22nd

INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

WESTIN CHICAGO RIVER NORTH

#IUCLS2025

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22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

Treatment options: Frontline Diffuse Large B-Cell Lymphoma

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Medical College of Wisconsin
April 4, 2025

Disclosures

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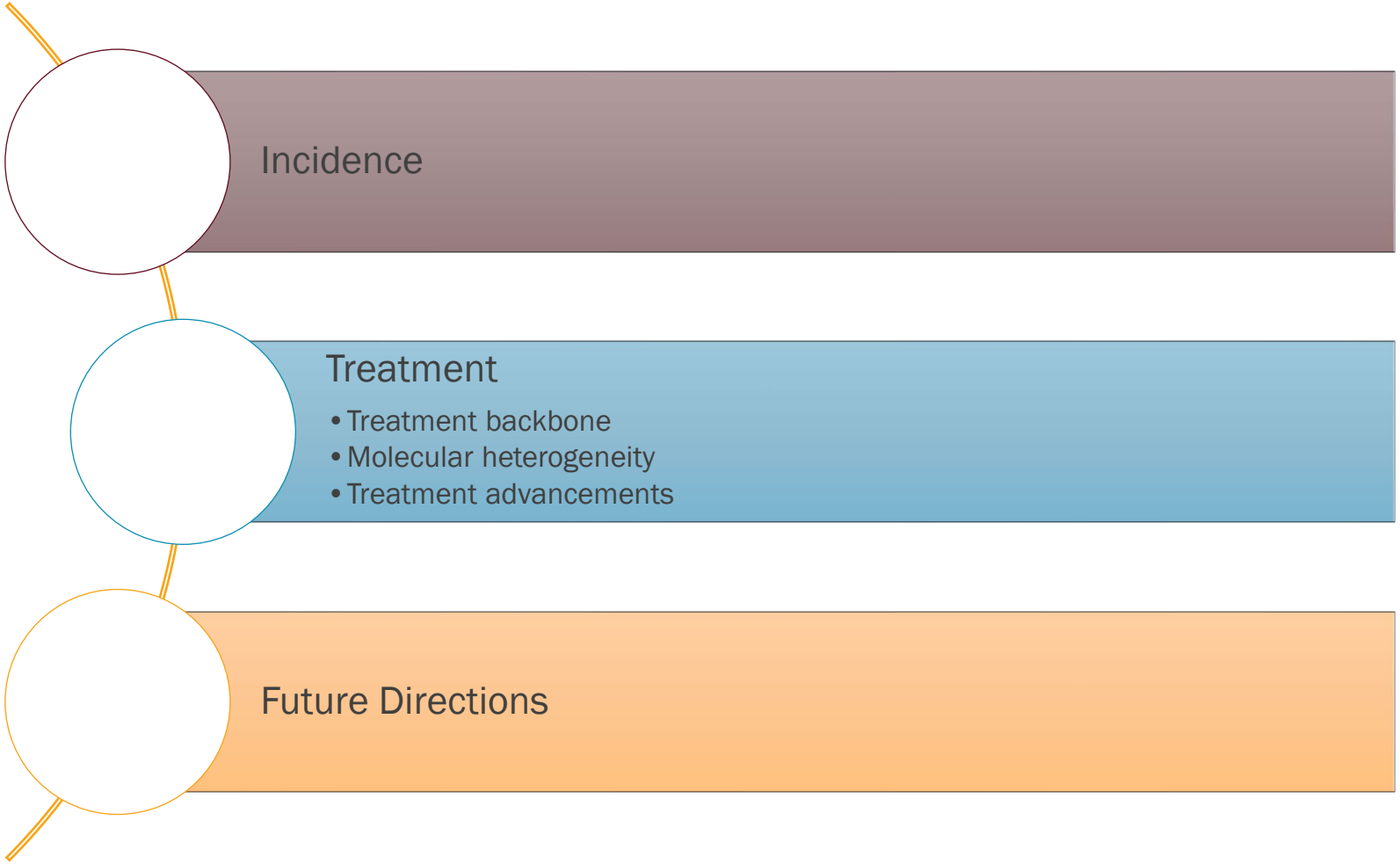
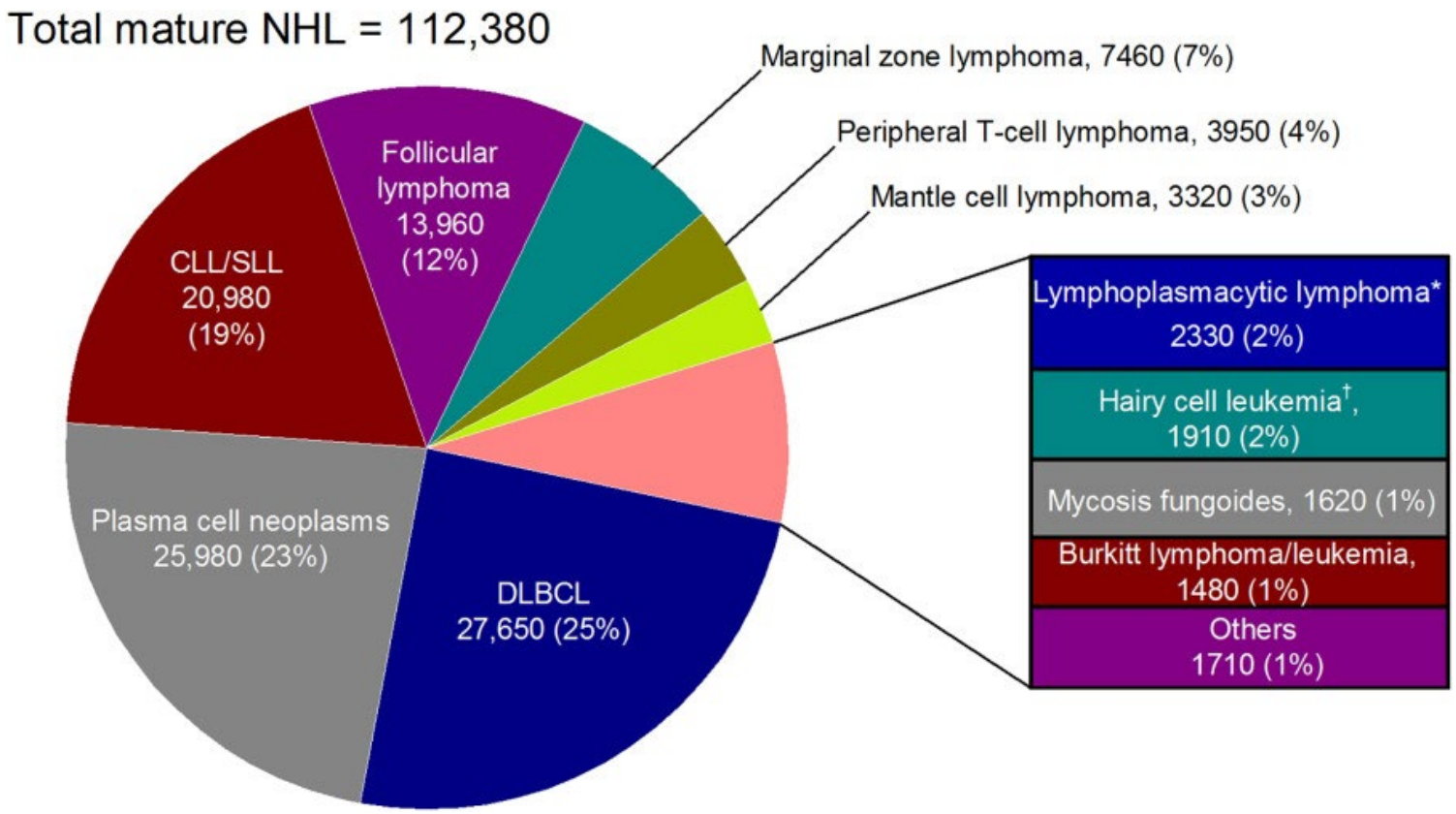
Disclosures impacting presentation: none

Front line DLBCL



U.S. NHL Cancer Stats



US cancer stats for lymphoid malignancies by WHO subtypes

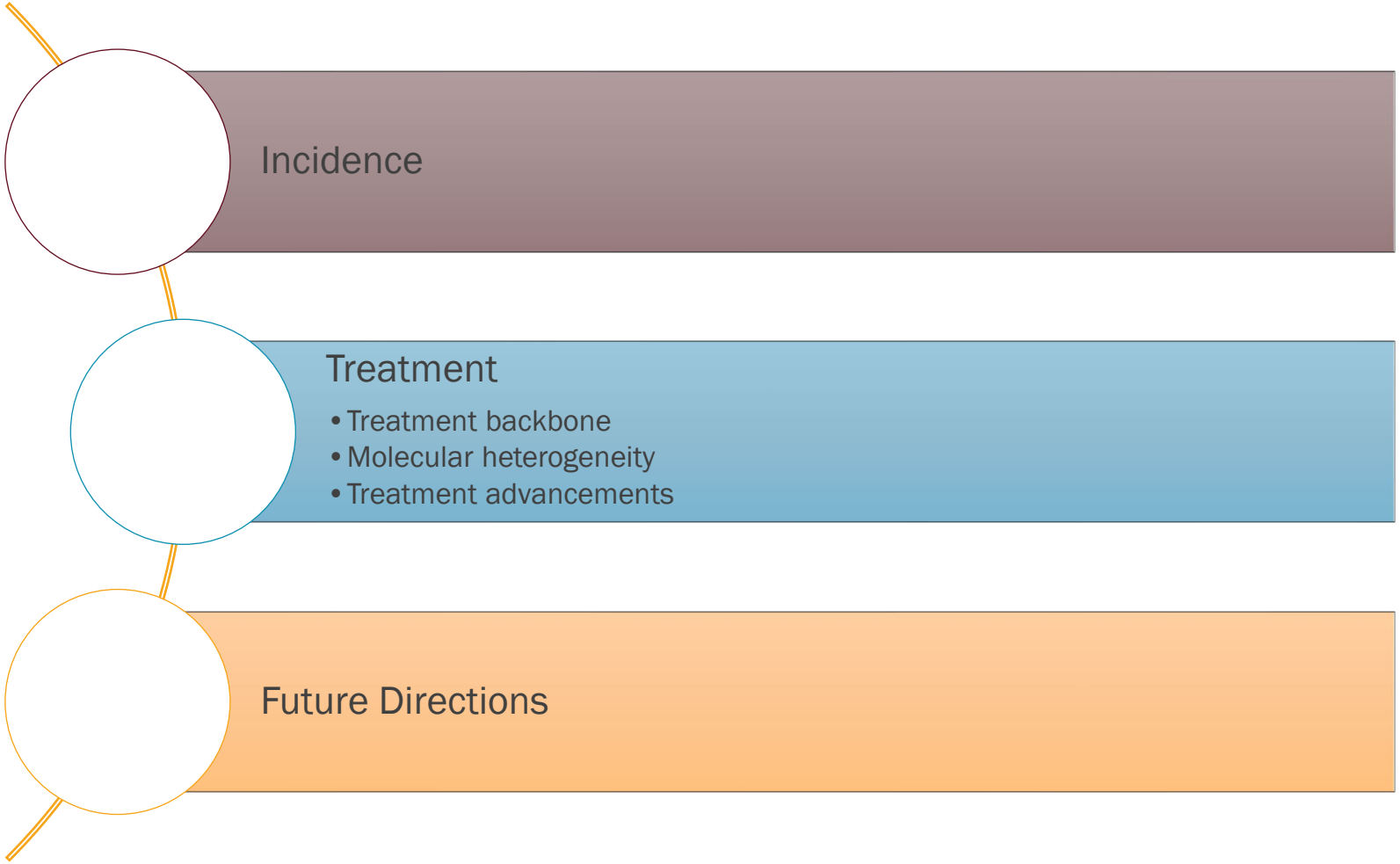
Most common form of NHL

Aggressive NHL

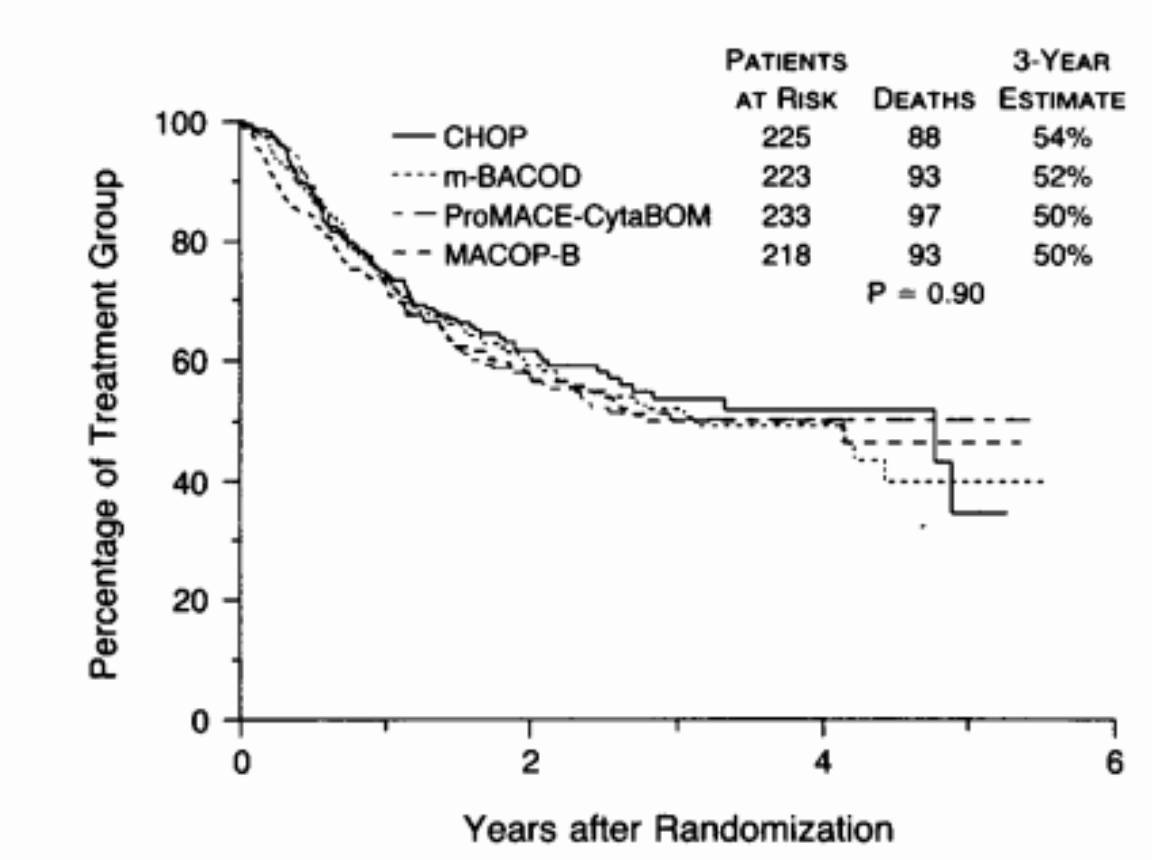
Peaks in the 6th decade

Ca Cancer J Clin 2016;66:443–459.

Front line DLBCL



CHOP: formalizing a backbone



Phase III, SWOG 8516 trial

Initiated 1986; N=1138

Overall survival

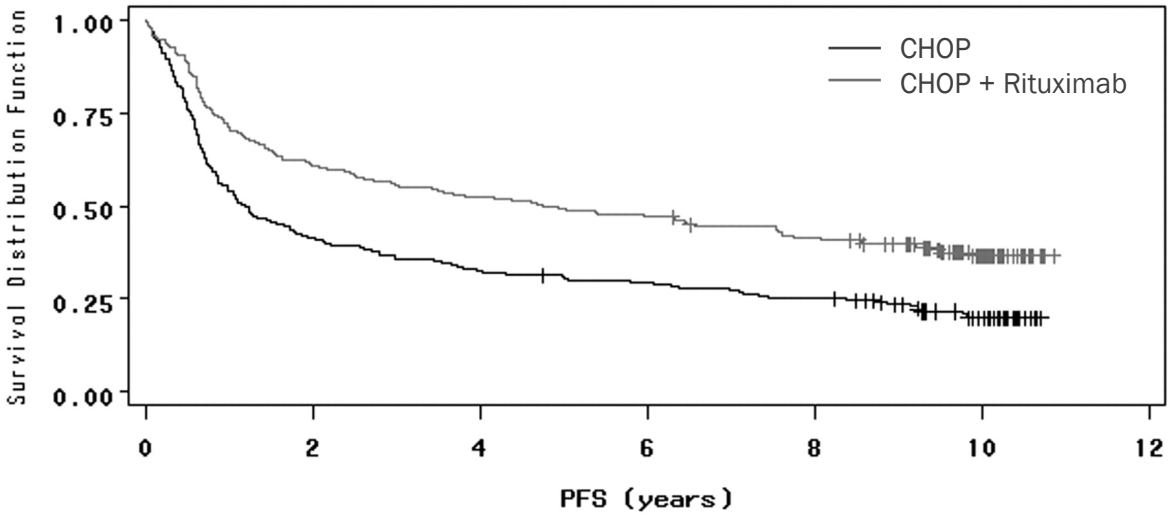
CHOP best available therapy

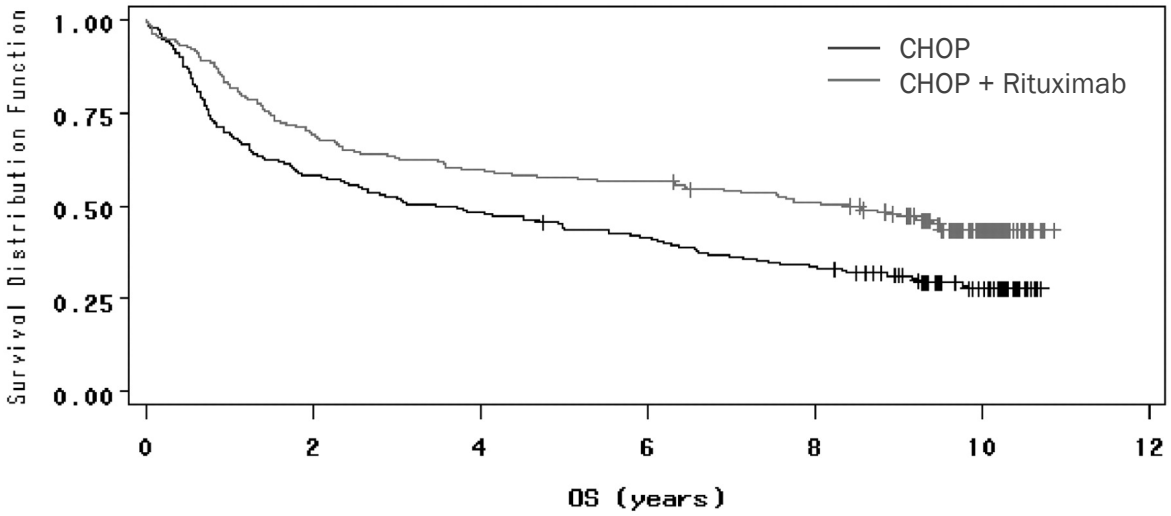
Toxicity	CHOP	m-BACOD	ProMACE-CytaBOM	MACOP-B
Death	1%	5%	3%	6%
G4	31%	54%	29%	43%

NEJM 1993;328:1002-1006

R-CHOP

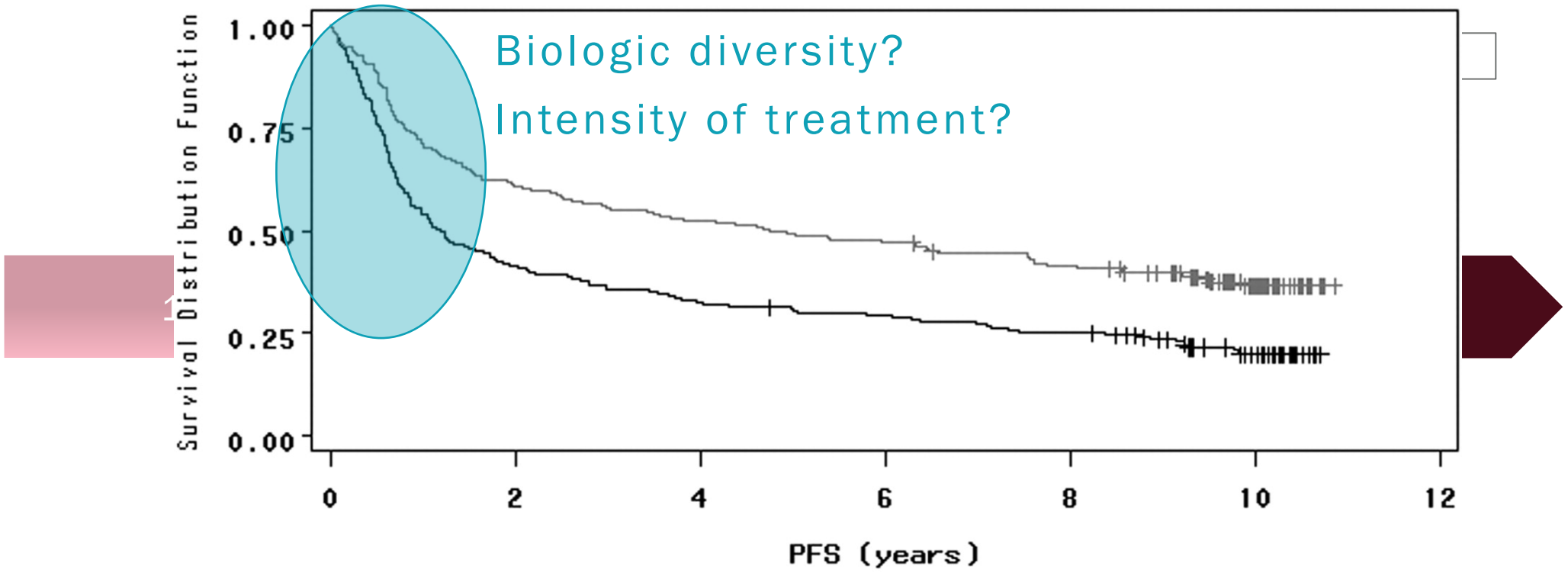
CHOP vs R-CHOP





N Engl J Med 2002;346:235-242.
Blood 2010;116 (12): 2040–2045.

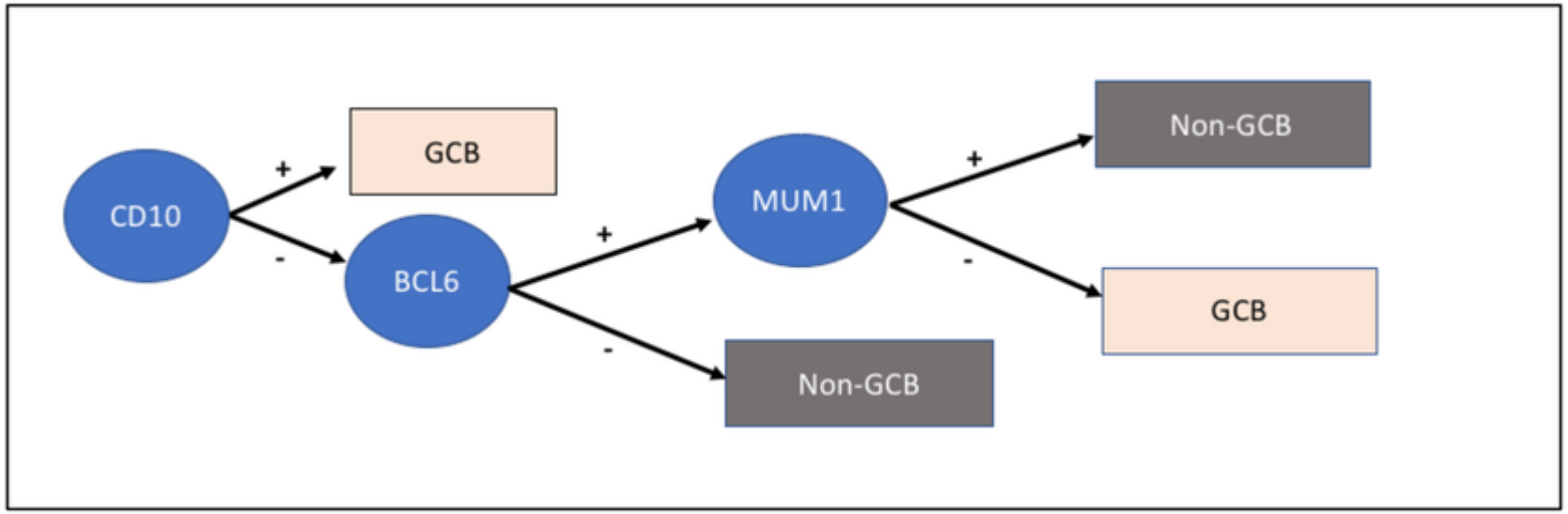
Evolution of DLBCL therapy



Cell of Origin - IHC

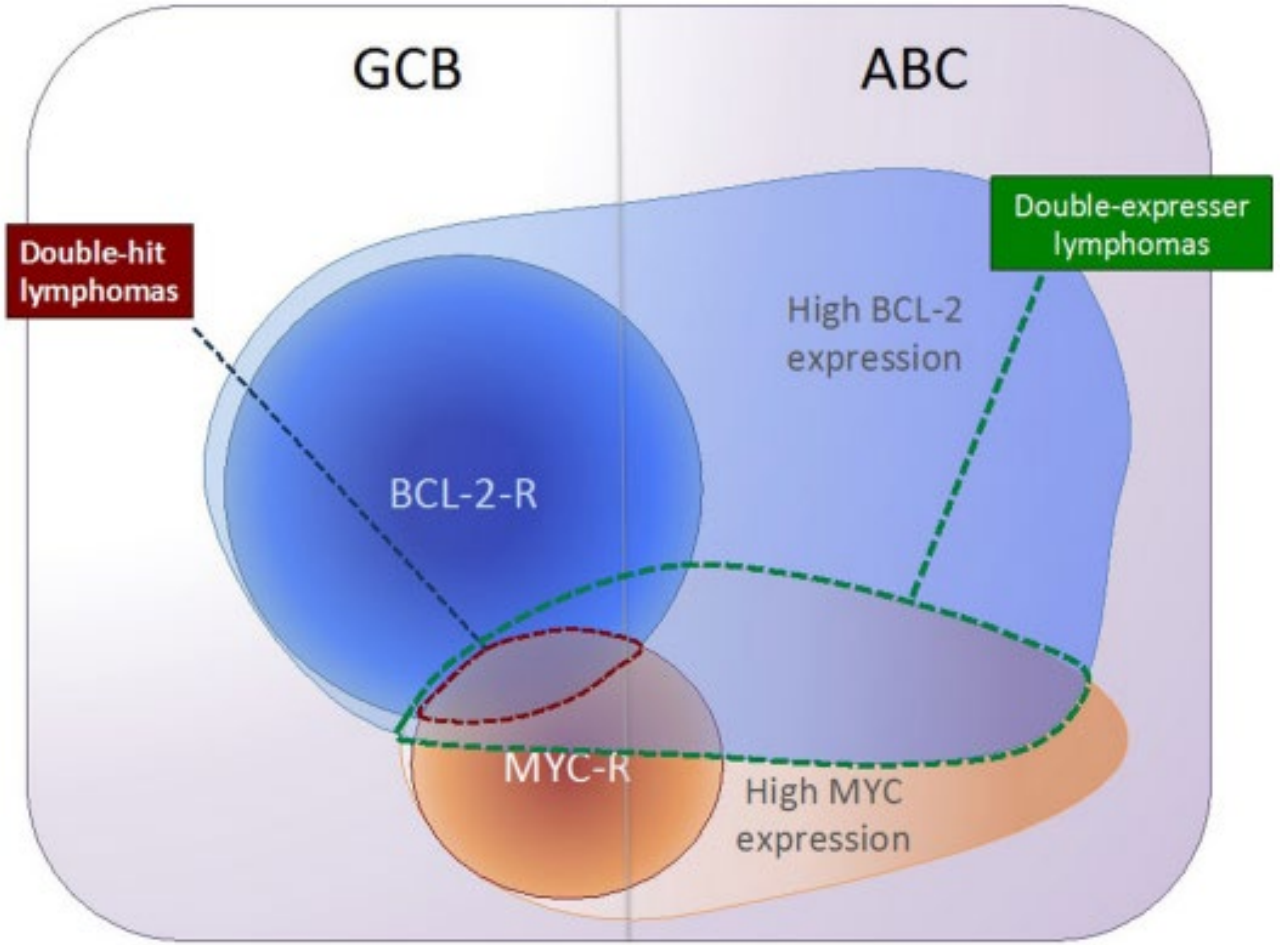
Hans algorithm – IHC based decision tree to classify GCB and non-GCB tumors

- ~70% concordance with GEP
- Does not recognize the 10-15% of tumors unclassified by GEP
- Some indeterminate cases seen clinically



Cell of Origin

GCB
favorable prognosis as compared to ABC.



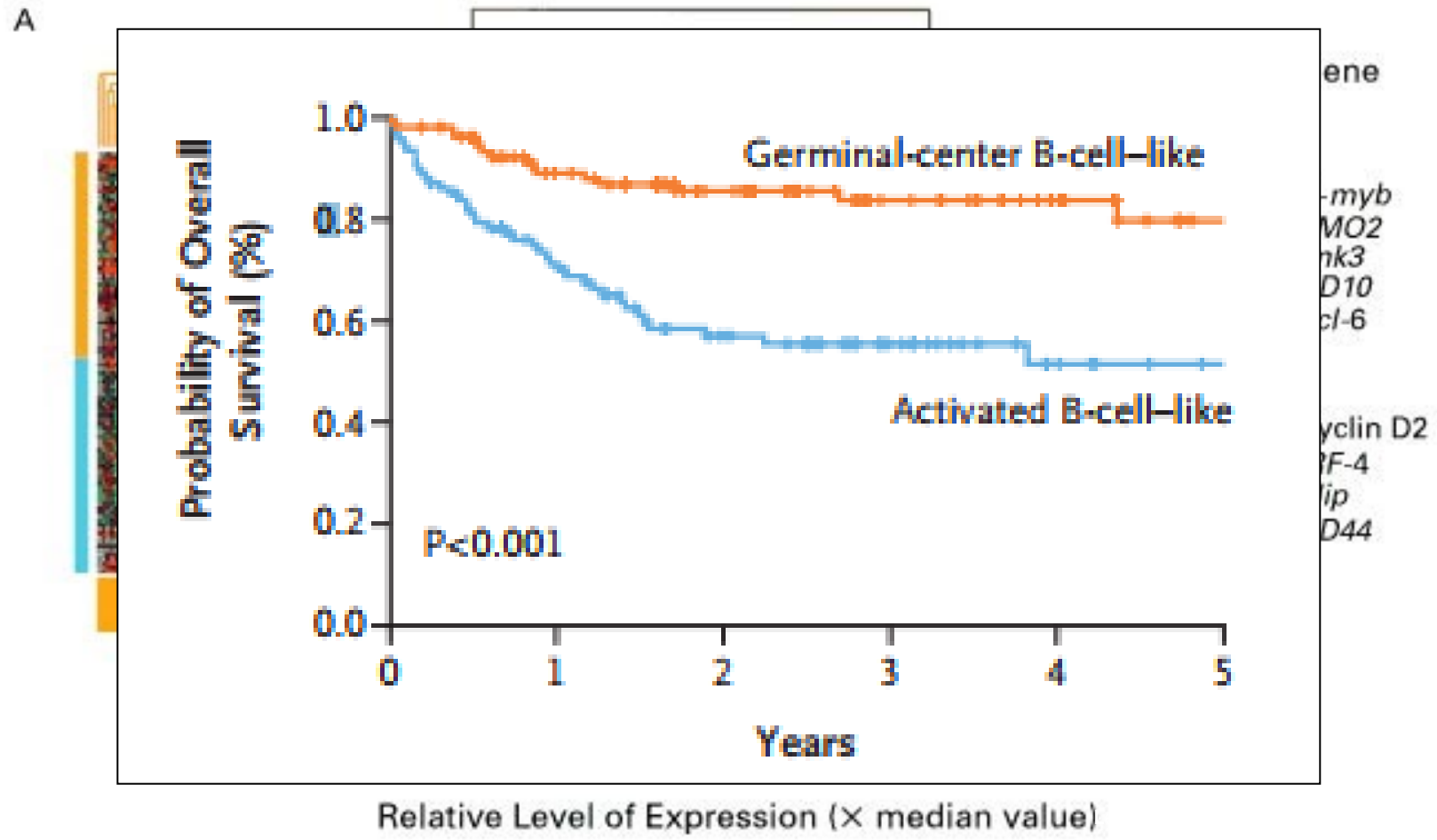
ABC
poor prognosis as compared to GCB. CNS involvement could be more likely

Double HIT
(FISH MYC & BCL2 rearrangements)
Very poor prognosis
CNS involvement likely

Double Expresser
(High MYC and BCL2 protein expression).
Poor prognosis

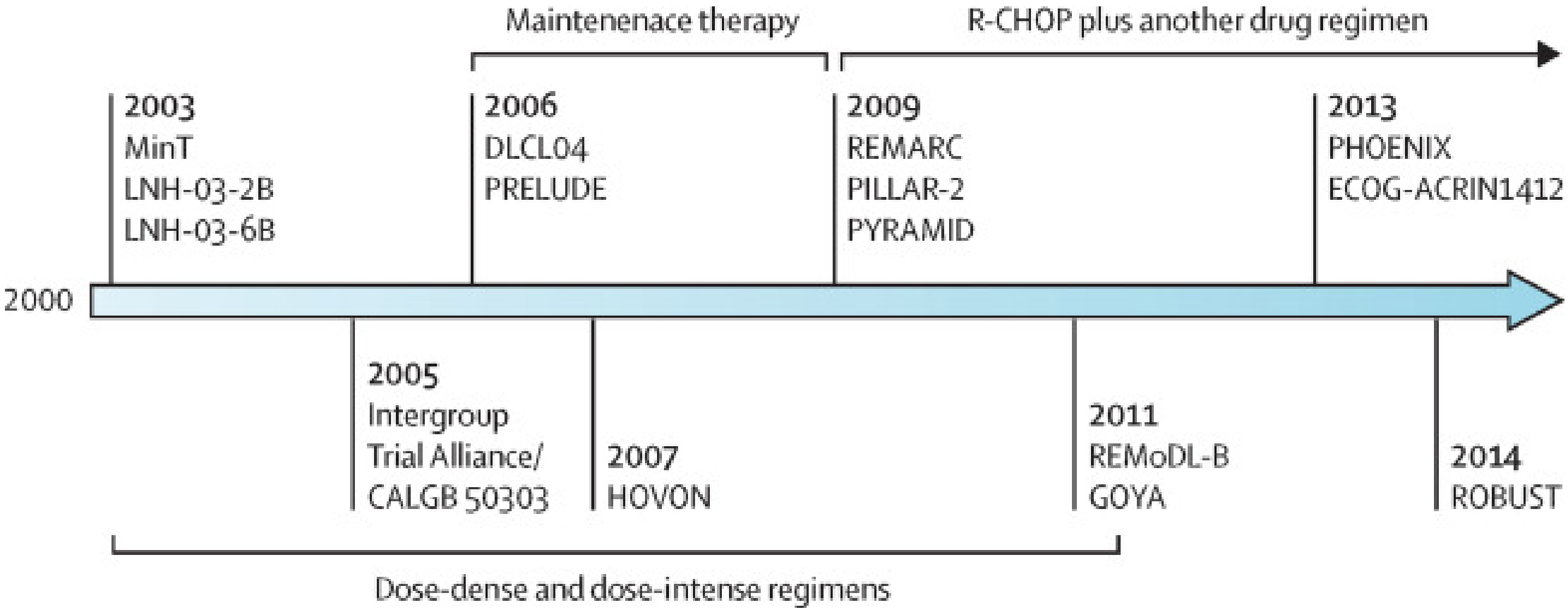
Curr. Treat. Options in Oncol.;2015,16: 58

Gene Expression Profiling



NEJM 2002; 346:1937-1947.
NEJM 2008;359:2313-2323.

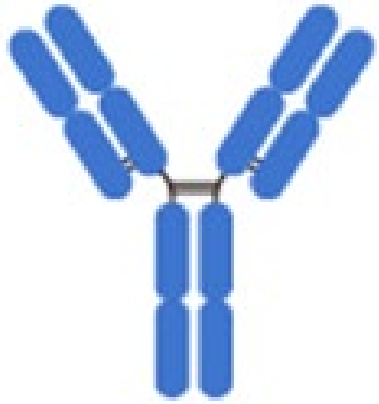
Attempts to improve the backbone



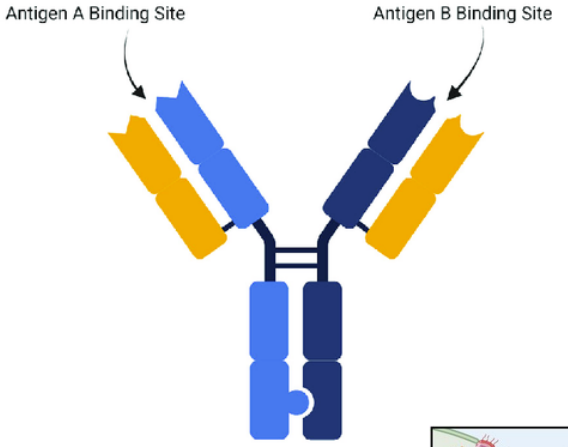
Lancet Haematol 2020; 7: e838–50

Novel therapy strategies

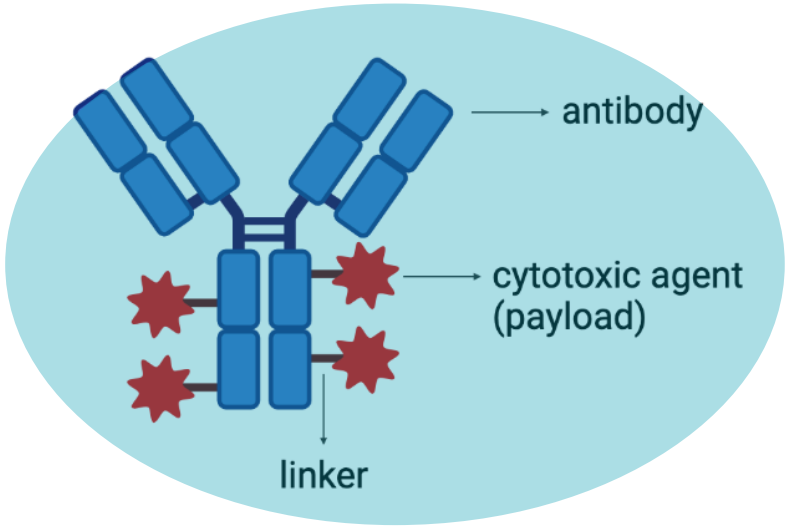
Monoclonal Antibodies



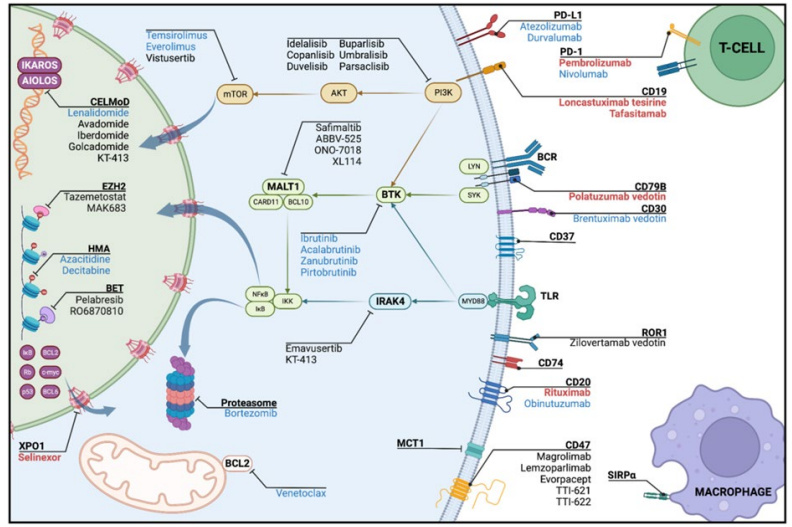
Bispecific Antibodies (BITE)



Antibody drug conjugate (ADC)

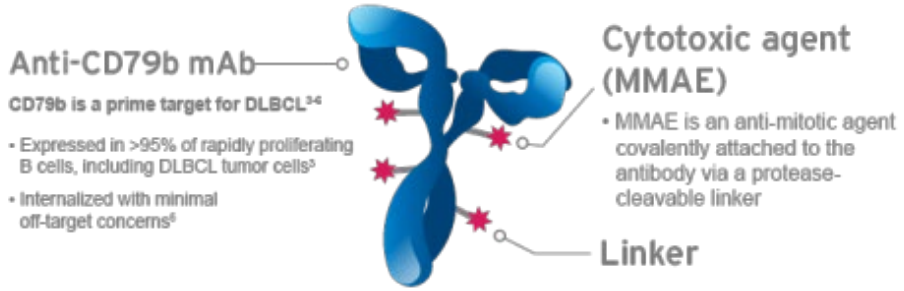


Targeted agents

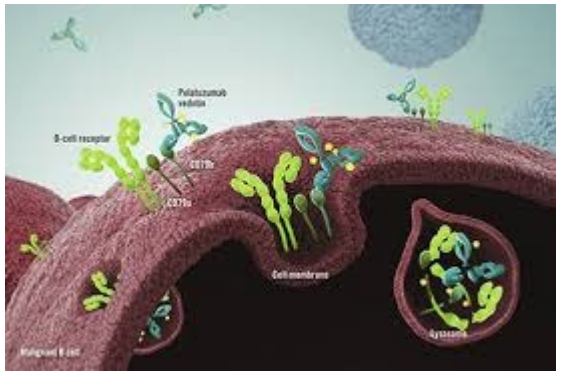


https://oncobites.blog/2023/09/27/antibody-drug-conjugate-revolution-in-cancer-treatment/
https://www.researchgate.net/figure/Monoclonal-and-bispecific-antibodies-for-targeted-treatment-Created-with-BioRendercom_fig5_364484166
Hematological Oncology, Volume: 41, Issue: S1, Pages: 92-106, First published: 09 June 2023, DOI: (10.1002/hon.3143)

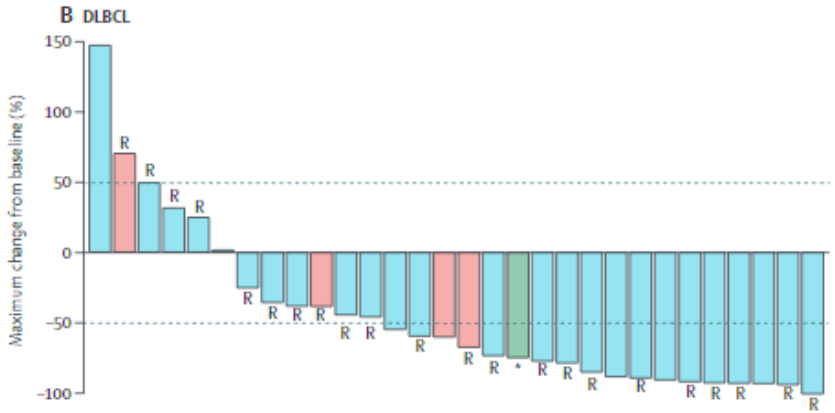
Polatuzumab Vedotin



- Antibody Drug Conjugate (ADC)
  - Humanized anti-CD79b monoclonal antibody
  - Conjugated with a monomethyl auristatin E (MMAE) payload
    - MMAE → Microtubule inhibitor
- Phase 1 study, Dose >1.8 mg/m2
- Main AEs
  - Neutropenia (G3-4)
  - Peripheral neuropathy (G1-2)



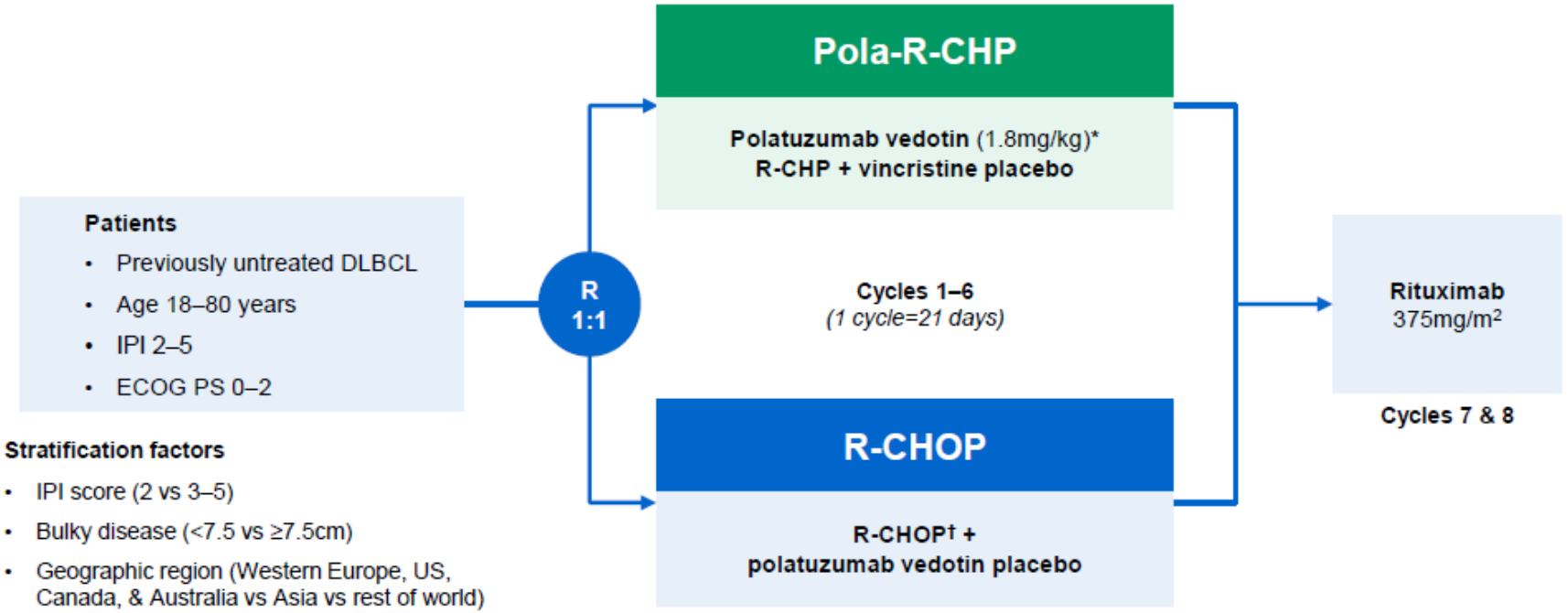
ORR	CR	mDOR
52%	13%	5.2 mo



Lancet Oncol 2015; 16: 704–15

POLARIX Trial

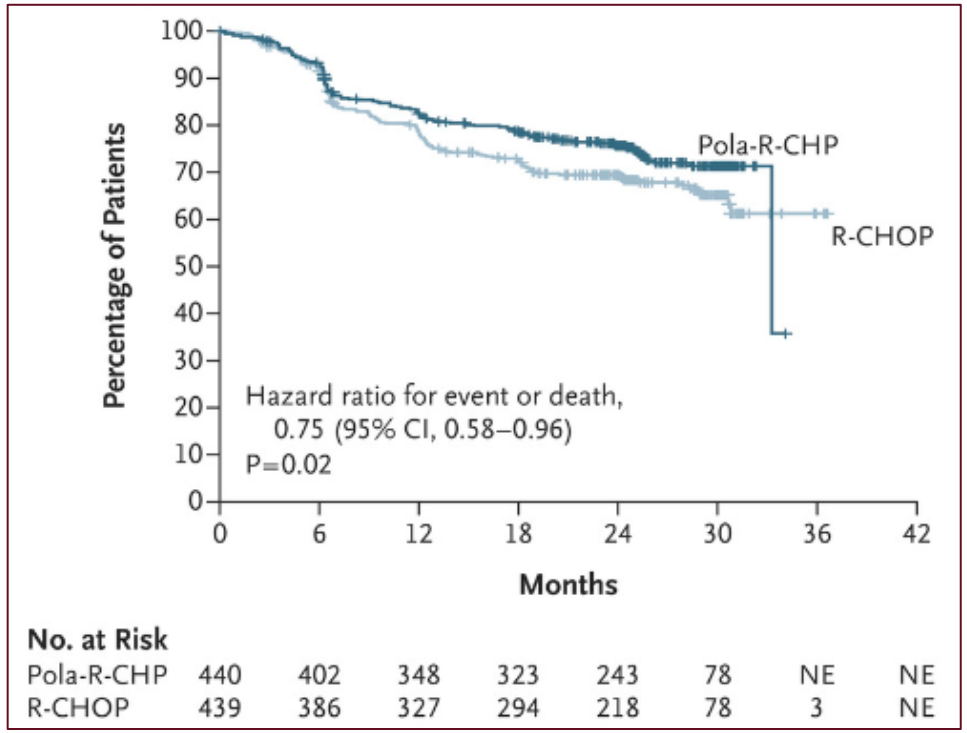
Randomized, double blind, phase III study



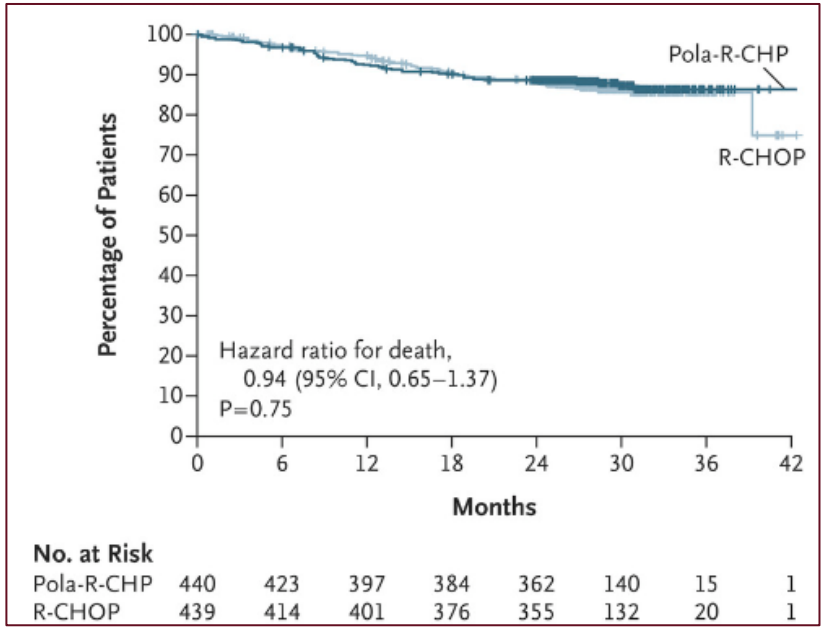
*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

N Engl J Med 2022;386:351-363

Polarix Trial: PFS and OS



- Pola-R-CHP showed 27% reduction in relative risk of disease progression, relapse, or death
- 24-month PFS
  - 76.7 vs 70.2%

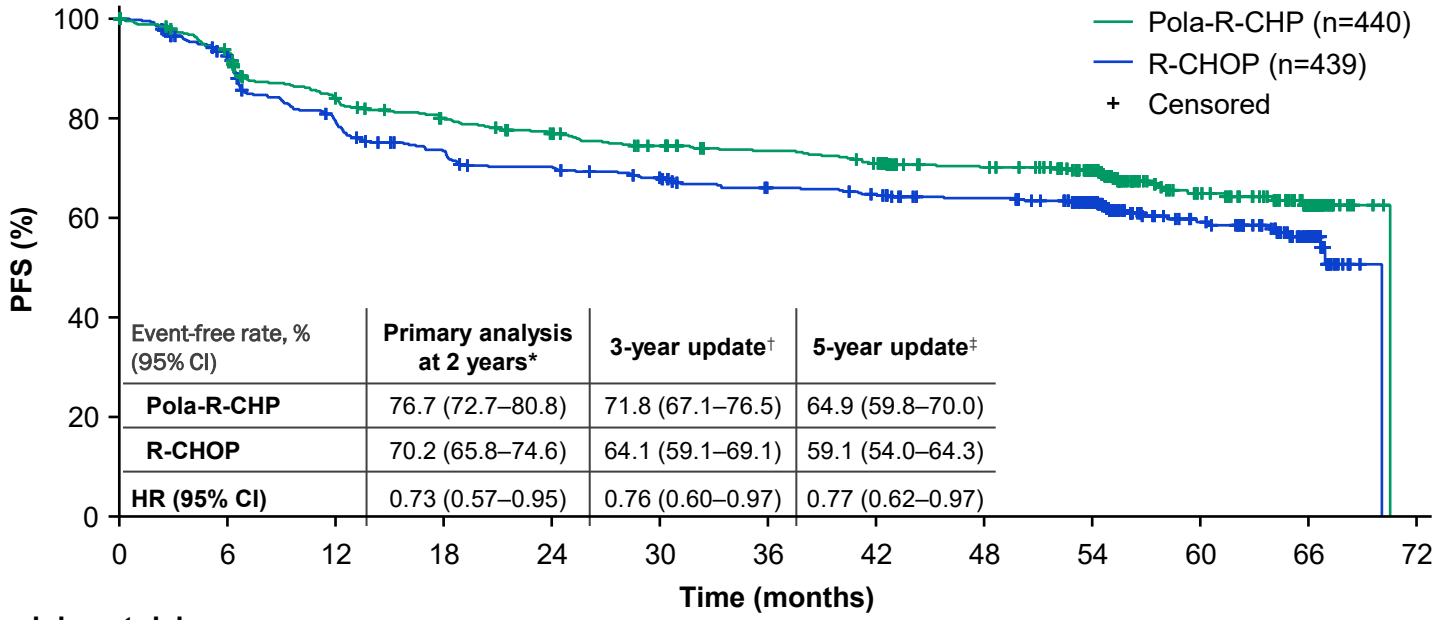


N Engl J Med 2022;386:351-363

POLARIX 5-yr update: PFS

PFS in the global ITT population

Sustained PFS benefit – confirmation of 2-yr primary analysis



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

Patients remaining at risk

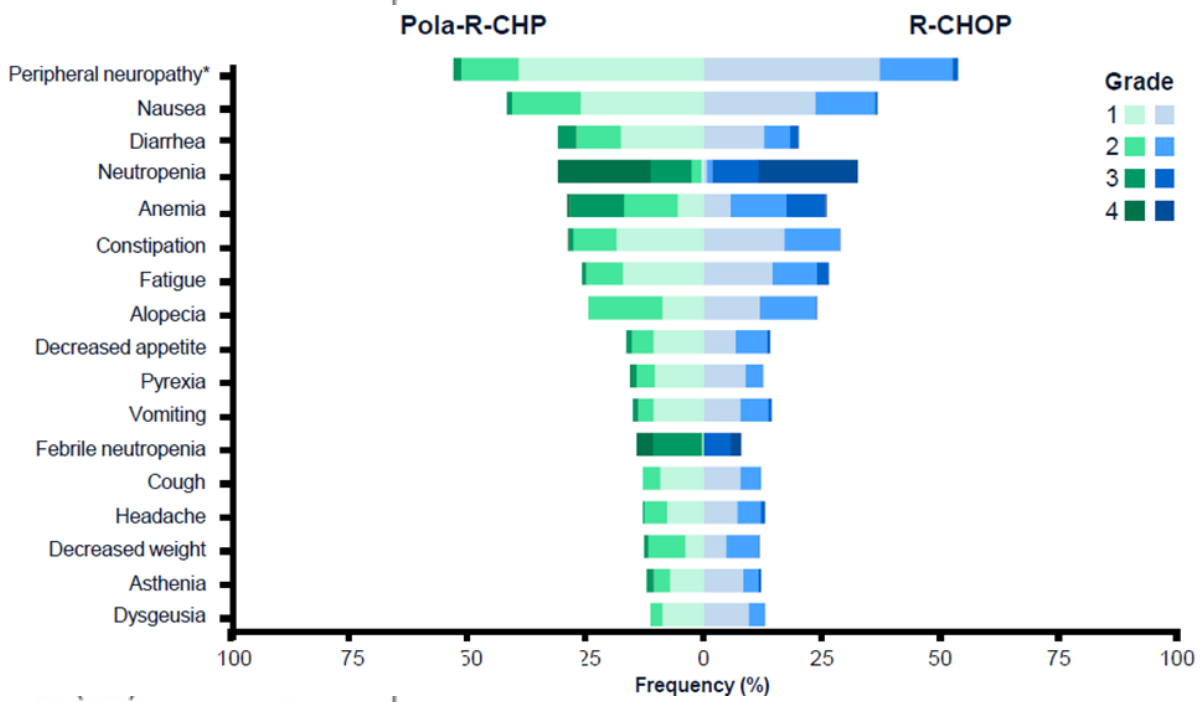
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

*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.

ASH 66th Annual meeting, oral presentation

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
		number of		
Peripheral neuropathy†	230 (52.9)	7 (1.6)		
Nausea	181 (41.6)	5 (1.1)		
Neutropenia	134 (30.8)	123 (28.3)		
Diarrhea	134 (30.8)	17 (3.9)		
Anemia	125 (28.7)	52 (12.0)		
Constipation	125 (28.7)	5 (1.1)		
Fatigue	112 (25.7)	4 (0.9)		
Alopecia	106 (24.4)	0		
Decreased appetite	71 (16.3)	5 (1.1)		
Pyrexia	68 (15.6)	6 (1.4)		
Vomiting	65 (14.9)	5 (1.1)		
Febrile neutropenia	62 (14.3)	60 (13.8)		
Headache	56 (12.9)	1 (0.2)		
Cough	56 (12.9)	0		
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0



N Engl J Med 2022;386:351-363

Evolution of DLBCL therapy

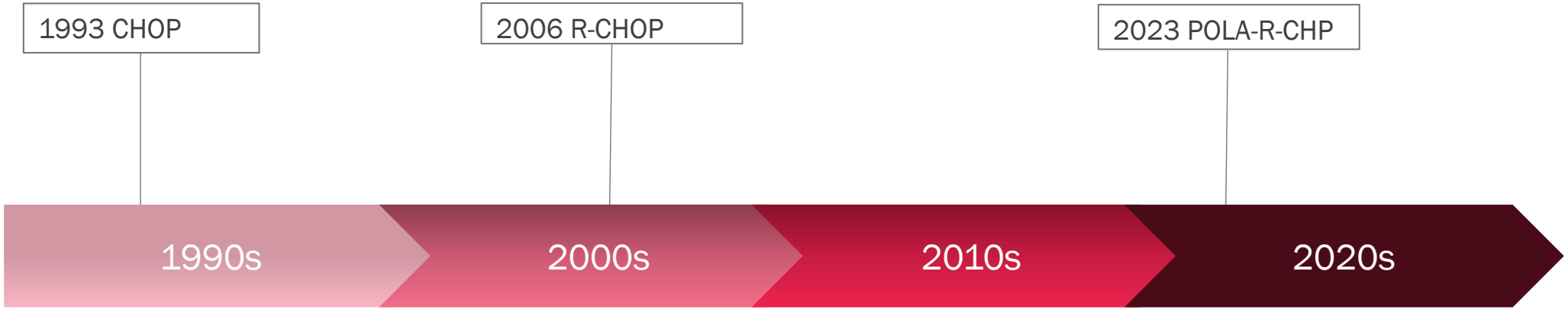
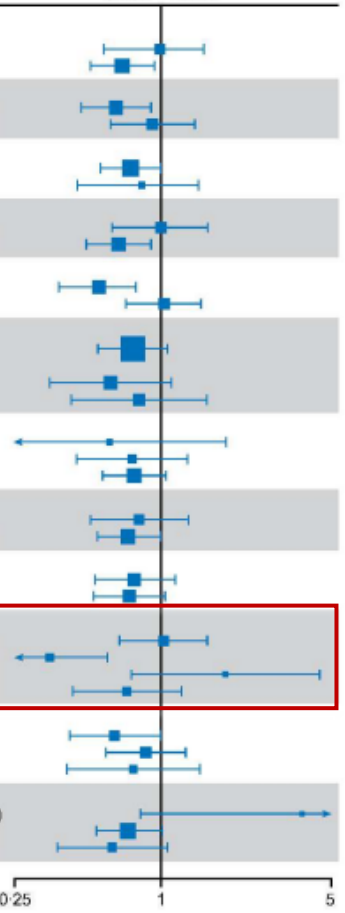


Figure S1. Subgroup Analysis of Investigator-assessed PFS (ITT Population).

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)

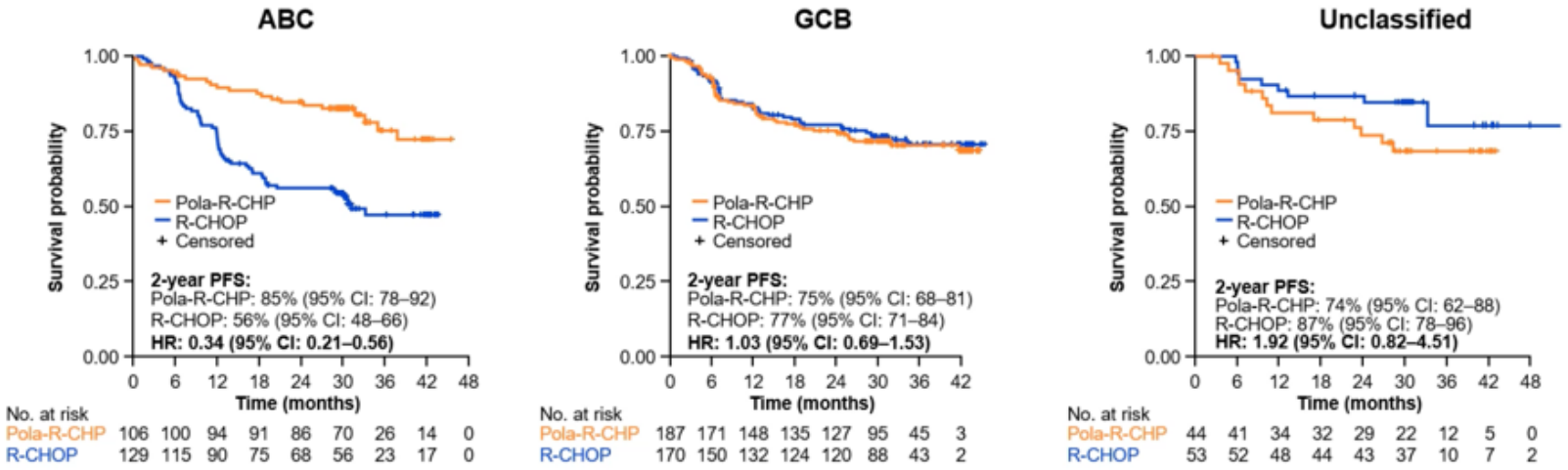


NEJM, 2022; 386: 351-363.

Polarix COO outcomes

Outcomes in COO subgroups

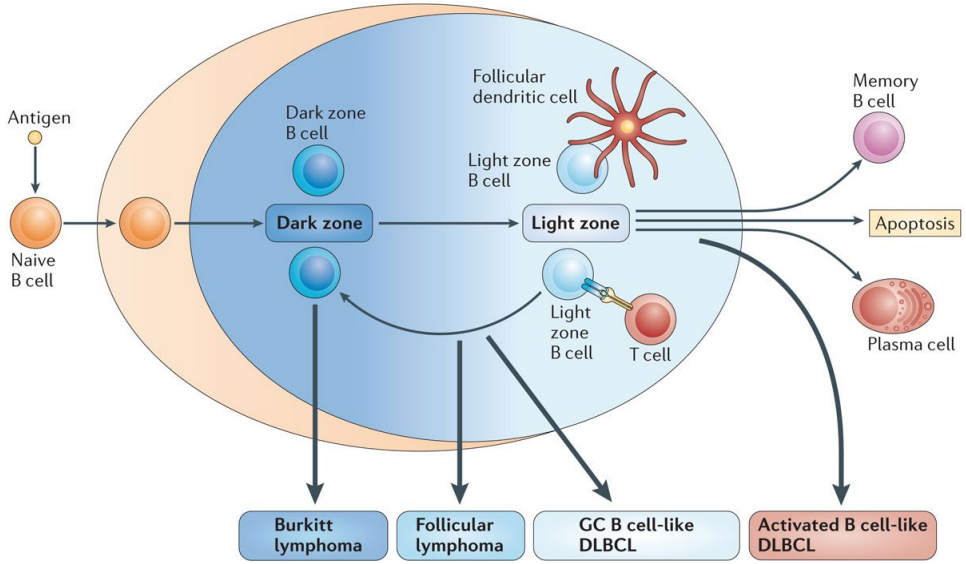
- COO status was determined in 689 patients in POLARIX (ABC, n=235; GCB, n=357; unclassified, n=97)
- Based on a data cutoff of June 15, 2022, with a median follow-up of 39.7 months, a **PFS difference between treatment groups** was observed in ABC-DLBCL, but not in GCB or the unclassified subgroups

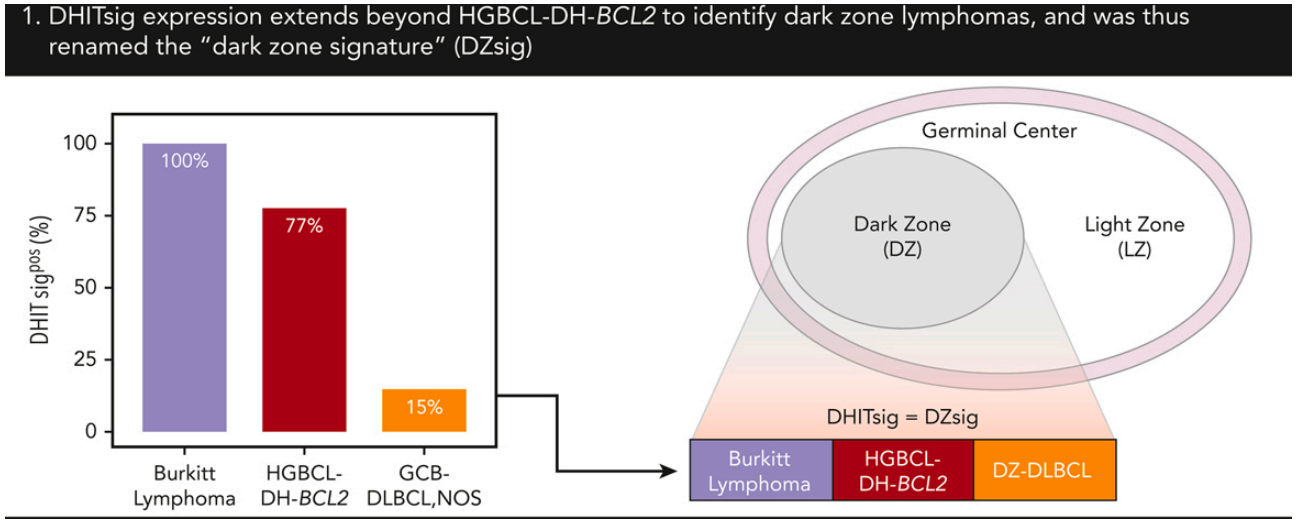


ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma GCB, germinal center B cell; HR, hazard ratio; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Morschhauser, ASH 2023, Poster 3000. As presented in Postercast.

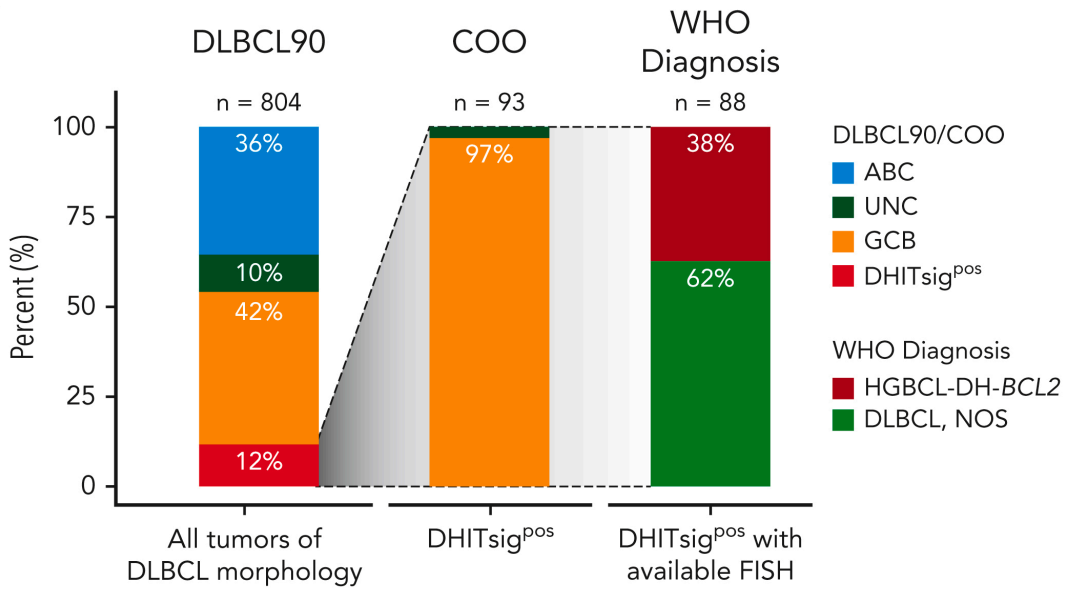
Other Molecular Signatures

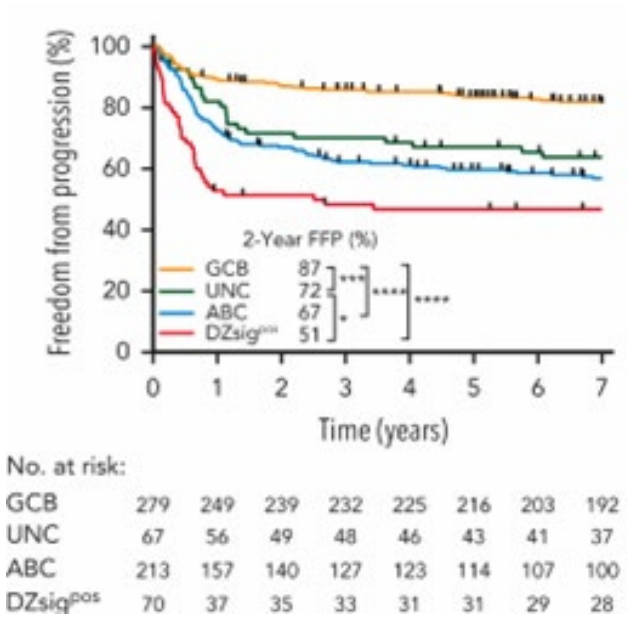




Nature Reviews Immunology, 2015;15: 172–184
Blood, 2023; 141 (20): 2493–2507.

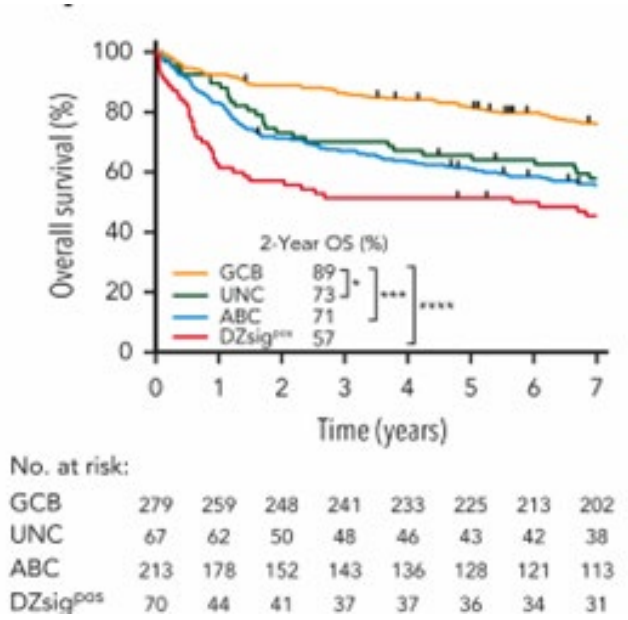
Other Molecular Signatures





No. at risk:

GCB	279	249	239	232	225	216	203	192
UNC	67	56	49	48	46	43	41	37
ABC	213	157	140	127	123	114	107	100
DZsig^{pos}	70	37	35	33	31	31	29	28



No. at risk:

GCB	279	259	248	241	233	225	213	202
UNC	67	62	50	48	46	43	42	38
ABC	213	178	152	143	136	128	121	113
DZsig^{pos}	70	44	41	37	37	36	34	31

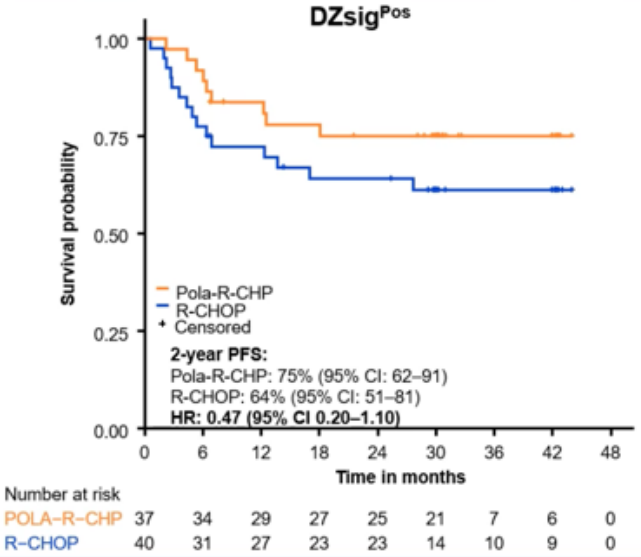
Blood, 2023; 141 (20): 2493–2507.

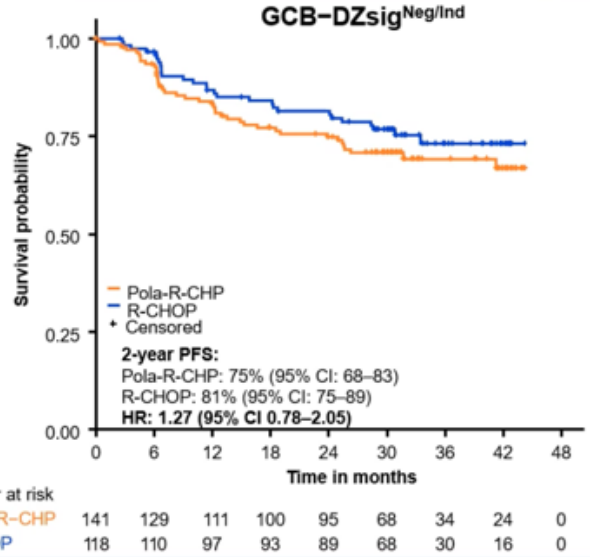
DZs

- GEP da
  -
  -
  -
  -

ABC
Unc
GCB
DZs

In DZsig^{Pos} DLBCL, a trend of higher 2-year PFS was observed with Pola-R-CHP vs R-CHOP





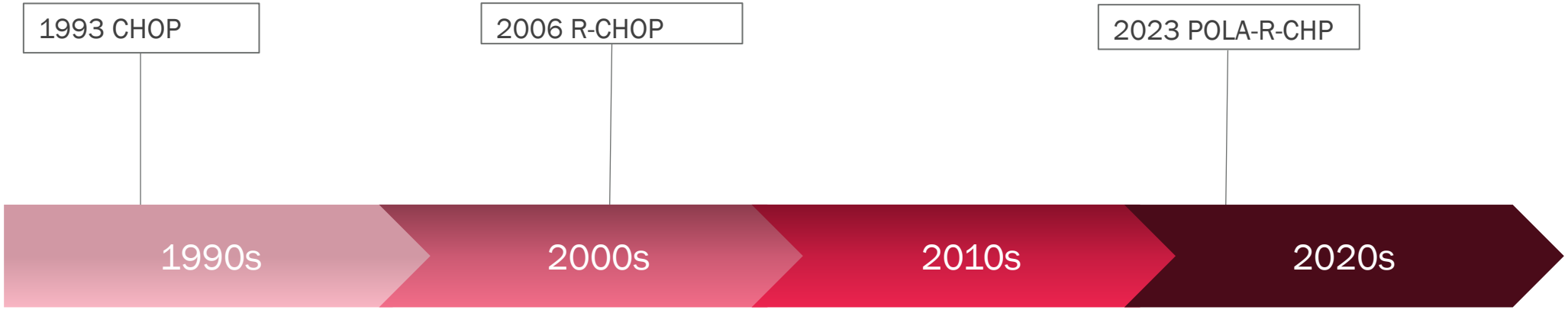
- In the R-CHOP arm, patients with DZsig^{Pos} DLBCL experienced poorer PFS vs those with DZsig$^{Neg/Ind}$ GCB-DLBCL (HR 2.04 [95% CI: 1.08–3.86]; 2-year PFS, 64% [95% CI: 51–81] vs 81% [95% CI: 75–89])
- The 2-year PFS trended in favour of patients with DZsig^{Pos} DLBCL treated with Pola-R-CHP vs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

CI, confidence interval; DLBCL; diffuse large B-cell lymphoma; DZsig, dark zone signature; HR, hazard rato; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone; DZsig^{Pos}, dark zone signature positive; DZsig$^{Neg/Ind}$, dark zone signature positive negative/indeterminate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

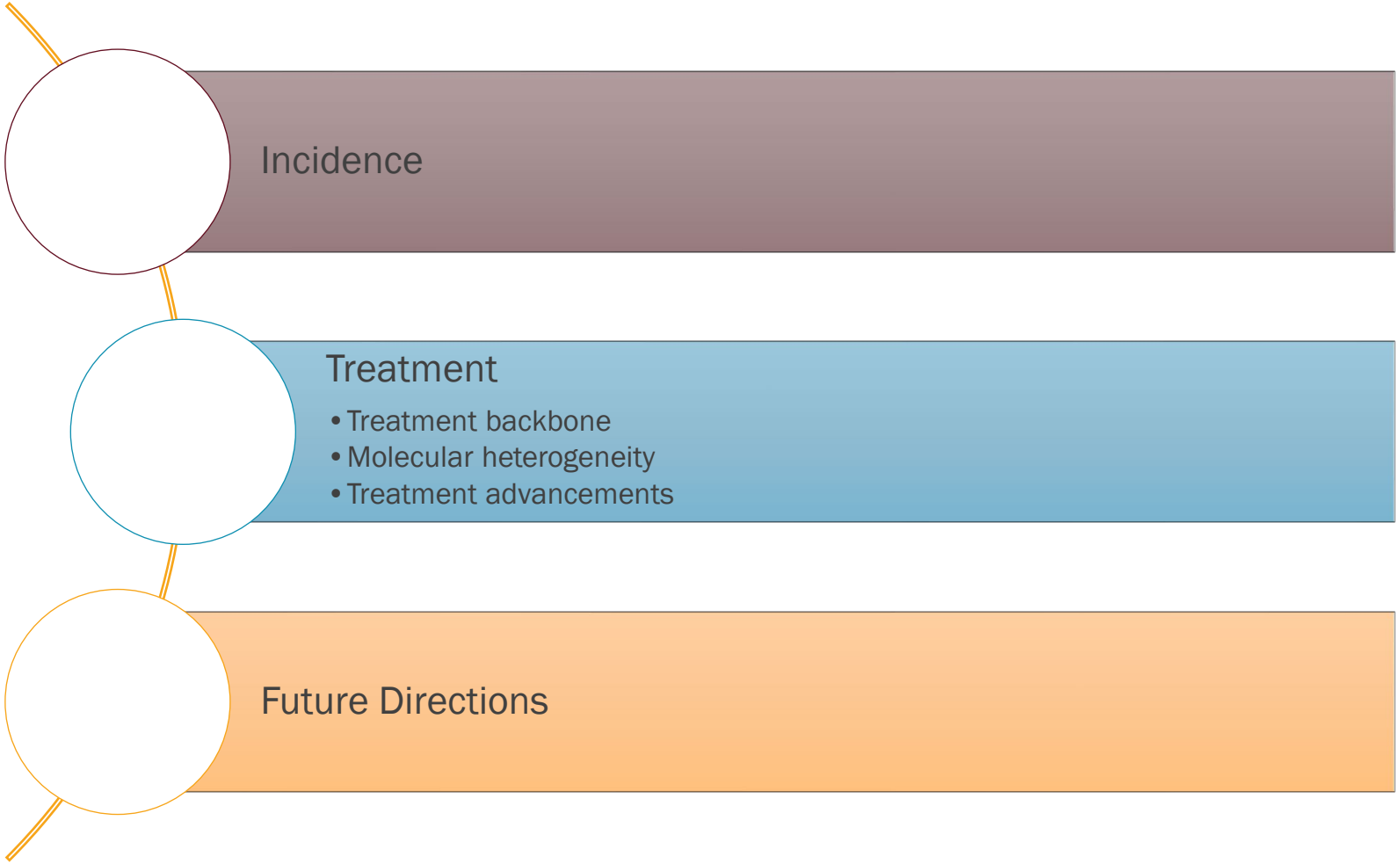
ABC, activated B cell; BN2, *BCL6* fusions and *NOTCH2* mutations; COO, cell of origin; DZsig^{Pos}, dark zone signature positive; GCB, germinal center B cell; GEP, gene expression programming; Pola-R-CHP, polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Morschhauser, ASH 2023, Poster 3000. As presented in Postercast.

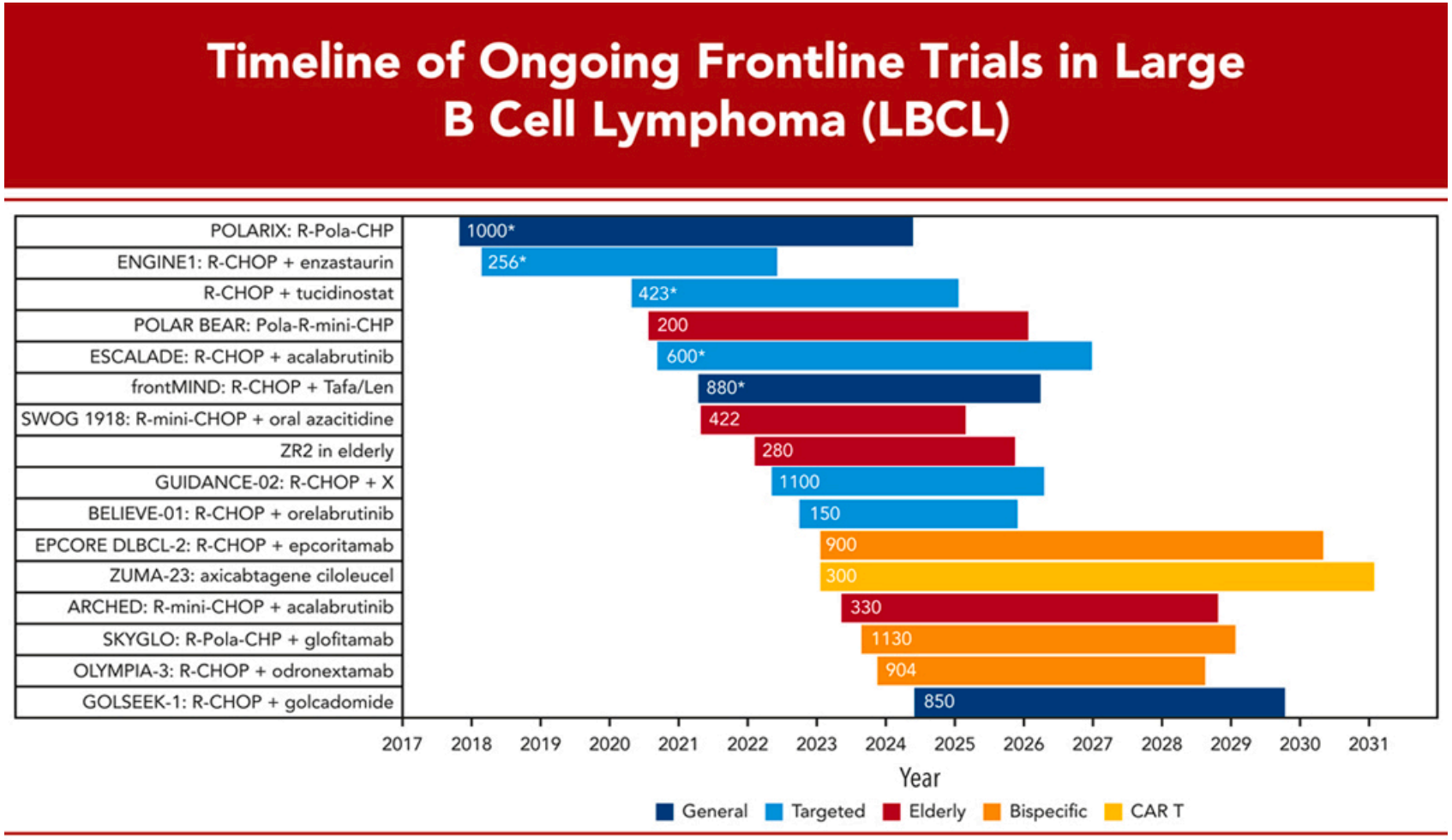
Evolution of DLBCL therapy



Front line DLBCL



The current landscape of frontline large B-cell lymphoma trials



Blood, 2025; 145 (2): 176–189.

Questions?

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22nd

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