NUOVE FRONTIERE NEI LINFOMI: IL PUNTO DI VISTA DEL CLINICO

TERAPIA DI PRIMA LINEA DEL DLBCL

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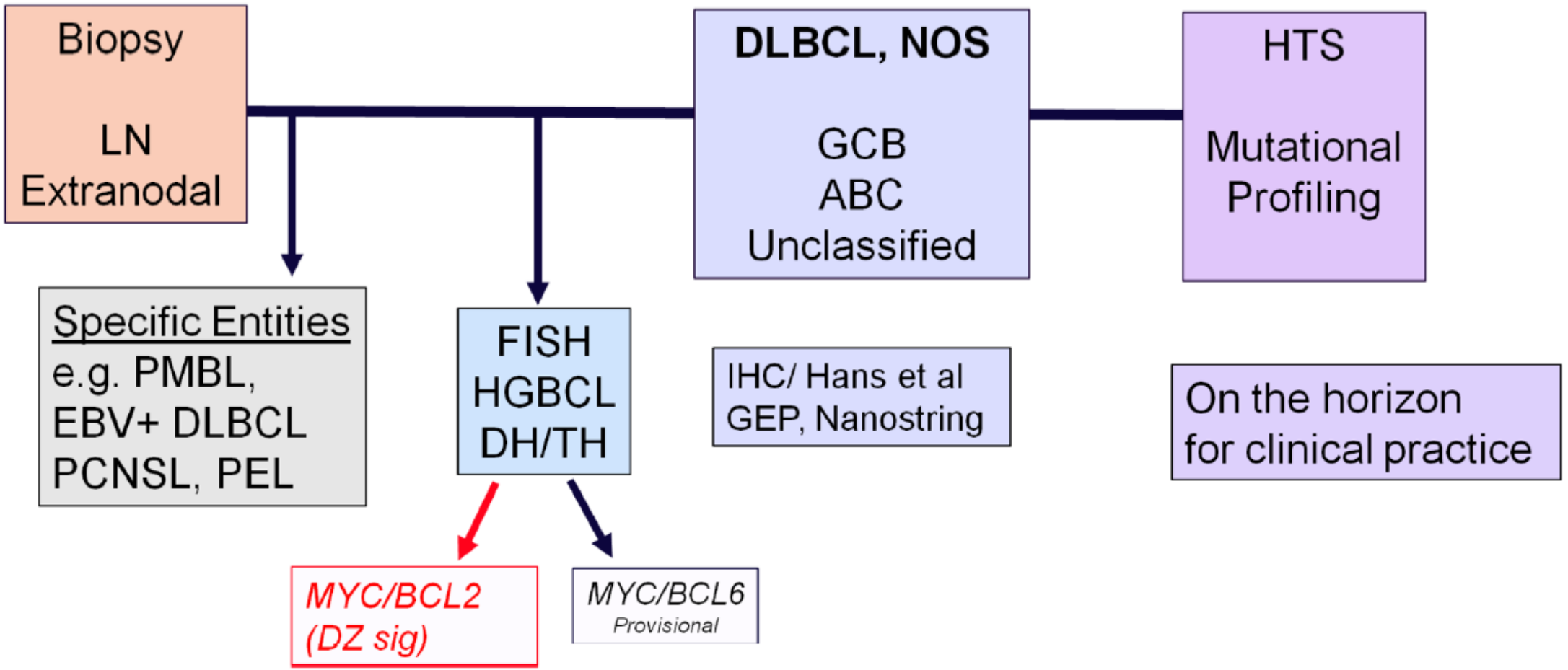
Disclosures of Alessandro Broccoli

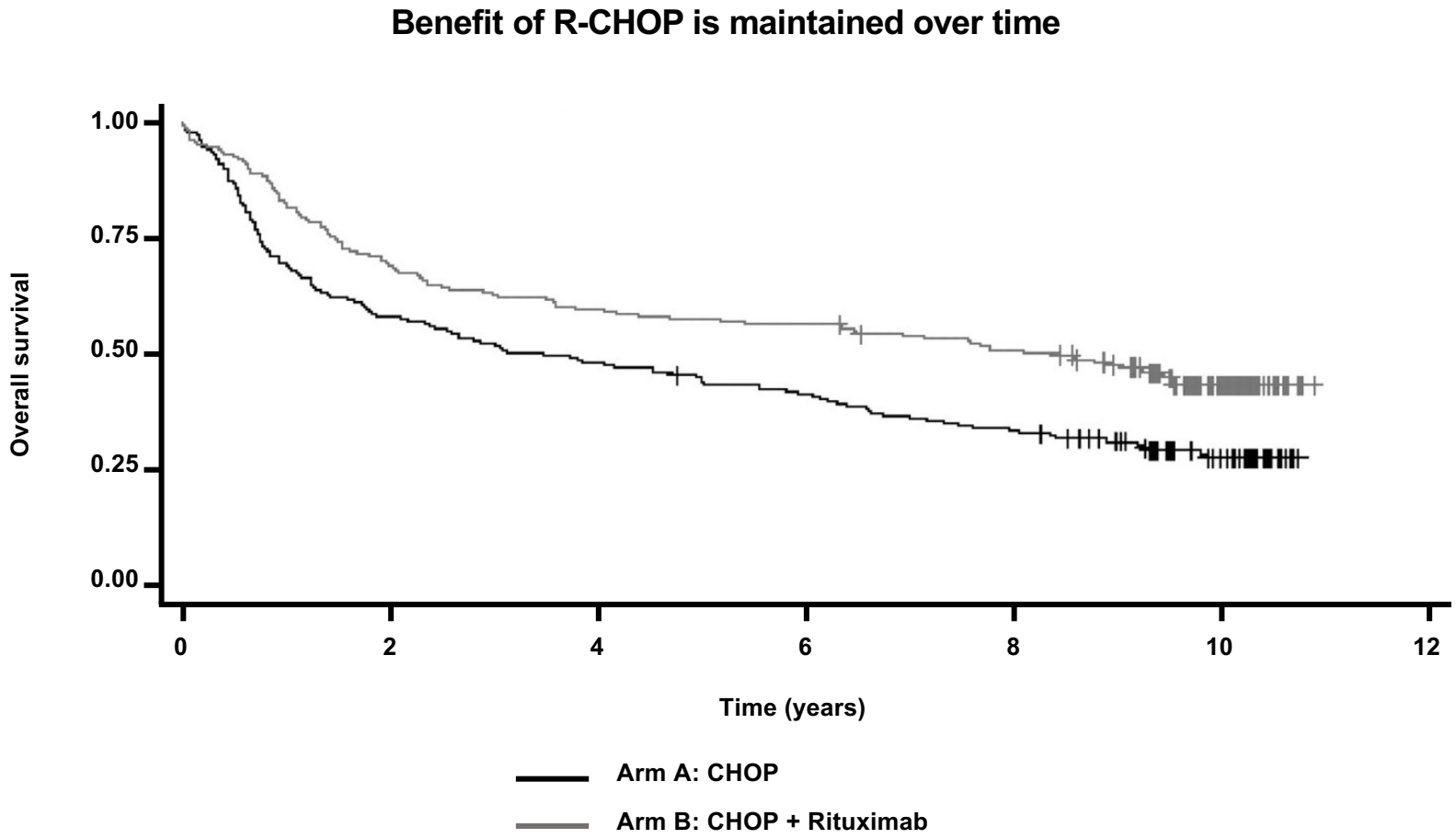
Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sandoz	X				X	X
Gilead				X	X	X
Merck	X					X
Janssen	X			X		X
Takeda		X		X	X	X
Kyowa Kirin	X			X	X	X
Incyte						X
Recordati						X
Astra Zeneca				X	X	
Roche				X		X
GlaxoSmithKline		X		X	X	
BeOne	X			X	X	X
Eli Lilly						X
SOBI				X		
SERB Pharma		X			X	

Diagnostic flow in large B-cell lymphomas



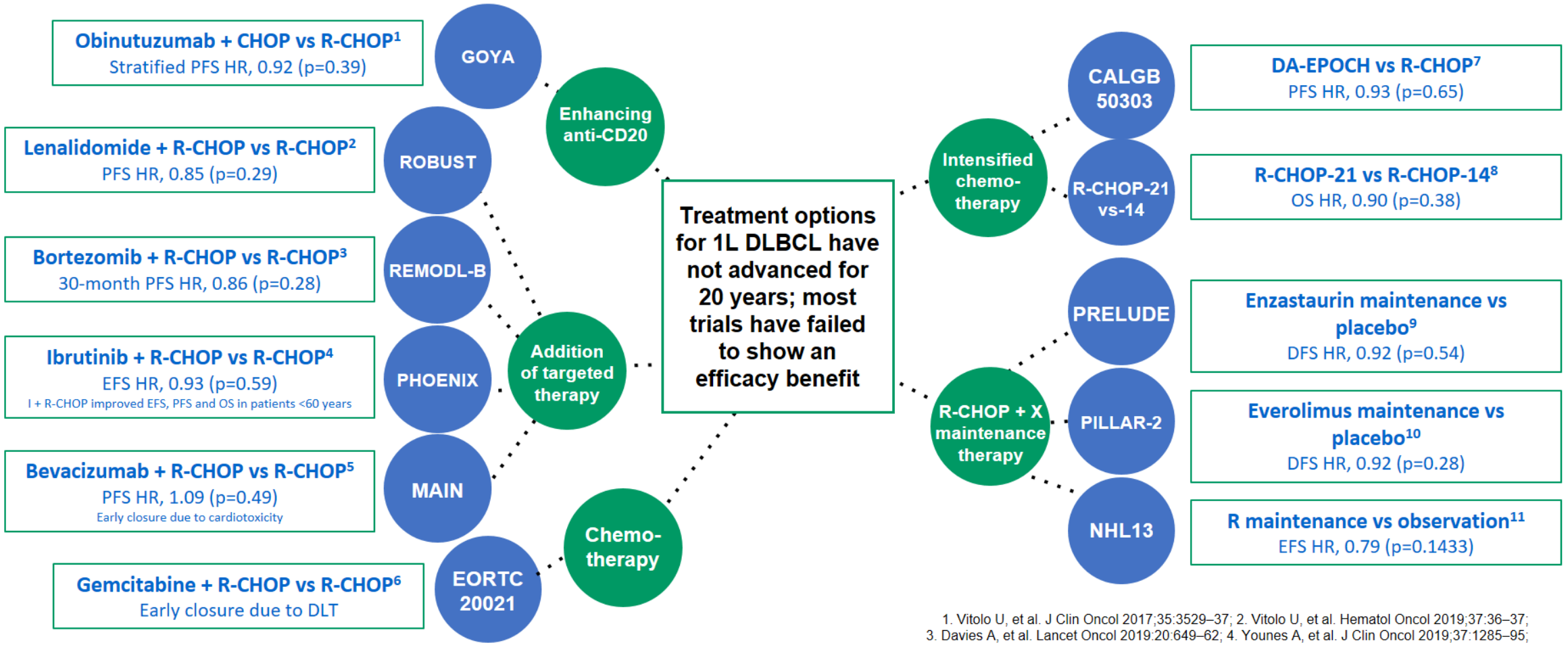
Jaffe ES. *Hemato*, 2024; 5: 157-170

R-CHOP is confirmed as the frontline standard of care



Coiffier B. *Blood*, 2010; 116: 2040-2045

How to increase the efficacy of frontline R-CHOP?

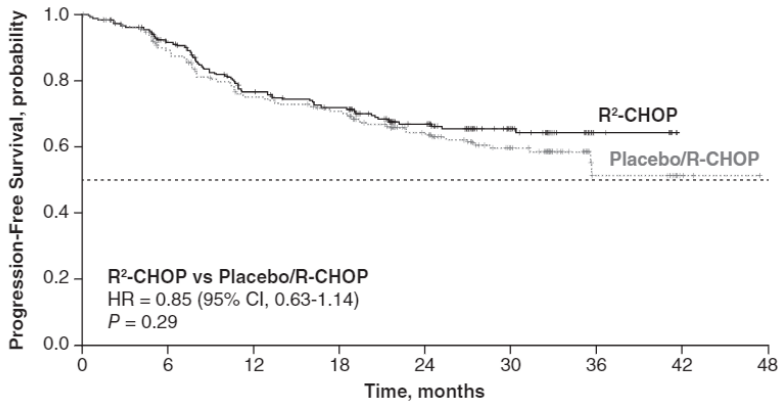


DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DFS, disease-free survival; DLT, dose-limiting toxicity; EFS, event-free survival; HR, hazard ratio; I, ibrutinib; MTD, maximum tolerated dose; OS, overall survival.

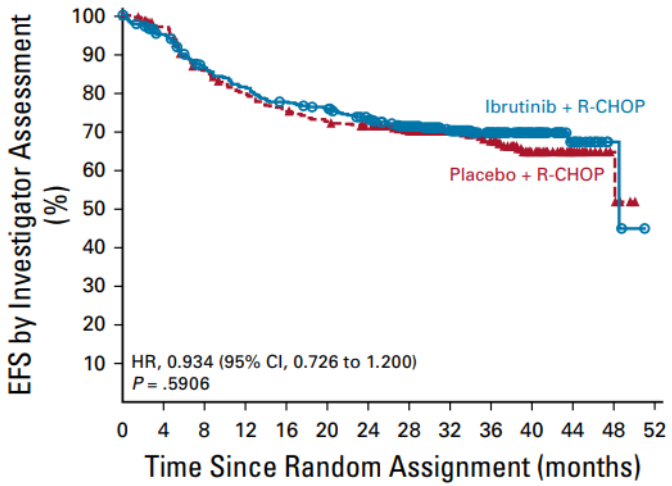
1. Vitolo U, et al. J Clin Oncol 2017;35:3529–37; 2. Vitolo U, et al. Hematol Oncol 2019;37:36–37; 3. Davies A, et al. Lancet Oncol 2019;20:649–62; 4. Younes A, et al. J Clin Oncol 2019;37:1285–95; 5. Seymour JF, et al. Haematologica 2014;99:1343–49; 6. Aurer I, et al. Eur J Haematol 2011;86:111–16; 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.

Frontline R-CHOP+X

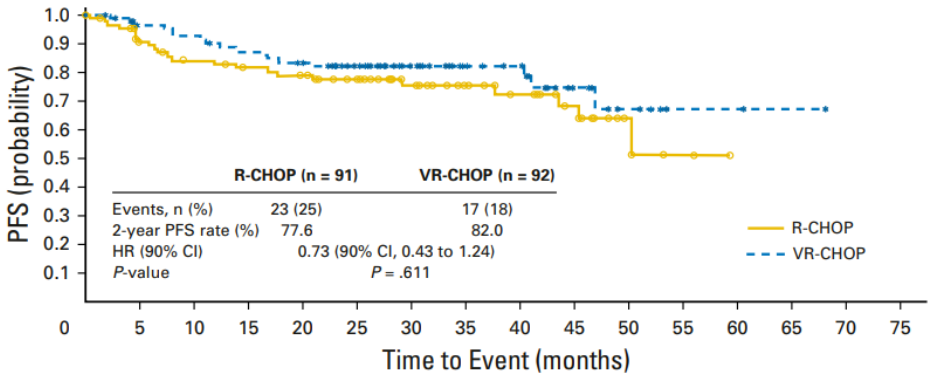
X = Lenalidomide

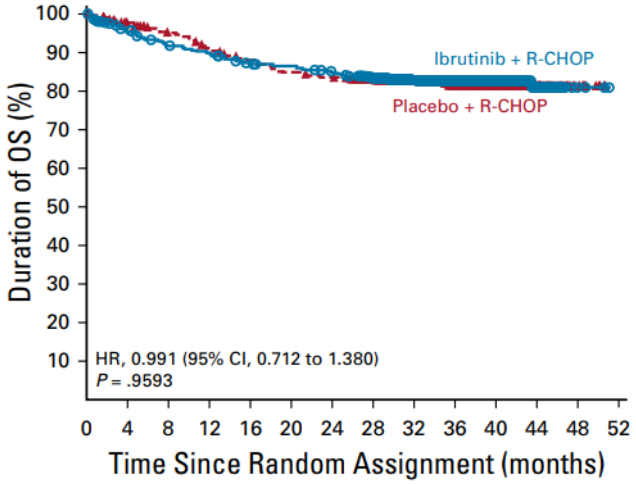


X = Ibrutinib



X = Bortezomib





Vitolo U. *Hematol Oncol (ICML meeting abstr)*, 2019; 37: 5 abstr

Leonard JP. *J Clin Oncol*, 2017; 35: 3538-3546

Younes A. *J Clin Oncol*, 2019; 37: 1285-1295

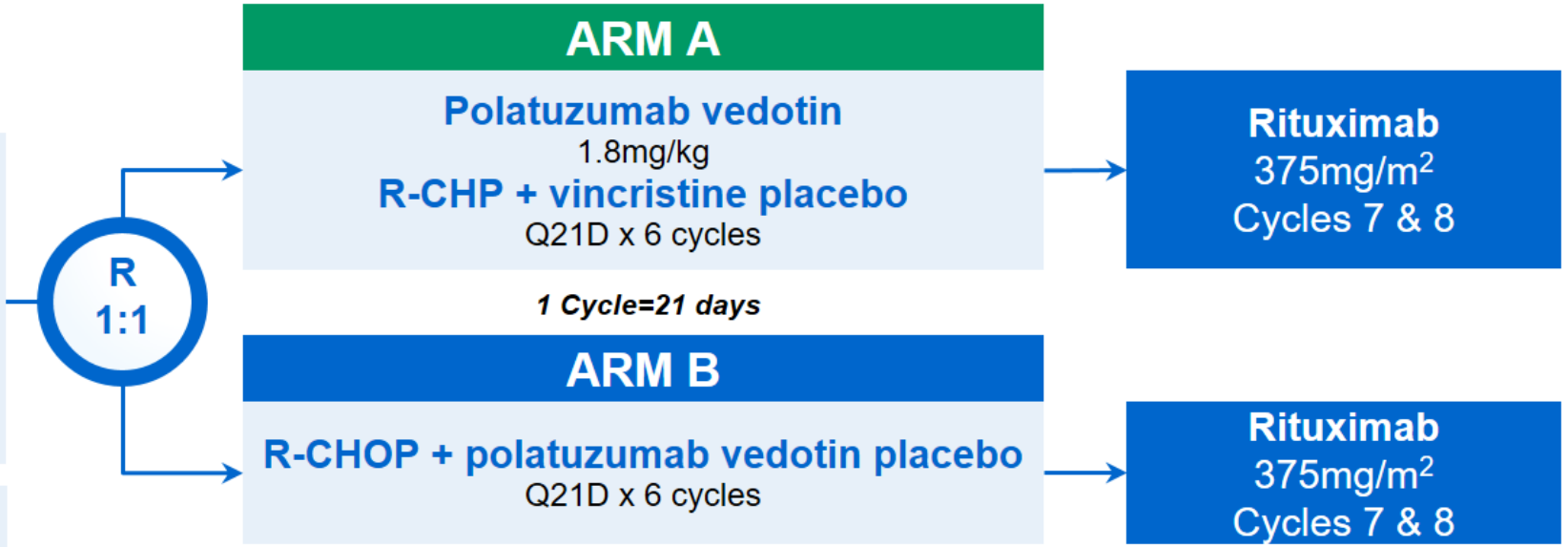
Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

- **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 (≥7.5cm vs absence)
- Geographic region



Primary endpoint	PFS by INV
Key secondary endpoints	$EFS_{efficacy}$ by INV, PET CR at EOT by BICR, OS, and safety

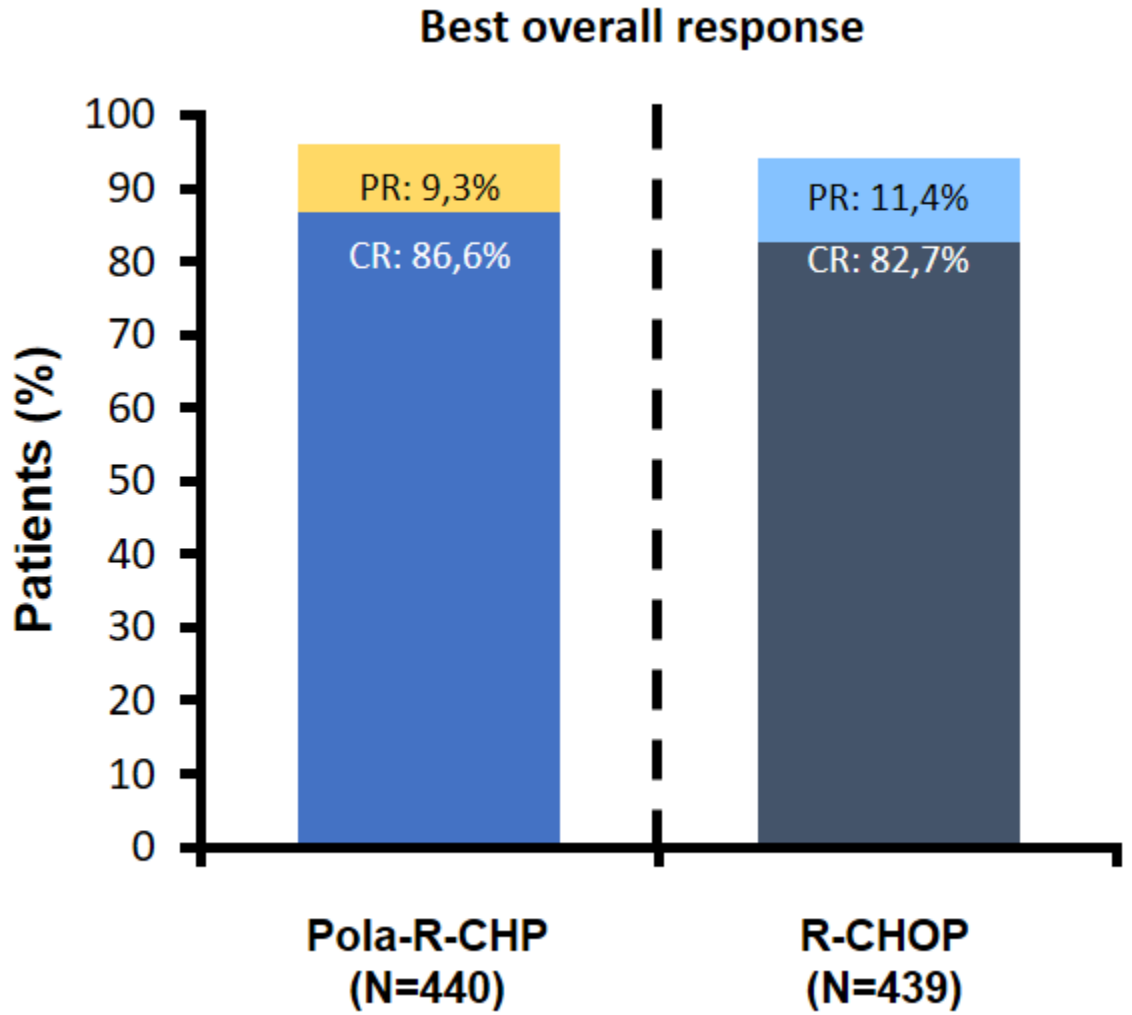
Tilly H. *N Engl J Med*, 2022; 386: 351-363

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

n (%), unless otherwise stated		Global population	
		Pola-R-CHP (n=440)	R-CHOP (n=439)
Age	Median, years (min–max) ≥65 years	65.0 (19–80) 231 (52.5)	66.0 (19–80) 236 (53.8)
Sex	Male	239 (54.3)	234 (53.3)
ECOG PS	0–1 2	374 (85.0) 66 (15.0)	363 (82.7) 75 (17.1)
IPI at screening	2 3–5	167 (38.0) 273 (62.0)	167 (38.0) 272 (62.0)
Bulky disease	≥7.5cm	193 (43.9)	192 (43.7)
Baseline lactate dehydrogenase	>1x upper limit of normal	291 (66.1)	284 (64.7)
Ann Arbor stage	III or IV	393 (89.3)	387 (88.2)
Number of extranodal sites	≥2	213 (48.4)	213 (48.5)
NHL histologic diagnosis reported by investigators	DLBCL NOS, ABC, GCB HGBCL, DHL/THL Other large B-cell lymphoma	373 (84.8)† 43 (9.8) 24 (5.5)	367 (83.6) 50 (11.4) 22 (5.0)
COO centrally reported by NanoString	n ABC by NanoString GCB by NanoString Unclassified by NanoString Unknown	330 102 (30.9) 184 (55.8) 44 (13.3) 110	338 119 (35.2) 168 (49.7) 51 (15.1) 101

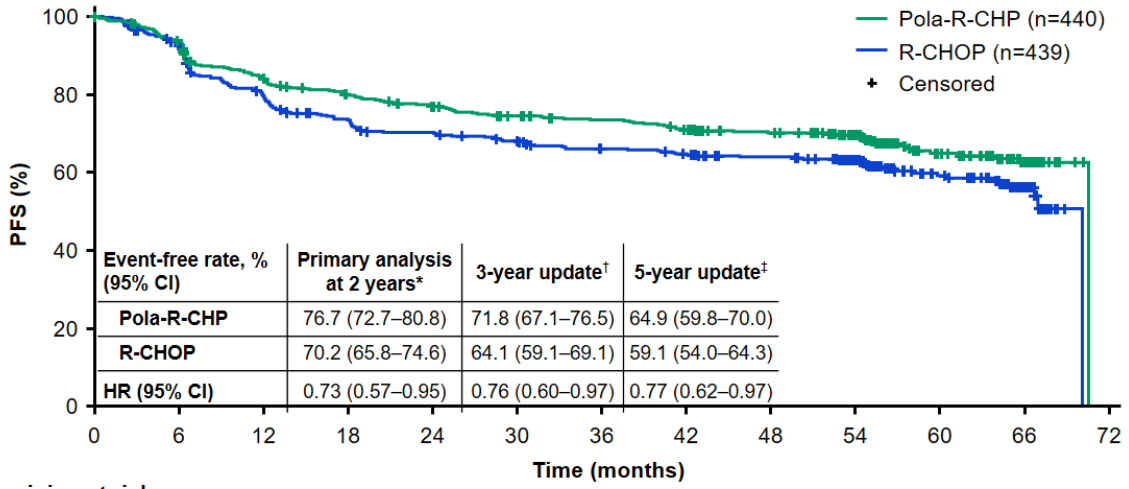
Tilly H. *N Engl J Med*, 2022; 386: 351-363

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma



Tilly H. *N Engl J Med*, 2022; 386: 351-363

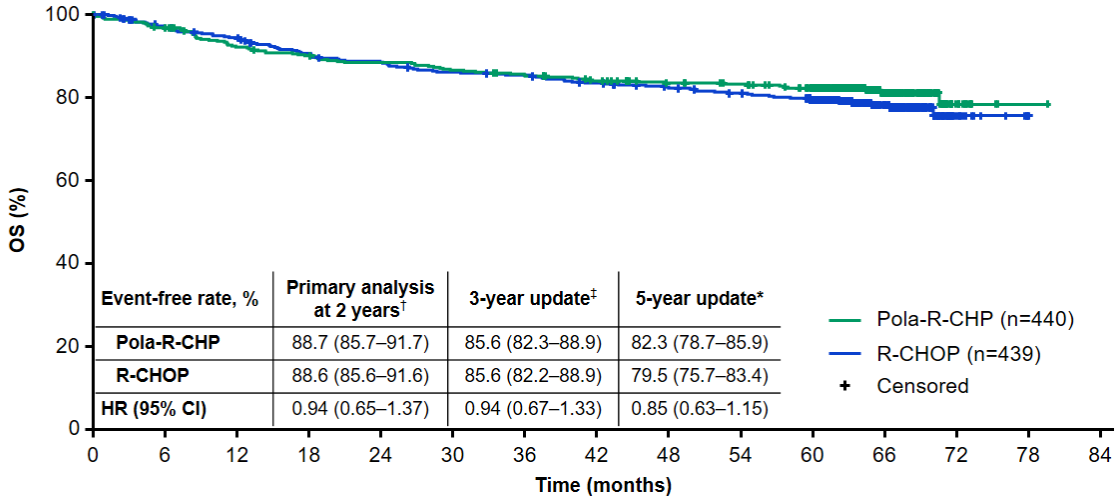
Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma



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



Event-free rate, %	Primary analysis at 2 years†	3-year update‡	5-year update*
Pola-R-CHP	88.7 (85.7–91.7)	85.6 (82.3–88.9)	82.3 (78.7–85.9)
R-CHOP	88.6 (85.6–91.6)	85.6 (82.2–88.9)	79.5 (75.7–83.4)
HR (95% CI)	0.94 (0.65–1.37)	0.94 (0.67–1.33)	0.85 (0.63–1.15)

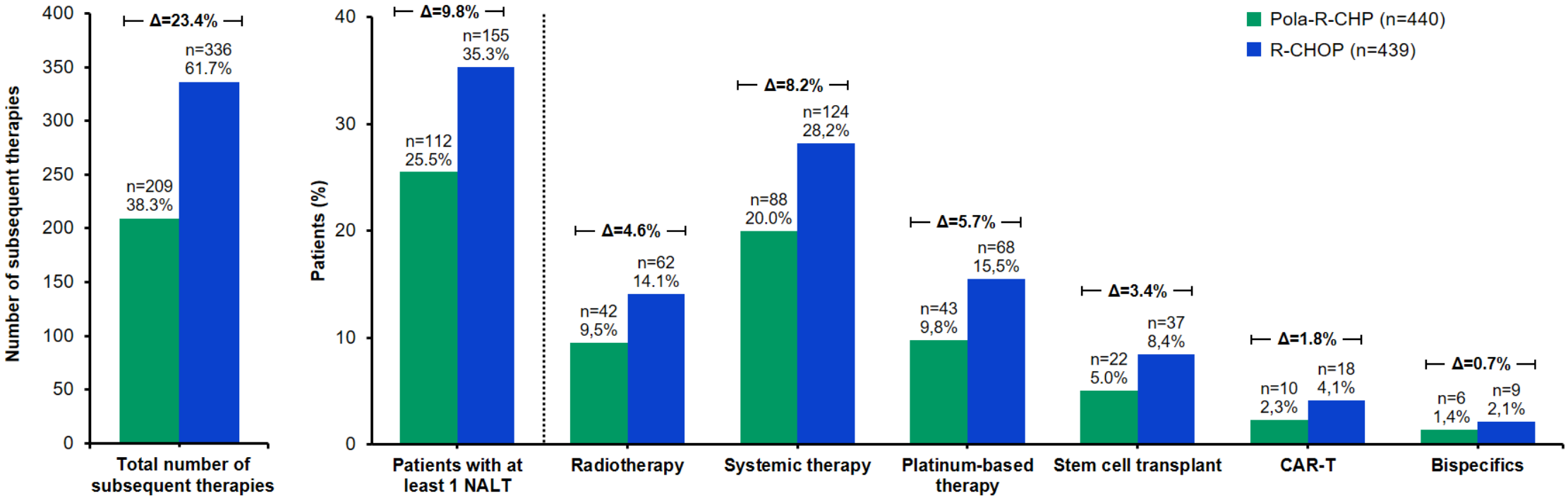
Patients remaining at risk

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

Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma

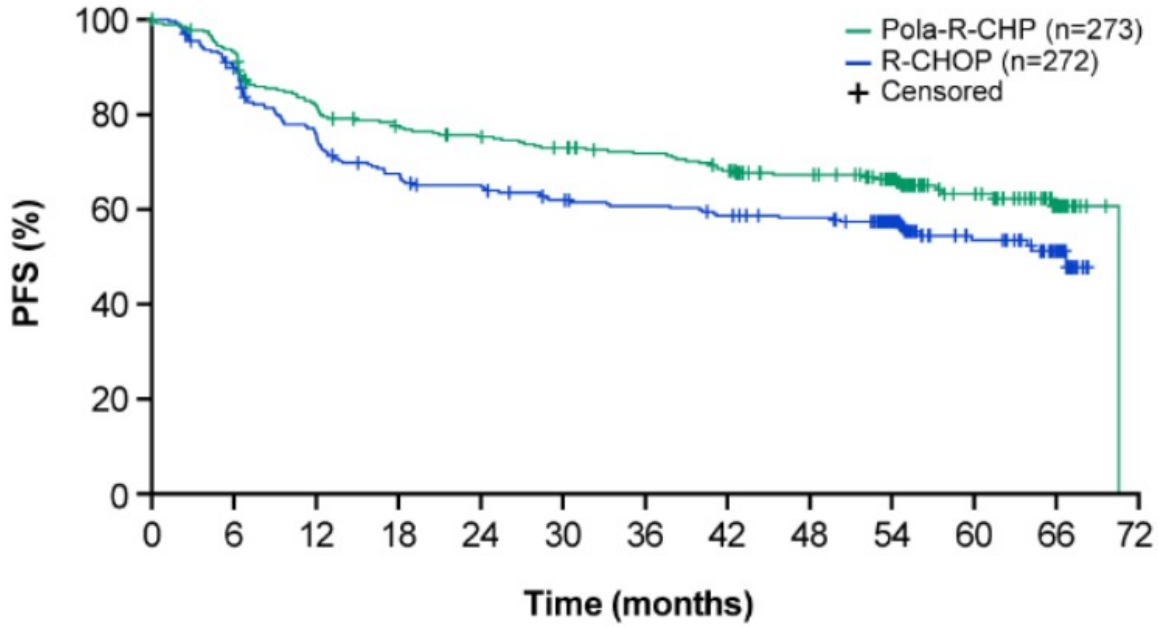
Subsequent therapies in the global ITT population



Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

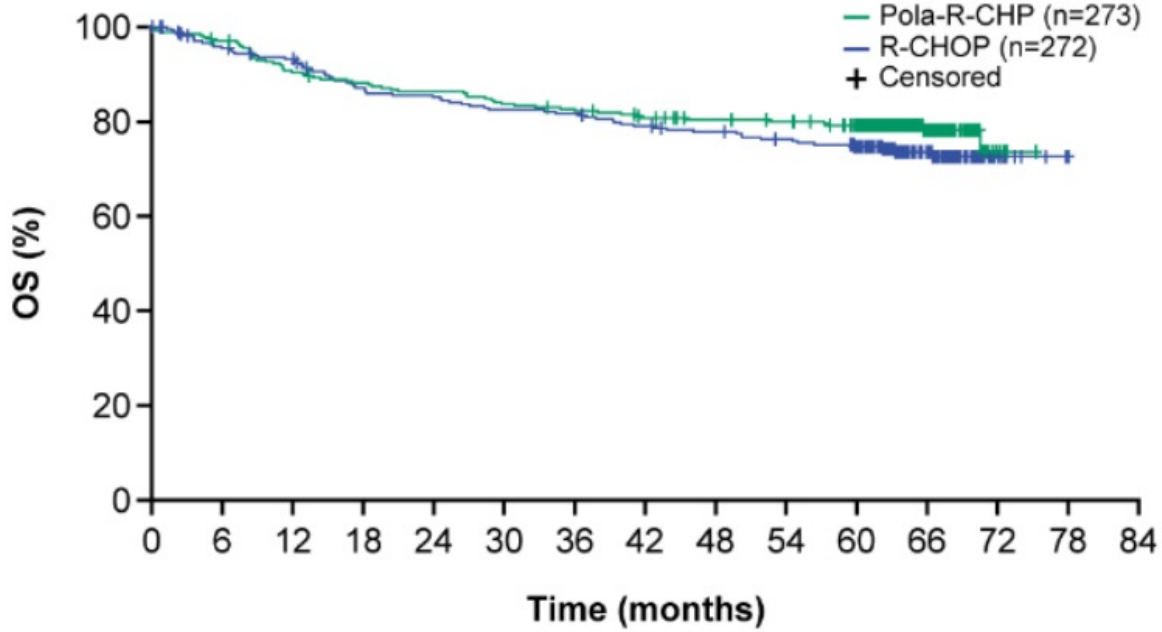
Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma

IPI 3-5



Patients remaining at risk

Pola-R-CHP	273	252	217	203	195	187	178	168	153	126	67	34	NE
R-CHOP	272	235	196	173	165	154	149	143	138	110	55	34	NE



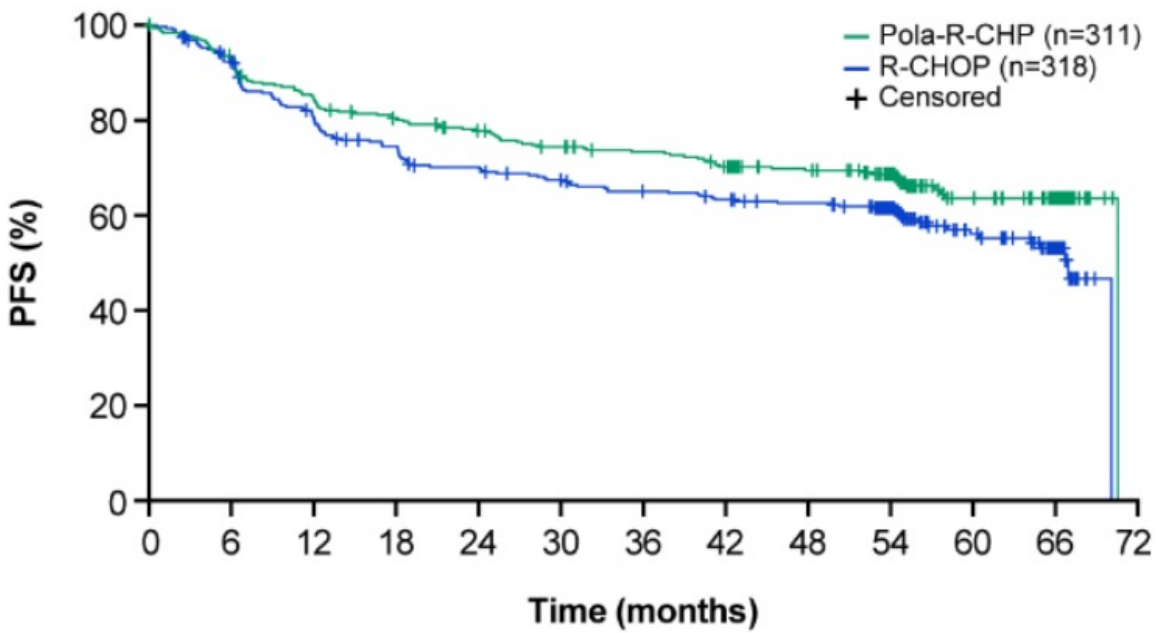
Patients remaining at risk

Pola-R-CHP	273	264	245	238	233	226	222	214	208	204	191	75	5	NE	NE
R-CHOP	272	254	246	227	222	215	213	205	200	194	182	81	9	1	NE

Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

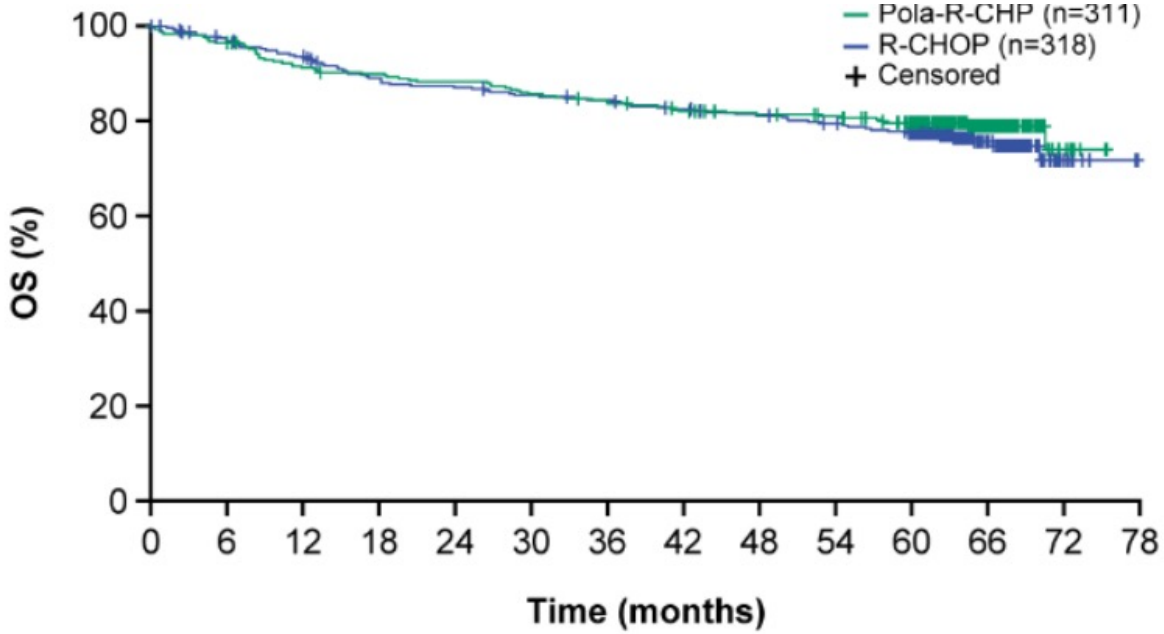
Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma

Age ≥ 60 years



Patients remaining at risk

Pola-R-CHP	311	287	258	243	231	219	210	199	182	149	70	46	NE
R-CHOP	318	283	244	223	208	197	188	182	175	142	65	38	NE

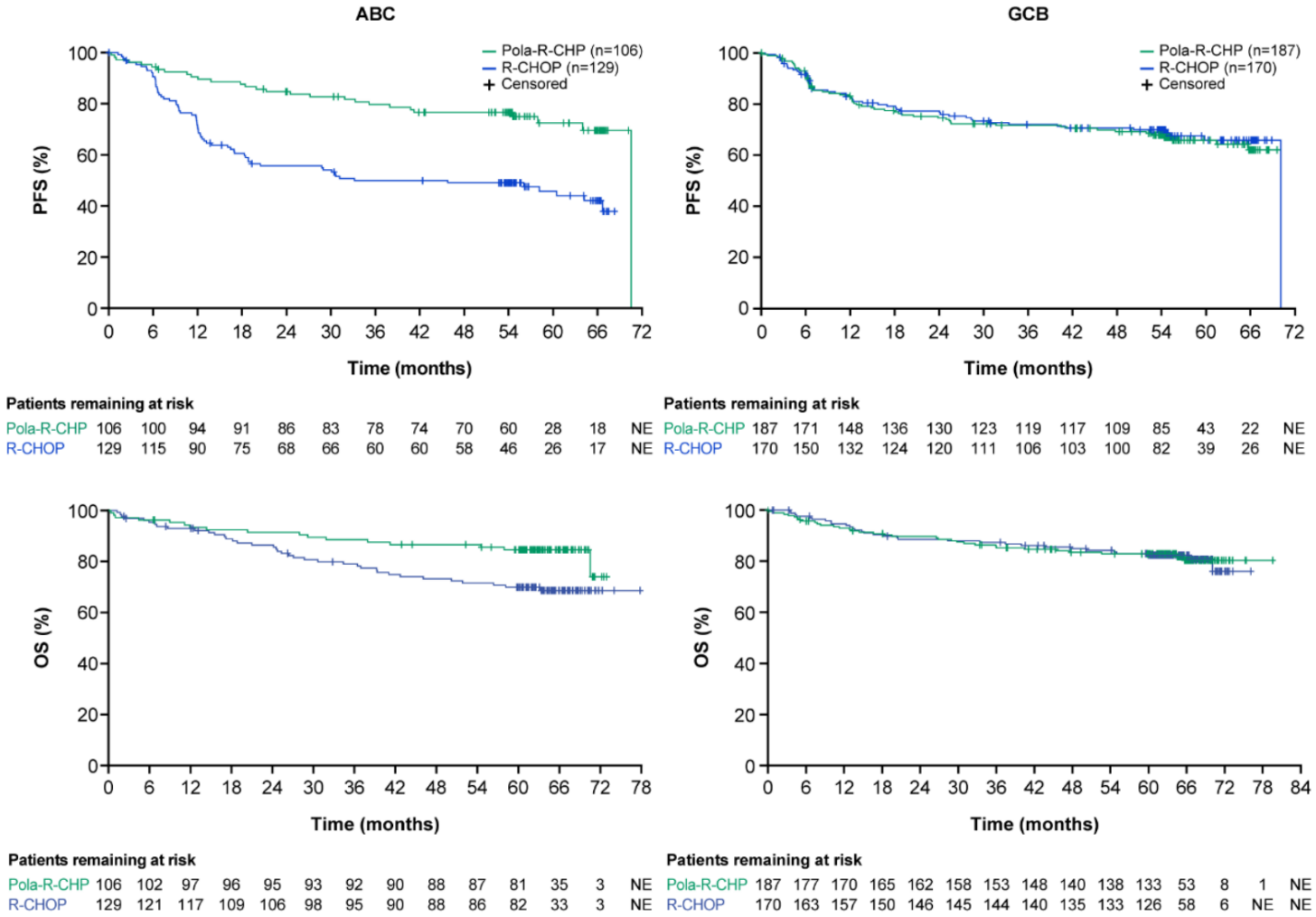


Patients remaining at risk

Pola-R-CHP	311	299	280	275	270	262	256	248	239	235	217	89	7	NE
R-CHOP	318	302	291	273	267	261	257	249	243	236	223	87	9	NE

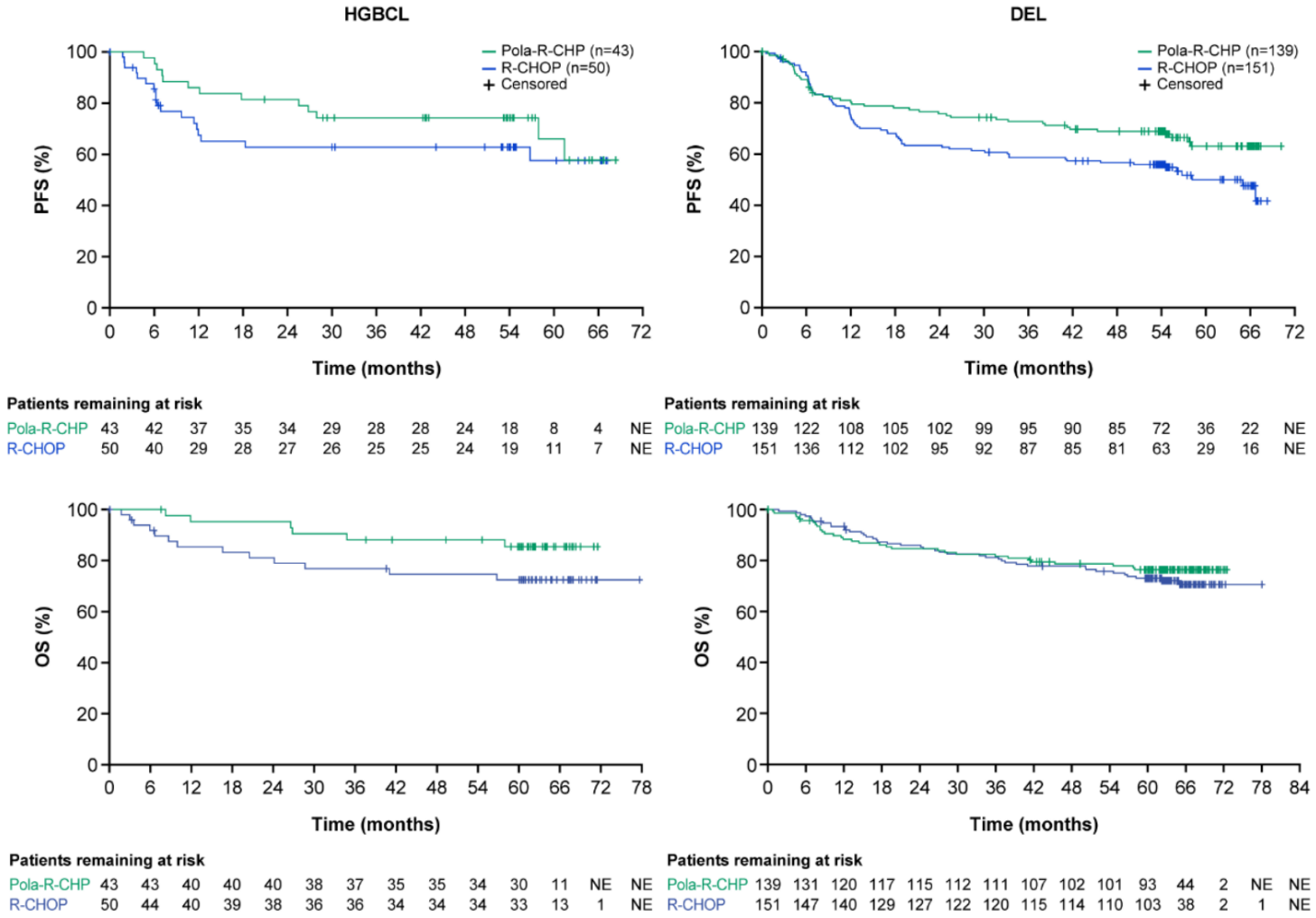
Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma



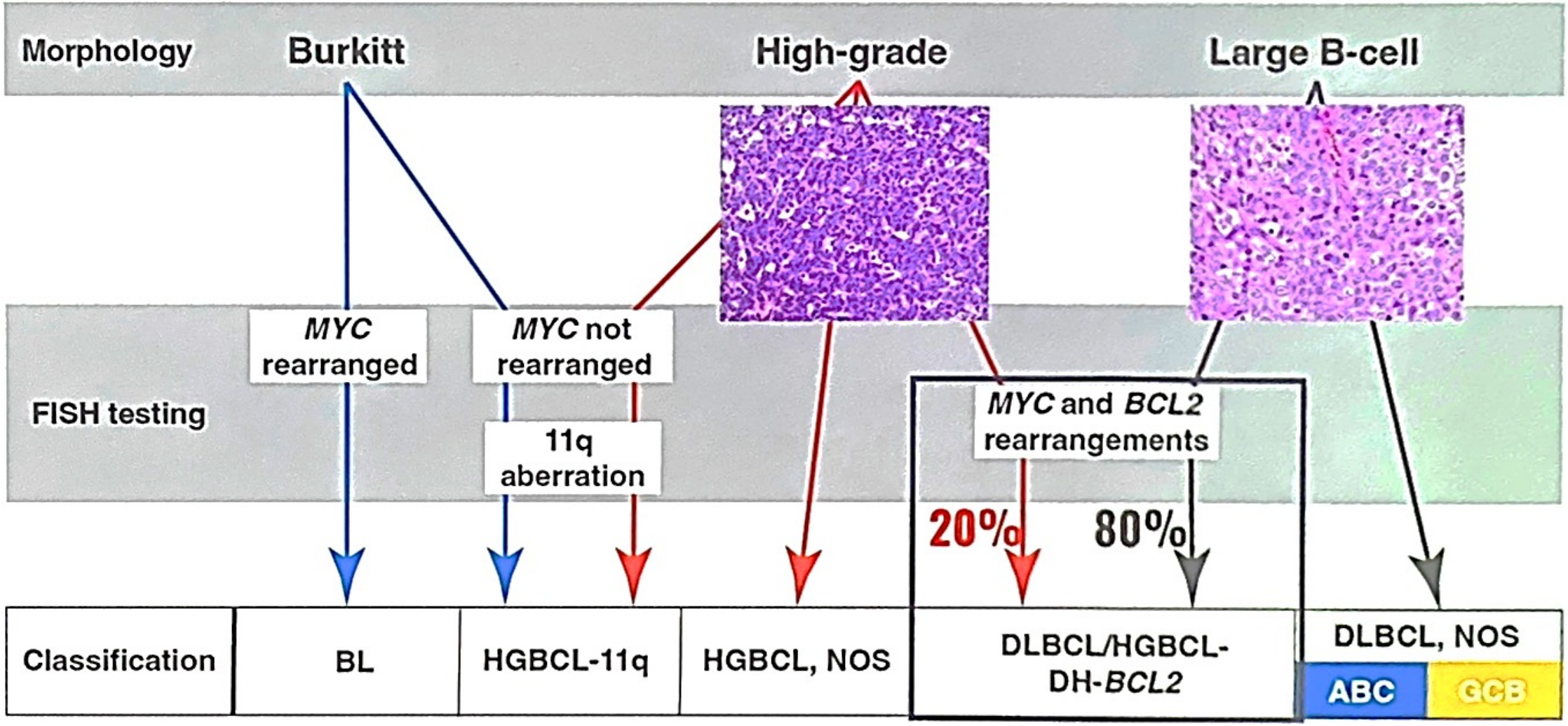
Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

Five-Year Outcomes of the POLARIX Study Comparing Pola-R-CHP and R-CHOP in Patients With Diffuse Large B-Cell Lymphoma



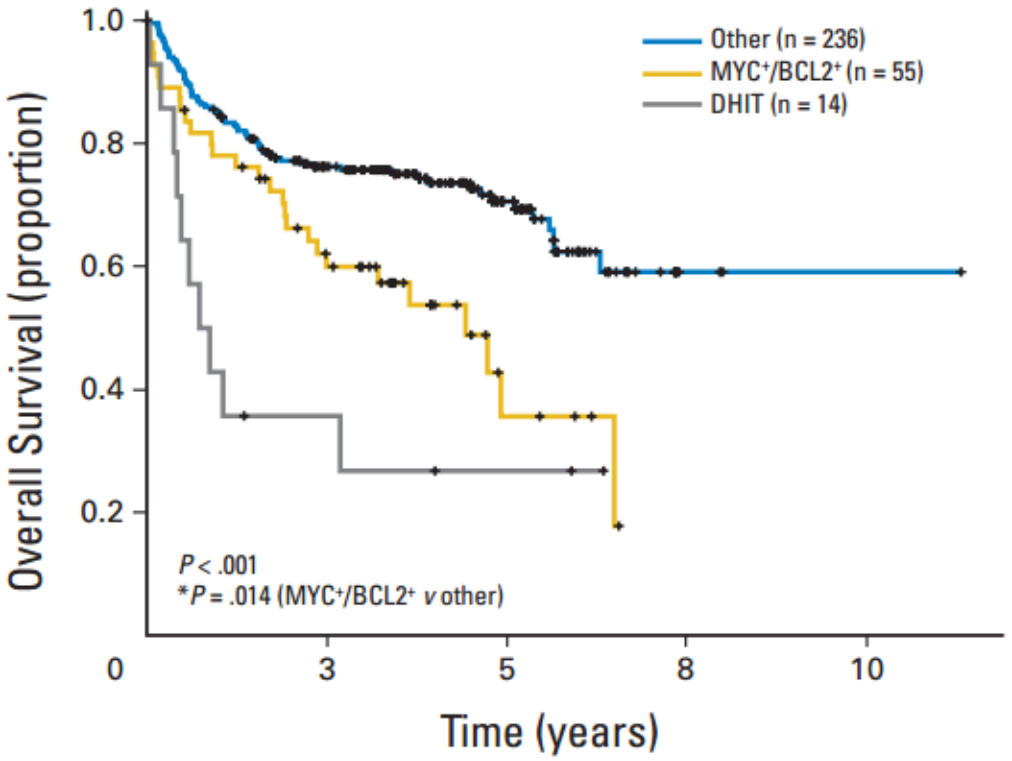
Morschhauser F. *J Clin Oncol*, 2025; 43: 3698-3705

The unmet needs in double-hit lymphomas



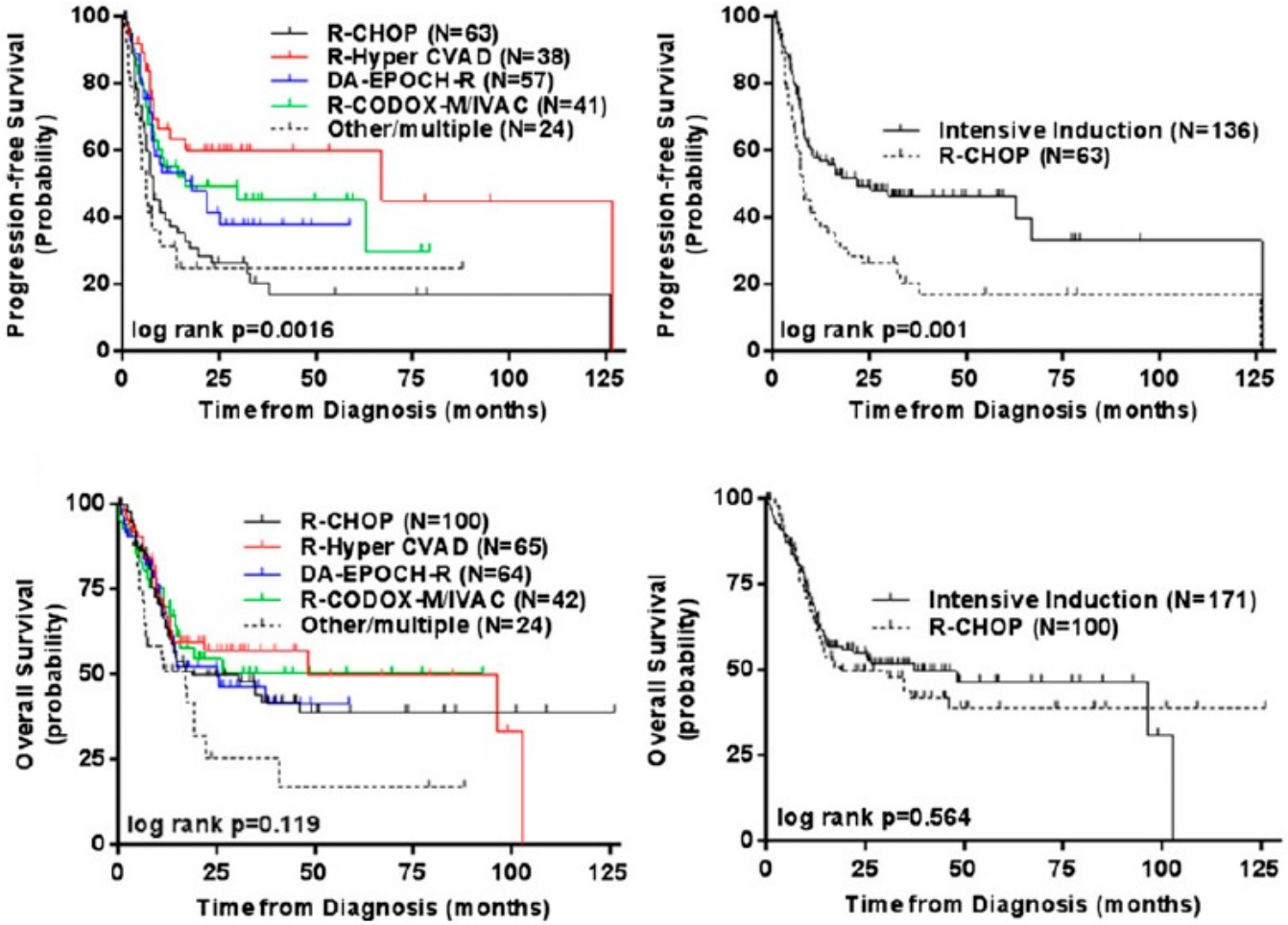
Alaggio R. *Leukemia*, 2022; 36: 1720-1748

Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone



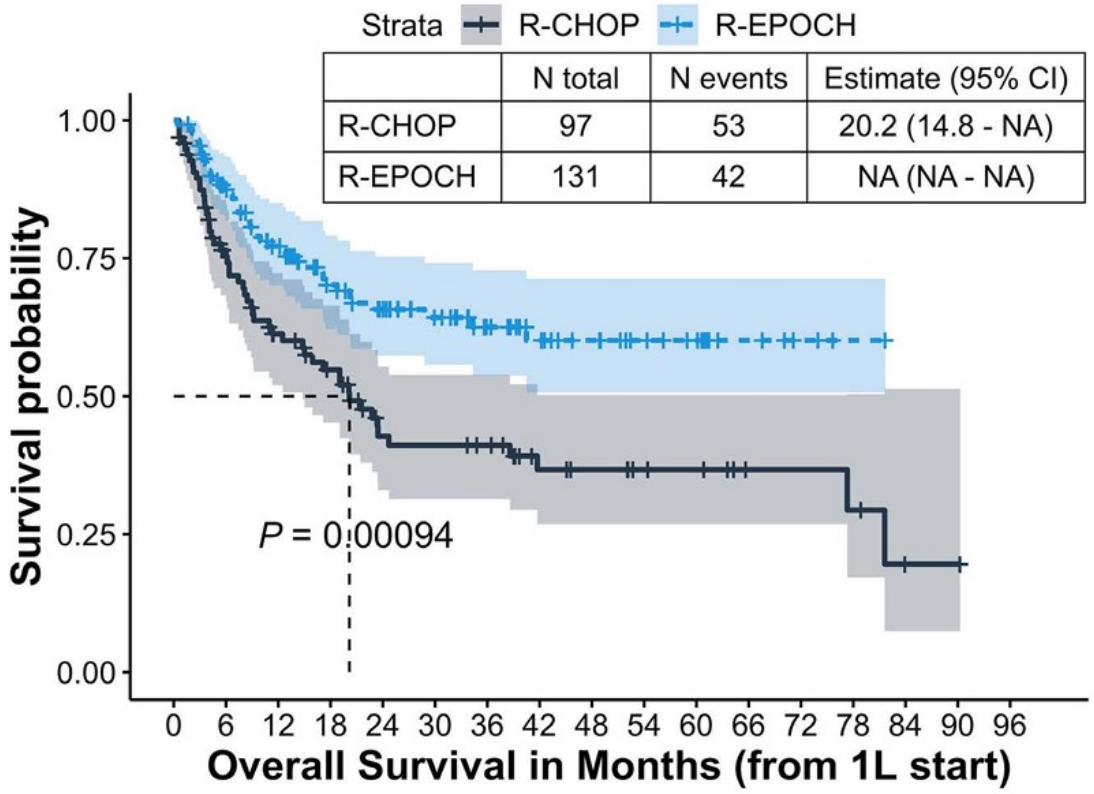
Johnson NA. *J Clin Oncol*, 2012; 30: 3452-3459

Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis



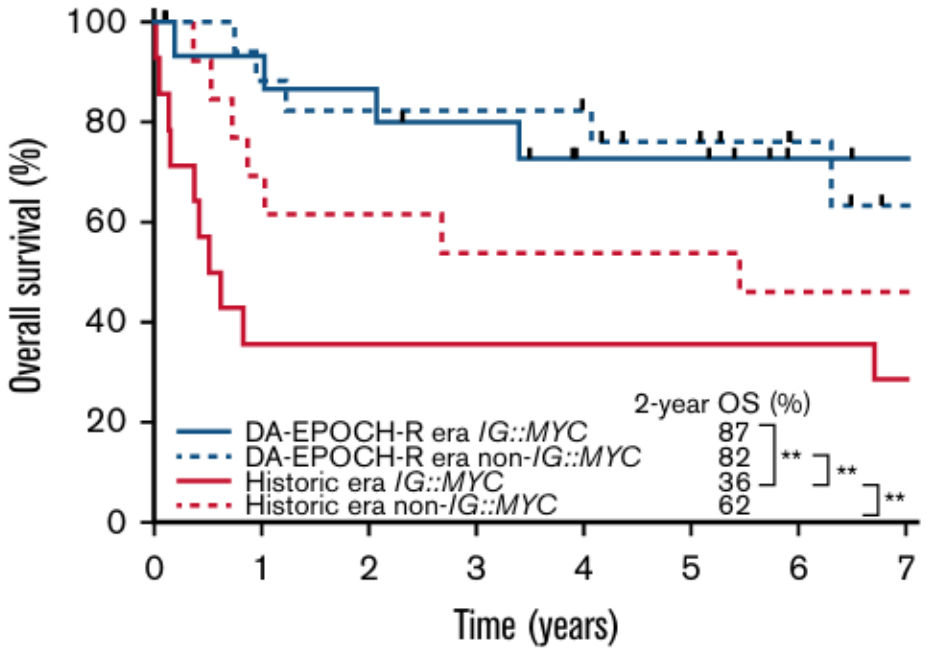
Petrich AM. *Blood*, 2014; 124: 2354-2361

Modern, real-world patterns of care and clinical outcomes among patients with newly diagnosed diffuse large B-cell lymphoma with or without double/triple-hit status in the United States



Goyal G. *Haematologica*, 2023; 108: 1190-1195

Population-wide introduction of dose-adjusted EPOCH-R in high-grade B-cell lymphoma with *MYC*/*BCL2* rearrangements, DLBCL morphology



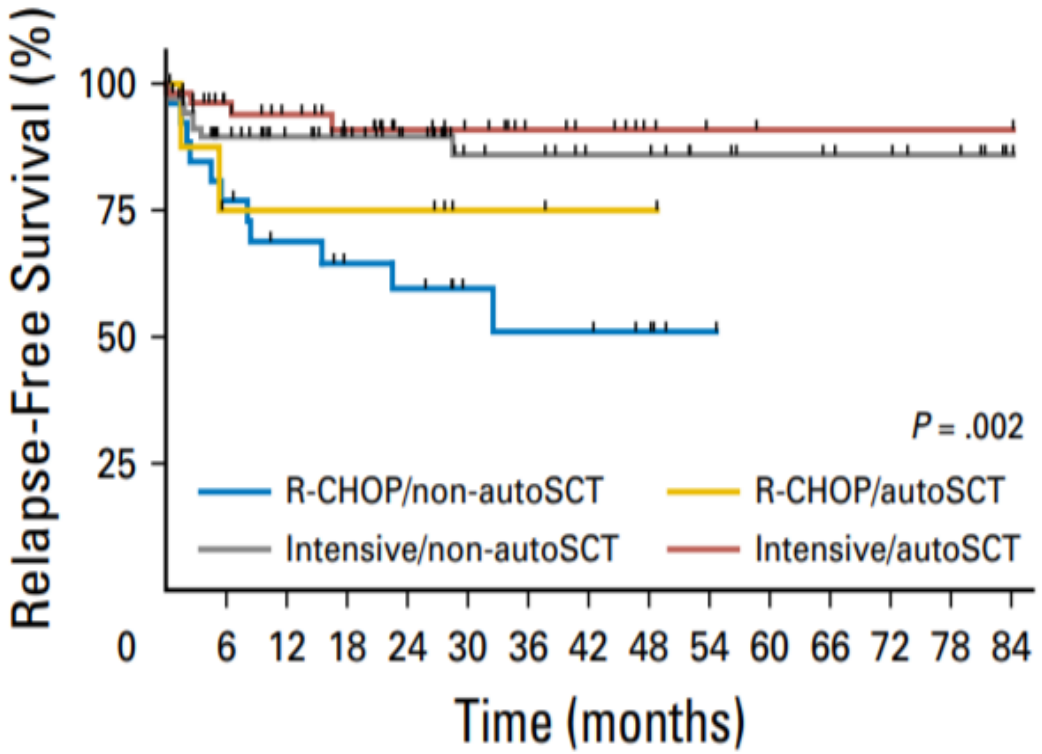
No. at risk:								
EPOCH IG	15	14	13	11	7	7	3	2
EPOCH non-IG	18	15	14	14	13	10	6	3
Hist IG	14	5	5	5	5	5	5	4
Hist non-IG	13	9	8	7	7	7	6	6

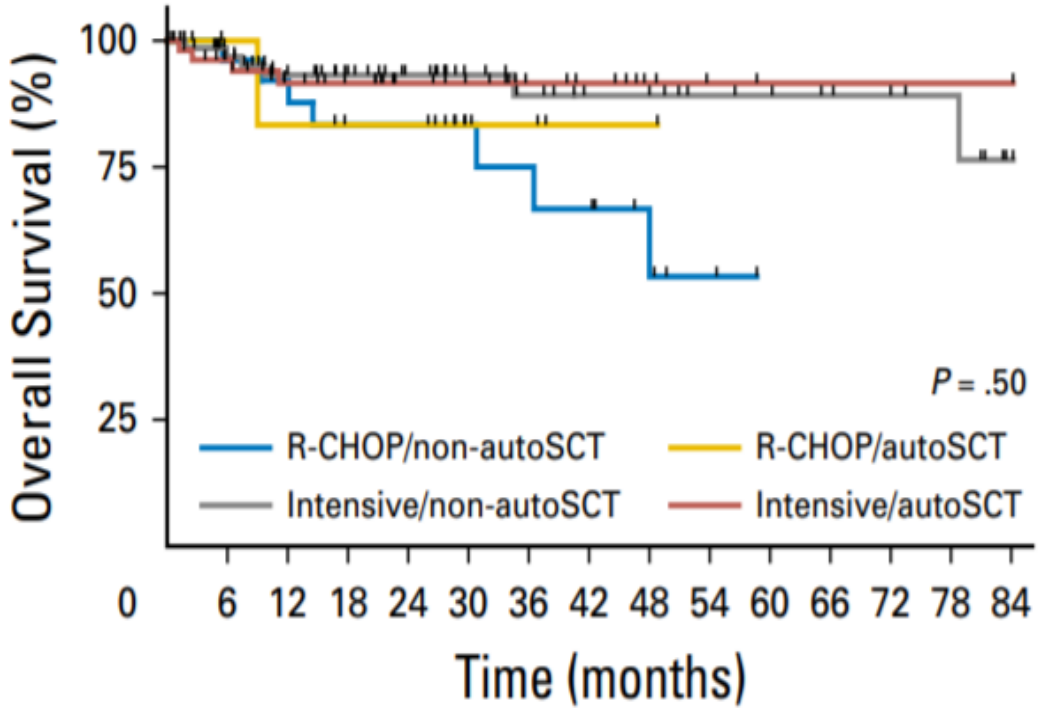
Alduaij W. *Blood Adv*, 2026; 10: 320-333

Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission

TIME 0 = 3 months after treatment completion
159 patients

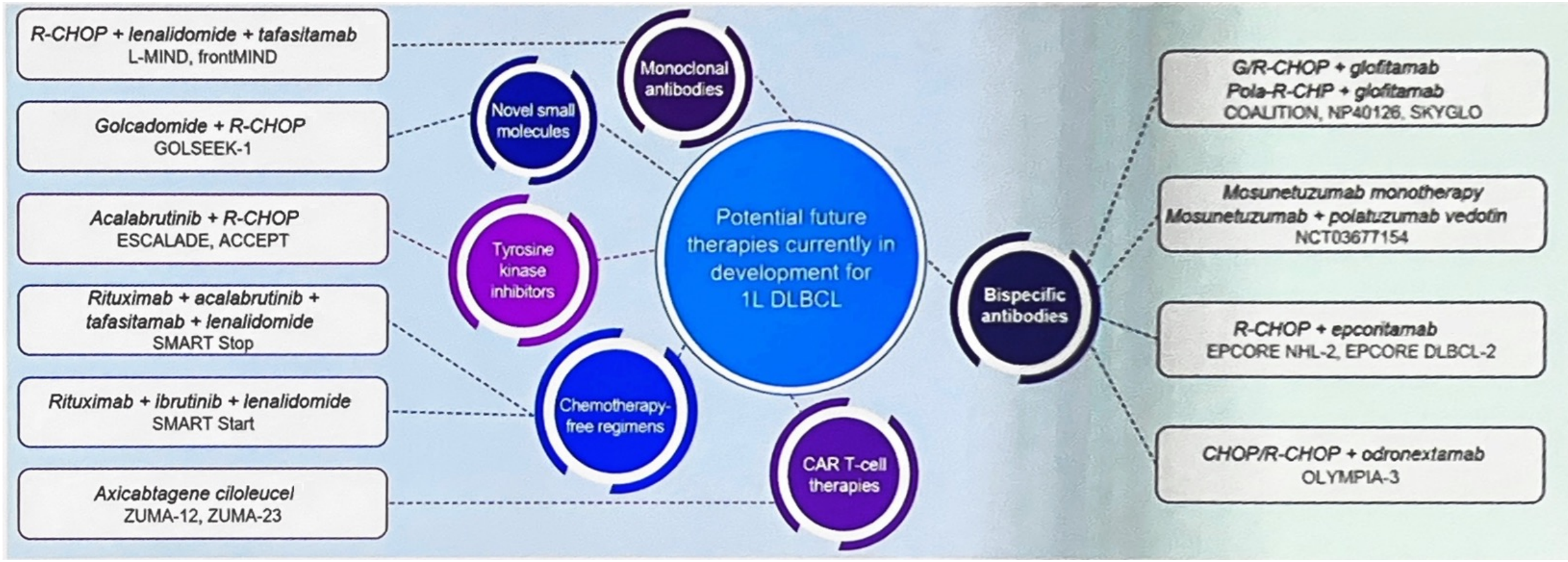
Suboptimal non-intense approaches would need consolidation





Landsburg DJ. *J Clin Oncol*, 2017; 35: 2260-2267

Potentially new frontline approaches



Selected ongoing phase 3 trials in untreated DLBCL

	Bispecific antibodies			CAR-T	Targeted		
	SKYGLO	EPCORE-DLBCL-2	OLYMPIA-3	ZUMA-23	frontMIND	ESCALADE	GOLSEEK-1
Trial design							
Experimental	Glofit-Pola-RCHP	Epco-RCHOP	Odro-CHOP	Axi-cel	Tafa-Len-RCHOP	Acalabrutinib-RCHOP	Golcadomide-RCHOP
Comparator	Pola-RCHP	RCHOP	RCHOP	RCHOP or EPOCH-R	RCHOP	RCHOP	RCHOP
Endpoint	PFS	PFS	PFS	EFS	PFS	PFS	PFS
Completion*	Dec 2027	June 2027	March 2028	March 2031	June 2025	February 2027	August 2028
Inclusion criteria							
COO	Any	Any	Any	Any	Any	non-GCB	Any
IPI	2-5	2-5	2-5	4-5	3-5	1-5	1-2HR, 3-5
Prior indolent	Excluded	Included	Included	Included	Excluded	Excluded	Excluded
HGBL	Included	Included	Included	Included	Included	Excluded	Included

NCT06047080, NCT05578976, NCT06091865, NCT05605899, NCT04824092, NCT04529772, NCT06356129

*estimated in clinicaltrials.gov

Fixed duration epcoritamab + RCHOP induces high complete response rates in patients with previously untreated diffuse large B-cell lymphoma with high-risk features: long-term results from the EPCORE NHL-2 trial

Key inclusion criteria

- Newly diagnosed CD20+ DLBCL
  - DLBCL, NOS
  - T-cell/histiocyte-rich DLBCL
  - Double-hit or triple-hit DLBCL
  - FL grade 3B
- IPI score ≥3
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: May 15, 2024
Median follow-up: 27.4 mo

Treatment regimen: concomitant fixed-duration epcoritamab 48 mg + R-CHOP

	Agent	C1–4	C5–6	C7+
	Epcoritamab SC 48 mg	QW	Q3W	Q4W Up to 1 year
R-CHOP	Rituximab IV 375 mg/m^2	Q3W		
	Cyclophosphamide IV 750 mg/m^2			
	Doxorubicin IV 50 mg/m^2			
	Vincristine IV 1.4 mg/m^2			
	Prednisone IV or oral 100 mg/d	D1–5 of each cycle		

- **Primary endpoint:** Overall response rate
- **Key secondary endpoints:** CR rate, time to response, time to CR, DOR, DOCR, PFS, OS, MRD negativity, and safety/tolerability
  - MRD was assessed using the exploratory AVENIO ctDNA method

Falchi L. *Blood (ASH annual meeting abstracts)*, 2024; 144: 581

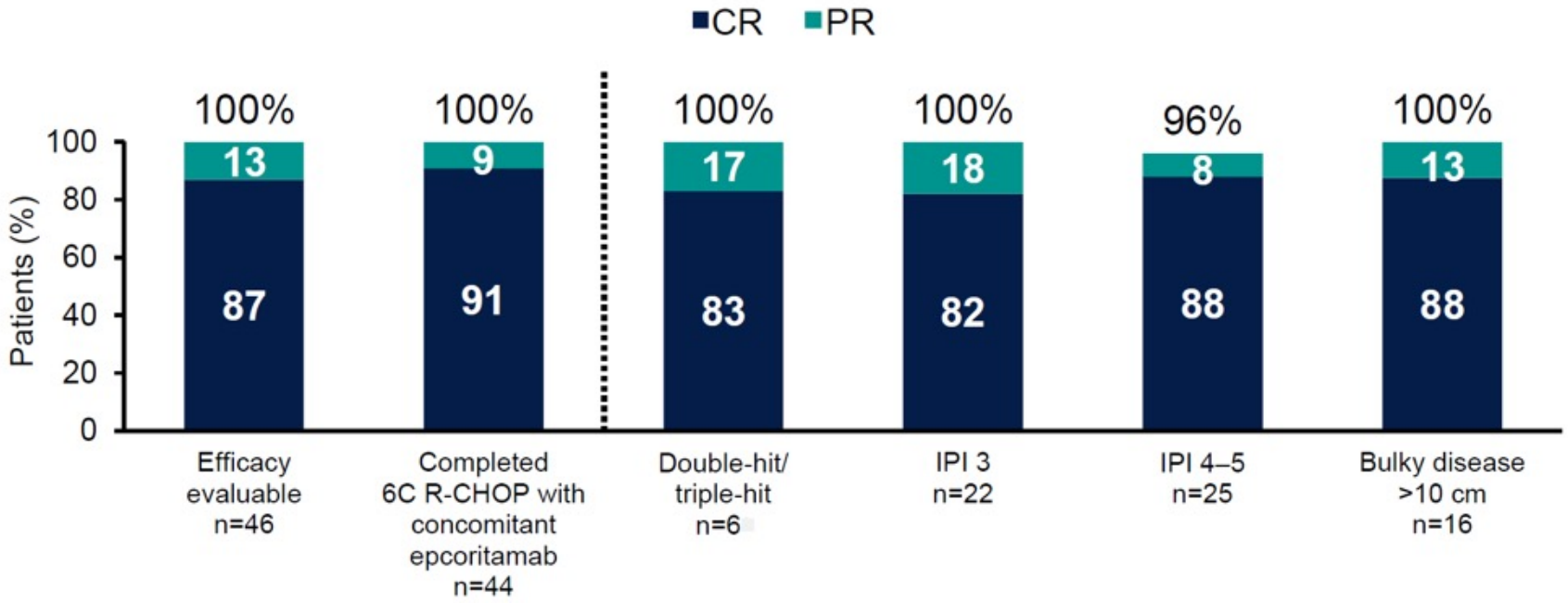
Fixed duration epcoritamab + RCHOP induces high complete response rates in patients with previously untreated diffuse large B-cell lymphoma with high-risk features: long-term results from the EPCORE NHL-2 trial

Characteristic	N=47
Median age, y (range)	64 (19–82)
≥75 y, n (%)	7 (15)
Male sex at birth, n (%)	23 (49)
Race, n (%)	
White	37 (79)
Asian	6 (13)
Ethnicity, n (%)	
Not Hispanic or Latino	19 (40)
Hispanic or Latino	1 (2)
ECOG PS, n (%)	
0–1	41 (87)
2	6 (13)
Ann Arbor stage, n (%)	
III	10 (21)
IV	37 (79)
IPI at screening, n (%)	
3	22 (47)
4–5	25 (53)

Characteristic	N=47
DLBCL, n (%)	47 (100)
De novo	39 (83)
Transformed	8 (17)
Double-hit/triple-hit by central lab, n/n (%)	6/28 (21)
Bulky disease, n (%)	
>10 cm	16 (34)
LDH, n (%)	
High	32 (68)
Extranodal disease at screening, n (%)	36 (77)
Cell of origin, n (%)	
Germinal center B-cell	28 (60)
Activated/non–germinal center B-cell	15 (32)
Unknown	4 (9)
Median time from initial diagnosis to first dose, wk (range)	4.0 (1.3–60.4)

Falchi L. *Blood (ASH annual meeting abstracts)*, 2024; 144: 581

Fixed duration epcoritamab + RCHOP induces high complete response rates in patients with previously untreated diffuse large B-cell lymphoma with high-risk features: long-term results from the EPCORE NHL-2 trial

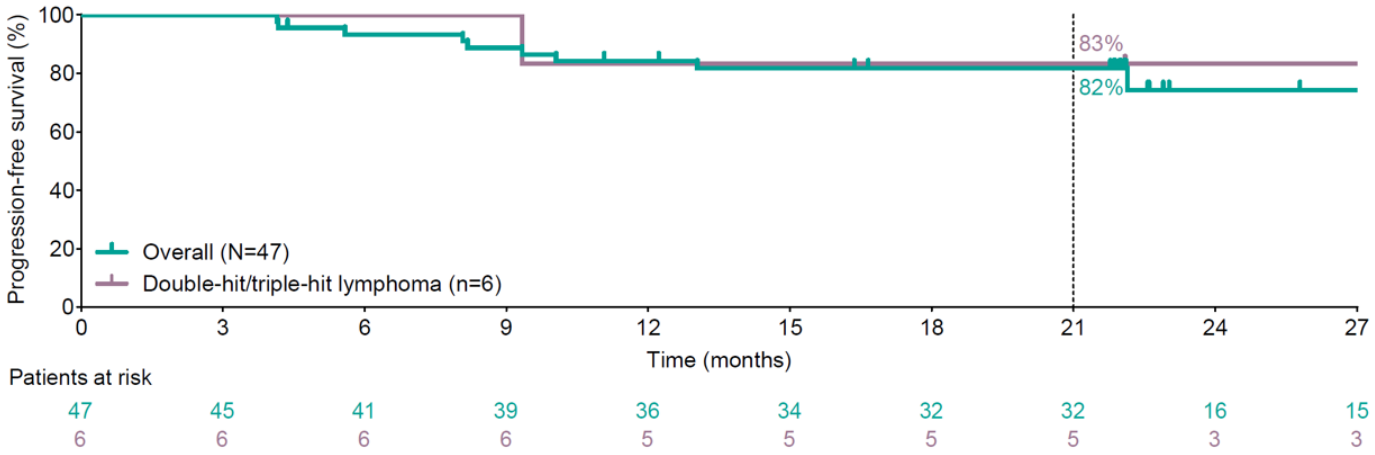


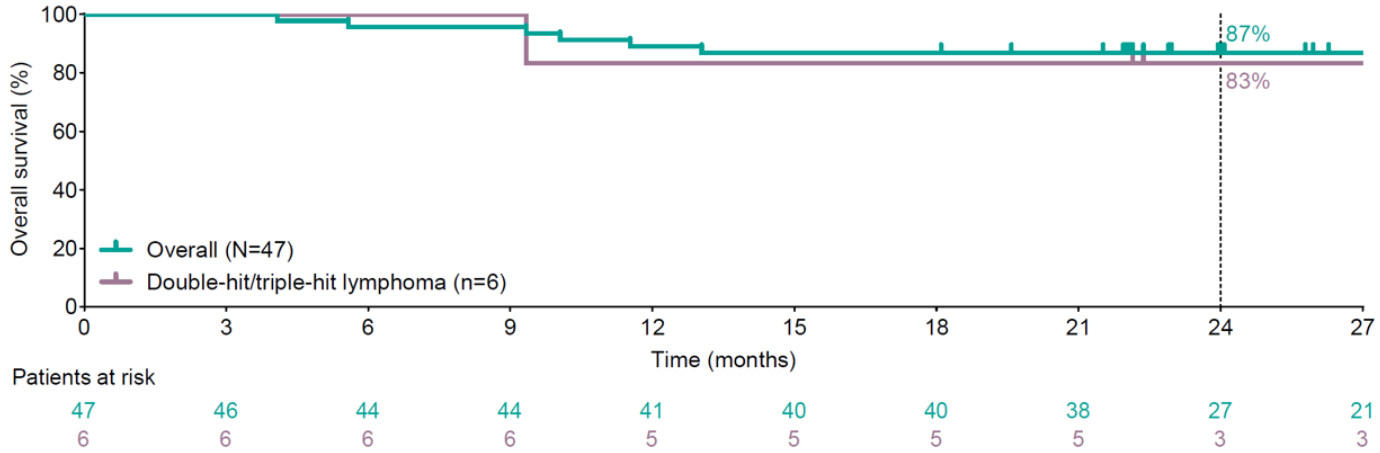
Exposure:

- Median duration of 11.5 mo of epcoritamab (range, 0.6–13.2)
- Median relative dose intensity of R-CHOP 95%–98% for all individual components
  - Three patients did not complete 6C due to withdrawal of consent, PD, and an AE (grade 5 COVID-19)

Falchi L. *Blood (ASH annual meeting abstracts)*, 2024; 144: 581

Fixed duration epcoritamab + RCHOP induces high complete response rates in patients with previously untreated diffuse large B-cell lymphoma with high-risk features: long-term results from the EPCORE NHL-2 trial



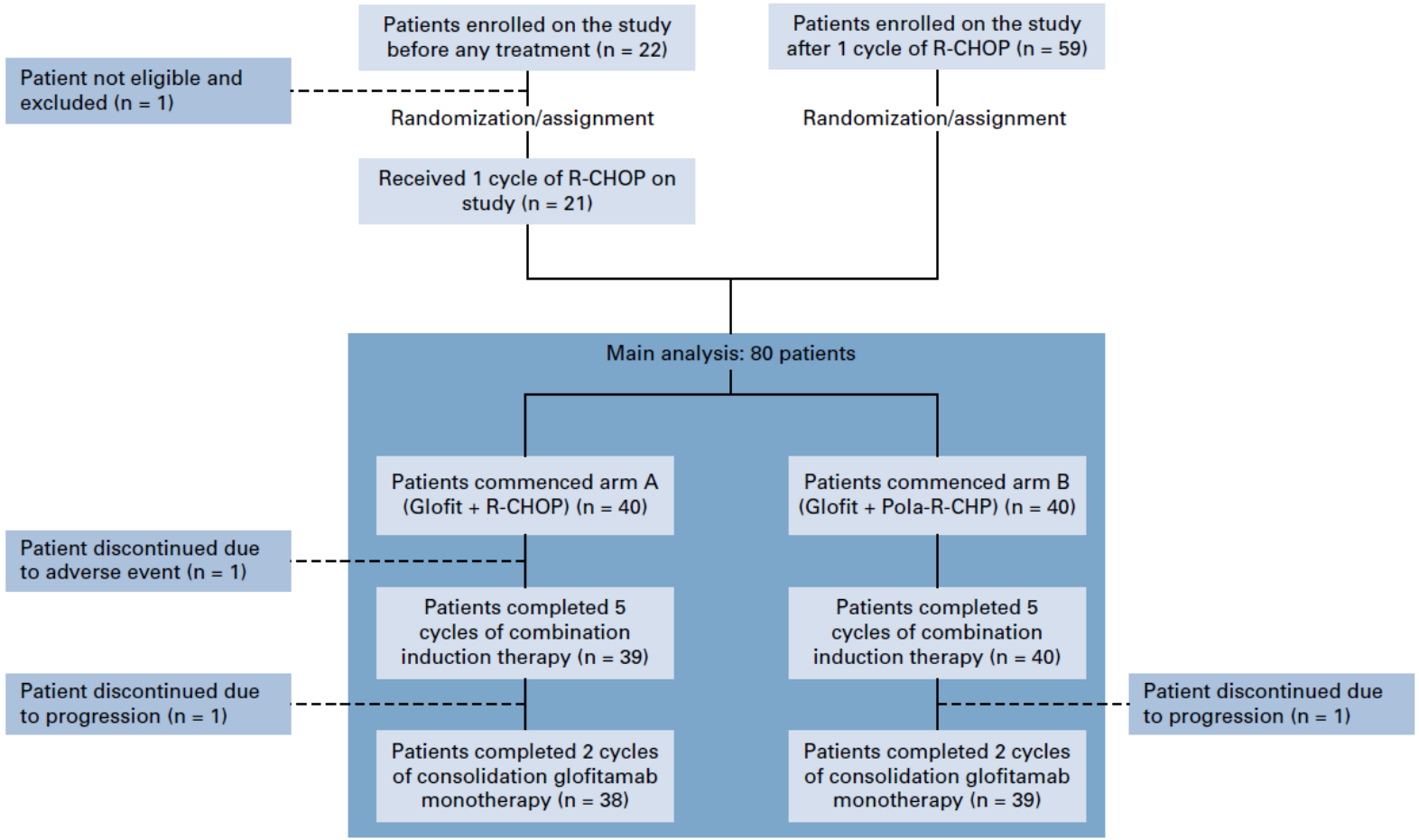


Falchi L. *Blood (ASH annual meeting abstracts)*, 2024; 144: 581

Glofitamab Combined With Pola-R-CHP or R-CHOP as First Therapy in Younger Patients With High-Risk Large B-Cell Lymphoma: Results From the COALITION Study

Age ≤ 65 years

High risk features:
- IPI ≥ 3, NCCN-IPI ≥ 4
- Rearrangements of *MYC* + *BCL2* ± *BCL6*



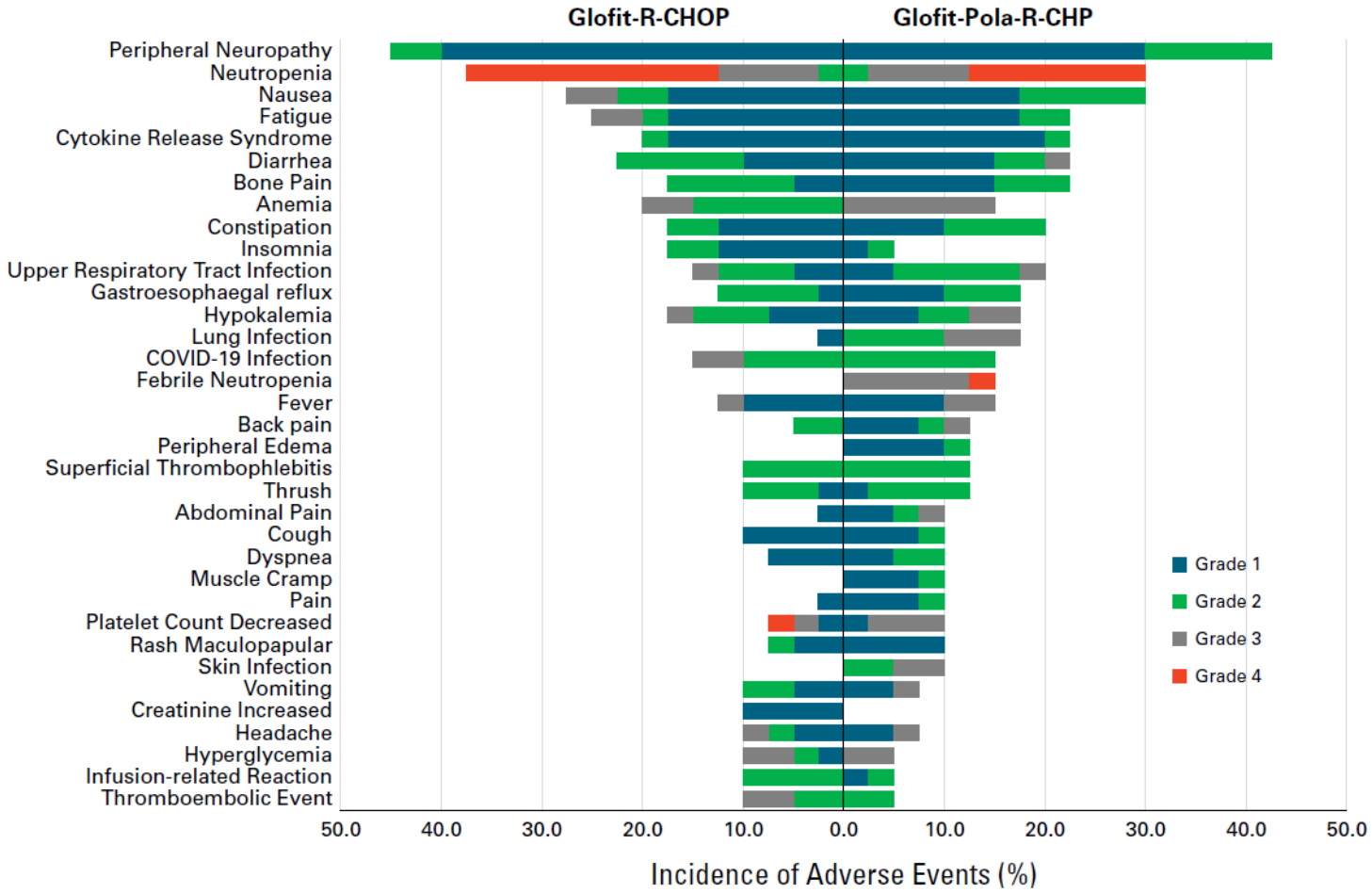
Minson A. *J Clin Oncol*, 2025; 43: 2595-2605

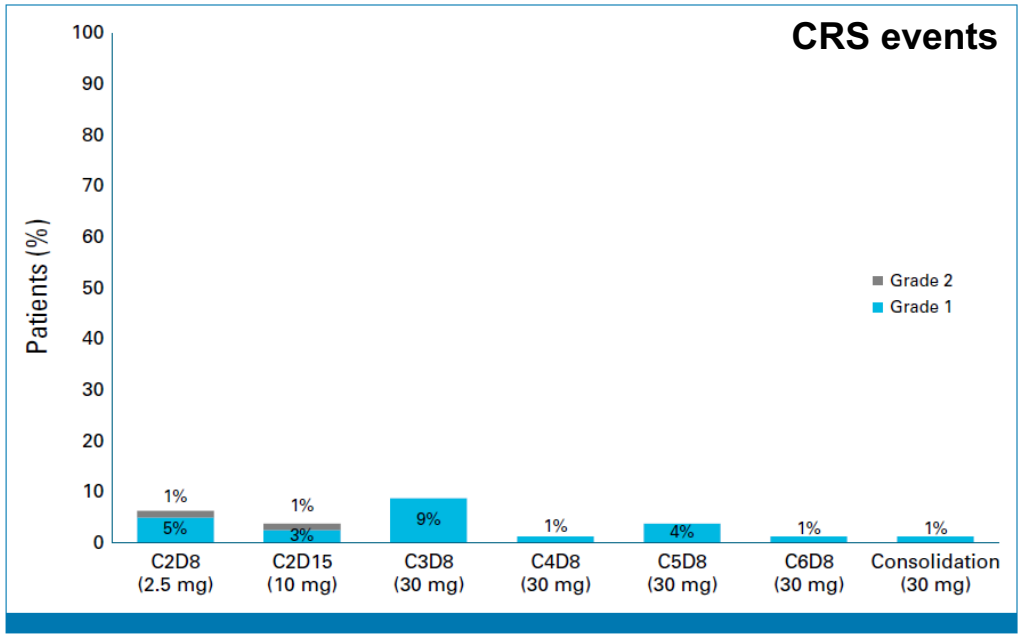
Glofitamab Combined With Pola-R-CHP or R-CHOP as First Therapy in Younger Patients With High-Risk Large B-Cell Lymphoma: Results From the COALITION Study

Responses to Therapy	All Patients (N = 80)	Arm A (Glofit-R-CHOP; n = 40)	Arm B (Glofit-Pola-R-CHP; n = 40)
End of induction response, No. (% [95% CI])			
CMR	59 (74% [63 to 83])	27 (68% [51 to 81])	32 (80% [64 to 91])
PMR	18 (23% [14 to 33])	11 (28% [15 to 44])	7 (18% [7 to 33])
PMD	2 (2% [0 to 9])	1 (2% [0 to 13])	1 (2% [0 to 13])
NE	0	1 (2% [0 to 13])	0
Best response across all visits, No. (% [95% CI])			
CMR	78 (98 [91 to 100])	39 (98 [87 to 100])	39 (98 [87 to 100])
PMR	2 (2 [0 to 9])	1 (2 [0 to 13])	1 (2 [0 to 13])
12-month PFS, % (95% CI)	92 (84% to 97%)	90 (75% to 96%)	95 (81% to 99%)
12-month OS, % (95% CI)	97 (90% to 99%)	98 (84% to 100%)	98 (84% to 100%)
24-month PFS, % (95% CI)	86 (75% to 93%)	86 (69% to 94%)	86 (65% to 95%)
24-month OS, %, (95% CI)	92 (80% to 97%)	92 (76% to 97%)	91 (67% to 98%)

Minson A. *J Clin Oncol*, 2025; 43: 2595-2605

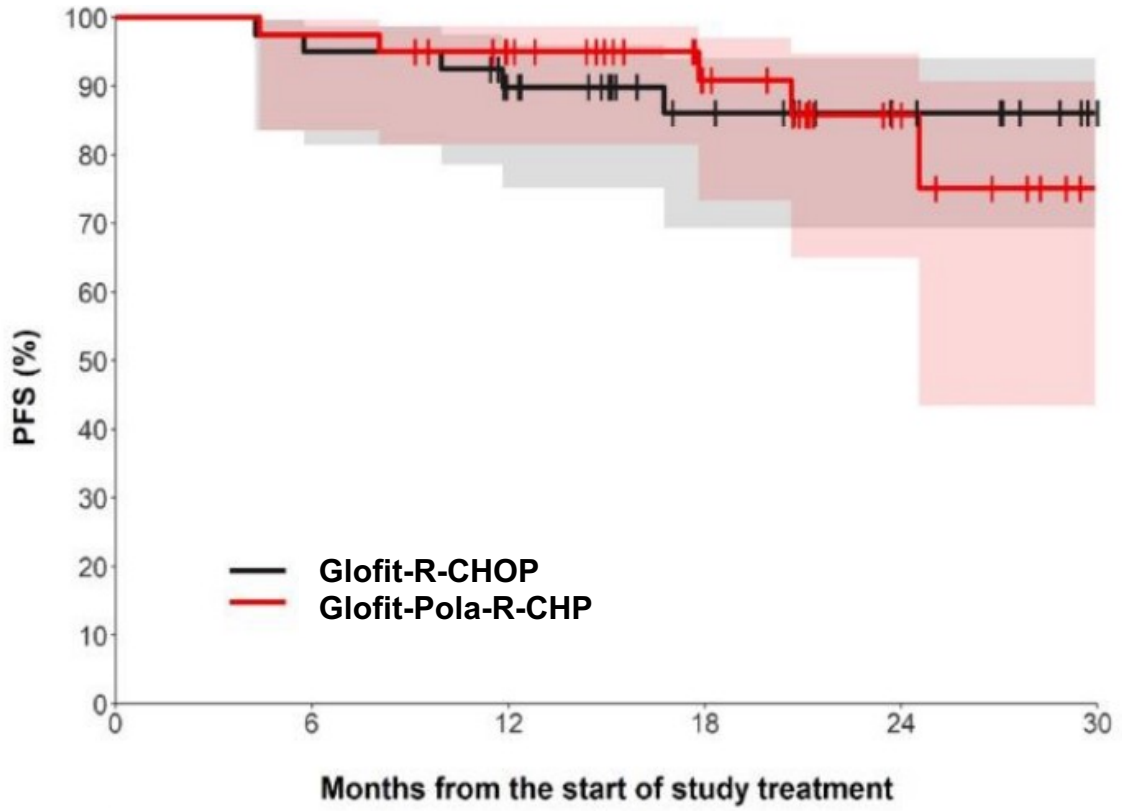
Glofitamab Combined With Pola-R-CHP or R-CHOP as First Therapy in Younger Patients With High-Risk Large B-Cell Lymphoma: Results From the COALITION Study





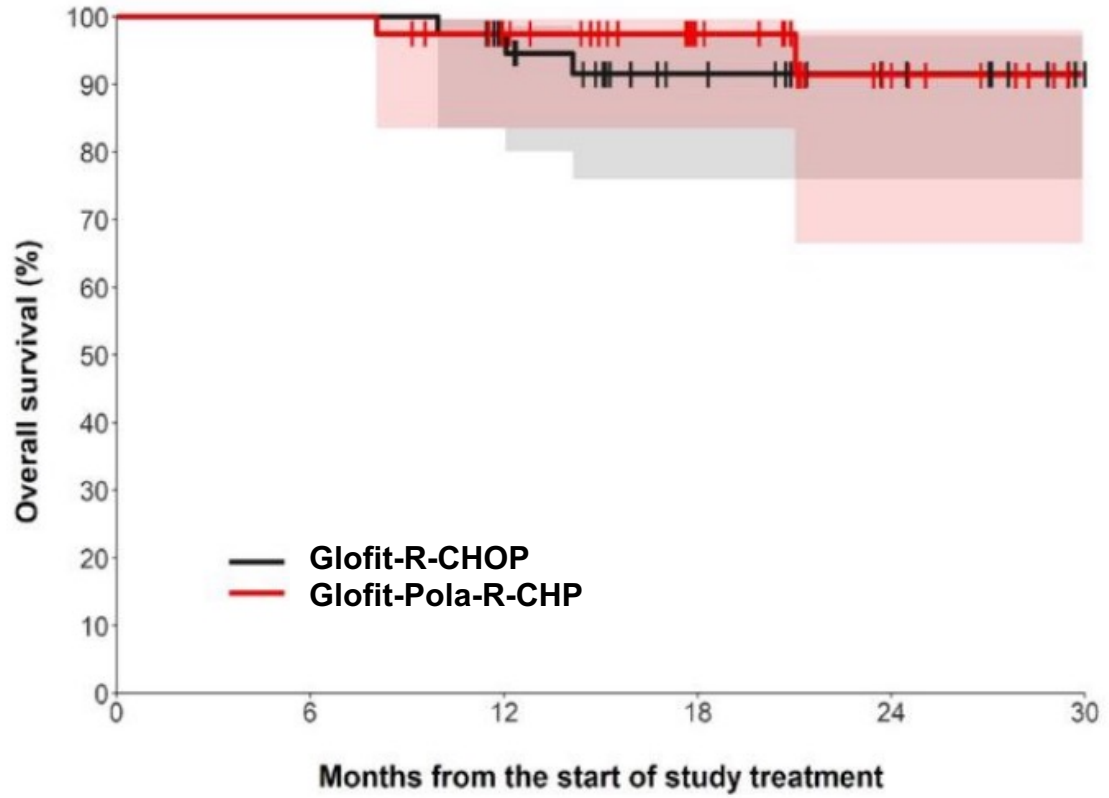
Minson A. *J Clin Oncol*, 2025; 43: 2595-2605

Glofitamab Combined With Pola-R-CHP or R-CHOP as First Therapy in Younger Patients With High-Risk Large B-Cell Lymphoma: Results From the COALITION Study



No. at risk (No. censored)

ARM A	40 (0)	38 (0)	32 (4)	22 (13)	14 (21)	4 (31)
ARM B	40 (0)	39 (0)	33 (5)	20 (17)	9 (27)	1 (34)



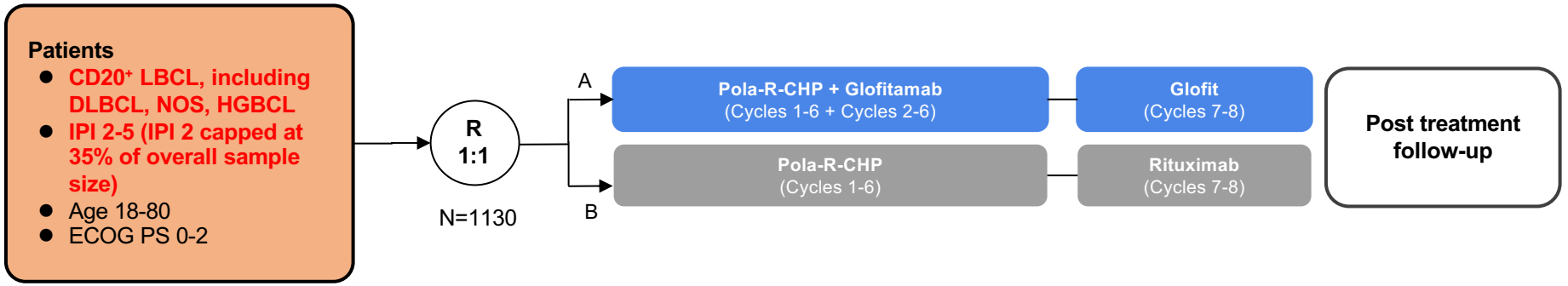
No. at risk (No. censored)

ARM A	40 (0)	40 (0)	34 (5)	22 (15)	14 (23)	4 (33)
ARM B	40 (0)	40 (0)	34 (5)	21 (18)	9 (29)	1 (37)

Minson A. *J Clin Oncol*, 2025; 43: 2595-2605

Glofitamab + chemoimmunotherapy: SKYGLO

SKYGLO: A Global Phase III Randomized Study Evaluating Glofitamab Plus Polatuzumab Vedotin + Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) Versus Pola-R-CHP in Previously Untreated Patients with Large B-Cell Lymphoma (LBCL)



Stratification Factors
- IPI 2 vs IPI 3-5
- bulky disease defined as one lesion ≳7.5 cm (present vs absent)

Primary EP: PFS with 2-year follow-up (IRC)

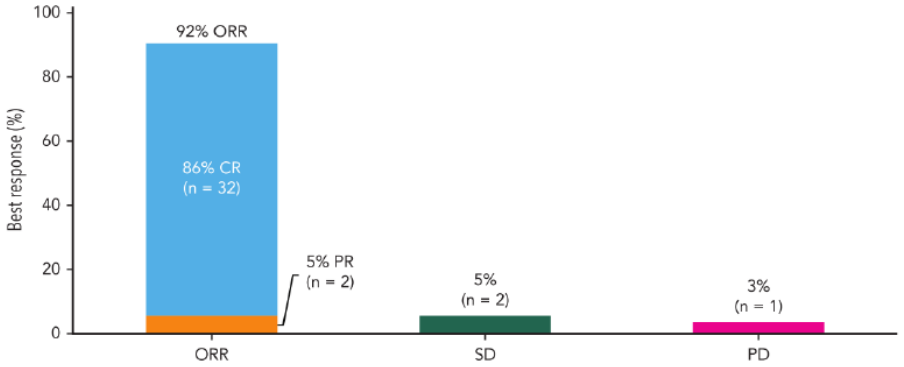
Key Secondary EPs: PFS in IPI 3-5 (IRC), OS, $EFS_{efficacy}$ (IRC)
Selected Secondary EPs (no adjustment for multiplicity): PFC (INV), ORR, DOR, DOCR, DFS, safety, PK, PROs, ctDNA

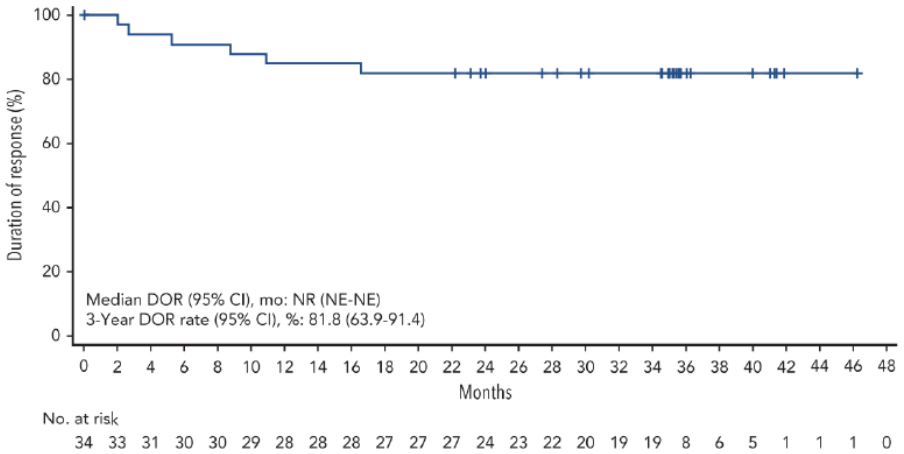
Exploratory: Biomarkers

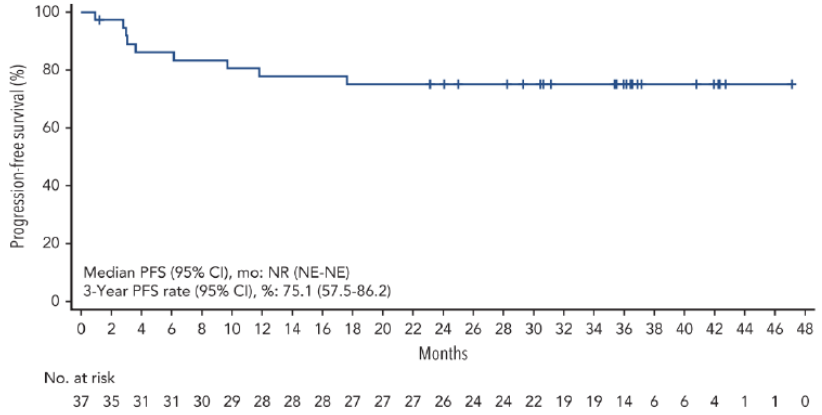
Advani RH. *Blood (ASH annual meeting abstracts)*, 2024; 144: 1718.1

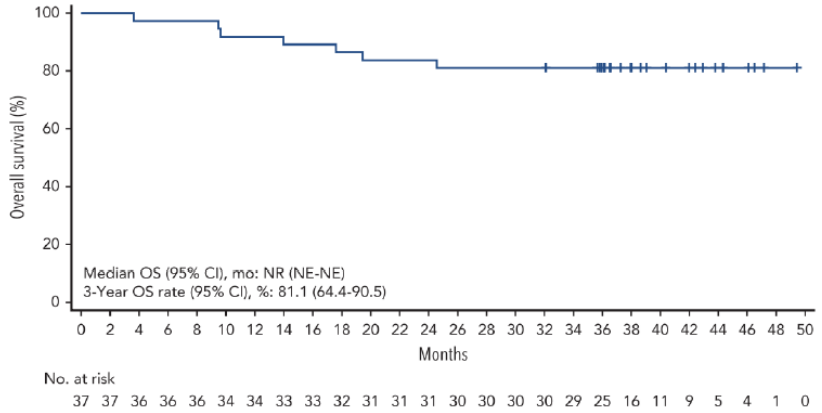
High risk features: IPI ≥ 3, rearrangements *MYC* + *BCL2* ± *BCL6*
2 initial chemoimmunotherapy cycles with anti-CD20 and anthracyclines
PET+2 Deauville score 4-5

Three-year follow-up analysis of first-line axicabtagene ciloleucel for high-risk large B-cell lymphoma: the ZUMA-12 study



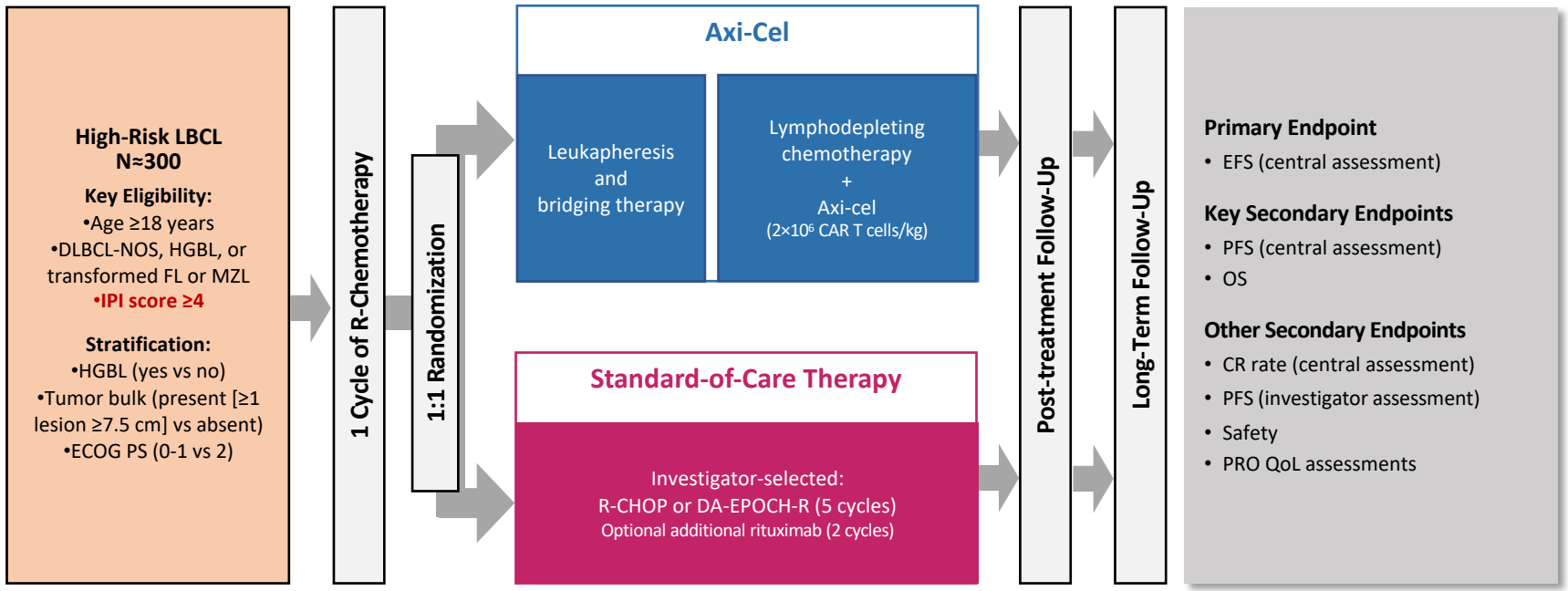






Chavez JC. *Blood*, 2025; 145: 2303-2311

PB2319 ZUMA-23: A GLOBAL, PHASE 3, RANDOMIZED CONTROLLED STUDY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE AS FIRST-LINE THERAPY IN PATIENTS WITH HIGH-RISK LARGE B-CELL LYMPHOMA



Westin JR. *Hemasphere (EHA annual meeting abstracts)*, 2023; 7: 4418-4419

Take home messages

- **R-CHOP** is the unsurpassed standard frontline combination in DLBCL; **Polatuzumab + R-CHP** yields better outcomes especially in some higher risk contexts and has become a new standard.

- The best treatment of **double hit DLBCL** is still debated, although it is known that R-CHOP-based inductions are unsatisfactory. The role of **autologous transplantation** is also unclear, particularly if more intensive regimens are applied as induction.

- **Bispecific antibodies** are moving from “right to left”, as they are now being incorporated in frontline approaches with chemotherapy ± monoclonal antibodies. Frontline standards for DLBCL are going to change in the next few years and so second and later salvage lines.

- New drugs, including CARTs, as part of induction, may confirm their potential benefit in patients with **high risk disease** in terms of IPI, histology, *MYC*/*BCL2*/*BCL6* rearrangements, early (*interim* PET) treatment failure.