

Hay un rol para Polar-CHP en LDCBG en entornos de bajos recursos?

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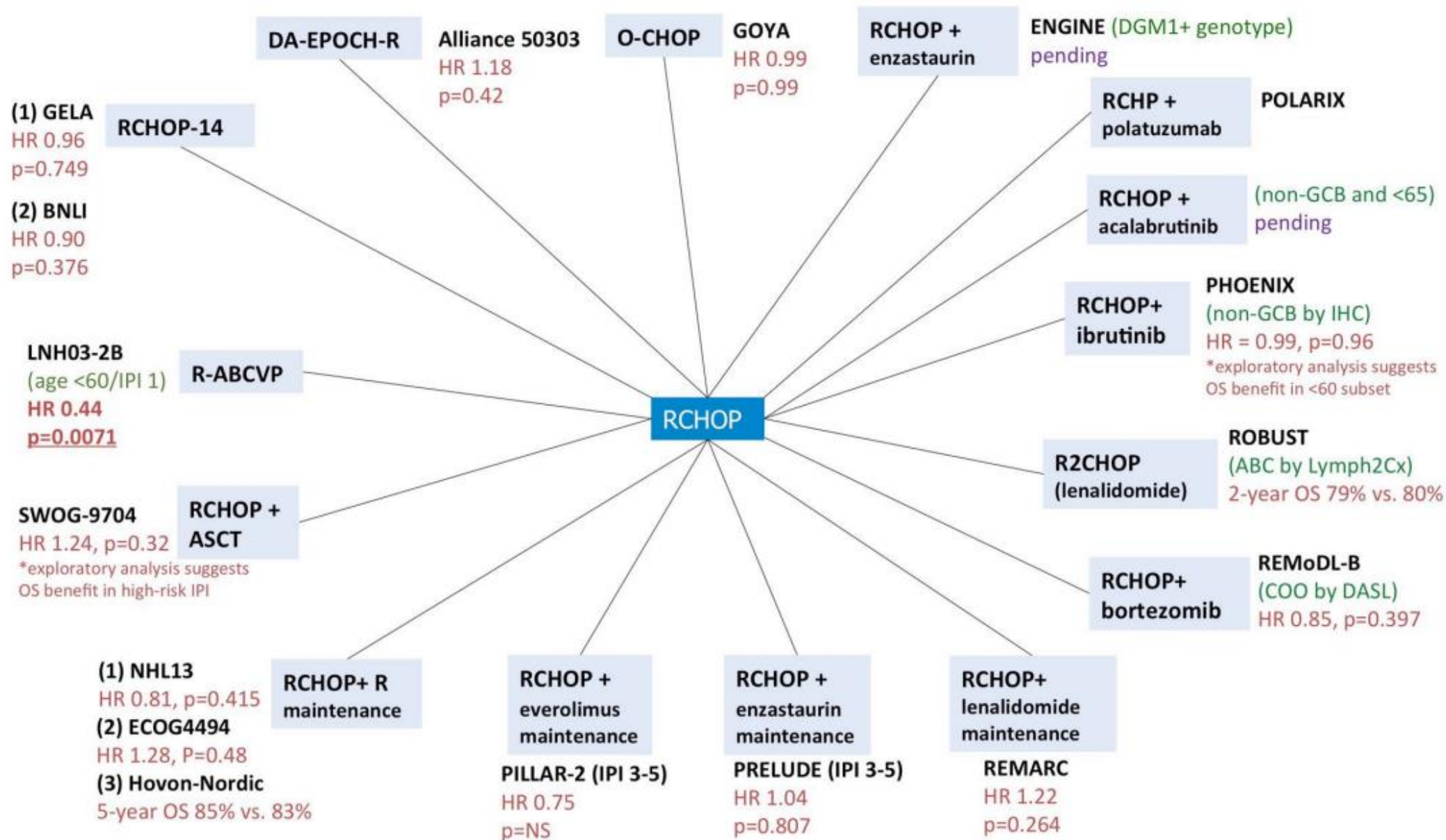
Conflitos de Interés

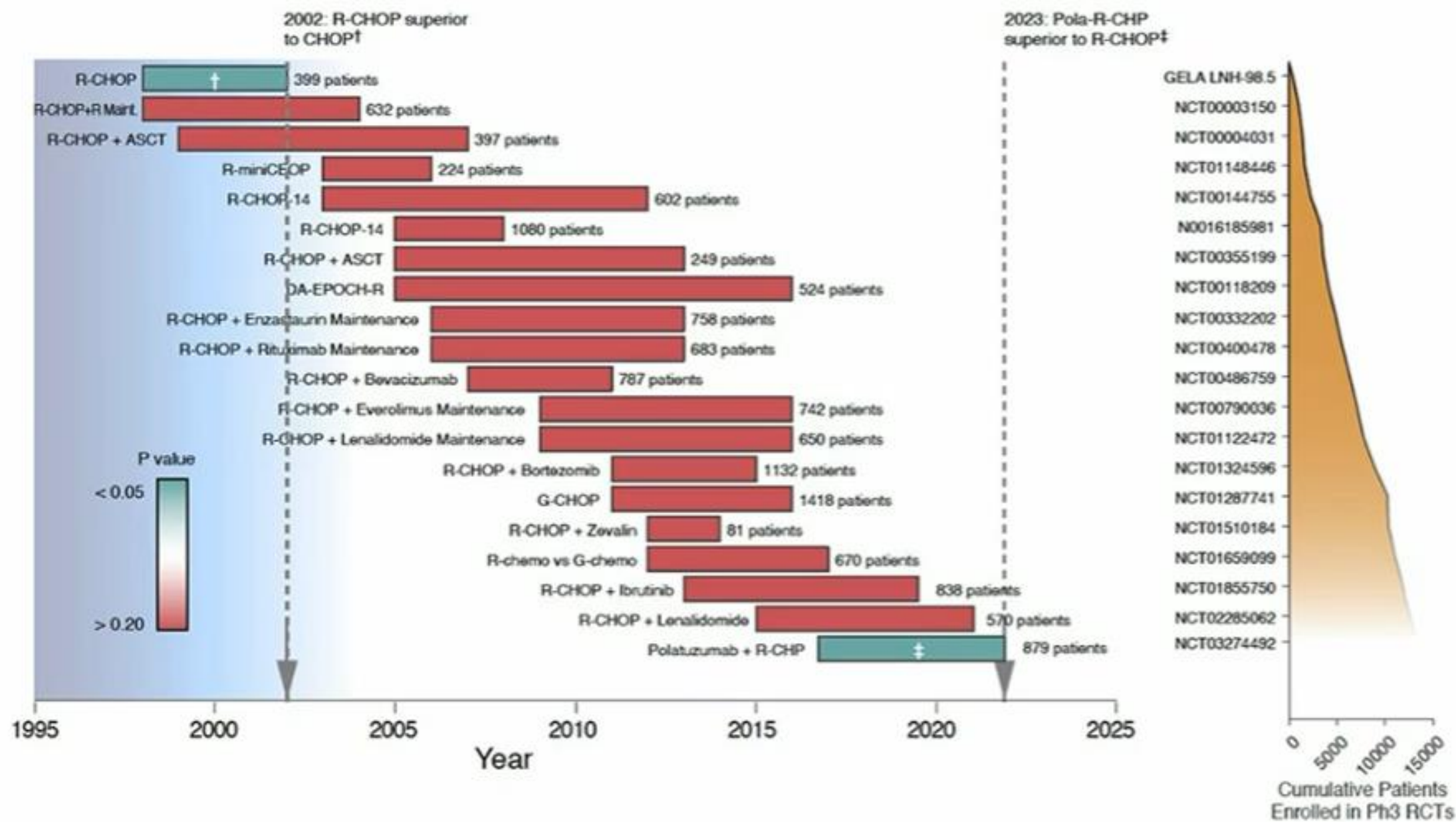
Speaker's Bureau: Janssen, Roche, Takeda, Abbvie, BMS, Lilly, BeiGene, Astra Zeneca, Abbvie

Educational Support: Janssen, Takeda, Roche, Abbvie

Advisory Board: Janssen, Roche, Abbvie, Astra Zeneca, Takeda

Research: Janssen, Millenium, Merck, BMS, BeiGene, MSD, Abbvie, Lilly, AstraZeneca



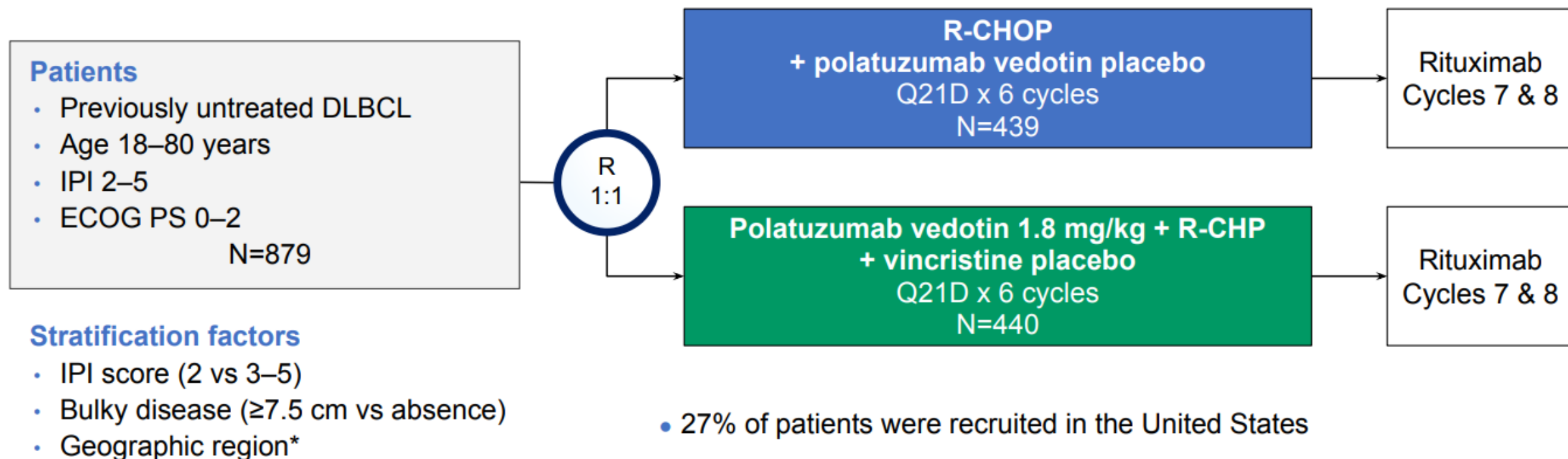


After Alizadeh and Kurtz; NEJM 2023

POLARIX is a Phase III Study Evaluating Pola+R-CHP vs R-CHOP

Multiregional, randomized, double-blind, active and placebo controlled trial

- Collaboration with the Lymphoma Study Association (LYSA) and Steering Committee.



*Western Europe, United States, Canada and Australia versus Asia versus Rest of World.

IPI, International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q21D, every 21 days.

Patient Demographics and Baseline Characteristics

Balanced between the 2 arms and representative of patients with 1L DLBCL

Intention-to-Treat population		R-CHOP (N=439)	Pola+R-CHP (N=440)
Age	Median (range), years	66 (19–80)	65 (19–80)
Sex, n (%)	Male	234 (53)	239 (54)
ECOG Performance Status, n (%)	0–1	363 (83)	374 (85)
	2	75 (17)	66 (15)
Bulky disease (≥7.5cm), n (%)	Present	192 (44)	193 (44)
Elevated LDH, n (%)	Yes	284 (65)	291 (66)
Time from diagnosis to treatment initiation	Median, days	27	26
Ann Arbor Stage, n (%)	III–IV	387 (88)	393 (89)
Extranodal sites, n (%)	≥2	213 (49)	213 (48)
IPI score, n (%)	2	167 (38)	167 (38)
	3–5	272 (62)	273 (62)
Cell-of-origin, n (%)*	ABC	119 (35)	102 (31)
	GCB	168 (50)	184 (56)
	Unclassified	51 (15)	44 (13)
MYC/BCL2 expression, n (%)*	Double expression	151 (41)	139 (38)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	19 (6)	26 (8)

*In the Pola+R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for MYC/BCL2/BCL6 rearrangements were 331 and 334.

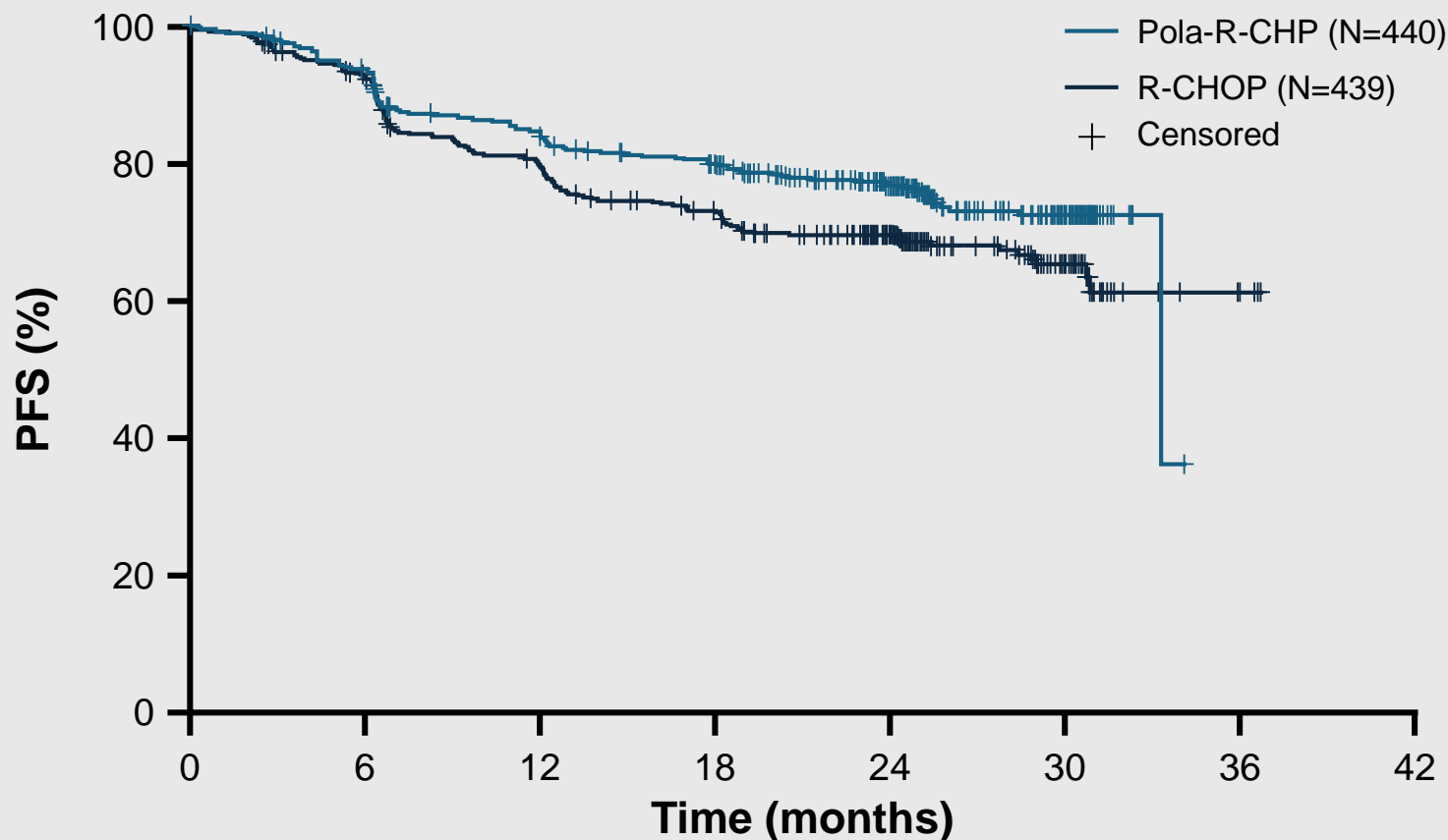
ABC, activated B-cell; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

POLARIX Primary Endpoint: Progression-Free Survival

INITIAL ANALYSIS



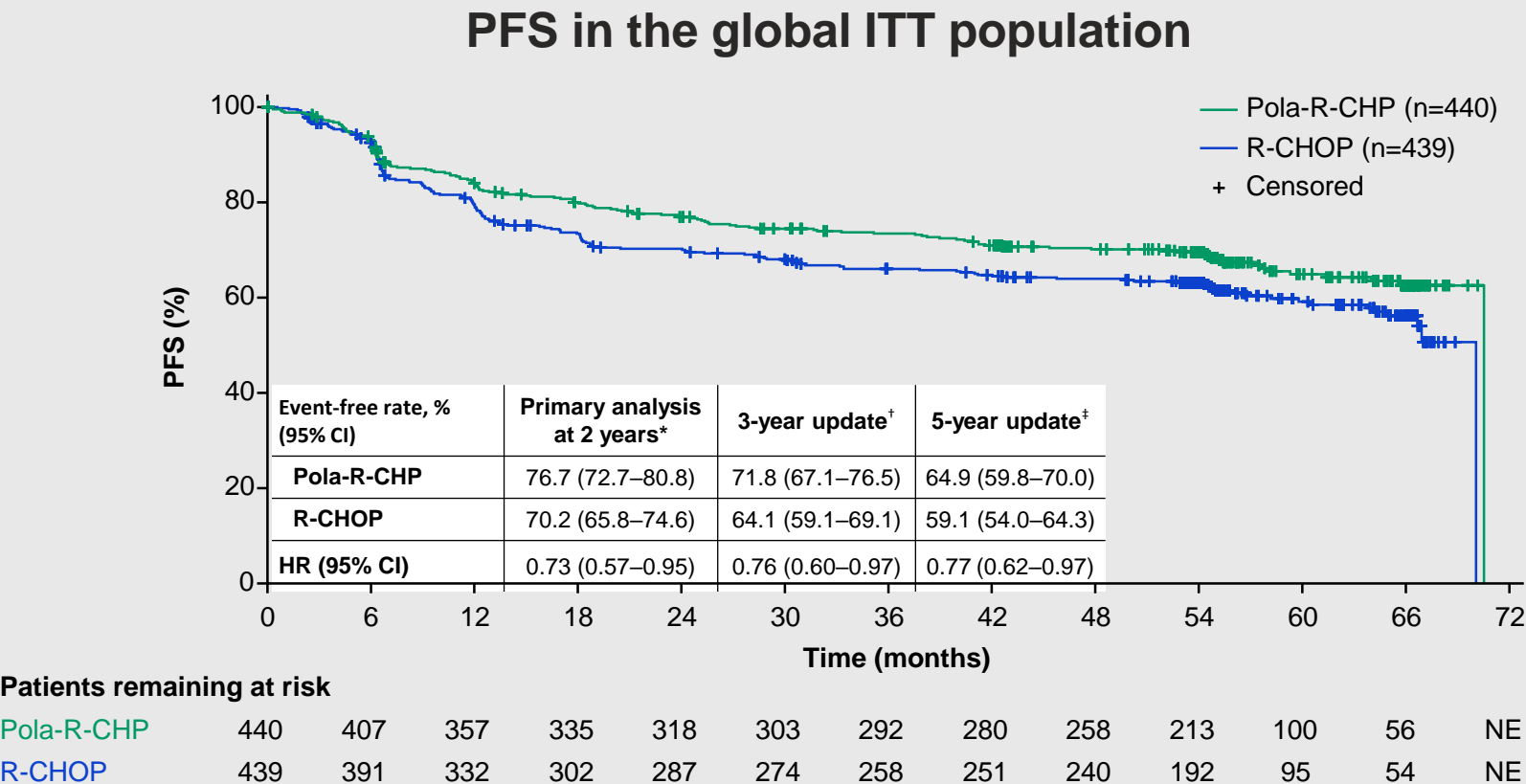
Pola-R-CHP Significantly Improved PFS Versus R-CHOP



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

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

Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years

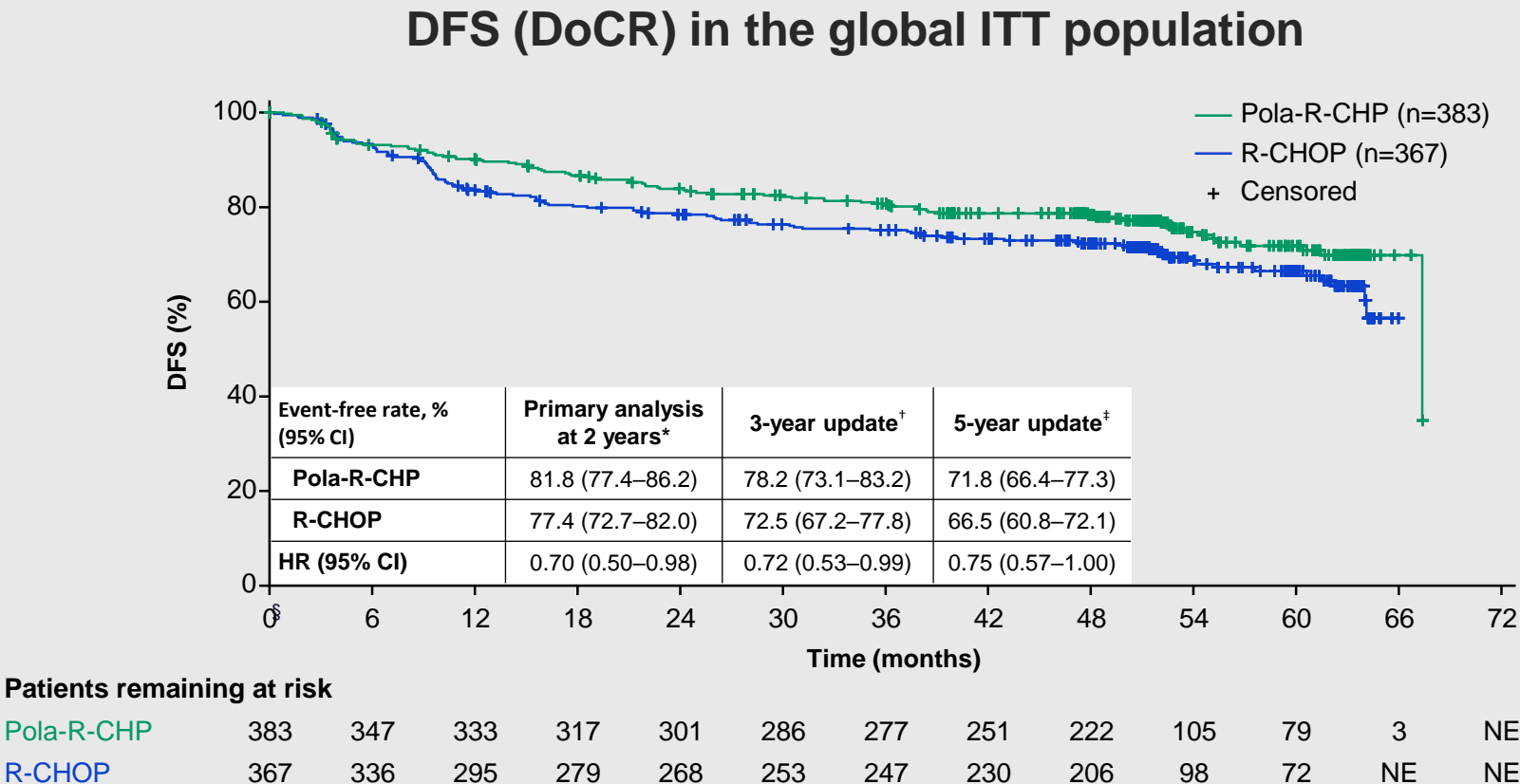


At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).¹

*Data cut-off: June 28, 2021; †Data cut-off: June 15, 2022; ‡Data cut-off: July 5, 2024.
CI, confidence interval; HR, hazard ratio; NE, not evaluable.



Complete remission obtained after Pola-R-CHP treatment is maintained with 5-year follow-up



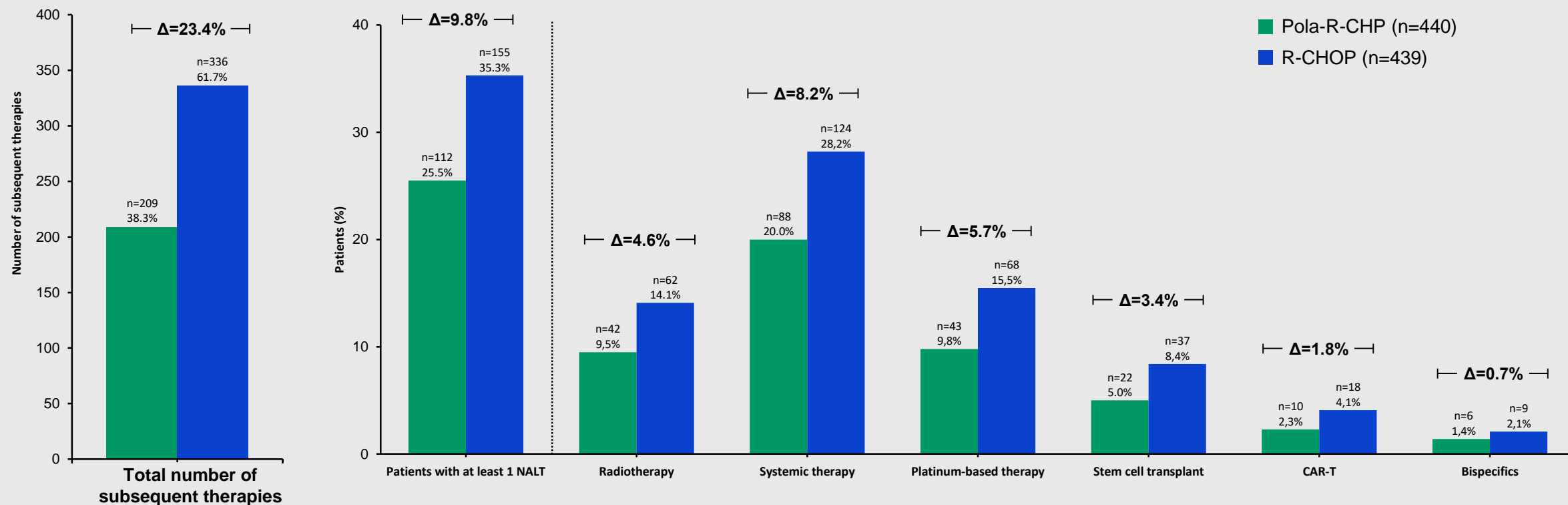
Complete remissions are durable and sustained with longer follow-up.

*Data cut-off: June 28, 2021; [†]Data cut-off: June 15, 2022; [‡]Data cut-off: July 5, 2024; §CR assessment occurred at the 0-month timepoint. CR, complete remission; DFS, disease-free survival; DoCR, duration of complete remission.



Patients treated with Pola-R-CHP required 23% fewer subsequent therapies versus patients treated with R-CHOP

Subsequent therapies in the global ITT population



Patterns of subsequent therapies received on study mirror routine clinical care at the time of study conduct.

Data cut-off: July 5, 2024.

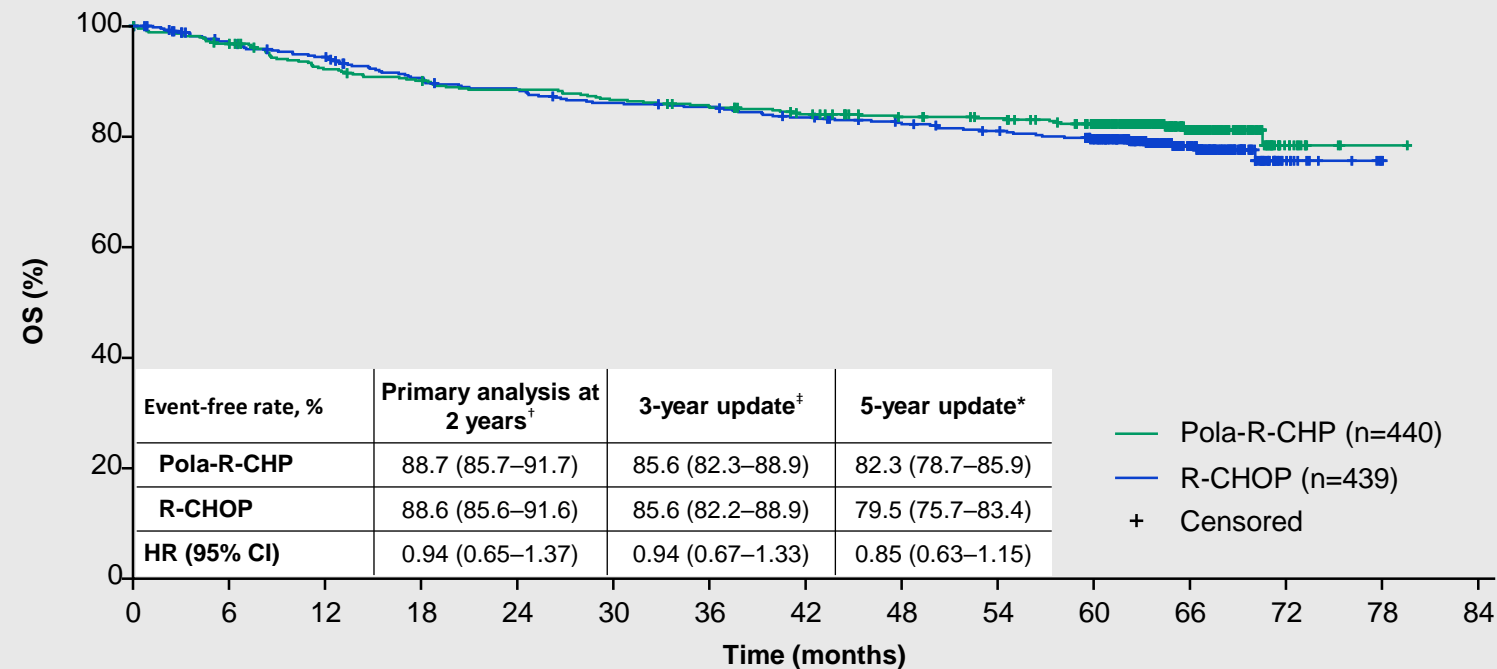
CAR-T, chimeric antigen receptor T-cell therapy; NALT, new anti-lymphoma treatment.

Morschhauser F. et al. JCO 2025.

5-year overall survival shows favorable results for Pola-R-CHP-treated patients



OS in the global 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

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



Deaths associated with lymphoma progression are numerically fewer with Pola-R-CHP vs R-CHOP in the global population

n (%)	Pola-R-CHP (n=440)	R-CHOP (n=439)
Total deaths	80 (18.2)	92 (21.0)
Progressive disease	40 (9.1)	51 (11.6)
Not disease related	23 (5.2)	28 (6.8)
Infection	7 (1.6)	12 (2.7)
Secondary malignancy*	7 (1.6)	5 (1.1)
Cardiovascular	4 (0.9)	4 (0.9)
COVID-19	2 (0.5)	4 (0.9)
Other [†]	3 (0.7)	3 (1.1)
Unknown [‡]	17 (3.9)	11 (2.5)

Most deaths were related to progressive disease (Pola-R-CHP, 50%; R-CHOP, 55%).
The nature and frequency of lymphoma-unrelated deaths were similar between treatment arms.

*Deaths due to secondary malignancies included colorectal cancer, melanoma, non-small cell lung cancer, pancreatic cancer, ovarian cancer, small bowel adenocarcinoma with liver metastases, and T-cell lymphoma in the Pola-R-CHP arm; and acute myeloid leukemia (2 patients), glioblastoma, metastatic pancreatic cancer, and unspecified second cancer in the R-CHOP arm; [†]Deaths due to other reasons included acute kidney injury, intestinal perforation, and respiratory failure in the Pola-R-CHP arm; and intracranial hemorrhage, liver failure, injury, other, and multiple organ dysfunction syndrome in the R-CHOP arm; [‡]Deaths due to unknown reasons included deaths reported by public records where reasons for death were not collected per reporting standards.



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

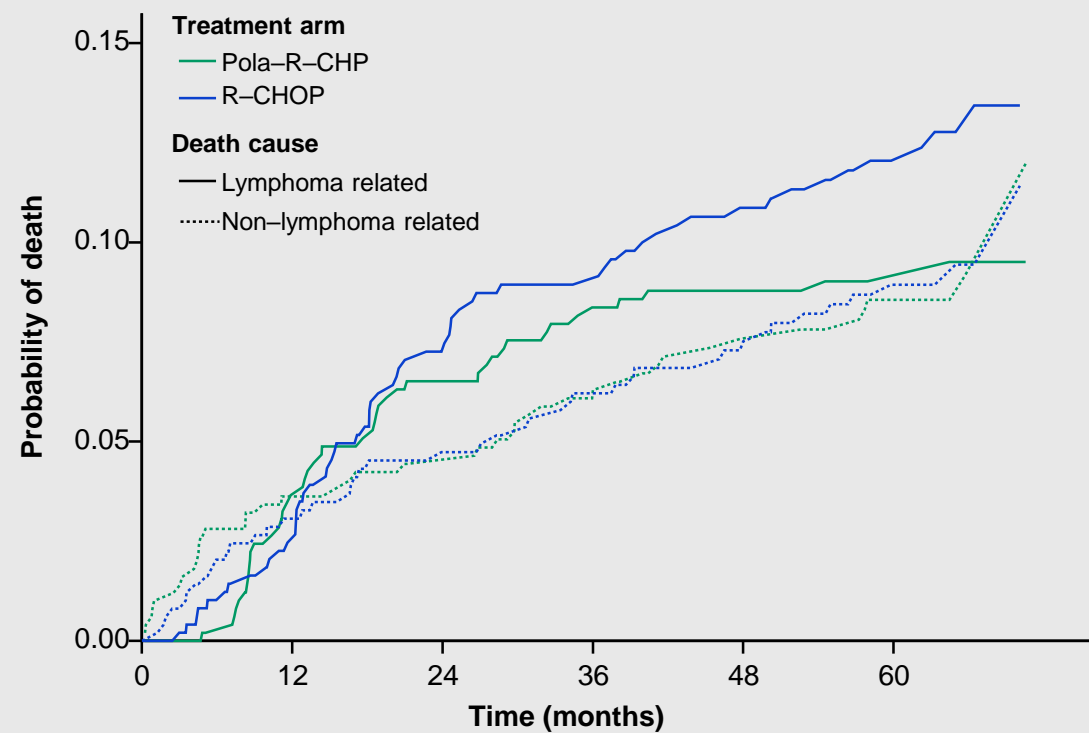
Baseline risk factors		PFS								OS							
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better	Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better
		n	60-month (%)	n	60-month (%)					n	60-month (%)	n	60-month (%)				
All patients		440	64.9	439	59.1	0.78	0.62–0.97			440	82.3	439	79.5	0.85	0.63–1.16		
Age group	≤65	225	69.6	219	64.3	0.80	0.57–1.11			225	89.1	219	84.7	0.73	0.44–1.21		
	>65	215	60.0	220	54.5	0.78	0.58–1.06			215	75.3	220	74.5	0.95	0.65–1.38		
Stratification – IPI score	2	167	67.2	167	68.3	0.91	0.61–1.36			167	87.6	167	87.4	0.96	0.53–1.75		
	3–5	273	63.2	272	53.5	0.72	0.55–0.94			273	79.2	272	74.7	0.81	0.57–1.15		
Stratification – bulky disease (≥ 7cm)	Absent	247	69.9	247	60.0	0.61	0.44–0.83			247	83.9	247	80.9	0.79	0.52–1.20		
	Present	193	58.5	192	57.9	1.02	0.73–1.41			193	80.3	192	77.9	0.92	0.60–1.43		
Baseline LDH	≤1xULN	146	65.3	154	64.8	0.83	0.55–1.23			146	88.7	154	87.9	0.85	0.45–1.61		
	>1xULN	291	64.3	284	55.7	0.77	0.59–1.01			291	79.0	284	74.9	0.85	0.60–1.19		
No. of extranodal sites	0–1	227	68.1	226	64.2	0.78	0.56–1.09			227	83.7	226	81.9	0.86	0.56–1.34		
	≥2	213	61.2	213	53.8	0.78	0.58–1.06			213	80.9	213	77.1	0.85	0.56–1.28		
NHL subtype	DLBCL, NOS, ABC, GCB	373	65.7	367	58.8	0.75	0.59–0.95			373	81.9	367	79.8	0.89	0.64–1.23		
	HGBL, NOS, DHL/THL	43	66.0	50	57.6	0.67	0.33–1.37			43	85.4	50	72.4	0.46	0.18–1.22		
	Other LBCL	24	49.7	22	70.3	1.86	0.69–5.04			24	83.3	22	90.9	1.93	0.35–10.52		
NanoString COO	NanoString GCB	187	65.9	170	65.8	1.07	0.74–1.56			187	82.9	170	82.3	0.99	0.60–1.61		
	NanoString ABC	106	72.5	129	45.8	0.38	0.24–0.59			106	84.6	129	69.9	0.49	0.28–0.88		
	NanoString UNC	44	55.2	53	70.8	1.60	0.79–3.25			44	76.9	53	94.2	4.46	1.23–16.21		
	Unknown	103	60.2	87	59.7	0.83	0.51–1.33			103	81.3	87	79.0	0.80	0.42–1.51		
Double expressor by IHC	DEL	139	63.1	151	50.0	0.65	0.45–0.94			139	76.4	151	73.0	0.84	0.53–1.33		
	Non DEL	223	66.6	215	64.7	0.89	0.64–1.24			223	86.3	215	82.8	0.81	0.51–1.30		
	Unknown	78	63.7	73	63.5	0.84	0.48–1.47			78	81.6	73	84.1	1.18	0.53–2.59		
		0.25 1 5 0.25 1 5															

- PFS and 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.



Competing risk analysis for deaths in the expanded population

Cumulative incidence plot of deaths due to lymphoma and from other causes



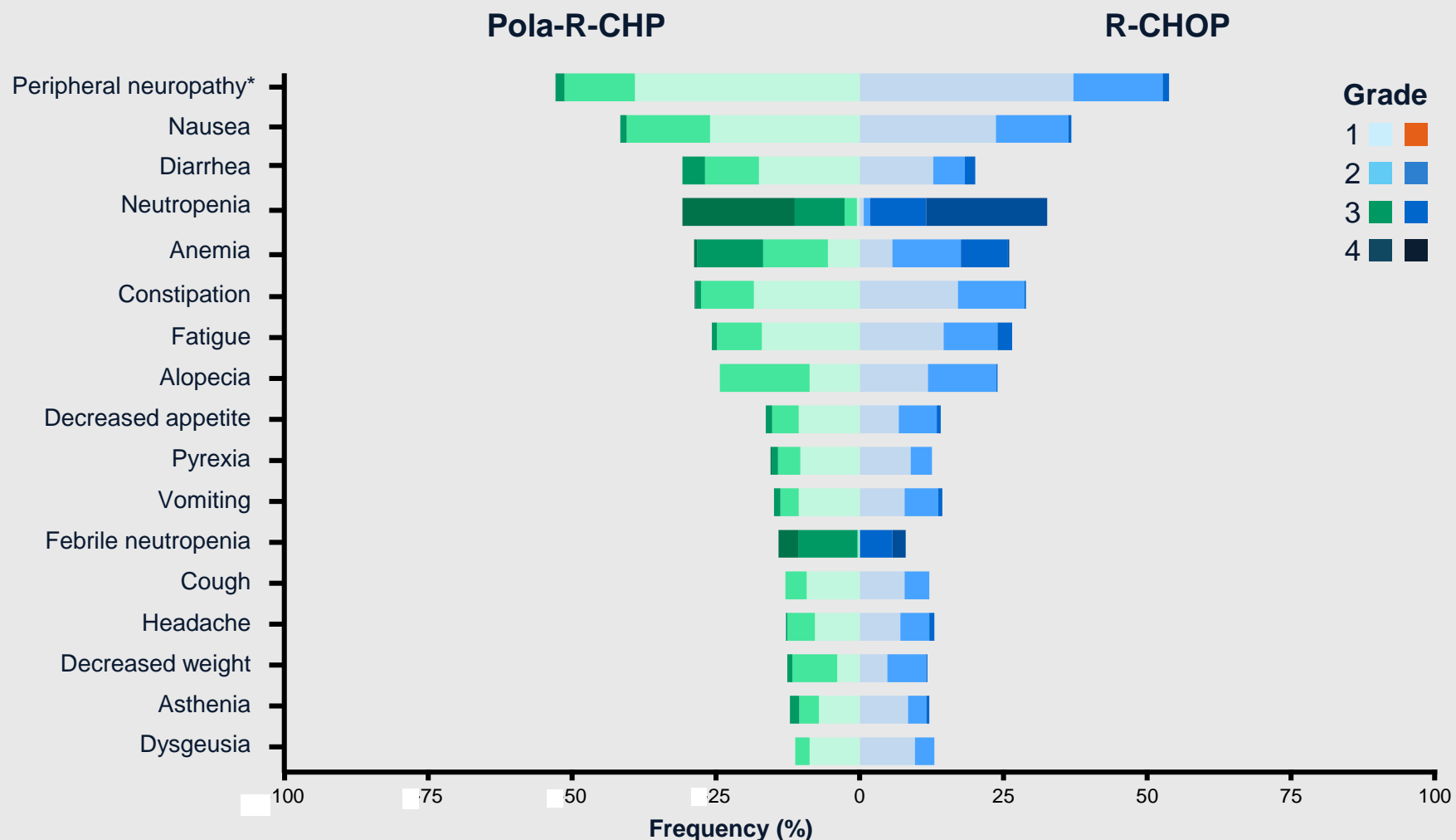
	Pola-R-CHP (n=500)	R-CHOP (n=500)
Probability of lymphoma-related deaths, %		
2 years	6.52	7.26
3 years	8.37	8.94
5 years	9.02	12.05
Probability of non-lymphoma-related deaths, %		
2 years	4.44	4.73
3 years	6.09	6.21
5 years	8.56	8.93

Cumulative incidence of lymphoma-related deaths was lower in patients treated with Pola-R-CHP versus R-CHOP (9.02% vs 12.05%).

Data cut-off: July 5, 2024. Competing risks for deaths were defined as deaths due to non-lymphoma related causes that prevent lymphoma-related deaths from occurring.



POLARIX: Common Adverse Events

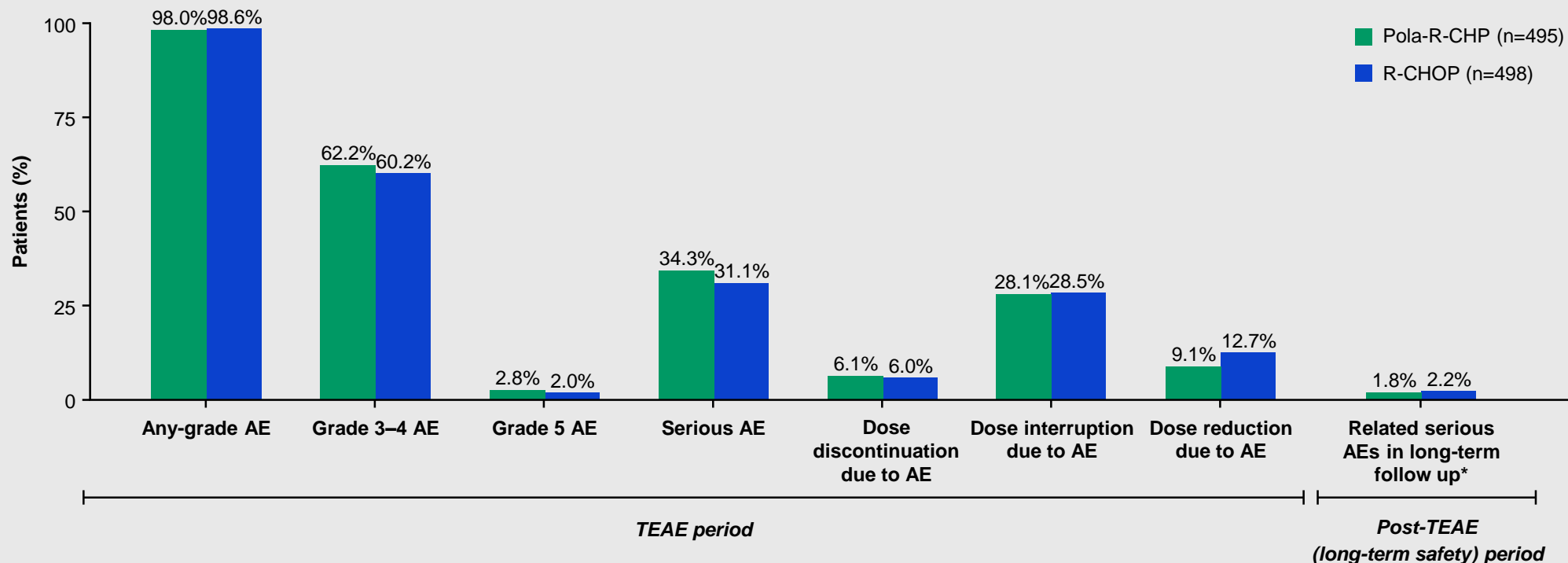


Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in $\geq 12\%$ of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.



Pola-R-CHP shows a favorable benefit–risk profile compared with R-CHOP in the expanded population

Safety summary



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. AE, adverse event; TEAE, treatment-emergent adverse event.



Select adverse events of particular interest in the expanded population

Patients, n (%)	Pola-R-CHP (n=495)	R-CHOP (n=498)
Peripheral neuropathy		
All grade	249 (50.3)	261 (52.4)
Grade 3–5	7 (1.4)	5 (1.0)
Infections		
All grade	237 (47.9)	219 (44.0)
Grade 3–5	75 (15.2)	66 (13.3)
Cardiac arrhythmias		
All grade	18 (3.6)	26 (5.2)
Grade 3–5	3 (0.6)	5 (1.0)
Carcinogenicity*		
All grade	5 (1.0)	12 (2.4)
Grade 3–5	5 (1.0)	9 (1.8)

Patients, n (%)	Pola-R-CHP (n=495)	R-CHOP (n=498)
Neutropenia		
All grade	240 (48.5)	228 (45.8)
Grade 3–5	216 (43.6)	205 (41.2)
Anemia		
All grade	165 (33.3)	150 (30.1)
Grade 3–5	56 (11.3)	49 (9.8)
Thrombocytopenia		
All grade	89 (18.0)	86 (17.3)
Grade 3–5	32 (6.5)	31 (6.2)

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.

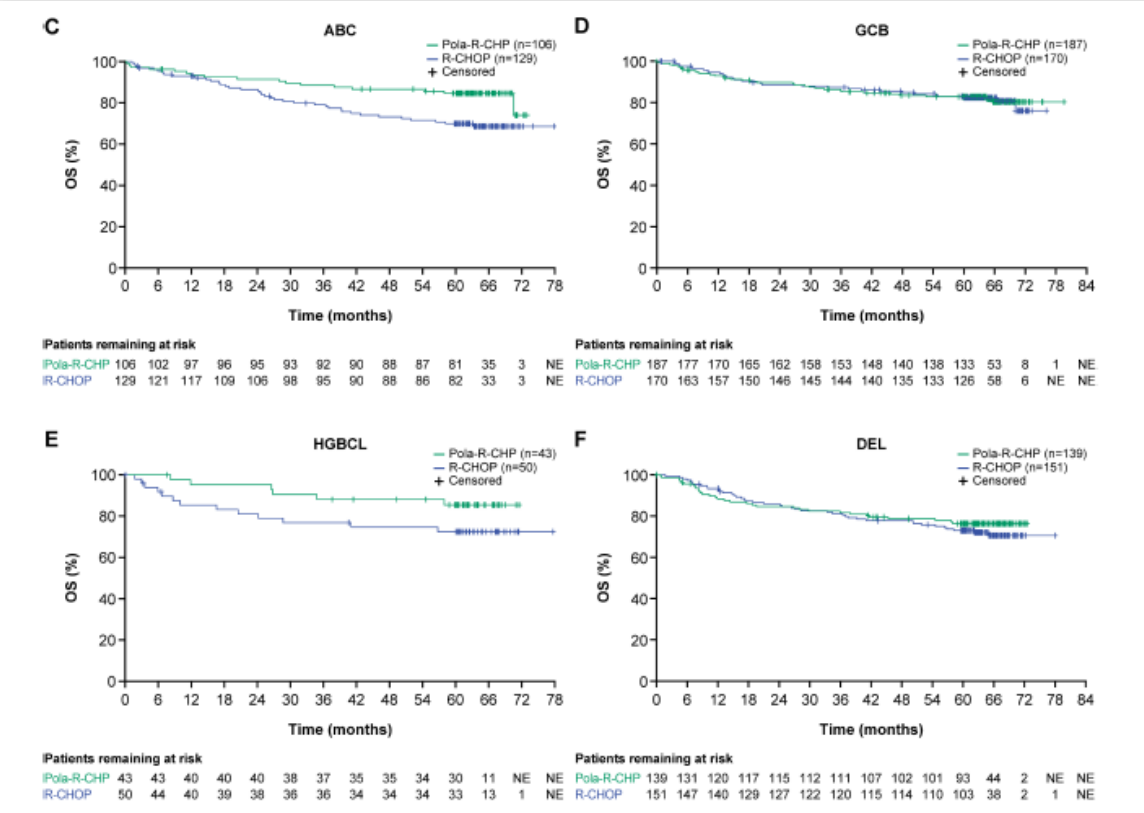
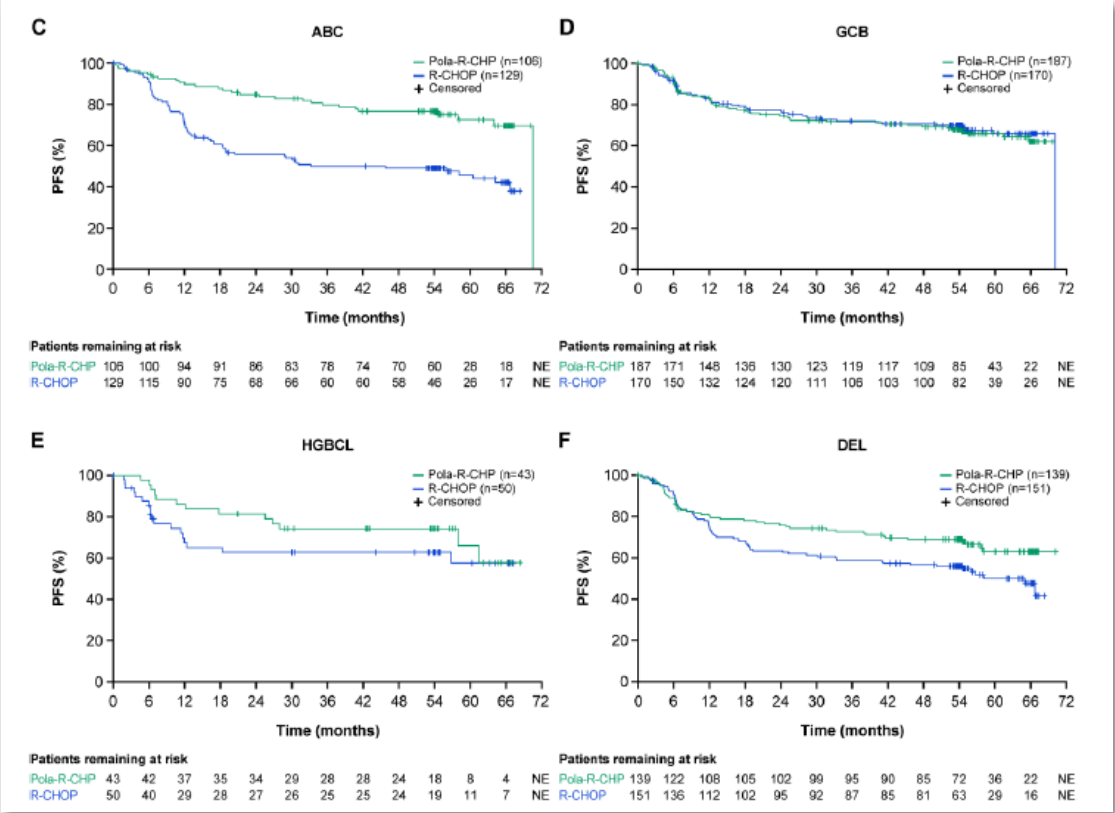
Data cut-off: July 5, 2024. *Carcinogenicity includes TEAEs with onset dates occurring during the AE reporting period and after the TEAE reporting period. The TEAE reporting period is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study 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.

POLARIX Study: Outcome in COO and other subtypes



Progression-Free Survival

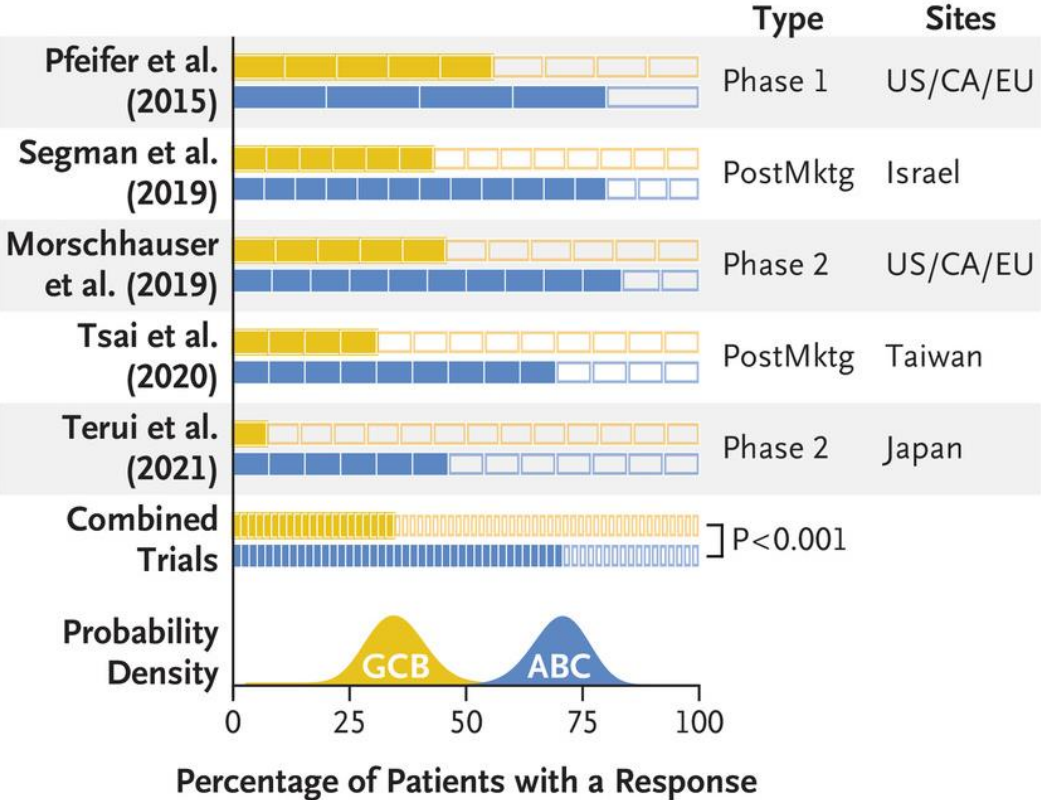
Overall Survival



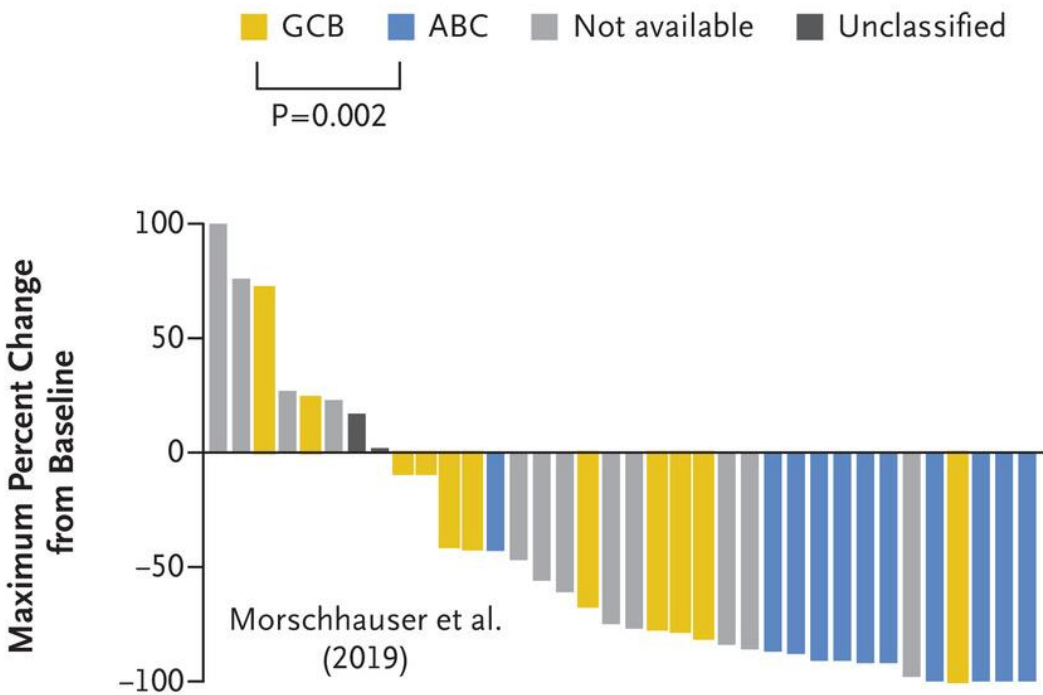


Pola en LNCBG subtipo ABC

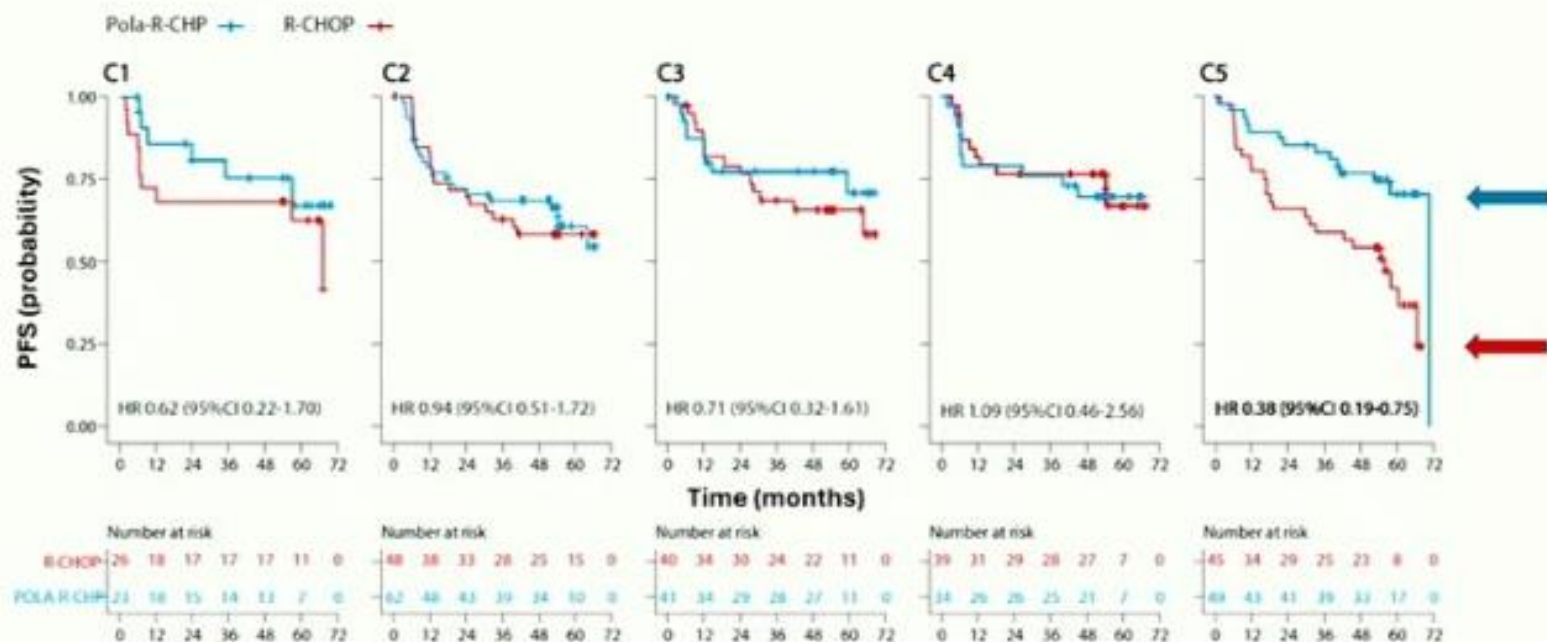
B Cell of Origin and Response to Polatuzumab Vedotin in DLBCL



C Cell of Origin and Response to Polatuzumab Vedotin Combined with Rituximab



Benefit of Pola-R-CHP in Patients with Cluster 5 DLBCLs



- 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



MCD/Cluster 5

Análise da Microscopia

Analísado o bloco de parafina de numeração AE23-064686. A amostra apresenta cerca de 90% de conteúdo tumoral no material avaliado.

Carga Mutacional Tumoral

10,2 mutações/Mb

Status Microssatélite

Instabilidade de microssatélites não detectada

Alterações Genômicas

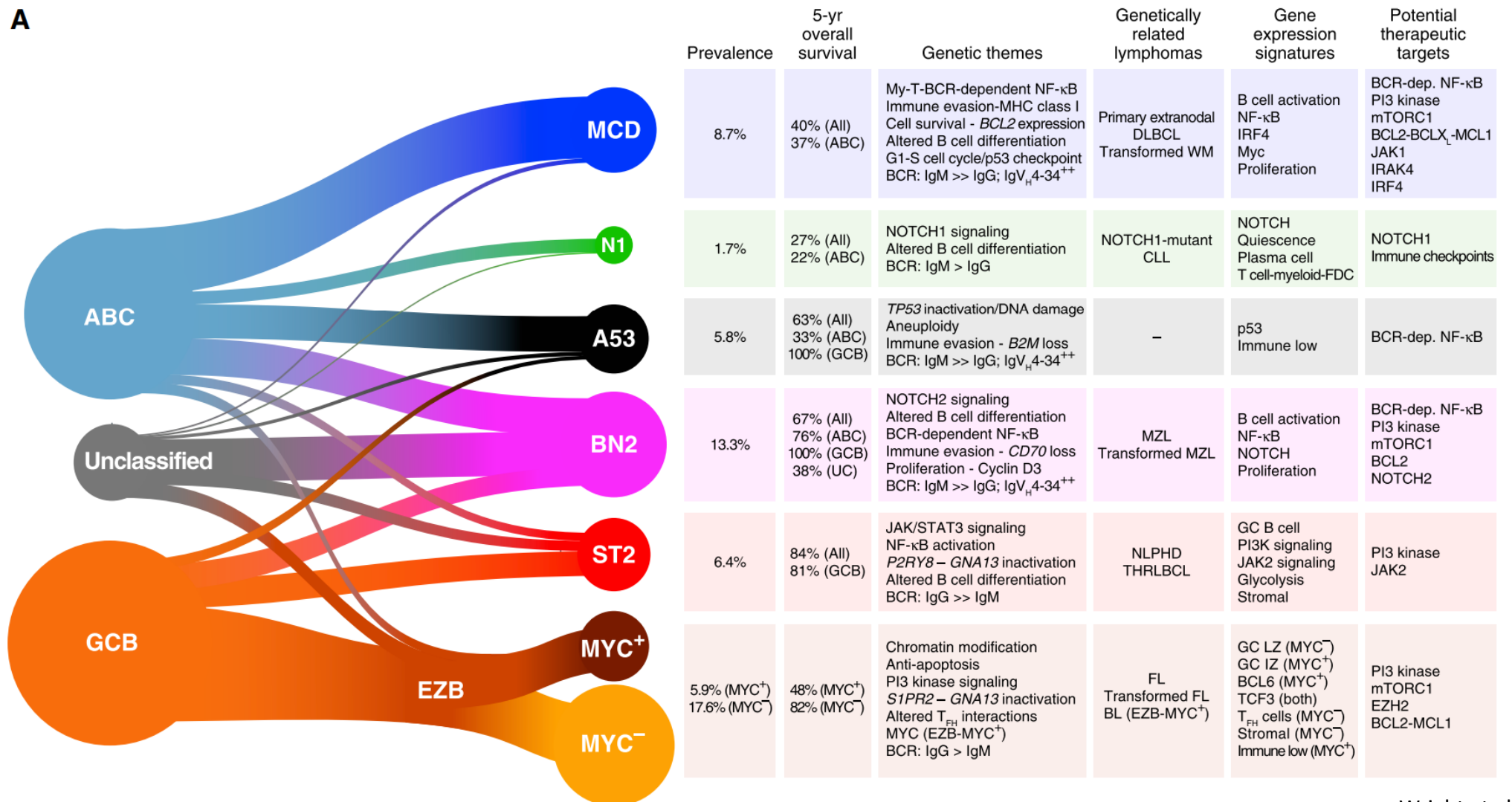
Foram encontradas variantes clinicamente relevantes envolvendo os genes MYD88, CD79B, HLA-C, ETV6, BTG1 e PIM1.

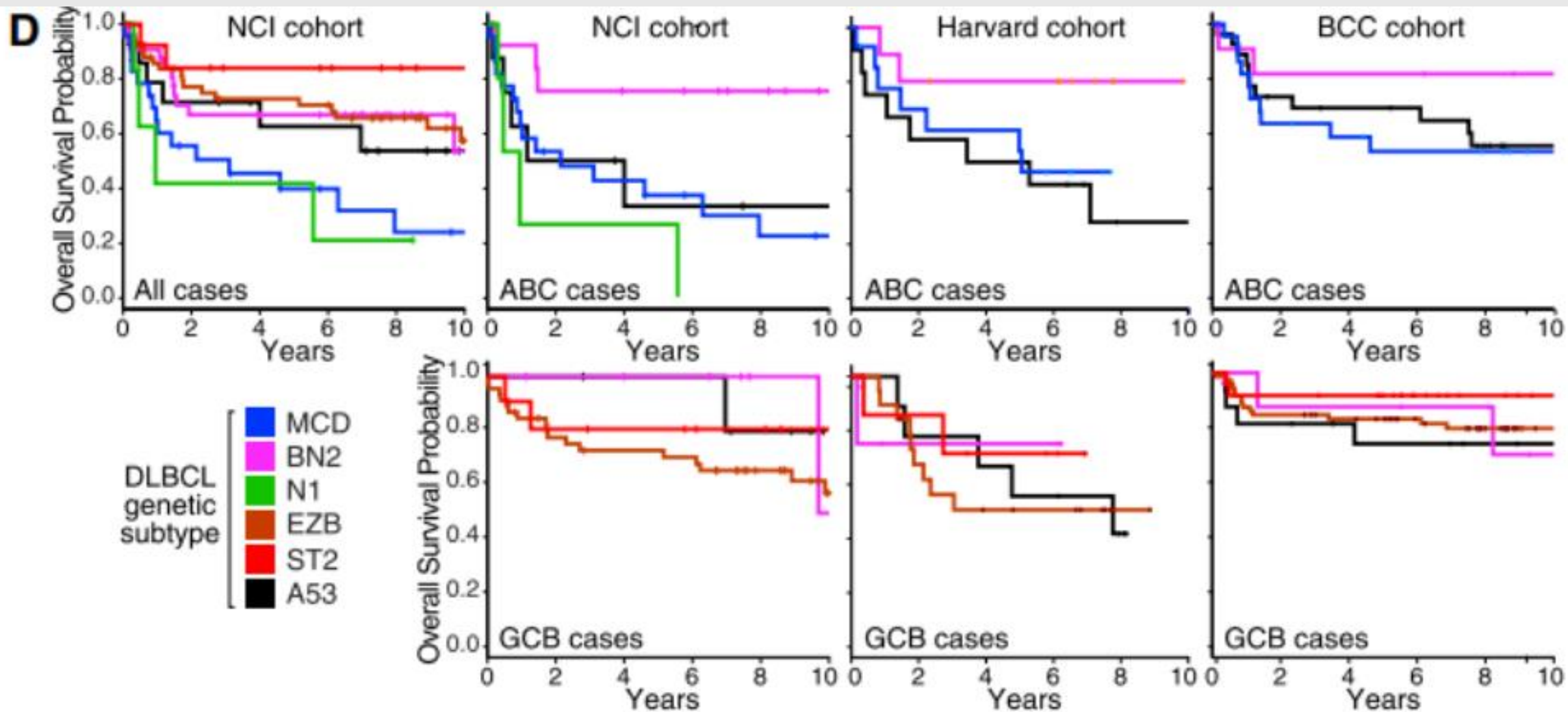
Variantes	Frequência Alélica	Terapias com potencial benefício clínico	Terapias potencialmente associadas a resistência	Ensaio clínico
MYD88 L265P	38,3%	-	-	-
CD79B Y196F	80,9%	-	-	NCT02503423
HLA-C Q78*	70,6%	-	-	-
ETV6 c.33+1G>A	38,1%	-	-	-
BTG1 E50K	36,9%	-	-	-
PIM1 E79D (variante de significado incerto)	42,8%	-	-	-

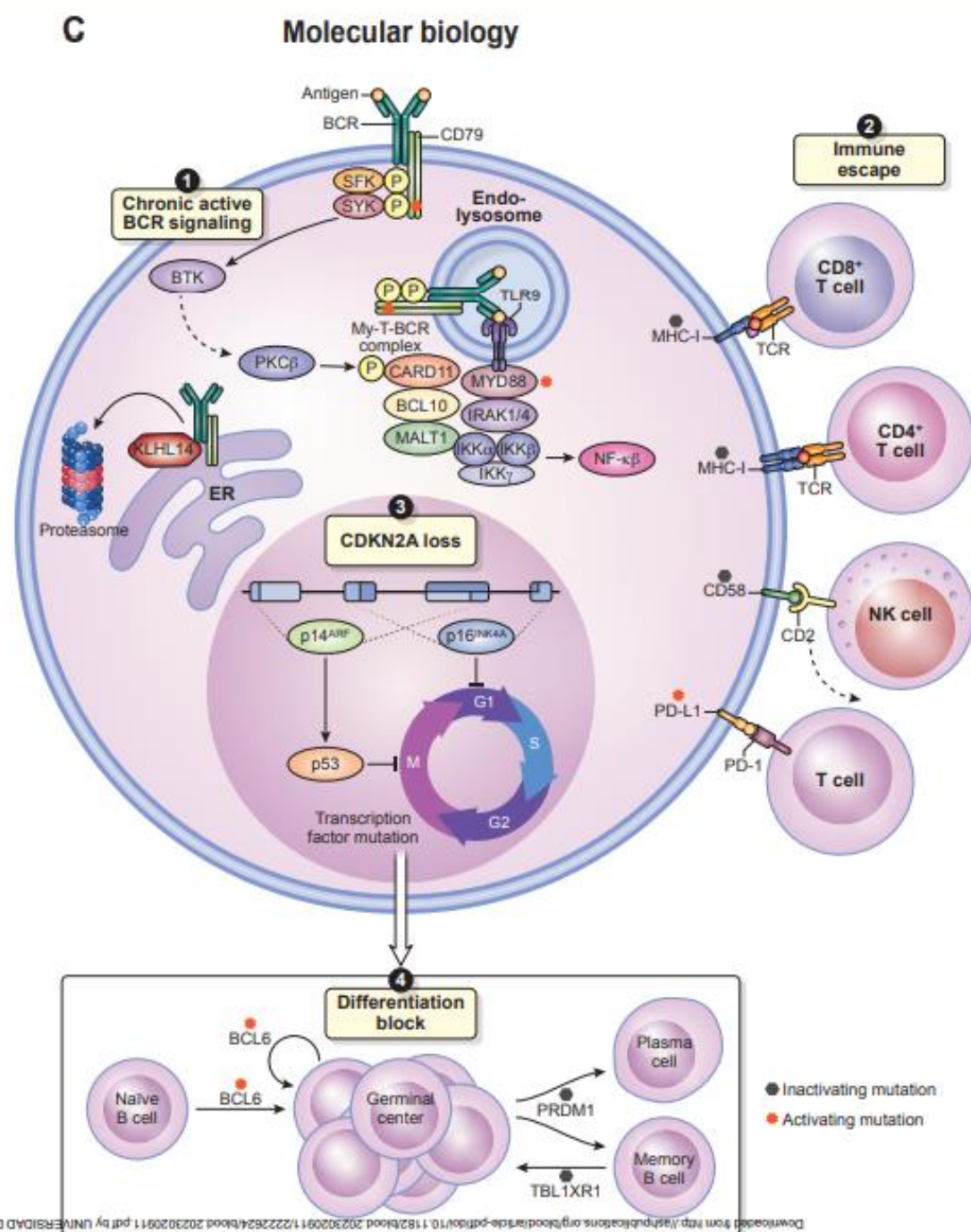
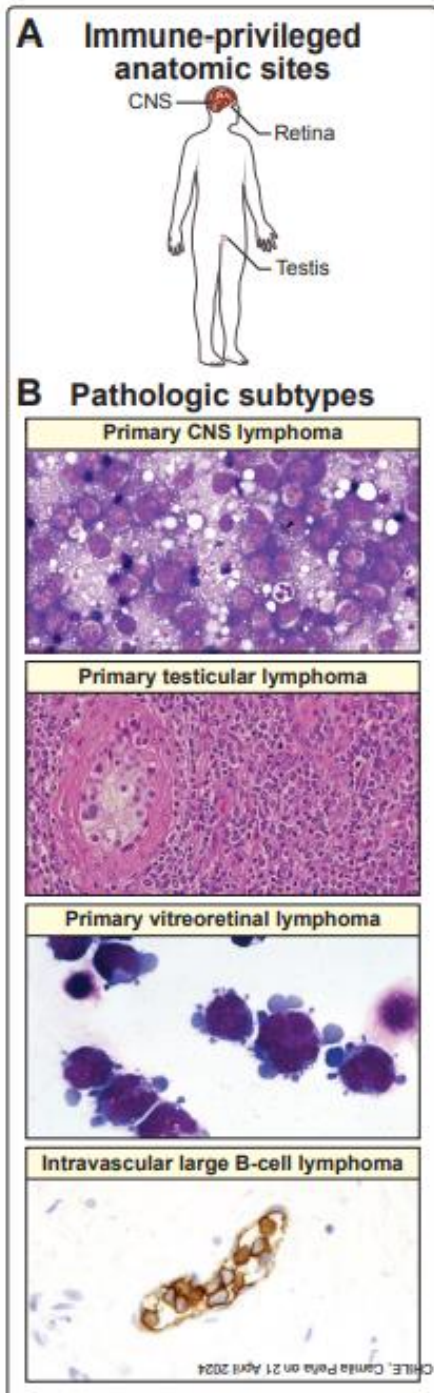




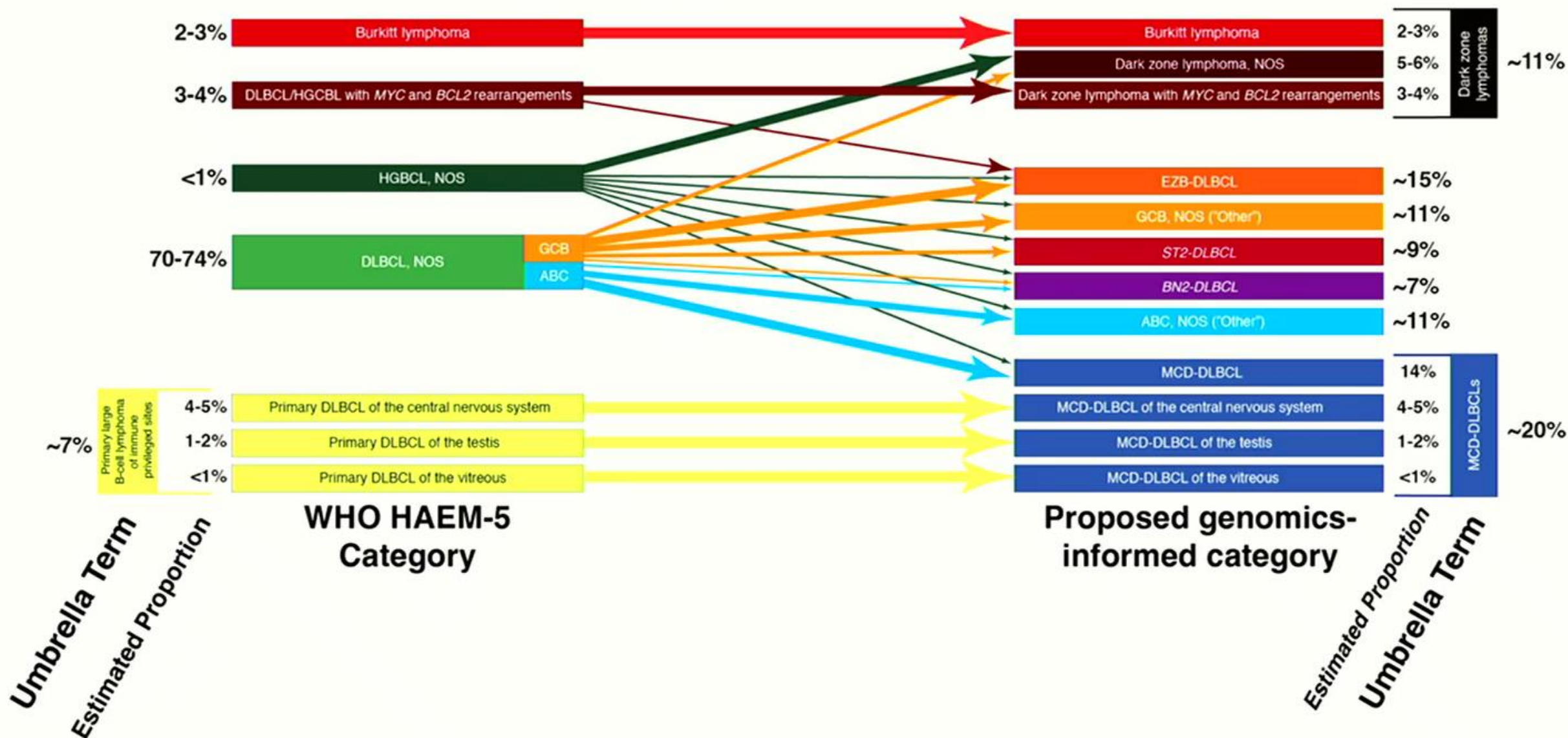
Molecular Classification of DLBCL







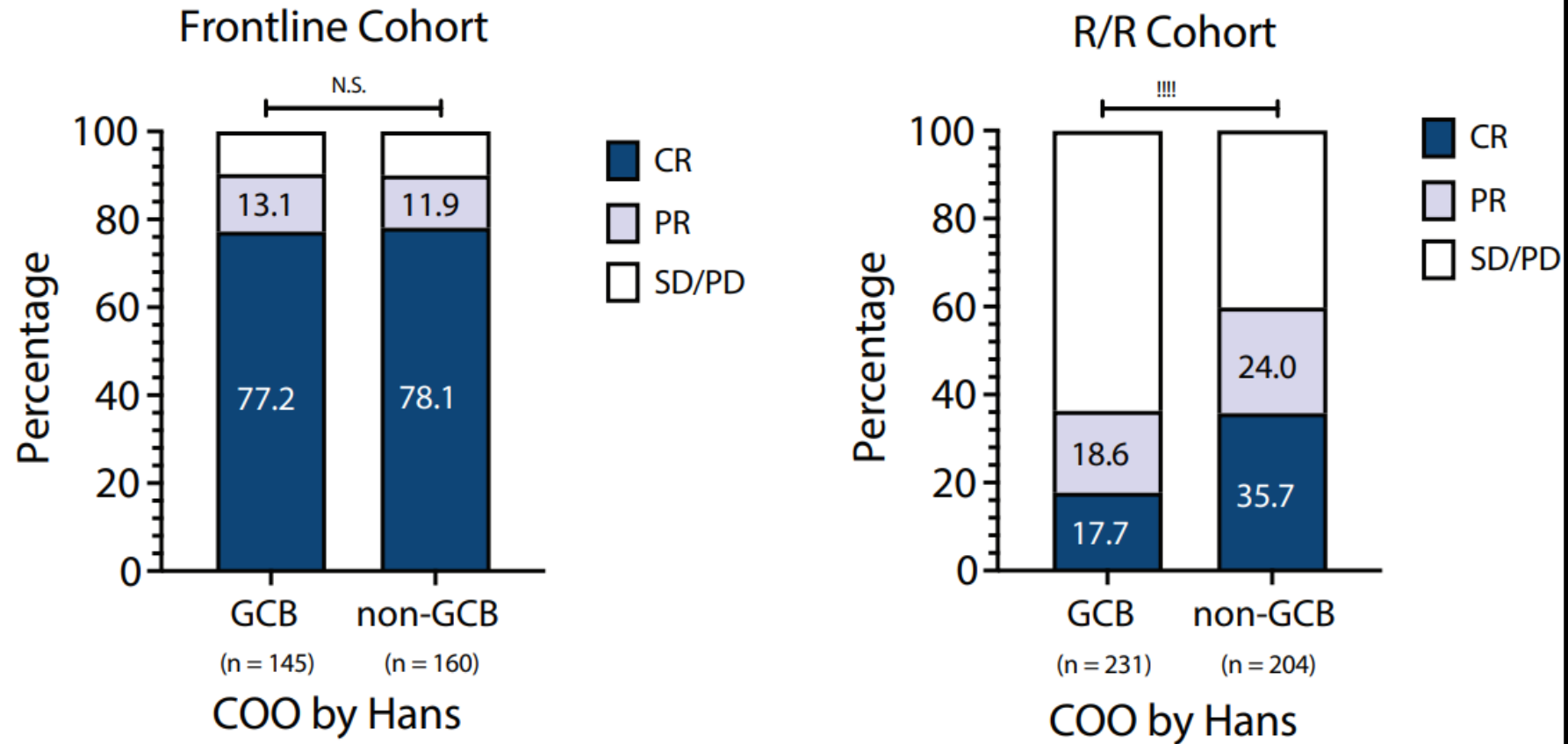
Draft of a genomics-informed classification





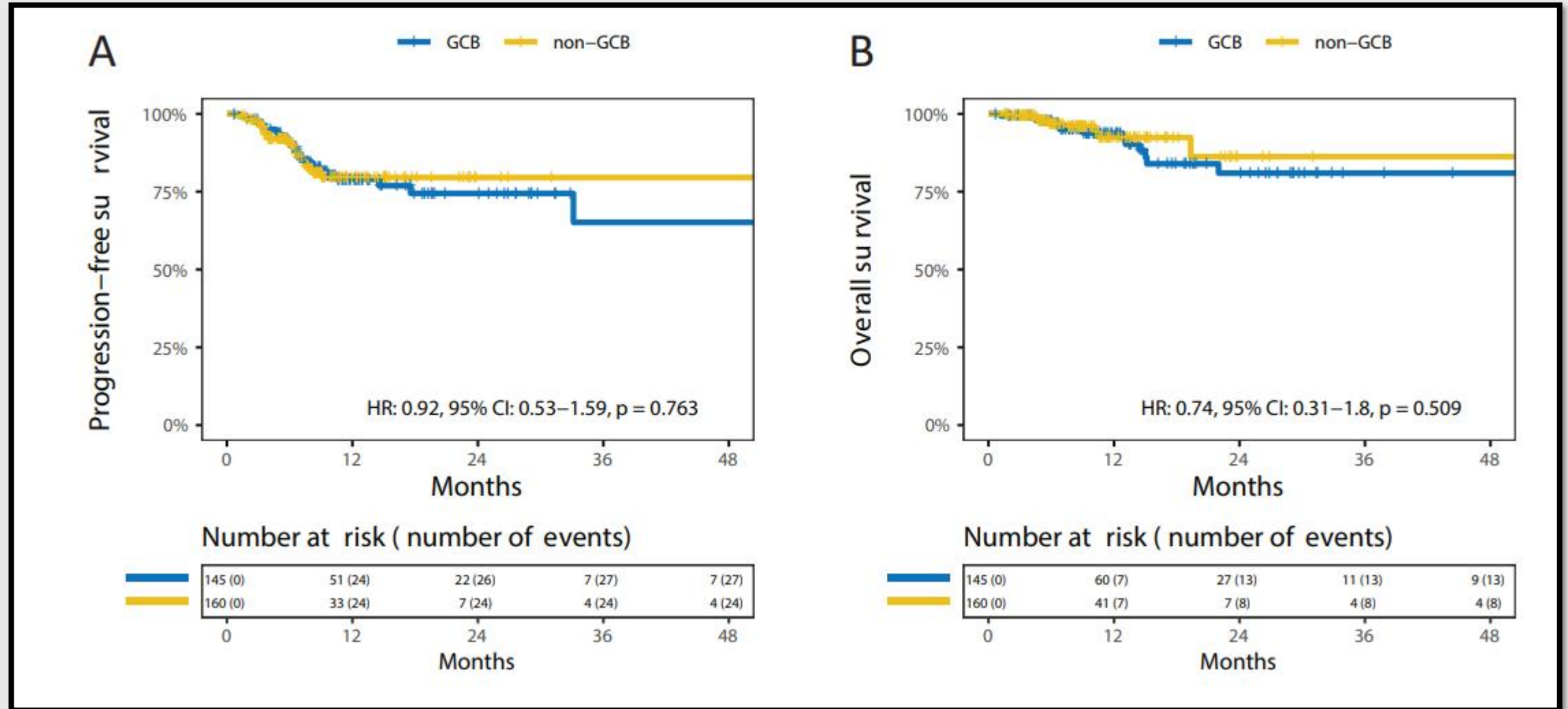
Podemos Utilizar COO por Hans?

Figure 1





Podemos Utilizar COO por Hans?

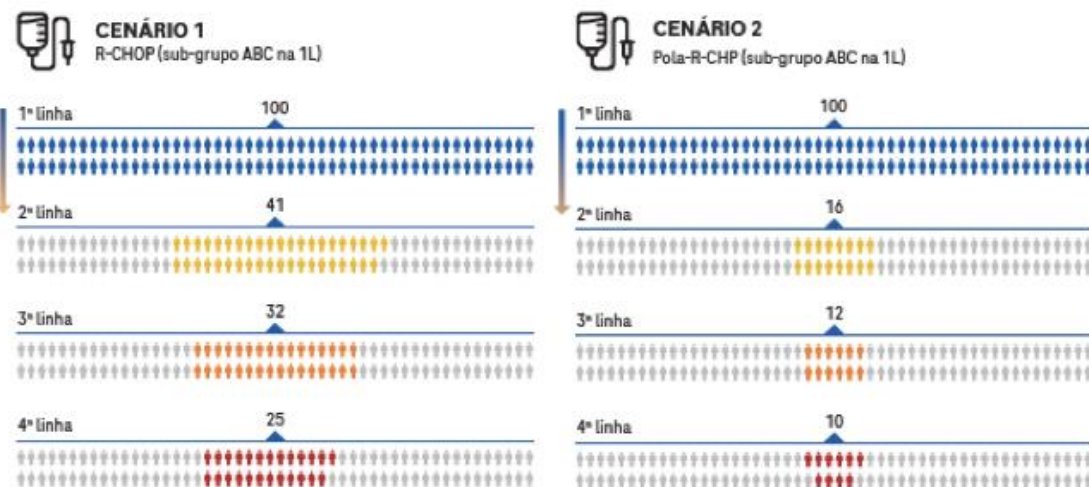




Impacto Orçamentário e benefício clínico de Polatuzumabe Vedotina na primeira linha de tratamento para o Linfoma Difuso de Grandes Células B no contexto Brasileiro

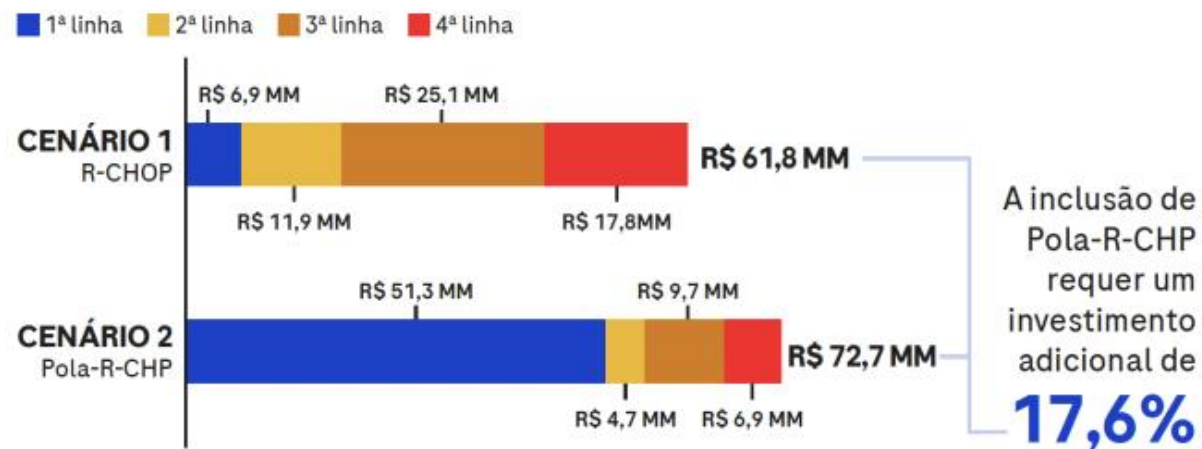
Impactos na progressão da doença

Nº de pacientes por linha de tratamento



A inclusão de Pola-R-CHP reduz em **61%** o número de pacientes que progridem à 2L na população ABC

Impacto orçamentário considerando o tratamento de 100 pacientes com LBCGB ABC





Conclusiones....

- Creo que, si possible, todos usaríamos Pola-R-CHP para todos
 - A Nadie le apasiona Vincristina!
 - Pero esta no és la realidad economica de nosotros
 - Elige bien para tenerlo disponible!
- Como hacemos en Einstein Hospital Israelita?
 - Pola-R-CHP para todos non-GCB
 - Si vas a hacer R-Mini-CHOP, hacemos Pola-R-MiniCHP
 - Si GCB y IPI>2, discutimos individualmente



Pola R-CHP en entornos de bajo recursos

- En un escenario con CART, Pola-R-CHP es viable economicamente en LGCBG
 - Pero no es nuestra realidad
 - Sin CART, el impacto economico és maior, pero mucho más pacientes se quedaran curados
 - Cual va a ser el impacto de Biespecíficos tanto em 1a línea quanto en la recaída?
- Devemos utilizar nuestros recursos con mas inteligencia:
 - Cuantos acá tienen COO para todos sus pacientes?
 - Testes moleculares?



Gracias! Muito Obrigado!

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Obrigado!

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