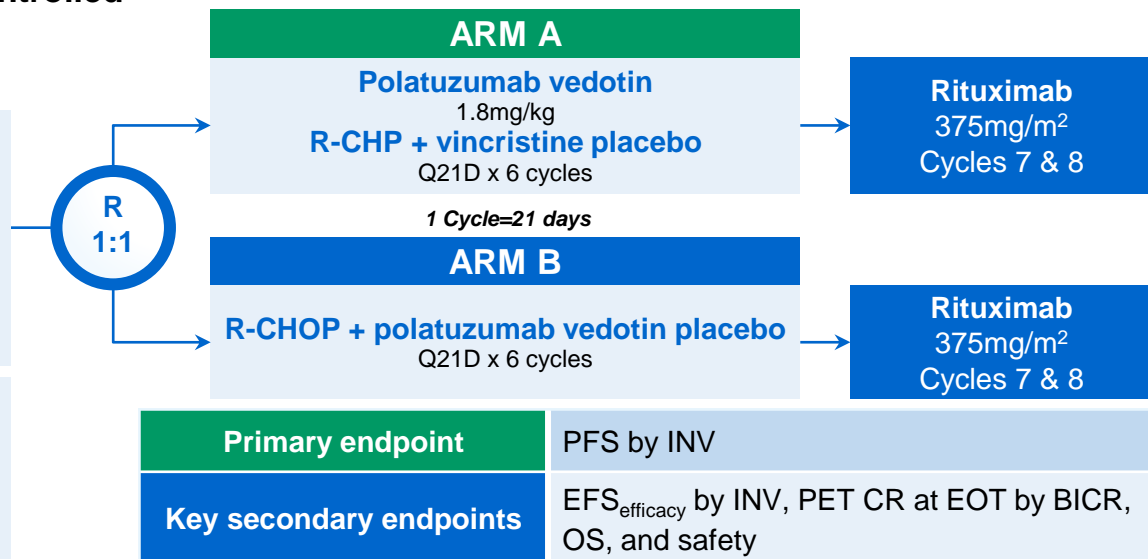
Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

N=879

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (≥ 7.5 cm vs absence)
- Geographic region*



*Western Europe, United States, Canada and Australia vs Asia vs Rest of World. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS_{efficacy}, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion)

Demographics and baseline characteristics were generally well balanced between arms – global ITT

		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age, n (%)	>60 years	300 (68.2)	308 (70.2)
Age, years	Median (Min–Max)	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54.3)	234 (53.3)
ECOG PS, n (%)	0–1	374 (85.0)	363 (82.7)
	2	66 (15.0)	75 (17.1)
	Unknown	0	1 (0.2)
Geographic region, n (%)	Asia	81 (18.4)	79 (18.0)
	Rest of World	57 (13.0)	59 (13.4)
	Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
IPI at screening, n (%)	2	167 (38.0)	167 (38.0)
	3–5	273 (62.0)	272 (62.0)
Bulky disease, n (%)	Absent	247 (56.1)	247 (56.3)
	Present	193 (43.9)	192 (43.7)
Baseline LDH, n (%)	≤1 x ULN	146 (33.2)	154 (35.1)
	>1 x ULN	291 (66.1)	284 (64.7)
	Unknown	3 (0.7)	1 (0.2)

Demographics and baseline characteristics were generally well balanced between arms – global ITT

		Pola-R-CHP (N=440)	R-CHOP (N=439)
NHL histologic diagnosis (local diagnosis), n (%)	DLBCL NOS (including ABC and GCB)	373 (84.8)	367 (83.6)
	HGBL, (including NOS and DHL/THL)	43 (9.8)	50 (11.4)
	Other large B-cell*	24 (5.5)	22 (5.0)
COO, [†] n (%)		N=330	N=338
	ABC	102 (30.9)	119 (35.2)
	GCB	184 (55.8)	168 (49.7)
	Unclassified	44 (13.3)	51 (15.1)
Double-expressor lymphoma, [†] n (%)		N=362	N=366
	DEL	139 (38.4)	151 (41.3)
	Non DEL	223 (61.6)	215 (58.7)
Double/triple-hit lymphoma, [†] n (%)		N=331	N=334
	DH/TH+	26 (7.9)	19 (5.7)
	DH/TH-	305 (92.1)	315 (94.3)

*Other large B-cell lymphomas by local diagnosis included EBV+ DLBCL NOS, and T-cell/histiocyte rich large B-cell lymphoma.

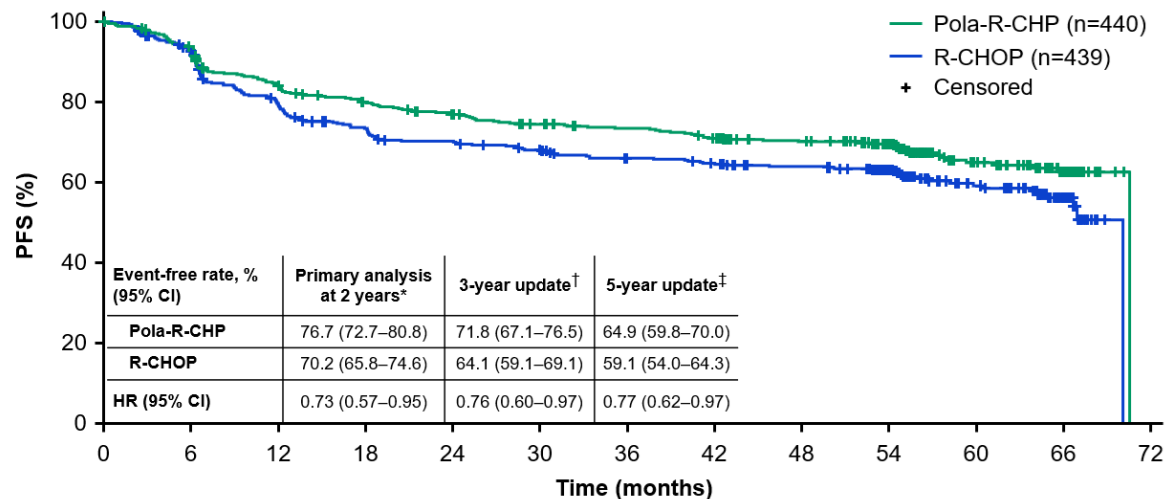
[†]Based on central review, and percentages are based on biomarker evaluable population (i.e. by excluding patients with unknown status).

Tilly H, et al. New Engl J Med 2022;386:351–63.

POLARIX: 5-year update analysis

Data cut-off: July 5, 2024

PFS (global ITT population)¹



Patients remaining at risk

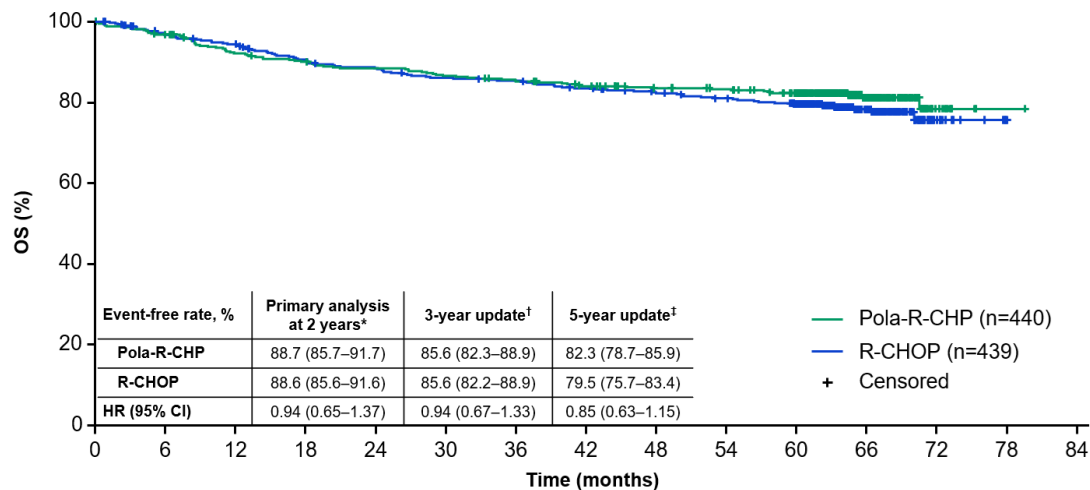
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years. At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73)²

*Data cut-off: June 28, 2021. [†]Data cut-off: June 15, 2022. [‡]Data cut-off: July 5, 2024.

1. Salles G et al. ASH 2024. Oral presentation 469;
2. Tilly H, et al. *N Eng J Med* 2022;386:351–63.

OS (global ITT population)



Deaths, n [§]	Pola-R-CHP (n=440)	R-CHOP (n=439)
Primary analysis at 2 years*	53	57
5-year update‡	79	91

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

5-year overall survival shows similar results for Pola-R-CHP and R-CHOP. After 5 years of follow-up, numerically fewer deaths were observed in the Pola-R-CHP versus R-CHOP arm, with an associated HR of 0.85 (0.63–1.15)

*Data cut-off: June 28, 2021. †Data cut-off: June 15, 2022. ‡Data cut-off: July 5, 2024; §In addition to the known deaths, there were two patients (one in the Pola-R-CHP arm and one in the R-CHOP arm) who died due to an unknown cause and an unknown death date and were not counted as death events in the OS analysis.

5-year PFS outcomes show consistent treatment effect of Pola-R-CHP across subgroups in the global population

Baseline risk factors		PFS							
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better
		n	60-month (%)	n	60-month (%)				
All patients		440	64.9	439	59.1	0.78	0.62–0.97		
Age group	≤65	225	69.6	219	64.3	0.80	0.57–1.11		
	>65	215	60.0	220	54.5	0.78	0.58–1.06		
Stratification – IPI score	2	167	67.2	167	68.3	0.91	0.61–1.36		
	3–5	273	63.2	272	53.5	0.72	0.55–0.94		
Stratification – bulky disease (≥ 7cm)	Absent	247	69.9	247	60.0	0.61	0.44–0.83		
	Present	193	58.5	192	57.9	1.02	0.73–1.41		
Baseline LDH	≤1xULN	146	65.3	154	64.8	0.83	0.55–1.23		
	>1xULN	291	64.3	284	55.7	0.77	0.59–1.01		
No. of extranodal sites	0–1	227	68.1	226	64.2	0.78	0.56–1.09		
	≥2	213	61.2	213	53.8	0.78	0.58–1.06		
NHL subtype	DLBCL, NOS, ABC, GCB	373	65.7	367	58.8	0.75	0.59–0.95		
	HGBL, NOS, DHL/THL	43	66.0	50	57.6	0.67	0.33–1.37		
	Other LBCL	24	49.7	22	70.3	1.86	0.69–5.04		
NanoString COO	NanoString GCB	187	65.9	170	65.8	1.07	0.74–1.56		
	NanoString ABC	106	72.5	129	45.8	0.38	0.24–0.59		
	NanoString UNC	44	55.2	53	70.8	1.60	0.79–3.25		
Unknown	Unknown	103	60.2	87	59.7	0.83	0.51–1.33		
	DEL	139	63.1	151	50.0	0.65	0.45–0.94		
	Non DEL	223	66.6	215	64.7	0.89	0.64–1.24		
Double expressor by IHC	Unknown	78	63.7	73	63.5	0.84	0.48–1.47		

0.25 1 5

- PFS by subgroups, including high-risk subgroups, generally favor Pola-R-CHP; however, subgroup analyses are exploratory and generally underpowered (especially for OS).
- Patient characteristics are multidimensional; therefore, translating univariate subgroup results into patient care should be applied with caution.

2-year PFS: ARR: 25.1%; RRR: 60%

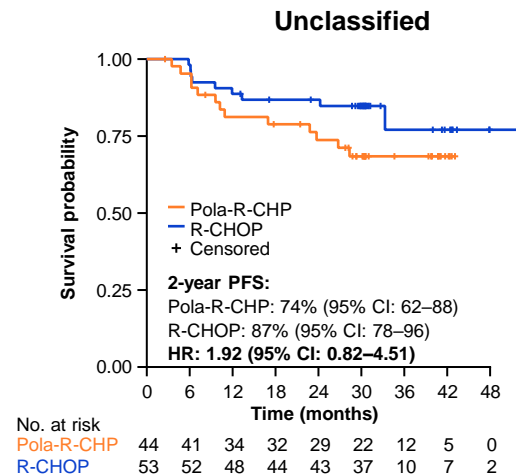
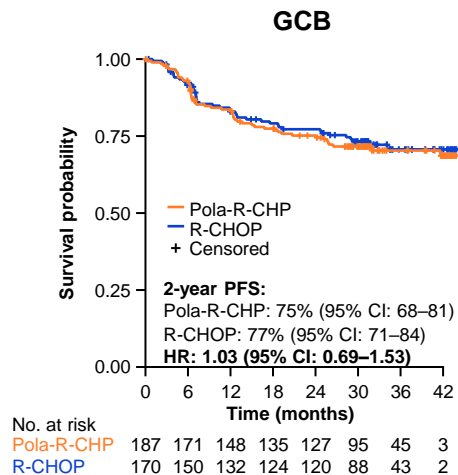
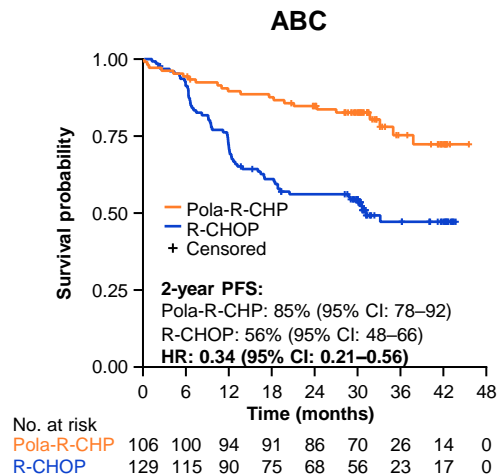
5-year PFS: ARR: 26.7%; RRR: 62%

2-year PFS	Total N	Pola-R-CHP (N=440)		R-CHOP (N=439)		HR	95% Wald CI
		n	2-year rate	n	2-year rate		
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)

5-Year PFS	Total N	Pola-R-CHP (N=440)		R-CHOP (N=439)		HR	95% Wald CI
		n	2-year rate	n	2-year rate		
Cell-of-origin							
GCB	352	187	65.9	170	65.8	1.07	0.74–1.56
ABC	221	106	72.5	129	45.8	0.38	0.24–0.59
Unclassified	95	44	55.2	53	70.8	1.60	0.79–3.25
Unknown	211	103	60.2	87	59.7	0.83	0.51–1.33

Investigator-Assessed PFS* by COO Subgroup

- COO status was determined in 689 patients in POLARIX (ABC, n=235; GCB, n=357; unclassified, n=97)
- Based on a data cutoff of June 15, 2022, with a median follow-up of 39.7 months, a **PFS difference between treatment groups** was observed in ABC-DLBCL, but not in GCB or the unclassified subgroups

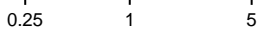


*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data.

5-year OS outcomes show consistent treatment effect of Pola-R-CHP across subgroups in the global population

Baseline risk factors		OS						Pola-R-CHP better	R-CHOP better
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI		
		n	60-month (%)	n	60-month (%)				
All patients		440	82.3	439	79.5	0.85	0.63–1.16		
Age group	≤65	225	89.1	219	84.7	0.73	0.44–1.21		
	>65	215	75.3	220	74.5	0.95	0.65–1.38		
Stratification – IPI score	2	167	87.6	167	87.4	0.96	0.53–1.75		
	3–5	273	79.2	272	74.7	0.81	0.57–1.15		
Stratification – bulky disease (≥ 7cm)	Absent	247	83.9	247	80.9	0.79	0.52–1.20		
	Present	193	80.3	192	77.9	0.92	0.60–1.43		
Baseline LDH	≤1xULN	146	88.7	154	87.9	0.85	0.45–1.61		
	>1xULN	291	79.0	284	74.9	0.85	0.60–1.19		
No. of extranodal sites	0–1	227	83.7	226	81.9	0.86	0.56–1.34		
	≥2	213	80.9	213	77.1	0.85	0.56–1.28		
NHL subtype	DLBCL, NOS, ABC, GCB	373	81.9	367	79.8	0.89	0.64–1.23		
	HGBL, NOS, DHL/THL	43	85.4	50	72.4	0.46	0.18–1.22		
	Other LBCL	24	83.3	22	90.9	1.93	0.35–10.52		
NanoString COO	NanoString GCB	187	82.9	170	82.3	0.99	0.60–1.61		
	NanoString ABC	106	84.6	129	69.9	0.49	0.28–0.88		
	NanoString UNC	44	76.9	53	94.2	4.46	1.23–16.21		
	Unknown	103	81.3	87	79.0	0.80	0.42–1.51		
Double expressor by IHC	DEL	139	76.4	151	73.0	0.84	0.53–1.33		
	Non DEL	223	86.3	215	82.8	0.81	0.51–1.30		
	Unknown	78	81.6	73	84.1	1.18	0.53–2.59		

- OS by subgroups, including high-risk subgroups, generally favor Pola-R-CHP; however, subgroup analyses are exploratory and generally underpowered (especially for OS).
- Patient characteristics are multidimensional; therefore, translating univariate subgroup results into patient care should be applied with caution.

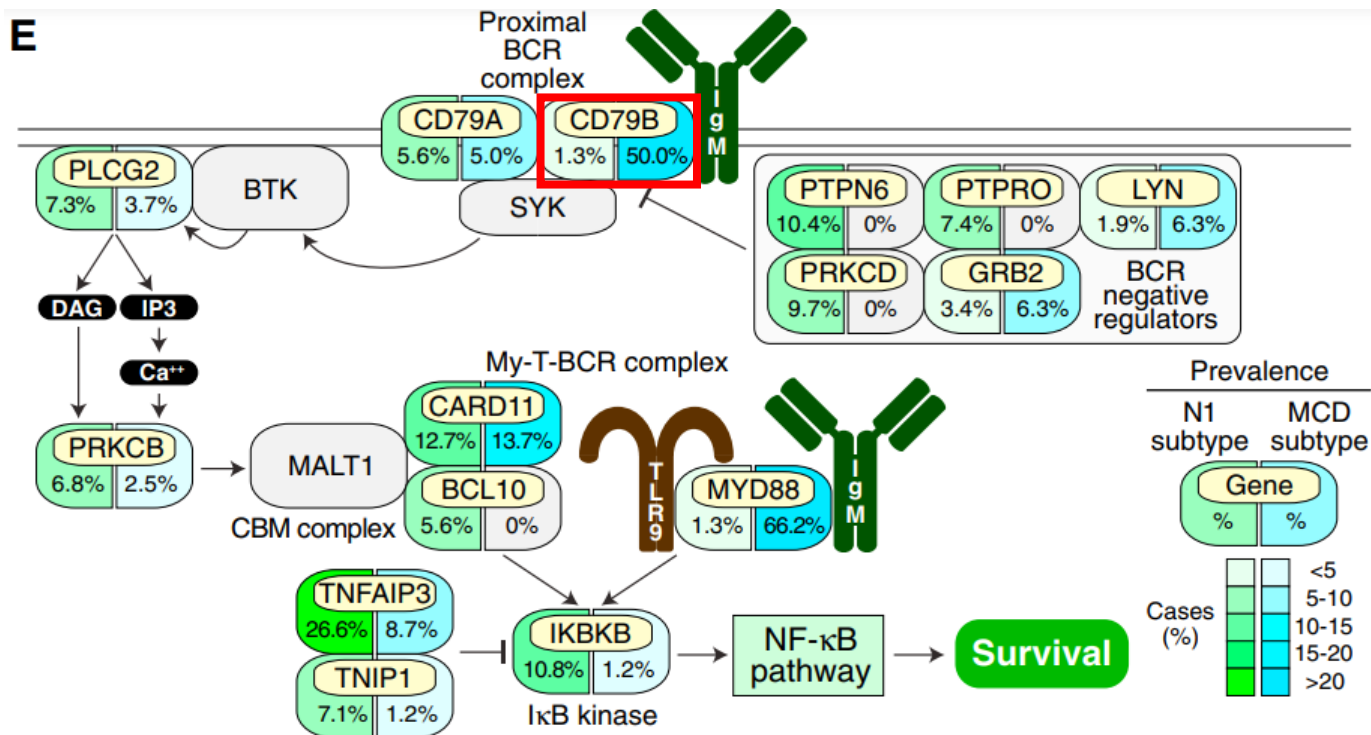


DEL, double-expressor lymphoma; IHC, immunohistochemistry; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; ULN, upper limit of normal; UNC, unclassified.

5-year OS - ARR: 14.7%; RRR: 51%

Baseline risk factors		OS					
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI
		n	60-month (%)	n	60-month (%)		
NanoString COO	NanoString GCB	187	82.9	170	82.3	0.99	0.60–1.61
	NanoString ABC	106	84.6	129	69.9	0.49	0.28–0.88
	NanoString UNC	44	76.9	53	94.2	4.46	1.23–16.21
	Unknown	103	81.3	87	79.0	0.80	0.42–1.51

ABC subtype rely upon chronic active BCR signaling

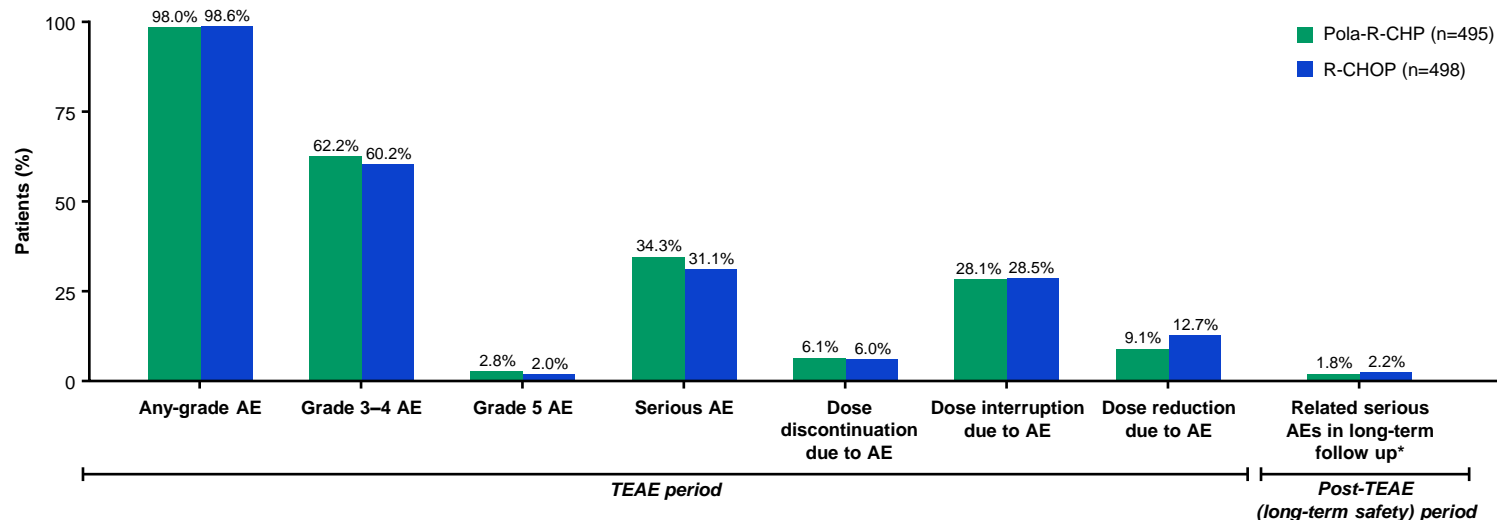


Pola-R-CHP for ABC subtype

Table 1. Notable studies showing greater benefit in patients with ABC (or non-GCB) COO DLBCL receiving polatuzumab

Variable	Tilly et al ¹	Morschhauser et al ¹⁰	Sehn et al ¹¹ and Sehn et al ¹²	Terui et al ¹³	Liu et al ¹⁴	Segman et al ^{15,16}	Tsai et al ¹⁷ and Wang et al ¹⁸
Trial identifier	POLARIX (NCT03274492)	ROMULUS (NCT01691898)	GO29365 (NCT02257567)	JapicCTI-184048	N/A	N/A	N/A
Study design	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective
Location	International	International	International	Japan	China	Israel	Taiwan
Clinical setting	Frontline DLBCL	Rel/ref DLBCL ≥1 prior therapies	Rel/ref DLBCL ≥1 prior therapies Ineligible for ASCT	Rel/ref DLBCL ≥1 prior therapies Ineligible for ASCT	Rel/ref DLBCL ≥2 prior therapies	Rel/ref DLBCL ≥2 prior therapies	Rel/ref DLBCL ≥2 prior therapies
Treatment	Pola-R-CHP vs R-CHOP	Polatuzumab + R	Polatuzumab + BR	Polatuzumab + BR	Polatuzumab + BR or R	Polatuzumab + B ± R	Polatuzumab + physician's choice chemotherapy
Sample size*	Pola-R-CHP: 440 R-CHOP: 439	23	32	35	28	34	40
ORR in ABC (or non GCB) vs GCB, %	2-y PFS [†] ABC: Pola-R-CHP: 83.9 vs R-CHOP: 58.8 GCB: Pola-R-CHP: 75.1 vs R-CHOP: 76.9	83.3 vs 45.5	58.8 vs 33.3	46.2 vs 7.1 (CRR)	70.6 vs 63.6	80 vs 43	65.0 vs 31.3
COO method	NanoString Lymph2Cx	Fluidigm targeted gene expression profiling assay	NanoString Lymph2Cx and Hans algorithm	NanoString Lymph2Cx	Hans algorithm	Hans algorithm	Hans algorithm

Safety summary (expanded population)



Safety profile remained comparable between treatment arms, with no increased risks with long-term follow-up.
There was no substantial change in the proportion of patients with AEs ($\geq 5\%$) compared with the global population

Data cut-off: July 5, 2024. *TEAEs are defined as new or worsening AE from the first dose of study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier. After this TEAE period, the post-TEAE period (i.e. long-term safety follow up) reporting requirement is only for serious AEs that the investigator believes to be related to prior study drug treatment.

Select adverse events of particular interest (expanded population)

Patients, n (%)	Pola-R-CHP (n=495)	R-CHOP (n=498)	Patients, n (%)	Pola-R-CHP (n=495)	R-CHOP (n=498)
Peripheral neuropathy			Thrombocytopenia		
All grade	249 (50.3)	261 (52.4)	All grade	89 (18.0)	86 (17.3)
Grade 3–5	7 (1.4)	5 (1.0)	Grade 3–5	32 (6.5)	31 (6.2)
Neutropenia			Cardiac arrhythmias		
All grade	240 (48.5)	228 (45.8)	All grade	18 (3.6)	26 (5.2)
Grade 3–5	216 (43.6)	205 (41.2)	Grade 3–5	3 (0.6)	5 (1.0)
Infections			Carcinogenicity*		
All grade	237 (47.9)	219 (44.0)	All grade	5 (1.0)	12 (2.4)
Grade 3–5	75 (15.2)	66 (13.3)	Grade 3–5	5 (1.0)	9 (1.8)
Anemia					
All grade	165 (33.3)	150 (30.1)			
Grade 3–5	56 (11.3)	49 (9.8)			

There was a <5% difference in hematological toxicities and infections in the Pola-R-CHP versus R-CHOP arm.
Fewer secondary malignancies were observed with Pola-R-CHP versus R-CHOP.

Data cut-off: July 5, 2024. *Carcinogenicity includes TEAEs with onset dates occurring during the AE reporting period and after the TEAE reporting period. The TEAE reporting period is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier. The carcinogenicity events in the R-CHOP arm included adenocarcinoma (2 patients), prostate cancer (2 patients), glioblastoma, basal cell carcinoma, malignant lung neoplasm, lymphocytic leukemia, in situ malignant melanoma, acute myeloid leukemia, glottis carcinoma, and Hodgkin's disease and in the Pola-R-CHP arm included adenocarcinoma of the colon (2 patients), colorectal cancer (2 patients), and papillary renal cell carcinoma.

Salles G et al. ASH 2024.
Oral presentation 469.

Cost effectiveness for
treatment of ABC-subtype
DLBCL

Direct medical costs = Total treatment cost

Direct medical costs:

- Drug treatment (generic/similar)
 - CMED Jul/24 PF
 - Biosimilar/Generic
- Monitoring/Follow up
- Key AEs



Average weight = 70 kg
Average height 171 cm
Body surface area = 1.82 m²

Budget impact

Scenario 2 = Patients on **Pola-R-CHP** in 1L
Vs
Scenario 1 = Patients on **R-CHOP** in 1L

- If **positive**, this means incremental **cost** with inclusion of Pola-R-CHP vs costing for Scenario 1
- If **negative**, means **savings** from including Pola-R-CHP vs costing from Scenario 1

References to disease progression data*

Response	Progression Rate*	References
R-CHOP ABC Subgroup	41.20%	Tilly H, et al. Polatuzumab vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. <i>N Engl J Med.</i> 2022; 386:351-363
Pola-R-CHP ABC Subgroup	16.10%	Tilly H, et al. Polatuzumab vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. <i>N Engl J Med.</i> 2022; 386:351-363
R-DA-EPOCH	28.00%	Jermann M, Jost LM, Taverna Ch, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. <i>Ann Oncol.</i> 2004 Mar;15(3):511-6. doi: 10.1093/annonc/mdh093.
R-ICE + autologous HSCT	47.00%	Gisselbrecht C, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. <i>J Clin Oncol</i> 2010;28:4184-4190.J, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. <i>Cancer Invest.</i> 2006 Oct;24(6):593-600. doi: 10.1080/07357900600814490.
R-DHAP + autologous HSCT	47.00%	Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. <i>J Clin Oncol</i> 2010;28:4184-4190.J
R-GDP + autologous HSCT	47.00%	Crump M, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. <i>Clin Oncol.</i> 2014 Nov 1;32(31):3490-6.
Axicabtagene ciloleuce (2nd line)	54.00%	Locke F et al. Axicabtagene Ciloleuce as Second-Line Therapy for Large B-Cell Lymphoma. <i>N Engl J Med.</i> 2022 Feb 17;386(7):640-654.
Axicabtagene ciloleuce (3rd line)	60.00%	Neelapu, s. et al. Axicabtagene Ciloleuce CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. <i>N Engl J Med.</i> 2017 Dec 28;377(26):2531-2544.
Tisagenlecleuce	62.00%	Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleuce in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicenter, open-label, single-arm, phase 2 study. <i>Lancet Oncol.</i> 2021 Oct;22(10):1403-1415. doi: 10.1016/S1470-2045(21)00375-2.
Tafasitamab + Lenalidomide	54.00%	Salles G et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicenter, prospective, single-arm, phase 2 study. <i>Lancet Oncol.</i> 2020 Jul;21(7):978-988.
Pola-BR	71.60%	Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. <i>J Clin Oncol.</i> 2020 Jan 10;38(2):155-165.
Eporitamab	72.20%	Thieblemont C, Phillips T, Ghesquieres H, et al. Eporitamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. <i>J Clin Oncol.</i> 2023 Apr 20;41(12):2238-2247. doi: 10.1200/JCO.22.01725.
R-GemOx	86.10%	Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy: a phase II Lymphoma Study Association trial. <i>Haematologica</i> 2013;98:1726-1731.

*For calculation of disease progression we use the formula Progression = 1-PFS. Where PFS is 2-year progression-free survival. The choice of this parameter is due to the recognition in the literature that patients free of progression in 2 years have overall survival clinically indistinguishable from healthy individuals matched by gender, age and country.^{1,2}
1- Maurer, M. et al, 2018. 2- Qian S. et al., 2018.

Impact of TRADITIONAL treatments on the cost of disease

Treatment line	Treatment	Progressive disease (%)	COST PER PATIENT
1L	R-CHOP (ABC subgroup)	41.2	BRL 67,236.39
2L	R-ICE + autologous HSCT*	47.0	BRL 48,351.33 + BRL 247,636.39
2L+	R-GemOx	86.1	BRL 81,654.61

*R-ICE, R-DHAP and R-GDP response rates as autologous transplant rescue have no statistically significant difference and their choice is idiosyncratic at each service. Progression rate for patients who responded to rescue therapy and underwent transplant is 47% (1-53%).^{3,4}

1. Crump, M. et al. 2014; 2. Gisselbrecht, C. et al. 2010.

IMPACT OF NEW TREATMENTS ON COSTS

Treatment line	Treatment	Progressive disease (%)	COST PER PATIENT	Proportion of increased cost vs Pola-R-CHP
1L	Pola-R-CHP (ABC subgroup)	16.1	BRL 511,974.35	-
2L	Axicabtagene Ciloleucel	54.0	BRL 2,519,822.95	4.9
2L+	Tafasitamab + Lenalidomide	54.0	BRL 920,811.96	1.8
3L	Eporitamab	72.2	BRL 2,417,572.92	4.7
	Axicabtagene Ciloleucel	60.0	BRL 2,499,379.33	4.9

INCREASED EFFICIENCY in resource allocation when patients with ABC profile are treated with Pola-R-CHP in 1L

Evaluation Scenarios

	Scenario 1	Scenario 2
1L treatment	R-CHOP (ABC subgroup)	Pola-R-CHP (ABC subgroup)
Market share	100%	100%
2L- 4L Treatments	Same treatments and market share	

Costs Scenario 1 (R-CHOP ABC subgroup in 1L)

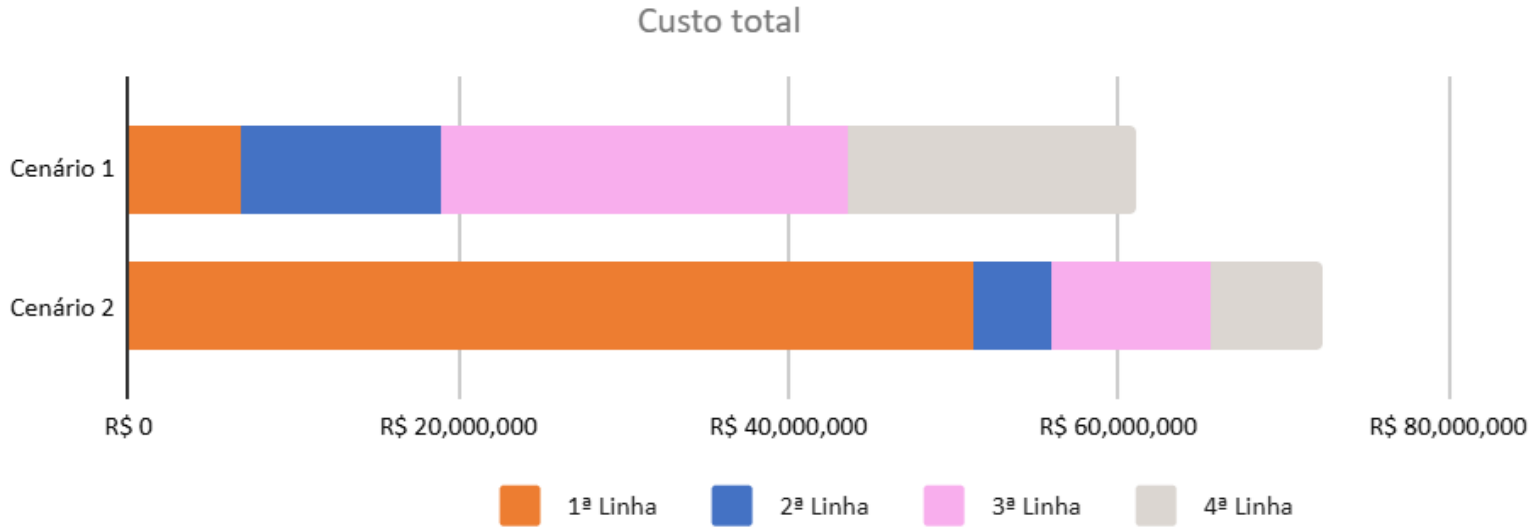
Treatment line	Number of patients	Cost of treatment	
		Per patient	For cohort
1ST	100	BRL 67,236	BRL 6,723,639
2ND	41	BRL 295,132	BRL 12,159,452
3RD	32	BRL 784,044	BRL 24,792,372
4TH	25	BRL 698,837	BRL 17,389,143
TOTAL			BRL 61,064,606

Costs Scenario 2 (Pola-R-CHP ABC subgroup in 1L)

Treatment line	Number of patients	Cost of treatment	
		Per patient	For cohort
1ST	100	BRL 511,974.35	BRL 51,197,435
2ND	16	BRL 295,132	BRL 4,751,631
3RD	12	BRL 784,044	BRL 9,688,281
4TH	10	BRL 698,837	BRL 6,795,272
TOTAL			BRL 72,432,619



Budget Impact Analysis



Enrollment of Pola-R-CHP requires an additional investment of 11.9%

Does the benefit of Polaris motivate first-line treatment change?

YES

- This is the first ph3 randomized study showing a PFS benefit versus R-CHOP.
- The PFS gain at 2 years is associated with better outcomes.
- The lack of OS benefit is related to the patient population, the high CR rate with R-CHOP, and subsequent therapies.
- Toxicity between the arms was mostly comparable.

ITT

NO

- The NNT at 5 years for progression, death, or subsequent therapy is 17.
- Pola-R-CHP was more associated with diarrhea, anemia, and febrile neutropenia than R-CHOP.
- Despite a 5-year follow-up, survival benefit was not observed.

ABC

- The benefit observed in high-risk subgroups (ABC, age > 60, and IPI > 2) demonstrates the efficacy of Pola-R-CHP and supports its use in "all scenarios".
- With 5-year FU, survival benefit was observed (HR 0.49, 0.28-0.88).
- The NNT at 5 years for progression, relapse or death is 4. For OS, is 7.
- Pola-R-CHP increases the cost of first-line treatment (~11.9%) with less than 25% patients progressing.

- Challenges with ABC diagnosis (methodology).
- This is a subgroup analysis and the study is not power for that conclusion.

CONCLUSIONS

- The addition of R to the CHOP protocol significantly improved efficacy and established **R-CHOP as the standard first-line treatment** for patients with DLBCL.
- In the POLARIX study, **Pola-R-CHP demonstrated superior PFS compared to R-CHOP**, a benefit that was confirmed at 5 years of follow-up.
- **Patients with an IPI score greater than 2 and with the ABC subtype** of COO appear to derive the greatest benefit from Pola-R-CHP versus R-CHOP.
- The advantage of Pola-R-CHP in the ABC subtype was reinforced by the 5-year follow-up of the POLARIX study, with **improvements observed in both PFS and OS**.
- Given emerging therapies that may offer enhanced efficacy in the ABC subtype, is there a need to develop more precise tools for COO classification in the daily practice?

Pesquisa de Satisfação





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M-BR-00019505 - Maio/2025

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HEMOCENTRO
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Obrigado!

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