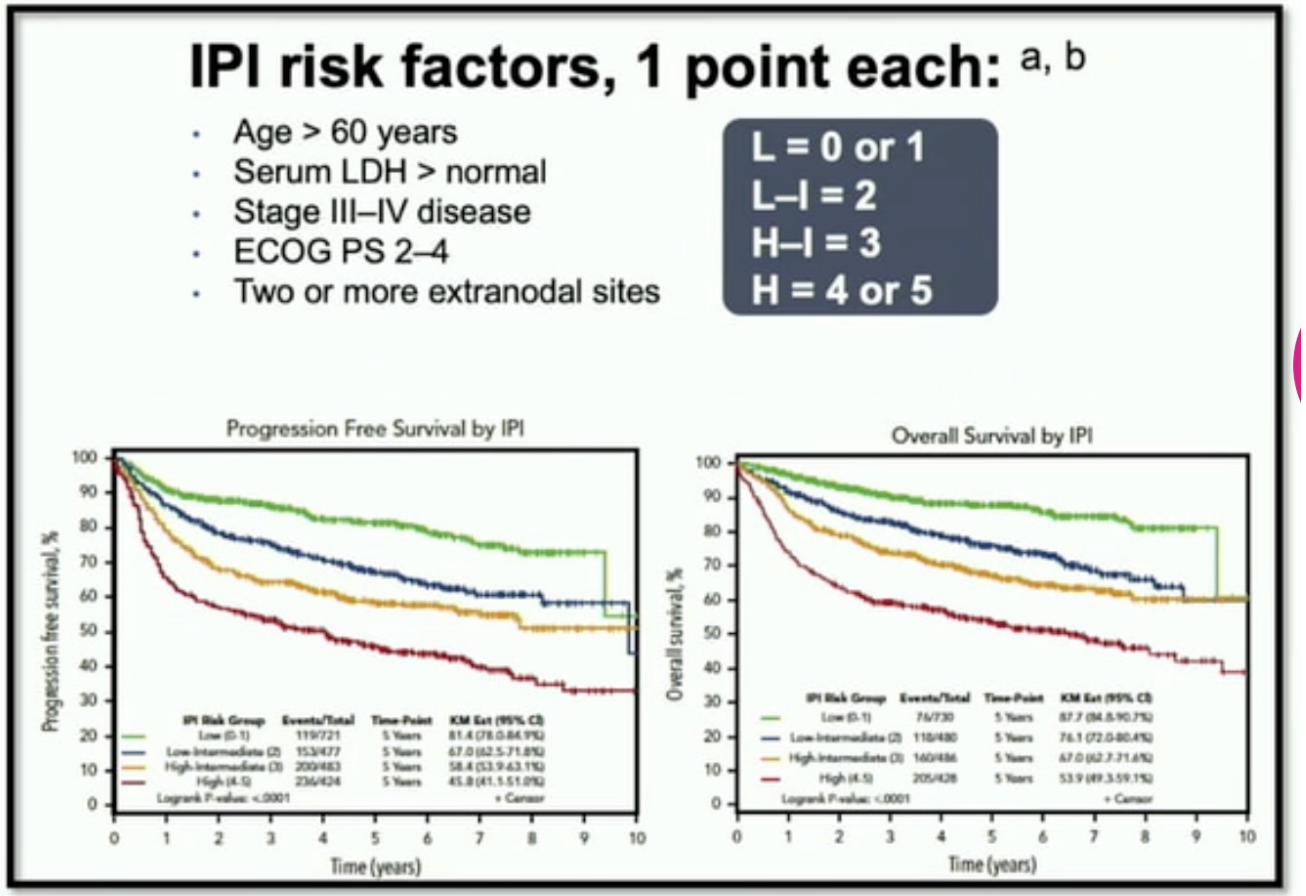
R-CHOP es insuficiente en LBCG de alto riesgo

Beatriz Wills, MD
Fundación Santa Fe de Bogotá

Características clínicas de nuestro paciente



3 points	55 %	53 %
Poor prognosis (R-IPI) High-intermediate risk group (IPI)	Overall survival (R-IPI) 49% overall survival (IPI)	Progression-free survival (R-IPI) 57% progression-free survival (IPI)

IPI 3

NCCN IPI 4

Riesgo alto-intermedio

Despite the ease in its **implementation, IPI does not fully represent disease heterogeneity**.
Therefore, efforts have **shifted to broad molecular profiles** that model and stratify risks of adverse outcomes.

a) The International NHL Prognostic Factors Project. N Engl J Med. 1993;329:987–94 ; b) Ruppert AS et al. Blood. 2020 Jun 4;135(23):2041-2048 ; c) Schmitz N et al., J Clin Oncol. 2016 Sep 10;34(26):3150-6

Índices clínicos pronósticos en LBCG tienen limitaciones

Análisis de 2124 pacientes.

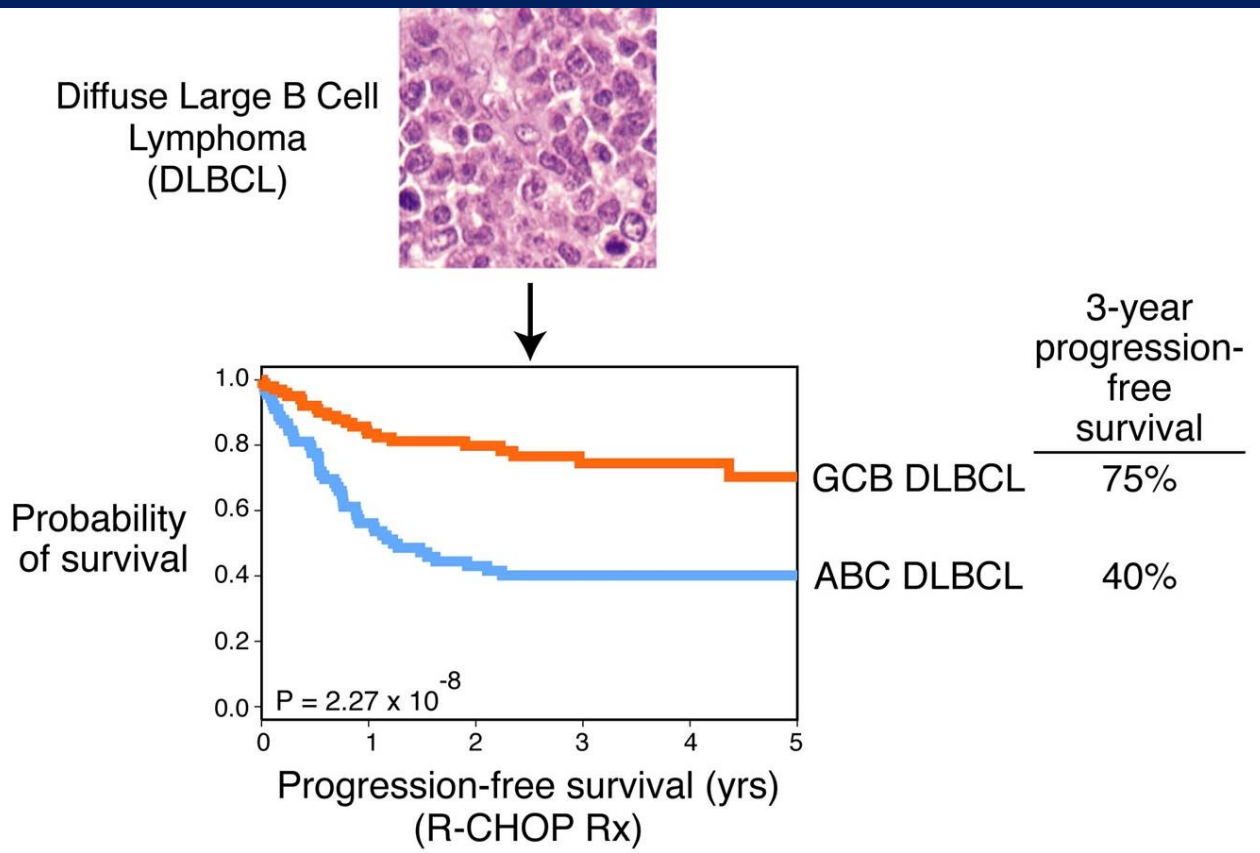
- Comparación de IPI, R-IPI, IPI NCCN

NCCN-IPI tuvo el mejor poder de discriminación para OS.

- No logró identificar un grupo de **pacientes de alto riesgo** con supervivencia global significativamente por debajo del 50%.

Ruppert AS et al. Blood. 2020

Linfoma Difuso de Células Grandes B, centro germinal

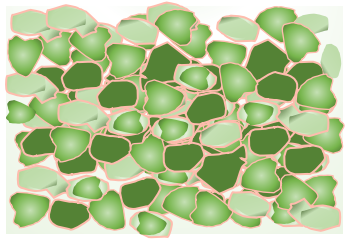


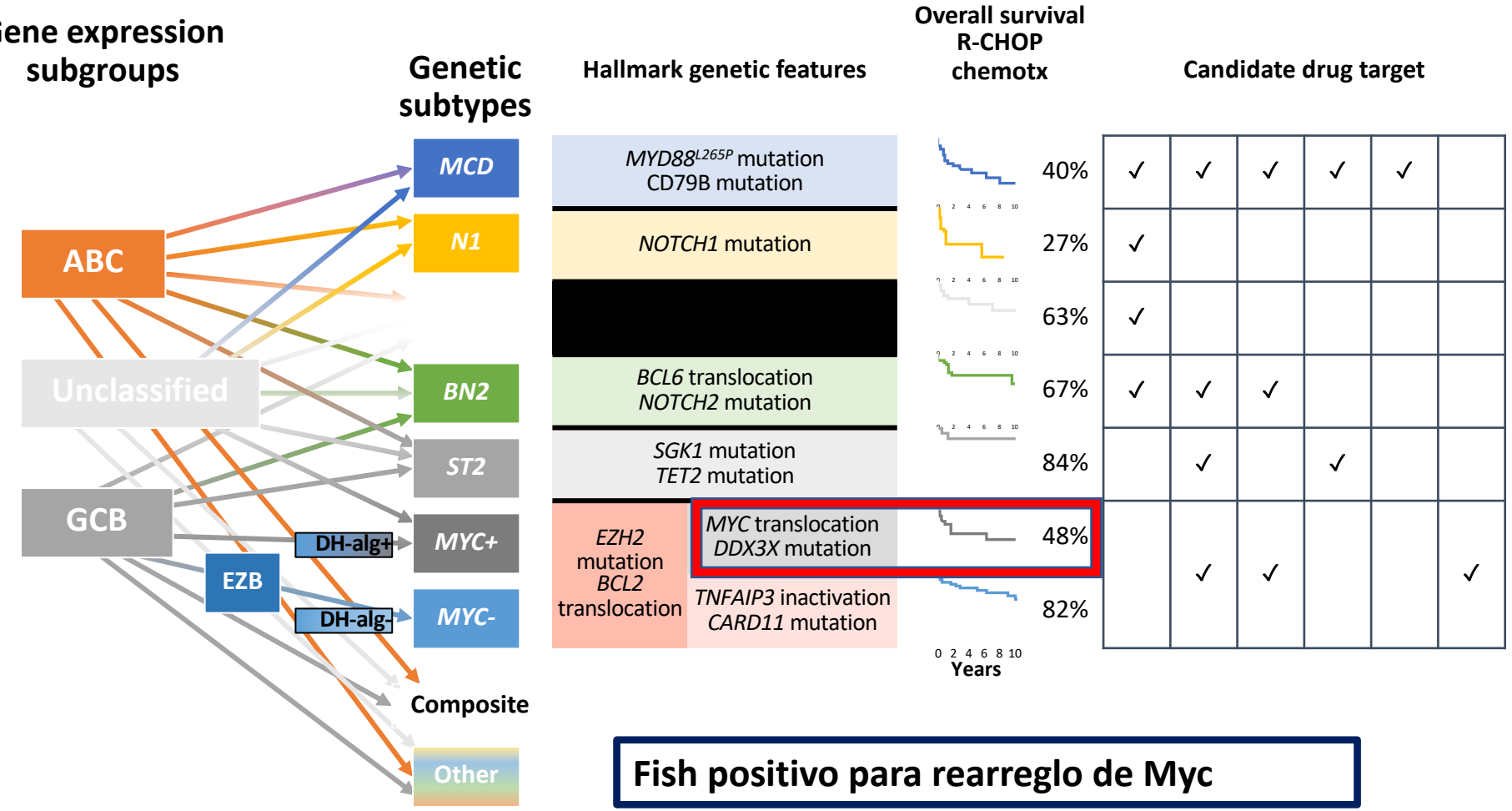
Subtype-specific response
To chemotherapy

Presented By Louis Staudt at 2016 ASCO Annual Meeting

Pero no todos los GCB se compartan igual…
¿Cuáles son las Características moleculares de nuestra paciente ?

Diffuse large B-cell lymphoma



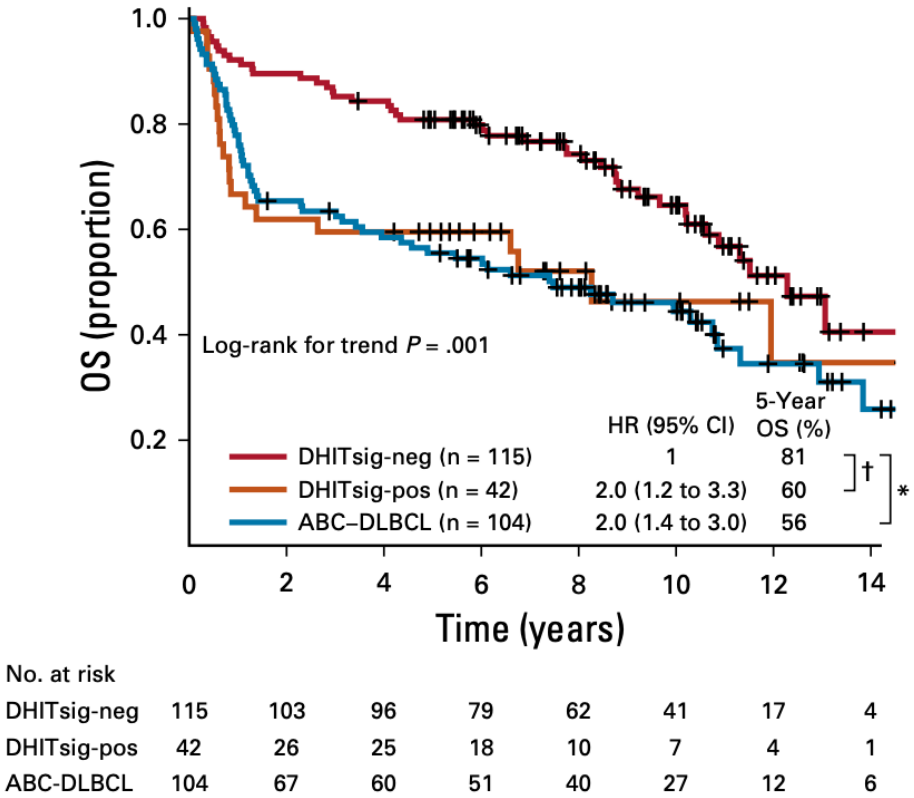


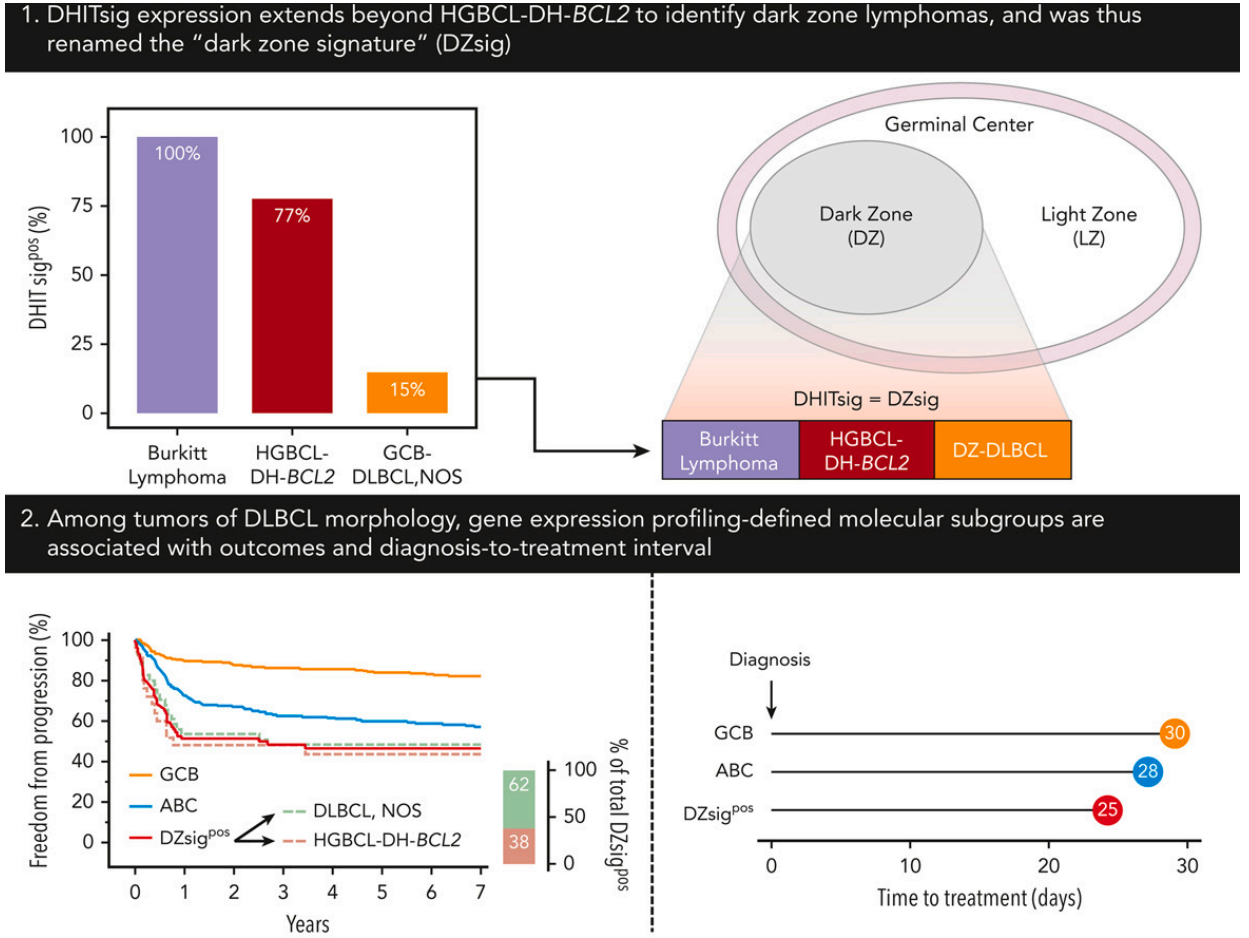
Fish positivo para rearreglo de Myc

Heterogeneity observed within the COO subtypes

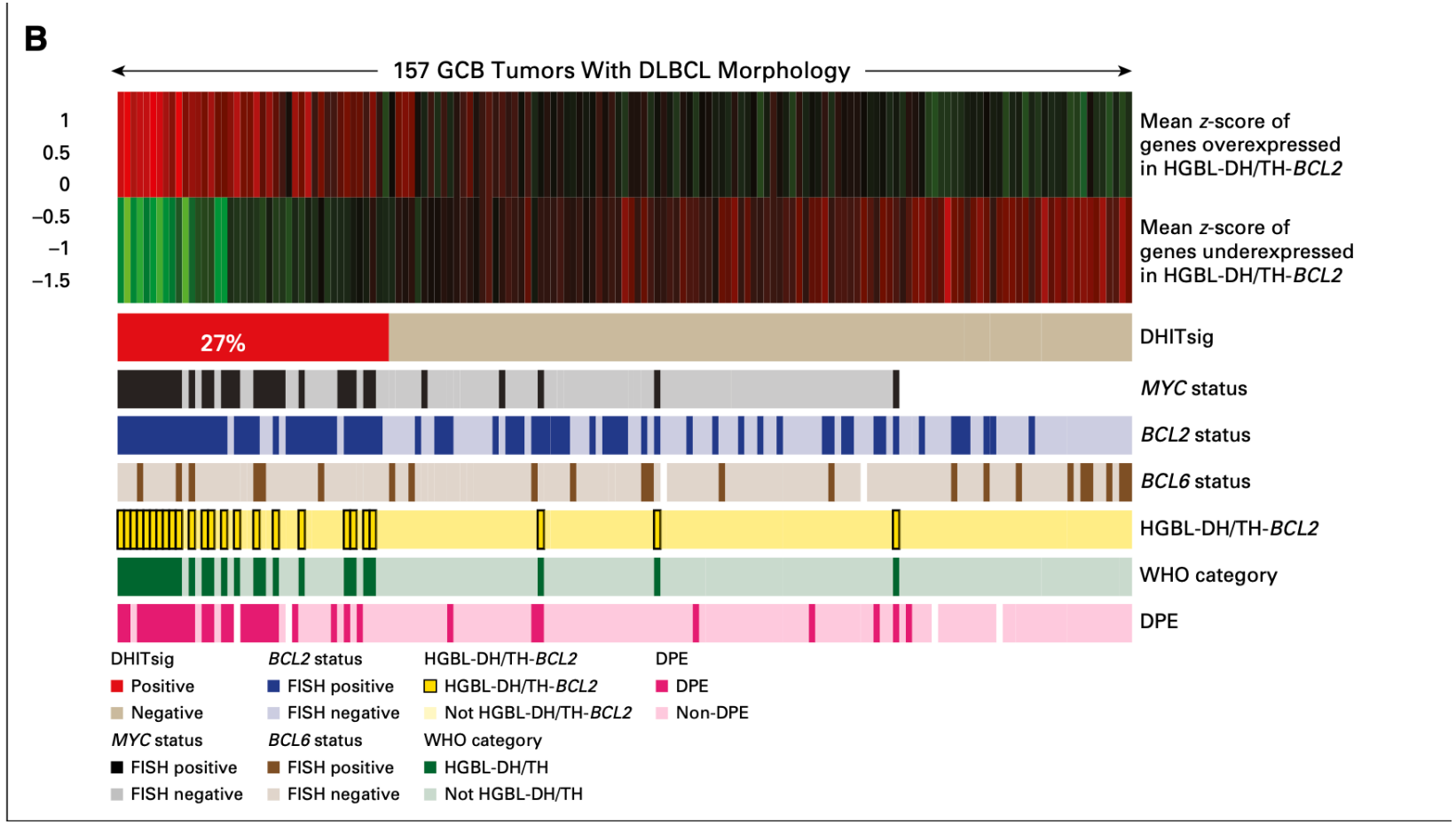
de Level. Blood. 2022

Subtipo agresivo de linfoma CG caracterizado por perfil molecular Dark zone +

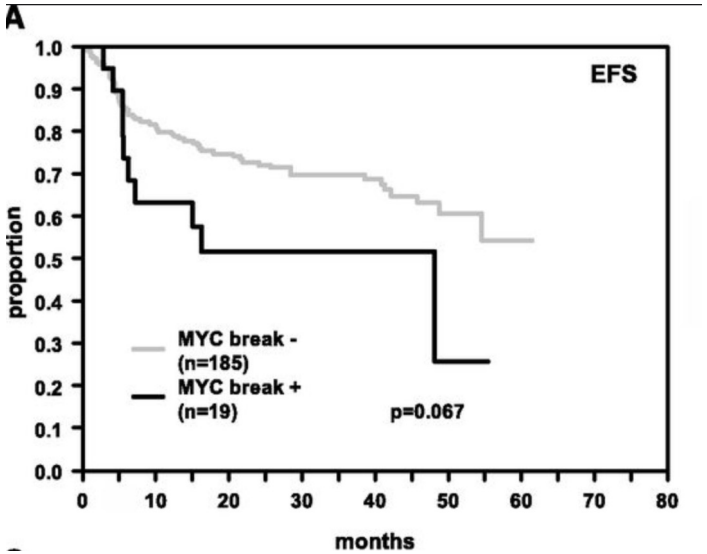


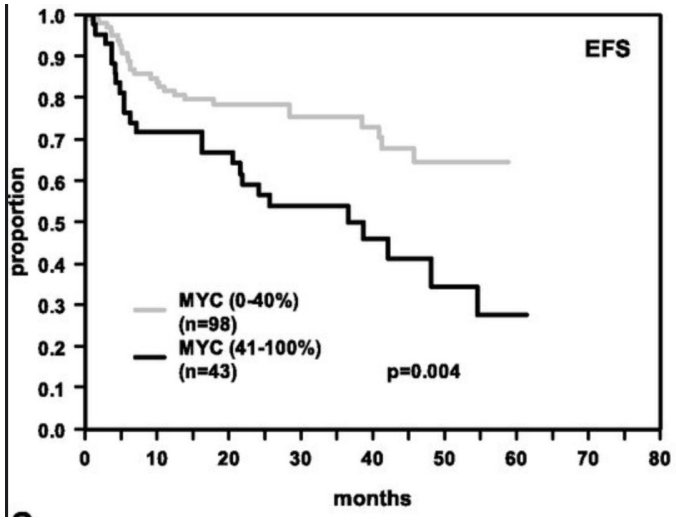


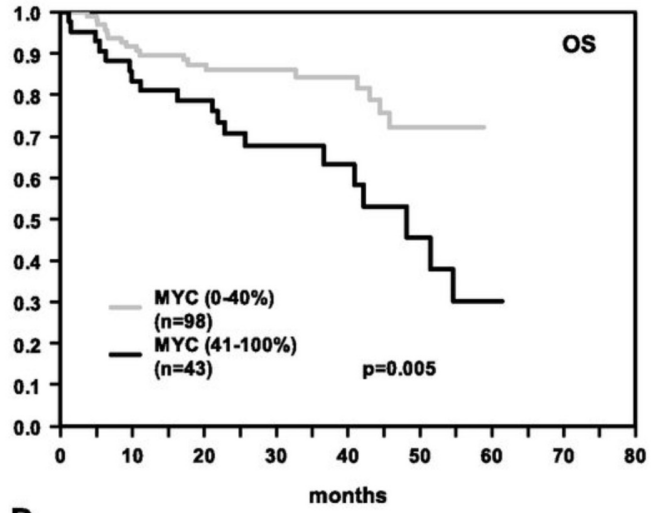
Alduaij, Blood 2023.
Ennishi . J Clin Oncol 37:190-201.

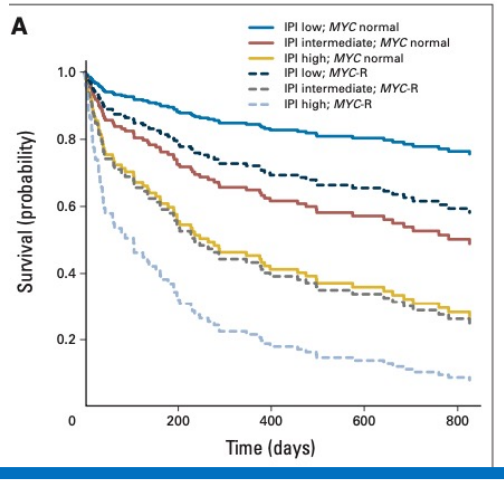

B
157 GCB Tumors With DLBCL Morphology
1
0.5
0
–0.5
–1
–1.5
Mean z-score of genes overexpressed in HGBL-DH/TH-BCL2
Mean z-score of genes underexpressed in HGBL-DH/TH-BCL2
27%
DHITsig
MYC status
BCL2 status
BCL6 status
HGBL-DH/TH-BCL2
WHO category
DPE
DHITsig
Positive
Negative
BCL2 status
FISH positive
FISH negative
HGBL-DH/TH-BCL2
HGBL-DH/TH-BCL2
Not HGBL-DH/TH-BCL2
DPE
DPE
Non-DPE
MYC status
FISH positive
FISH negative
BCL6 status
FISH positive
FISH negative
WHO category
HGBL-DH/TH
Not HGBL-DH/TH

Alteraciones en *MYC*--> fenotipo más agresivo y peores desenlaces







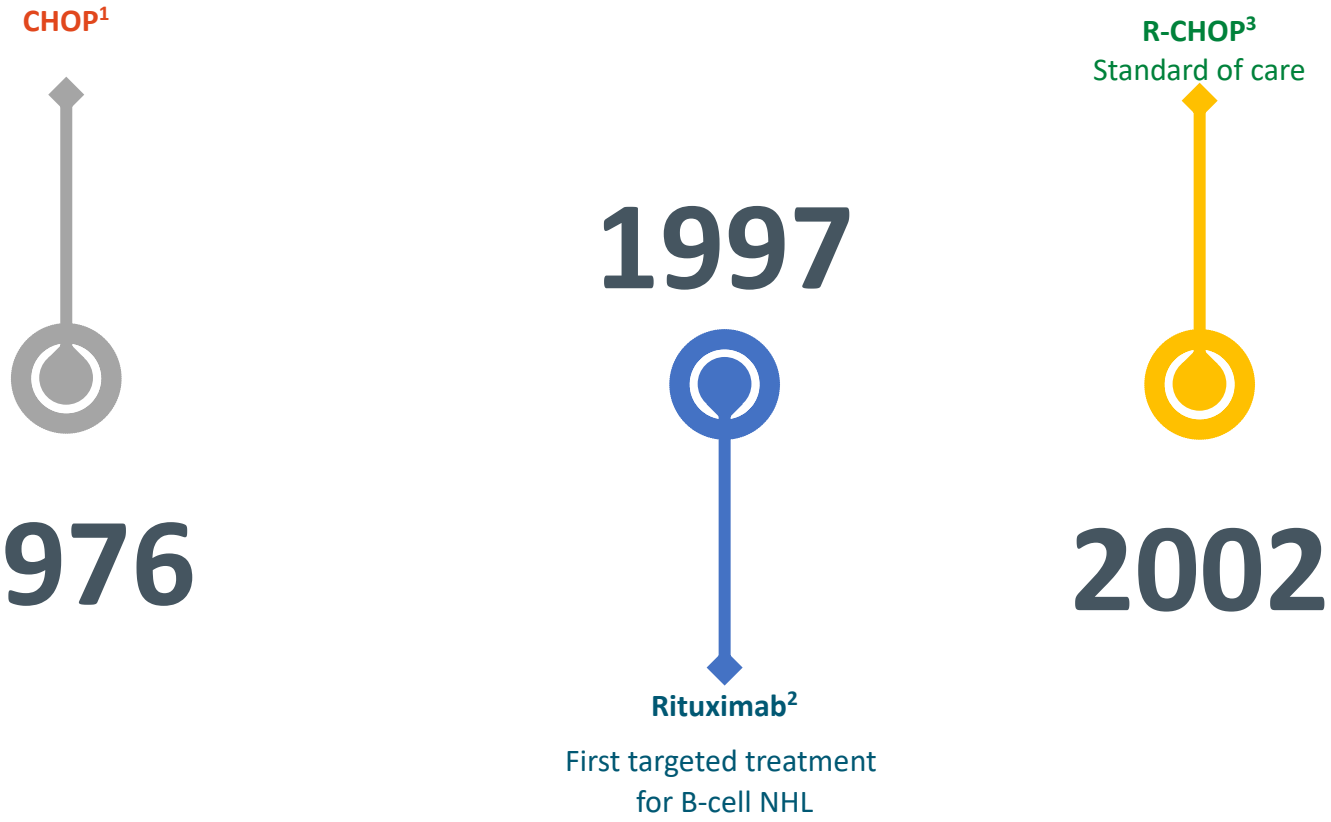


rMYC +IPI → factor pronóstico desfavorable

Nuestra paciente:
IHC MYC 40%
FISH rearreglo de Myc
Pobre factor pronostico

Rosenwald, NEJM, 2002
Barrans, JCP 2010

A pesar de entender mejor la biología de LBCG…
Seguí(a)mos tratando a los pacientes con LDCBG igual por más de 20 aNos …

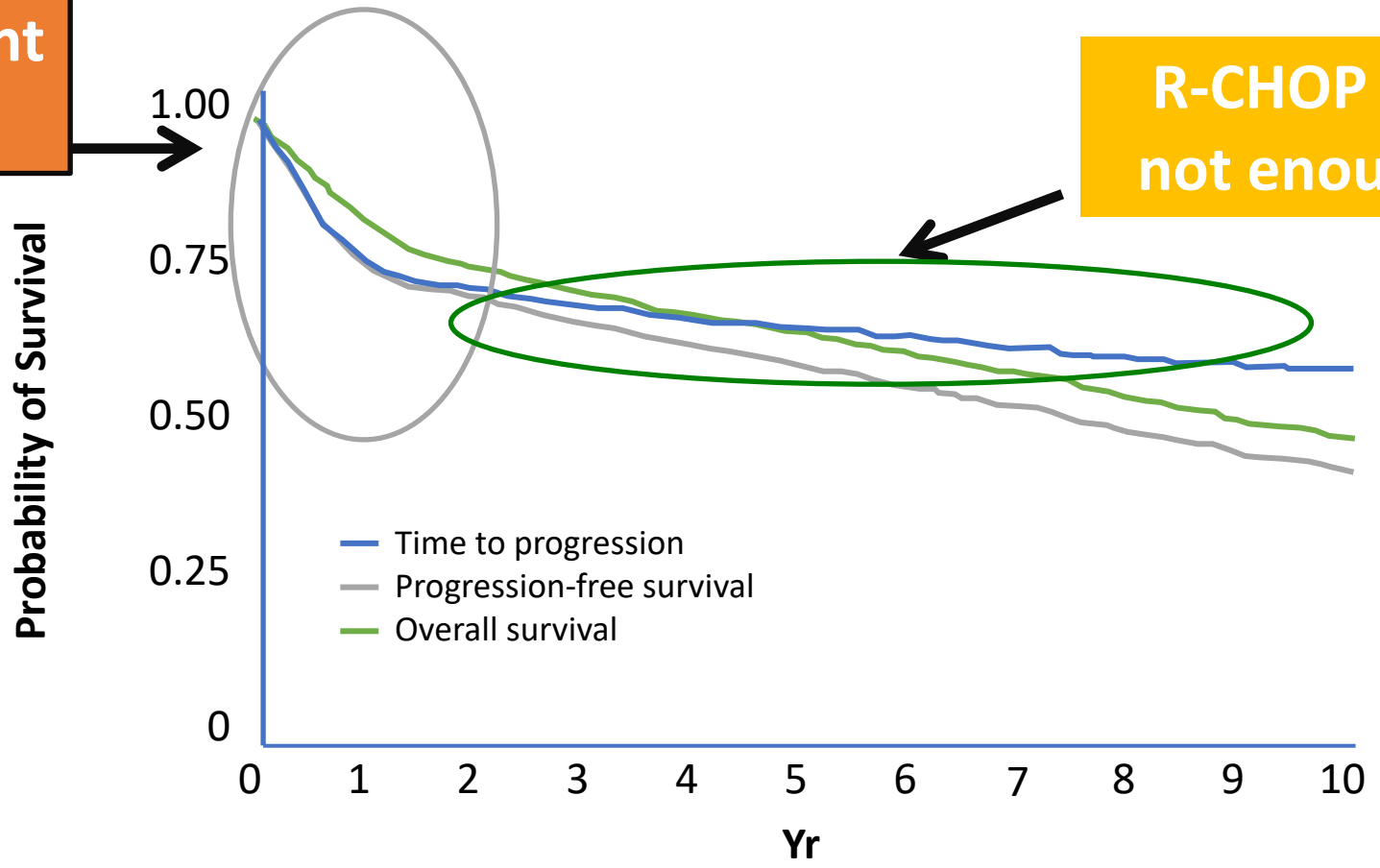


McKelvey. Cancer. 1976;38:1484. 2. McLaughlin. JCO. 1998;16:2825. 3. Coiffier. NEJM. 2002;346:235.

Desenlaces con R-CHOP en primera línea para DLBCL

Treatment-resistant disease

R-CHOP fine, but not enough for all



Sehn. NEJM. 2021;484:842.

Resistencia al tratamiento a primera línea es multifactorial

Tumor Heterogeneity

Genetic and/or epigenetic changes in cancer cells generate spatial and temporal diversity to confer resistance to treatment

R/R DLBCL

Expansion of preexisting resistant clones and cells with acquired resistance

Examples of genetic and/or epigenetic alterations in R/R DLBCL

Genetic modifications

Cell cycle regulation
CCND3, CDKN2A, CDKN2B

DNA damage response
TP53

Epigenetic regulation
EZH2, CREBBP, MEF2B, KMT2C, KMT2D

Immune surveillance
B2M, CD58, HLA-A, MS4A1

Oncogenes
MYC, PIM1, PRKCQ, GATA3, MLLT10, ABI1

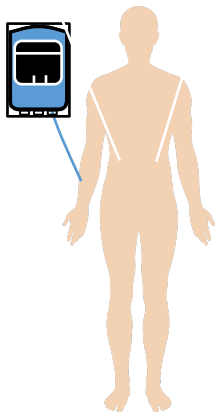
Signaling pathway activation
STAT6, SOCS1, FOXO1, MYD88, CD79B, NFKBIE, NFKBIZ

Epigenetic modifications

DNA methylation
Histone methylation/acetylation

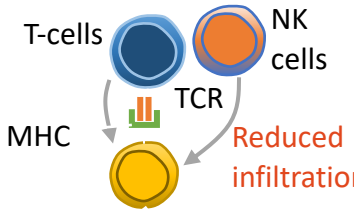
Therapy

DLBCL



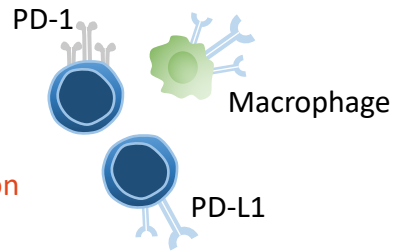
Immune dysfunction and supportive stromal cells promote a protumor environment for treatment resistance

Deficiency in TIICs



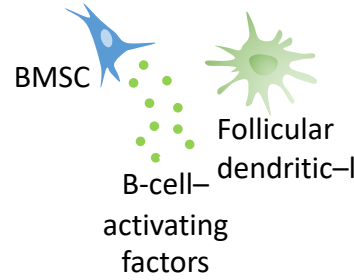
Inadequate apoptosis

Upregulation of inhibitory immune checkpoint molecules



Dysfunctional immune TME

Inhibition of apoptosis by cell adhesion-mediated resistance



Protection from apoptosis

Host variabilities

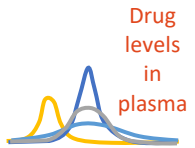
Interpatient variabilities represented from multiple host-specific factors lead to highly variable responses to treatment

Demographic and physical factors

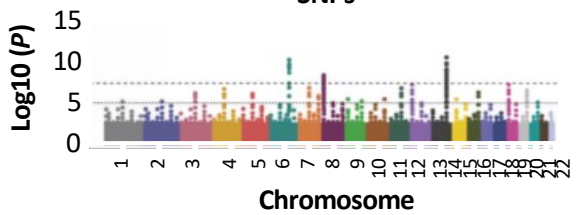
Age
Body weight
Gender

PK

Absorption
Distribution
Metabolism
Excretion



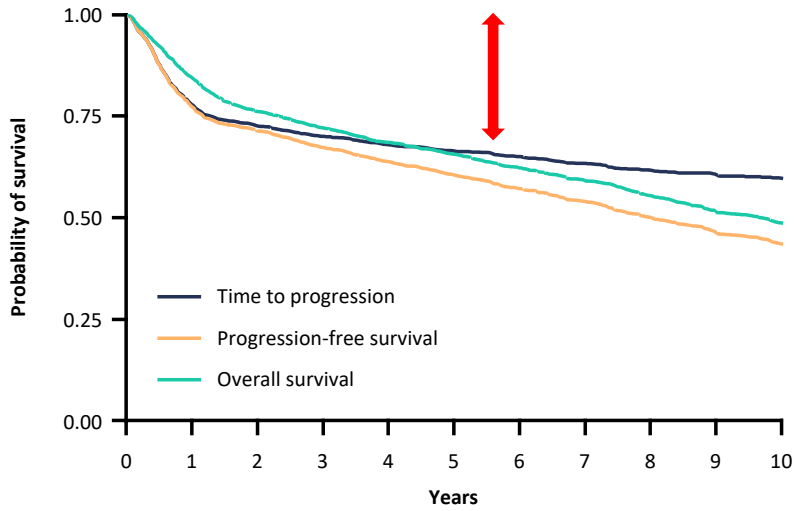
SNPs



Y. HeLeukemia (2021)

La mayoría de esfuerzos de mejorar R-CHOP han fallado

R-CHOP-21



Intensificar terapia:
ASCT[1], CHOP-14[2], ACVBP[3], DA-R-EPOCH[4]

Adicionar agente adicional:
bortezomib[5], ibrutinib[6] and lenalidomide[7]

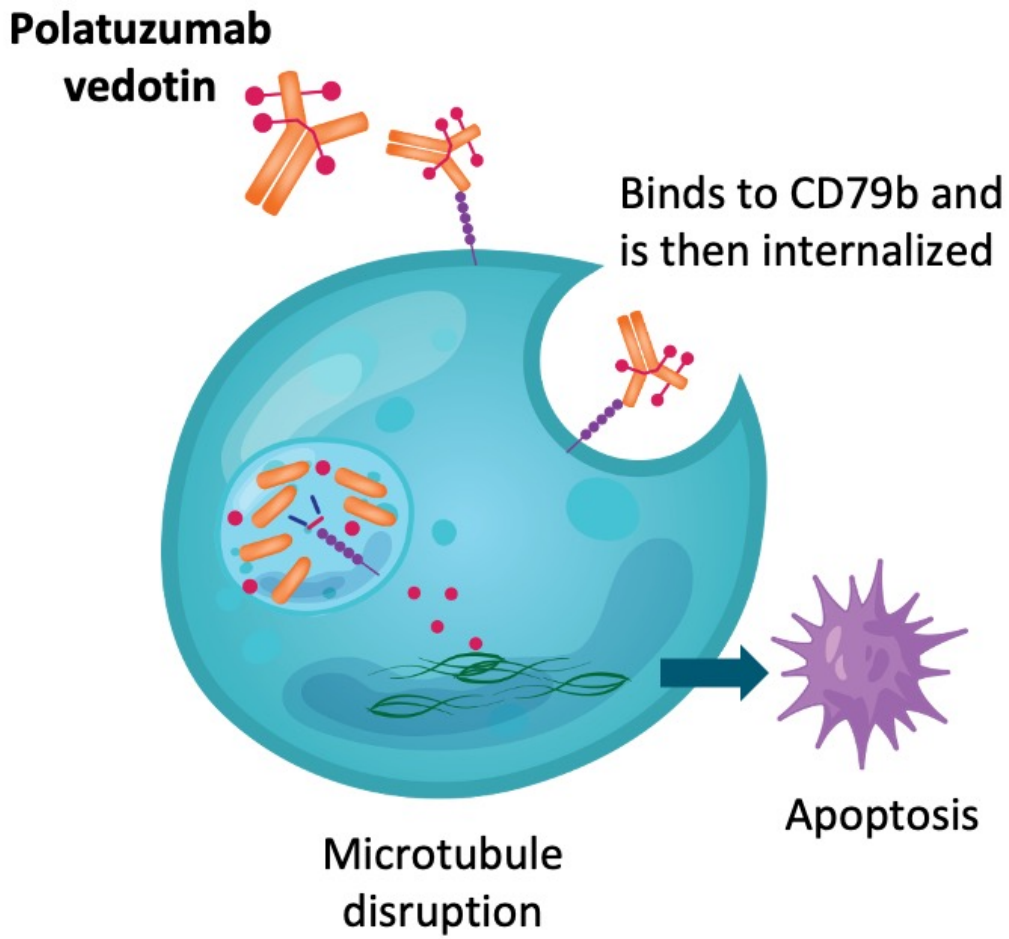
Mantenimiento
rituximab[8], lenalidomide[9], enzastaurin[10], everolimus[11]

Remplazar un componente
bortezomib[12], obinutuzumab[13]

1: Schmitz 2012; Stiff, 2013 ; Chiapella 2017 ; 2: Cunningham, 2013 ; Delarue 2013; 3 Recher 2011; 4: Bartlett, 2019 ; 5: Leonard, 2019 ; Davies, 2019 ; 6: Younes, 2019 ; 7: Nowakowski, 2021 ; 8: Habberman, 2006; Jaeger, 2015 ; 9 :Thieblemont 2017 ; 10: Crump 2018 ; 11: Witzig 208 ; 12: Offner 205 ; 13 : Vitolo, 2017.

Mecanismo de acción Polatuzuman Vedotin

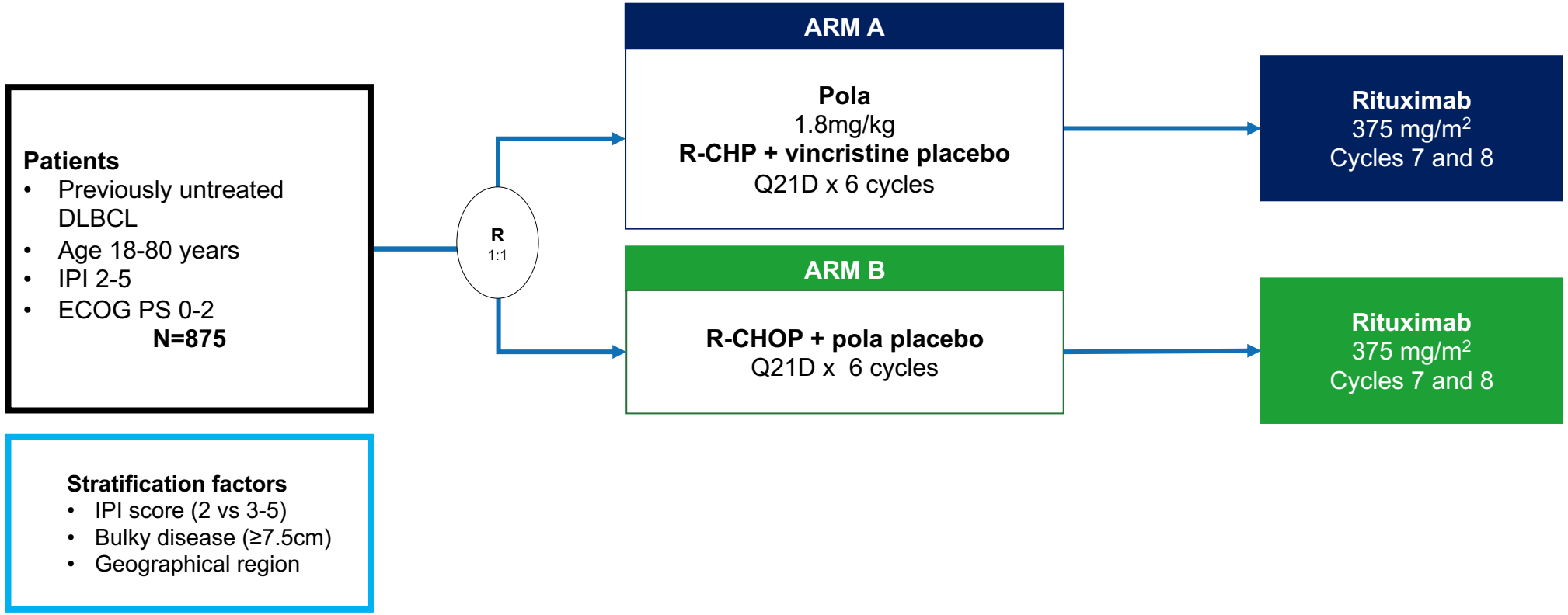
Anticuerpo monocolonal anti-CD79b
conjugado a monometin auristatin E (MMAE)



Sawalha. Onco Targets Ther. 2020;13:5123.

POLARIX: Diseño del estudio

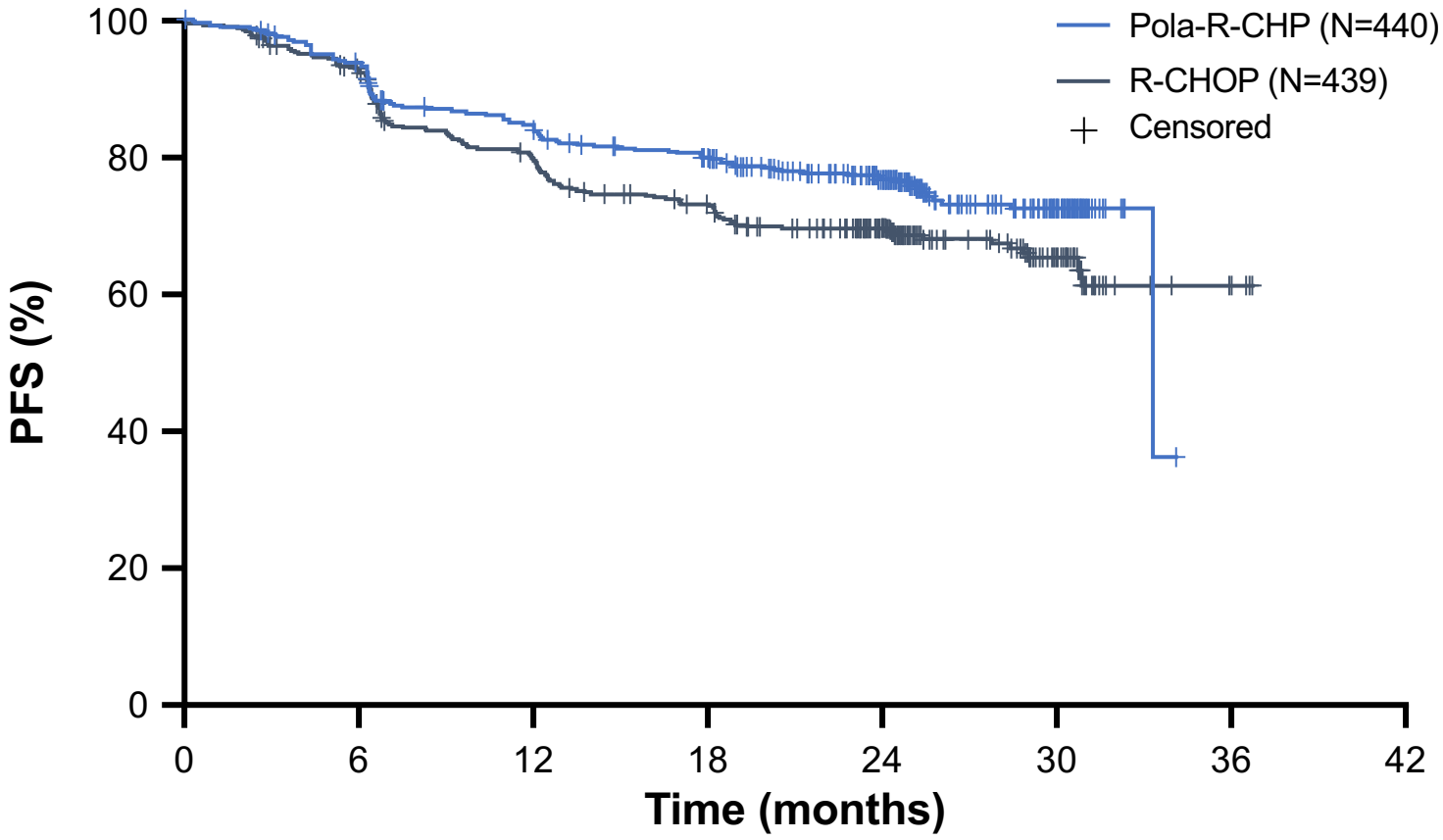
Ensayo doble ciego, fase 3, controlado con placebo



ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, international prognostic index; LYSA, Lymphoma Study Association; LYSARC, Lymphoma Academic Research Organisation; Q21D, every 21 days; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Collaboration with LYSA and LYSARC

POLARIX: Pola-R-CHP mejoró significativamente la supervivencia libre de enfermedad frente a R-CHOP.



No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

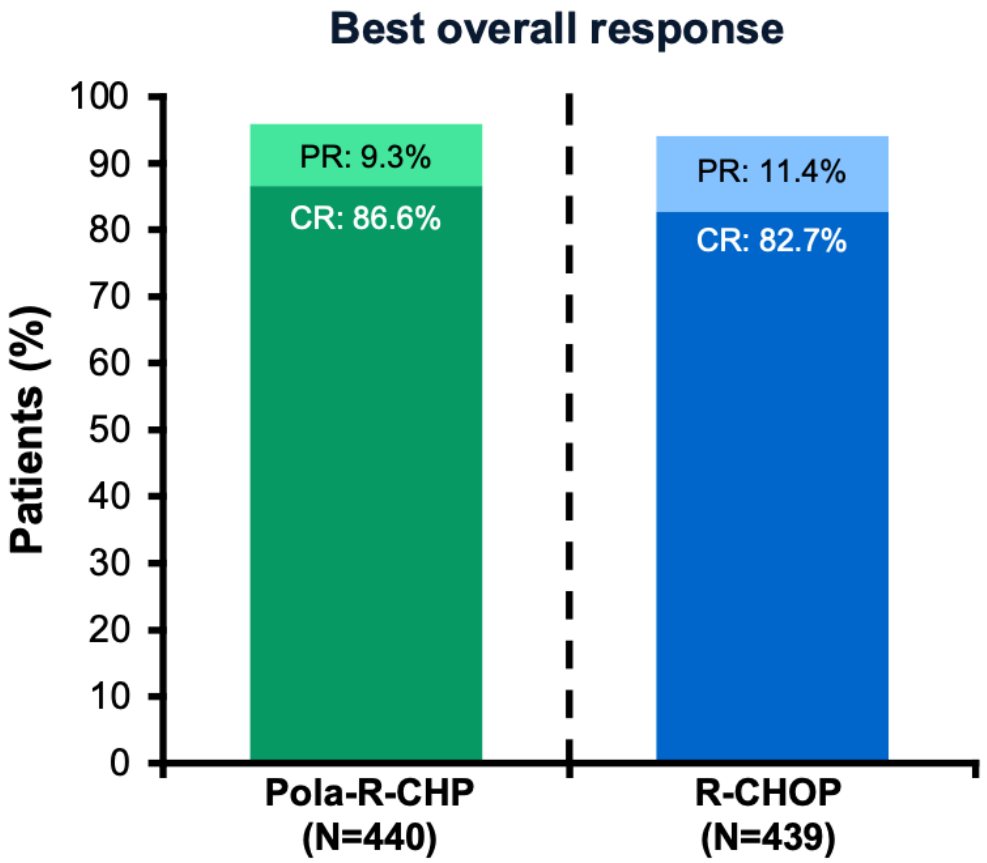
HR 0.73 **95% CI, 0.57, 0.95**

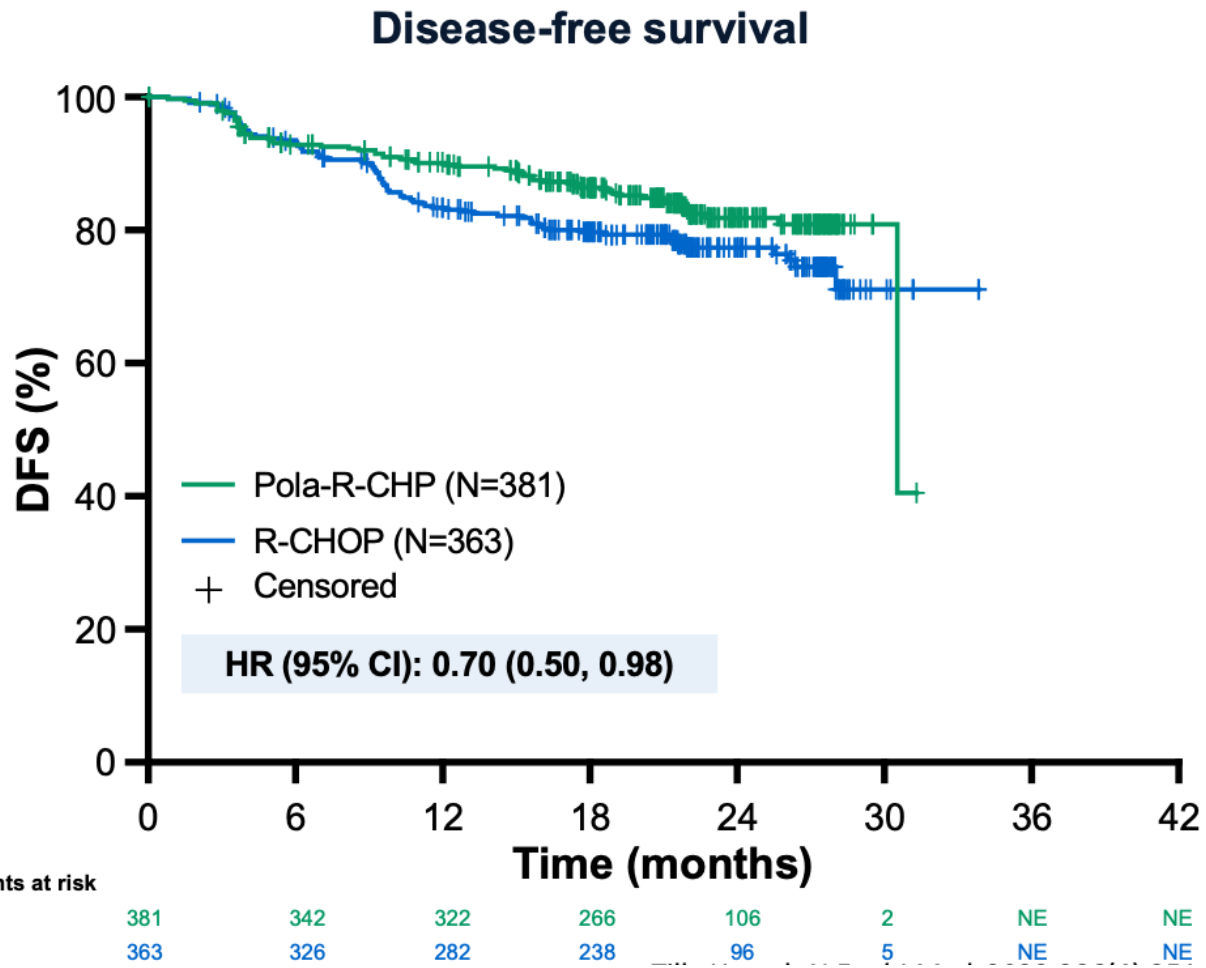
- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

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

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

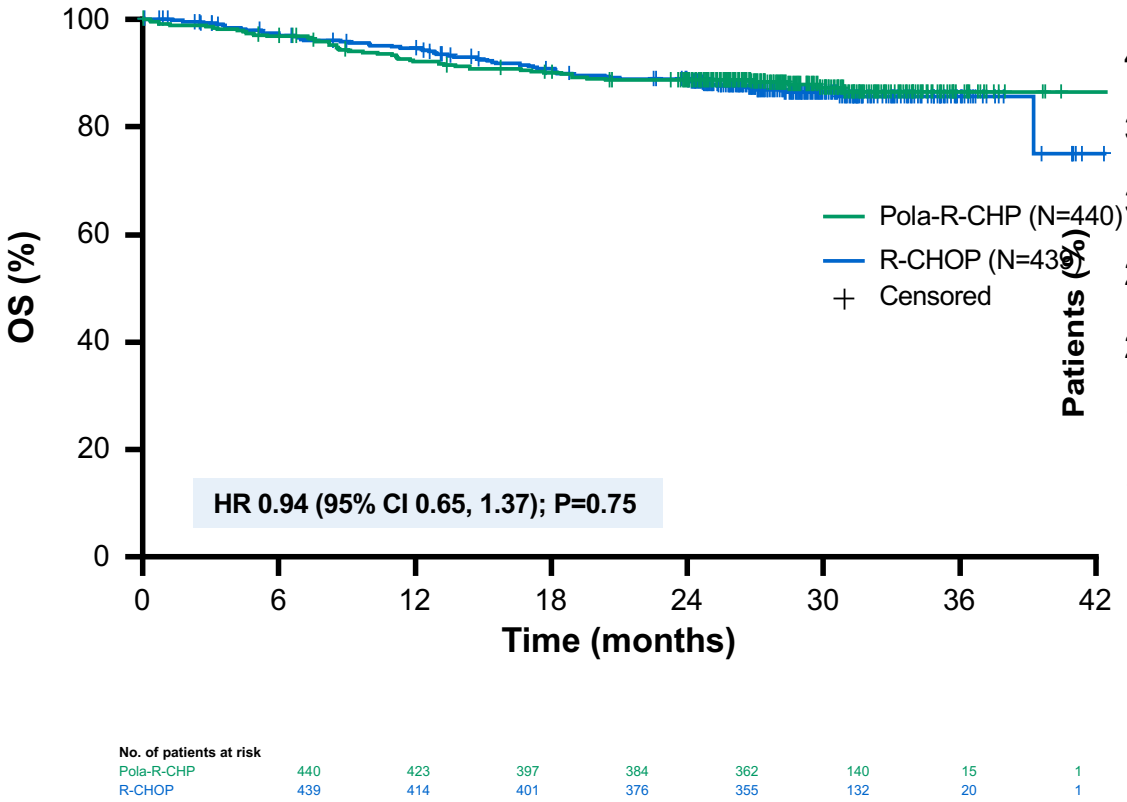
Tasas de respuesta y supervivencia libre de enfermedad



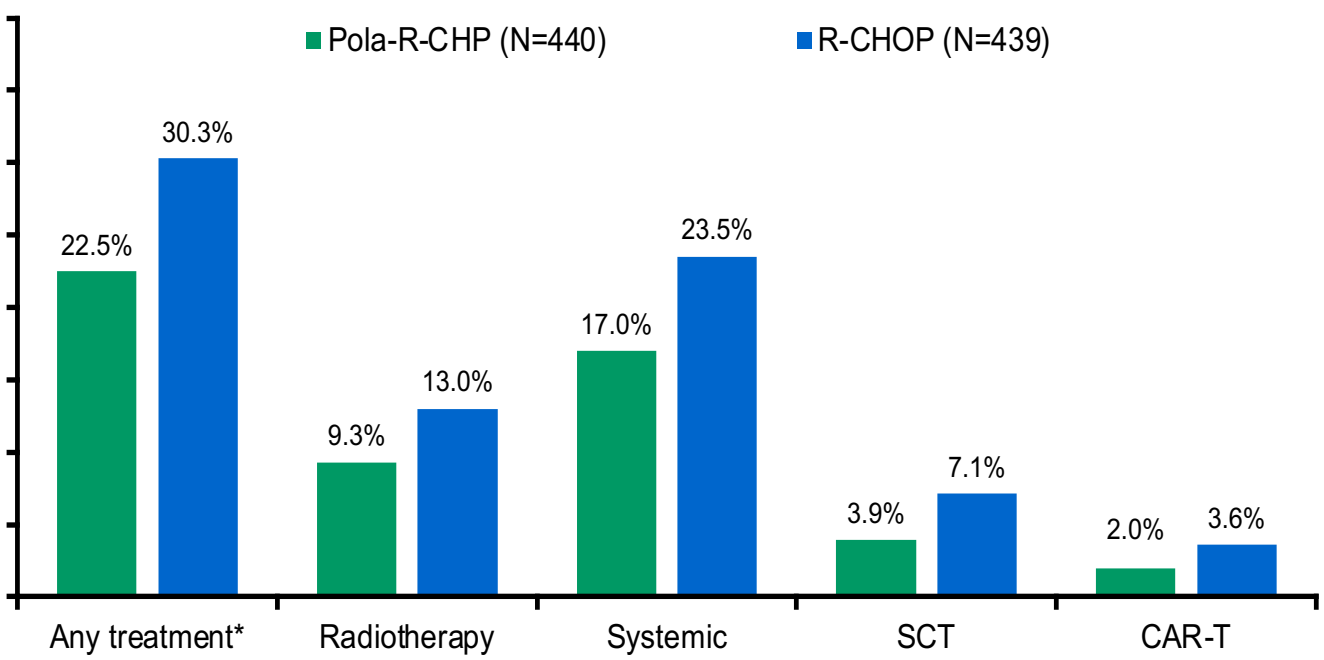


Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

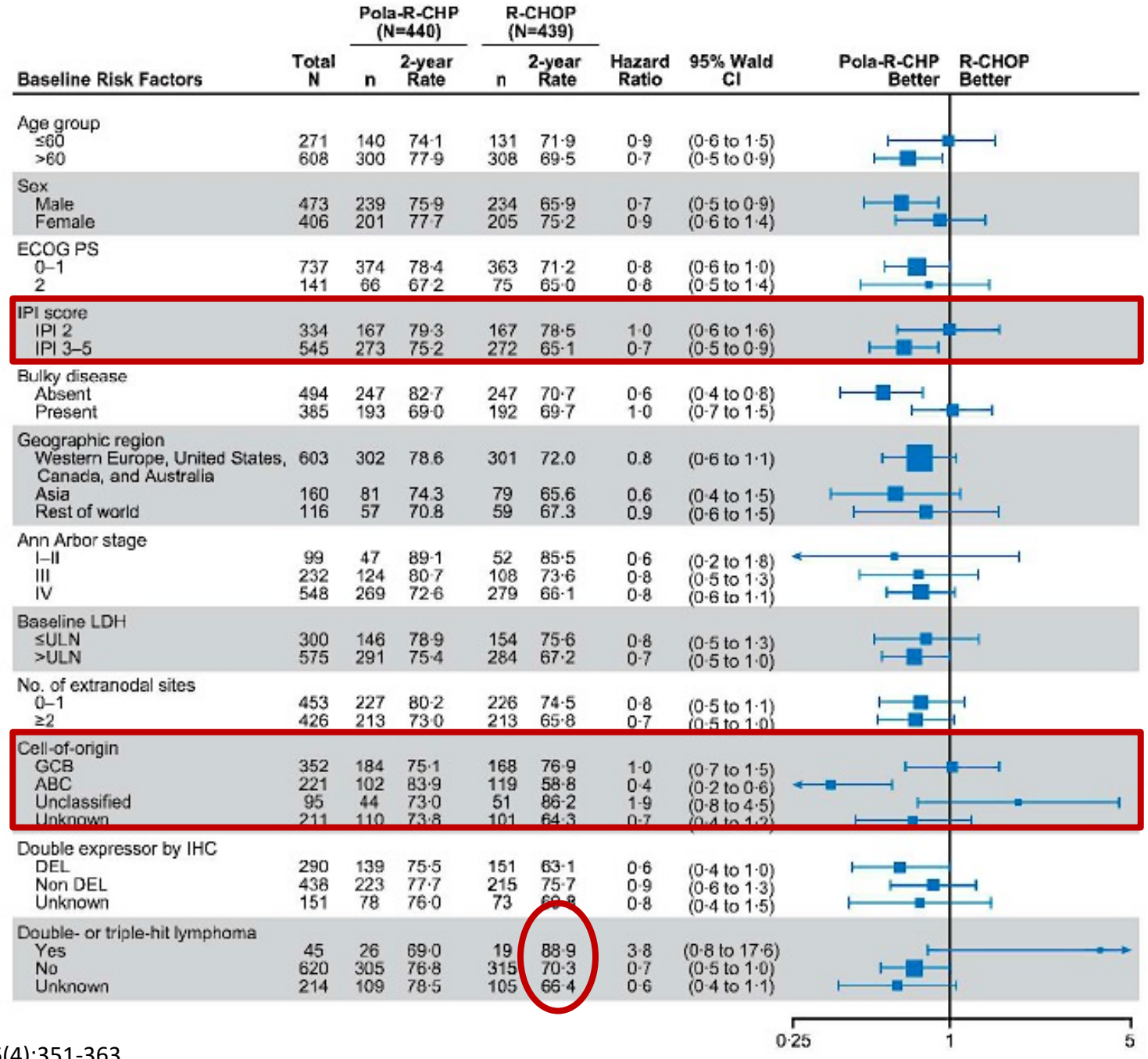
POLARIX: Supervicencia global y necesidad de tratamientos adicionales



Necesidad de tratamiento adicionales



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



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78·6	301	72·0	0·8	(0·6 to 1·1)
Asia	160	81	74·3	79	65·6	0·6	(0·4 to 1·5)
Rest of world	116	57	70·8	59	67·3	0·9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

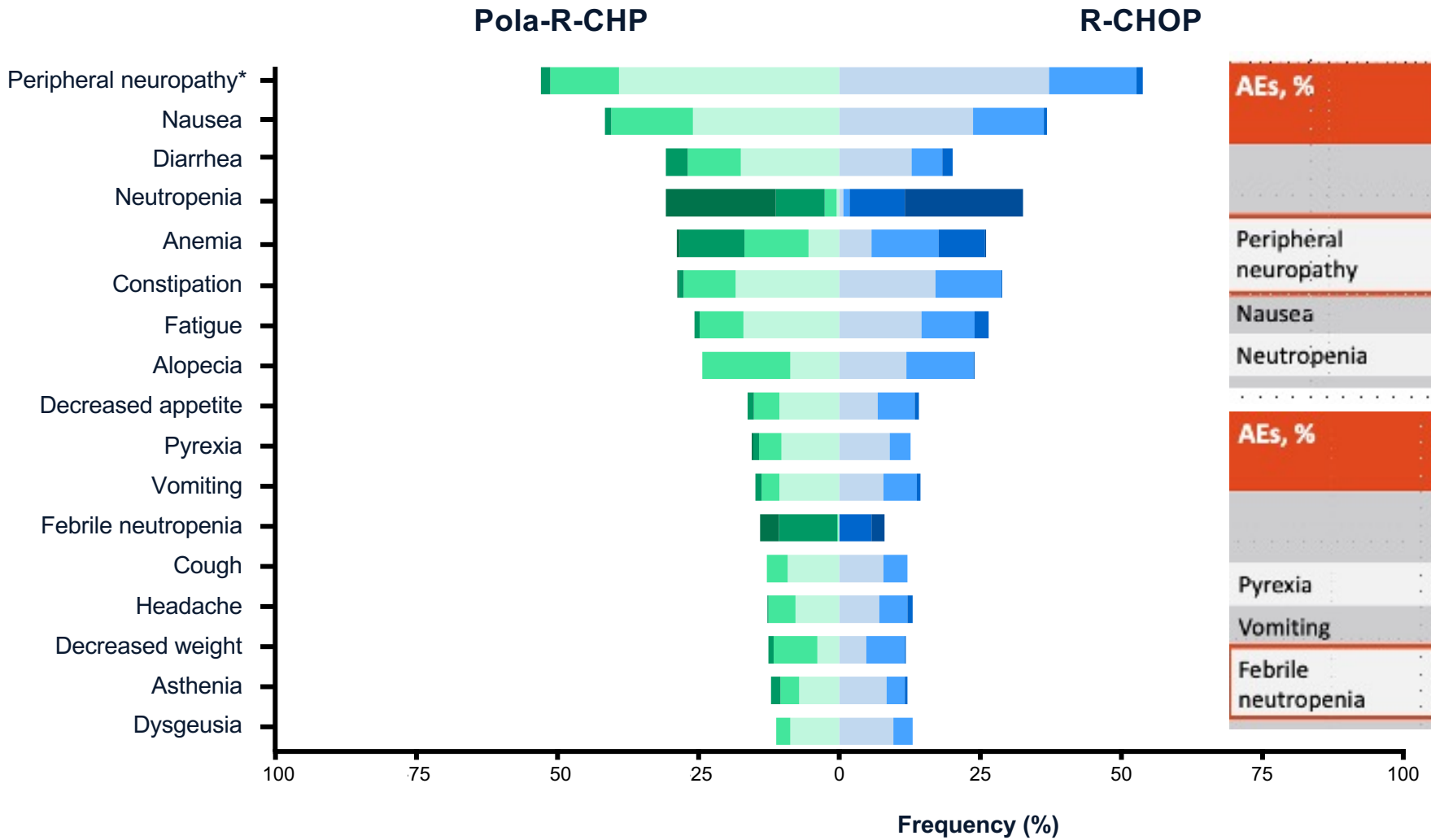
10% PFS difference in pts with IPI 3-5

15% PFS difference in pts with ABC DLBCL

Unusual outcome for control arm pts with DH/TH

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

POLARIX: Efectos adversos son similares



AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8.0	8.0

- 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 ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

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

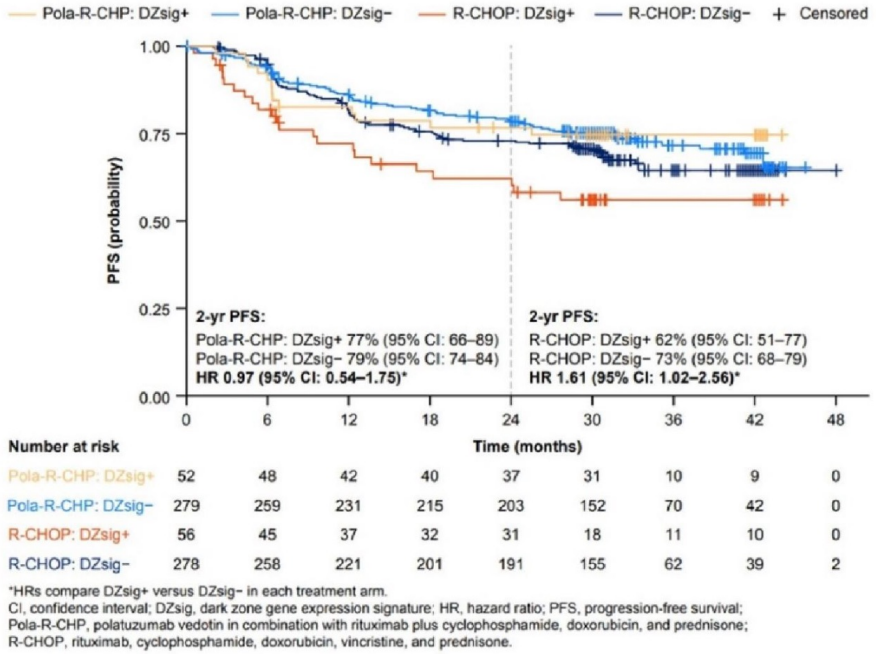
Deciphering the Clinical Benefit of Pola-R-CHP versus R-CHOP in Different Genetic Subtypes Beyond Cell of Origin in the POLARIX Study

Franck Morschhauser, Wilfred Leung, Vibha Raghavan, Georg Lenz, Fabrice Jardin, Alex F. Herrera, Laurie H. Sehn, Jeff P. Sharman, Christopher R. Flowers, Jonathan W. Friedberg, Marek Trněný, Hervé Tilly, Charles Herbaux, Samuel Tracy, Christopher R. Bolen, Will Harris, Jamie H. Hirata, Calvin Lee, Yanwen Jiang, Gilles Salles

Blood (2023) 142 (Supplement 1): 3000.

https://doi.org/10.1182/blood-2023-178623

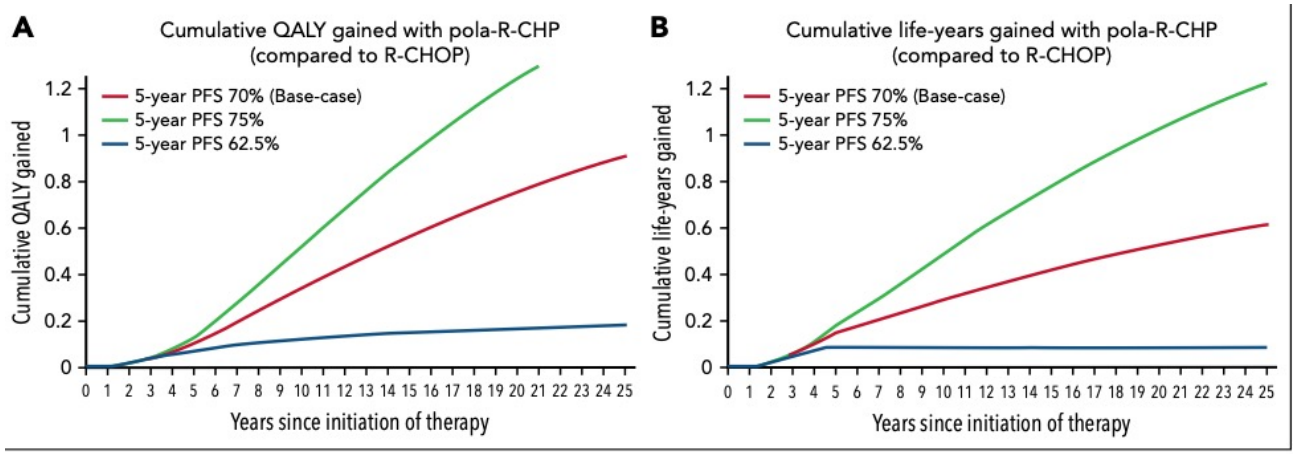
- Ciertos subtipos moleculares (independiente del COO) se han asociado con mal pronostico con R-CHOP
  - *EZH2* mutations/*BCL6* translocations (EZB), *MYD88*/*CD79B*, dark zone gene expression (DZ)
- Análisis post hoc POLARIX.
  - Pts con GCB DLBCL DZsig+ beneficio significativo Pola-R-CHP vs R-CHOP.
- DZsig refines cell-oforigin classification by identifying patients within GCB-DLBCL with inferior outcomes and shorter time to treatment.



POLARIX: costo-efectividad de Polatuzumab Vedotin + R-CHP comparado con R-CHOP

Treatment	Cost Effectiveness					
	Life, yr	Effectiveness, QALYs	Incremental effectiveness	Cost in 2021, $	Increase in cost, $	Incremental cost effectiveness ratio, $/QALY
R-CHOP	11.4	10.89	--	342,833	--	--
Pola-R-CHP	11.9	11.80	0.91	419,769	76,936	84,308

- Compared with R-CHP, Pola-R-CHP is **cost-effective ($84,308)** at a willingness-to-pay (WTP) level of $150,000/QALY, **if a PFS** improvement is maintained with Pola-R-CHP in the long term (5-yr PFS: 70%)
- Pola-R-CHP has an **incremental effectiveness** of 1.23 life-years and 1.16 QALYs
- Cost effectiveness of Pola-R-CHP depends largely on the **high cost of CAR T-cell therapy**
- Further efforts are needed **to reduce the cost of pola** and other novel therapies in DLBCL.



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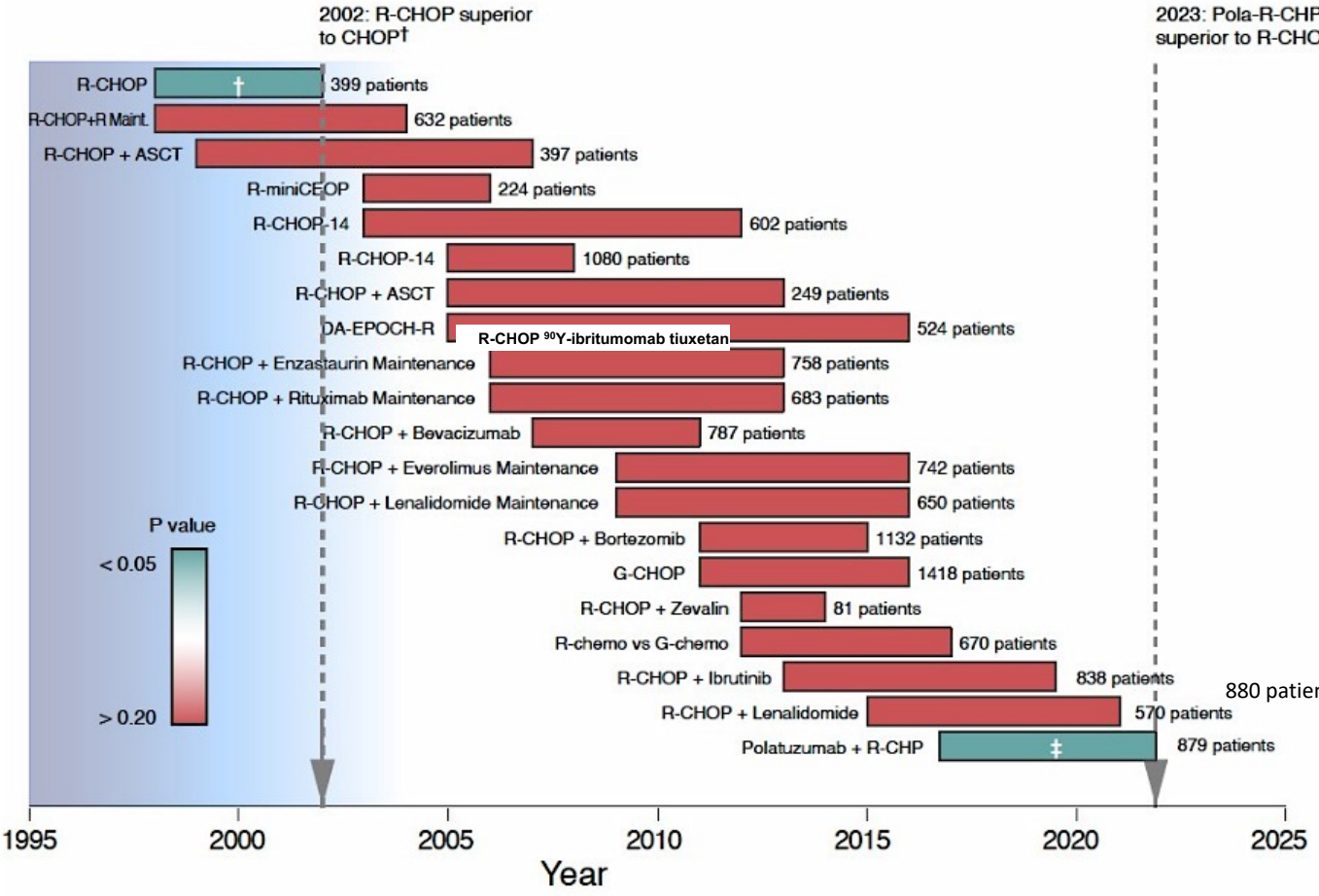
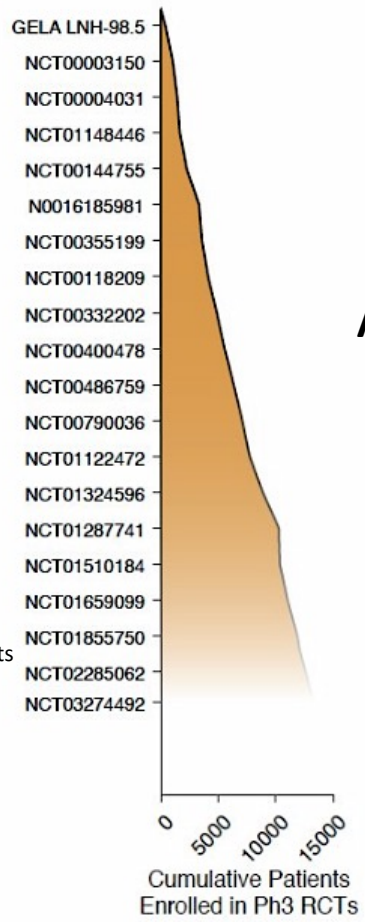
¿Más allá de RCHOP – Terapia guiada por perfil Molecular o agnóstico?





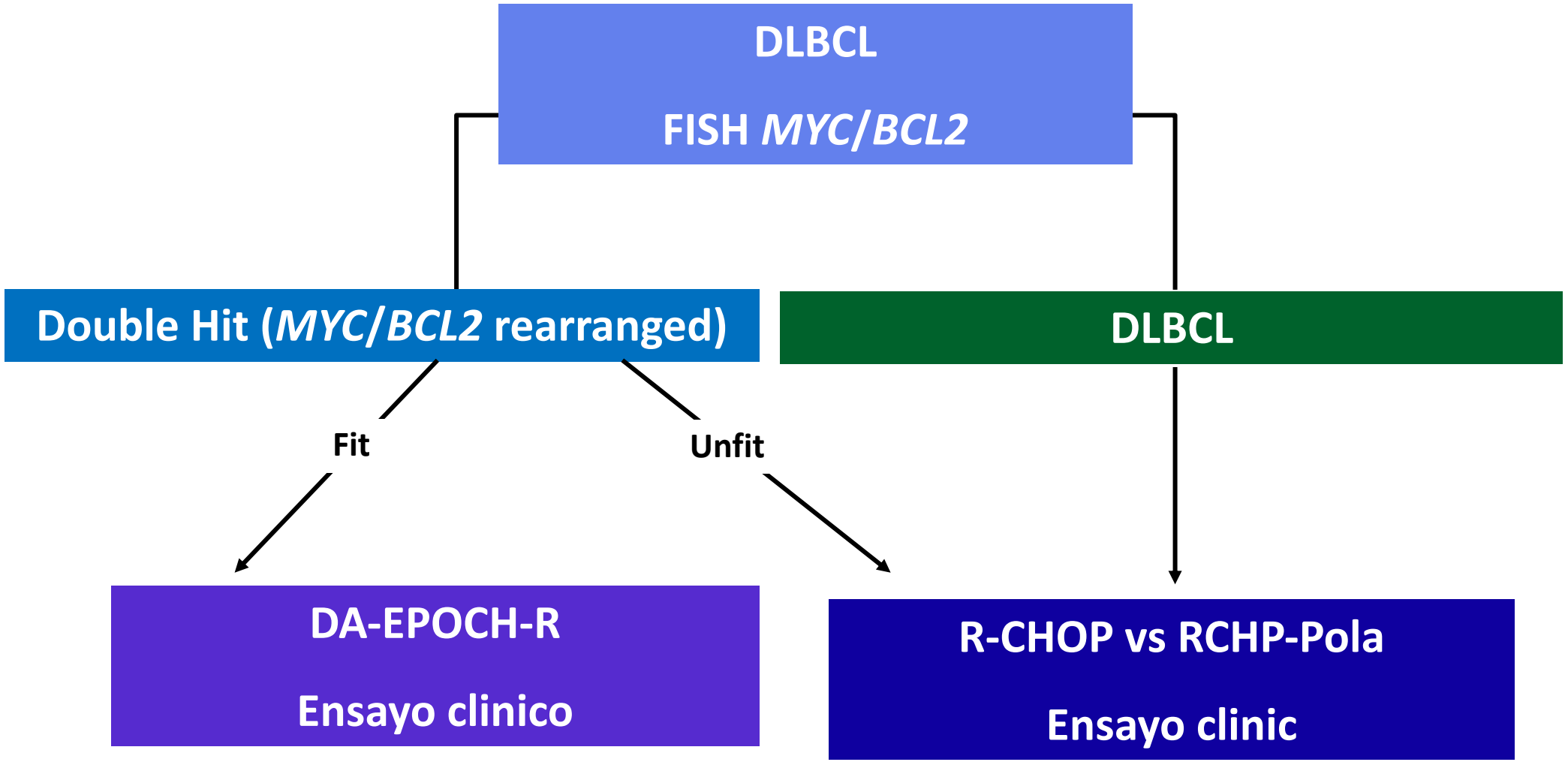
Molecularly Agnostic

- CAR T-cell therapy
- Tafasitamab/ lenalidomide
- Bispecifics
- COO agnostic small molecules

Molecularly selected

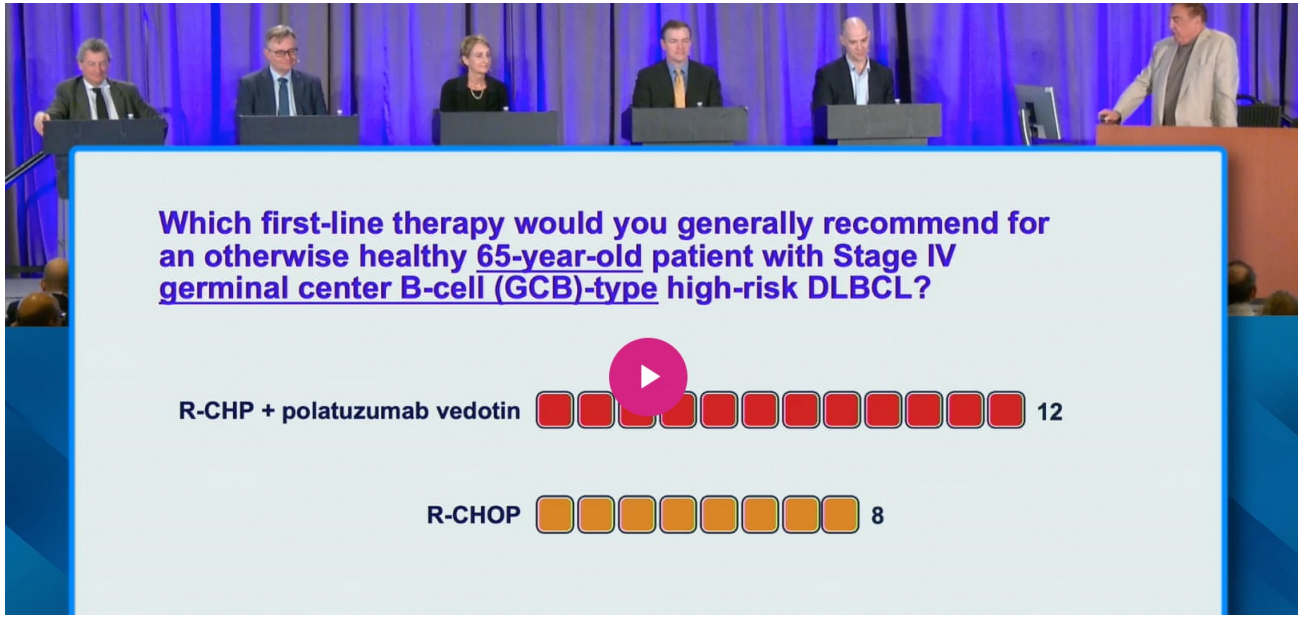
- BTK inhibitors
- PI3K inhibitors
- BCL2 inhibitors
- Others

Mi enfoque en este caso



Conclusion

- La terapia de primera línea para (DLBCL) **con Pola R-CHP es prometedora**
  - Hay margen para mejorar
  - No hay suficiente evidencia para excluir GCB del beneficio de Pola RCHP
- El uso de terapias **guiadas por el perfil molecular/ctDNA/MTV** es importante para optimizar y personalizar la terapia
- Debemos analizar la costo efectividad en nuestro contexto



C), genetic classification is yet to be optimized for routine clinical application.[12]