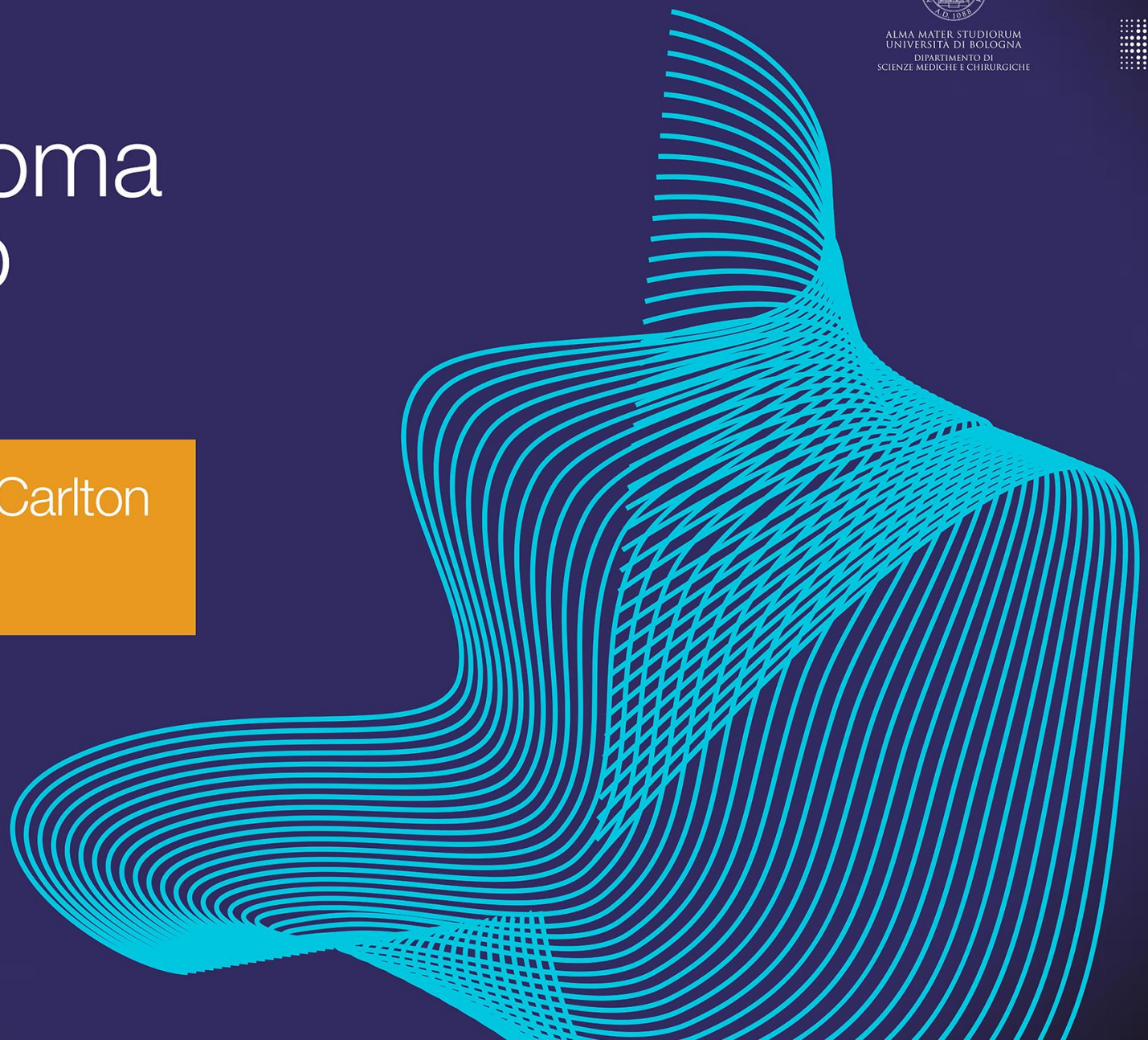
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

Moving Beyond RCHOP

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Disclosure of Grzegorz S. Nowakowski

Employment: None
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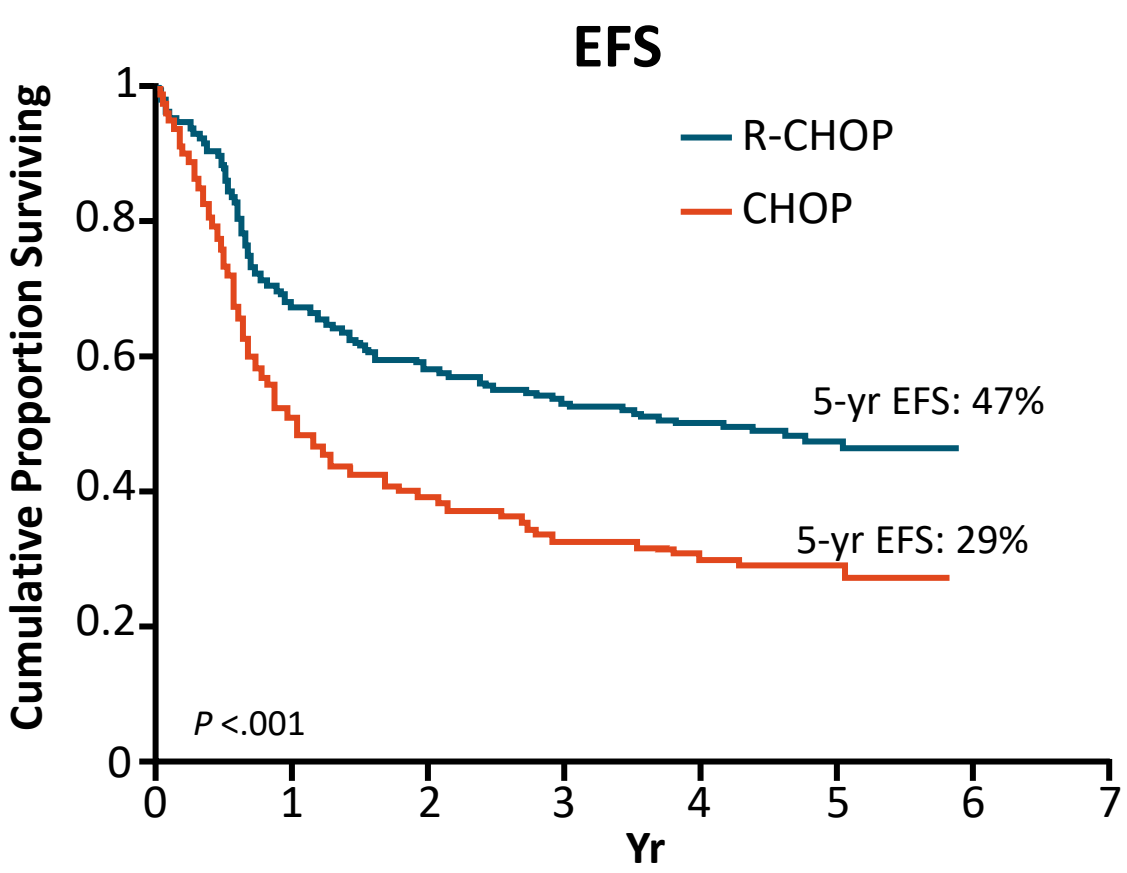
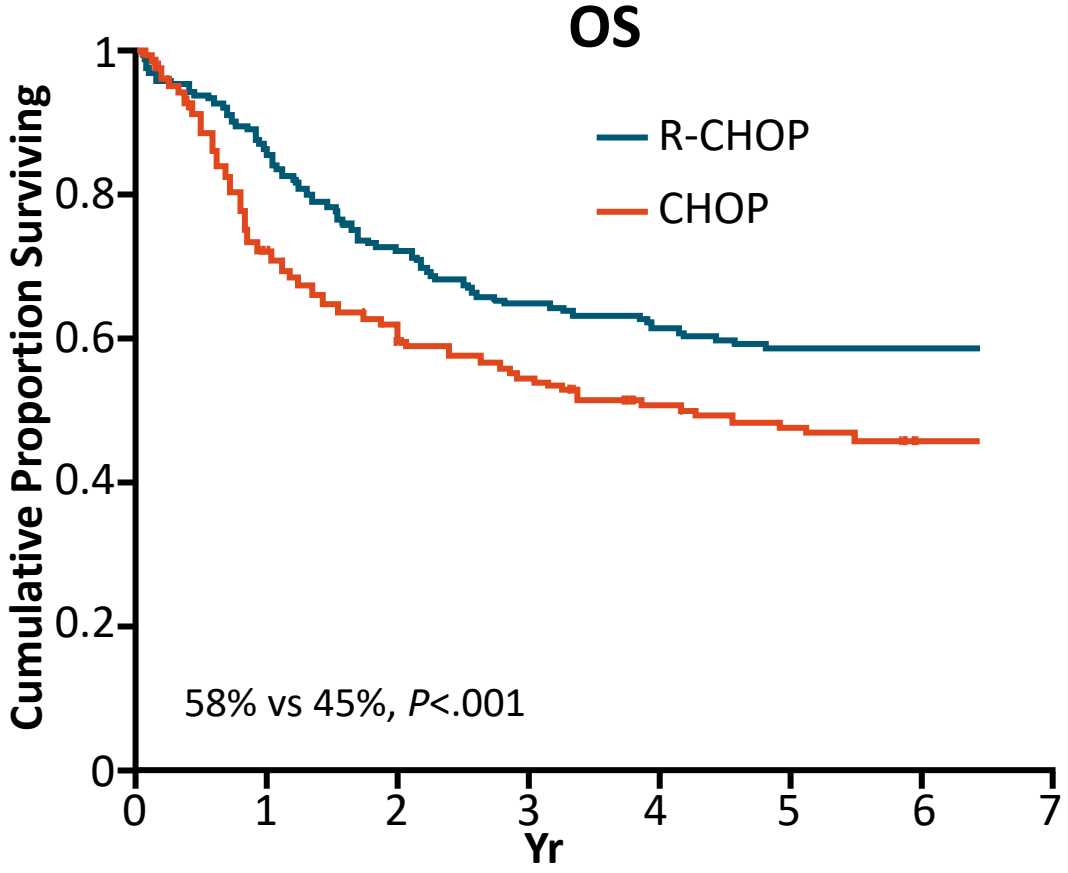
R-CHOP Has Been the Standard Initial Therapy for DLBCL for >20 Yr

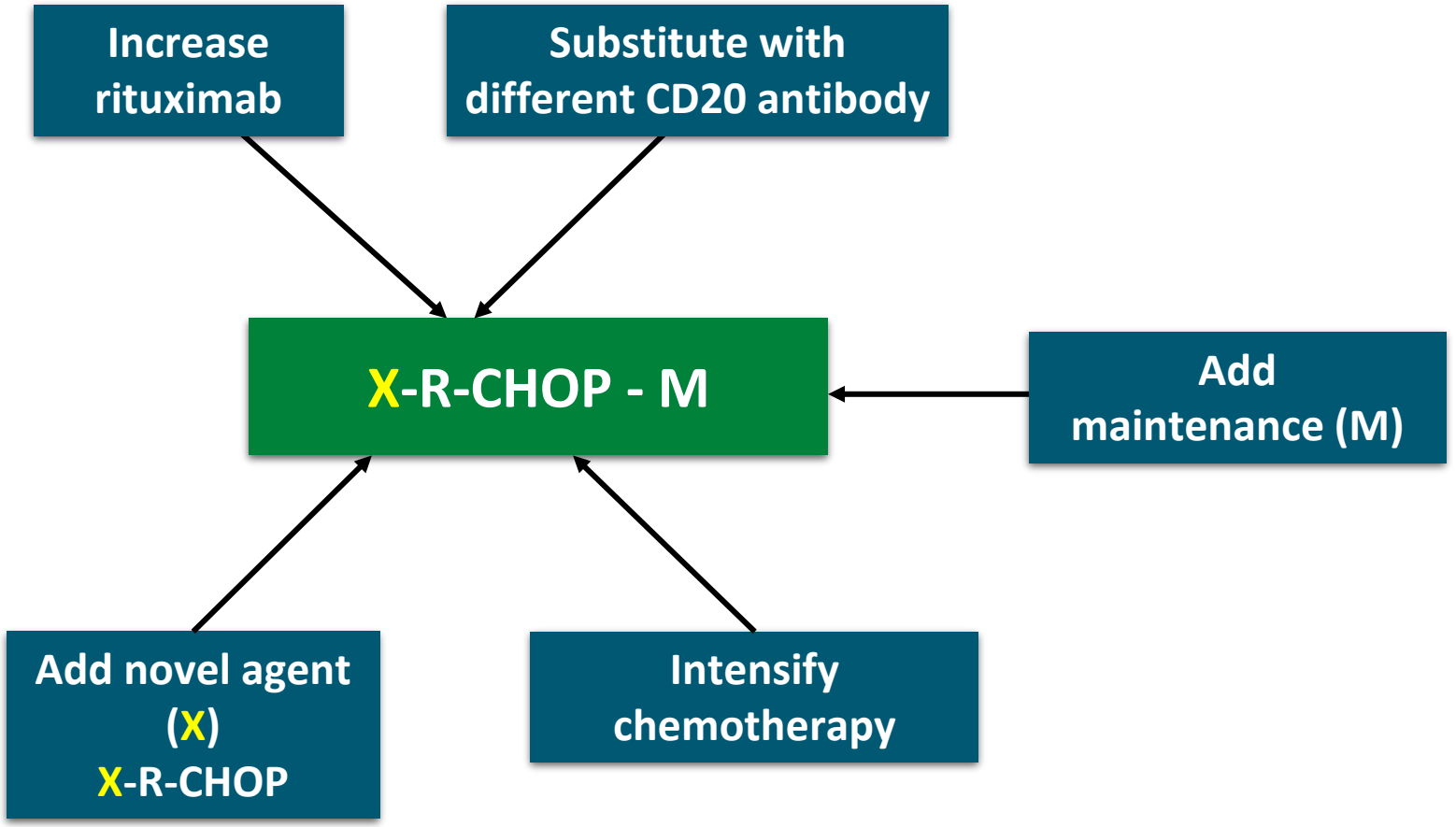
- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL



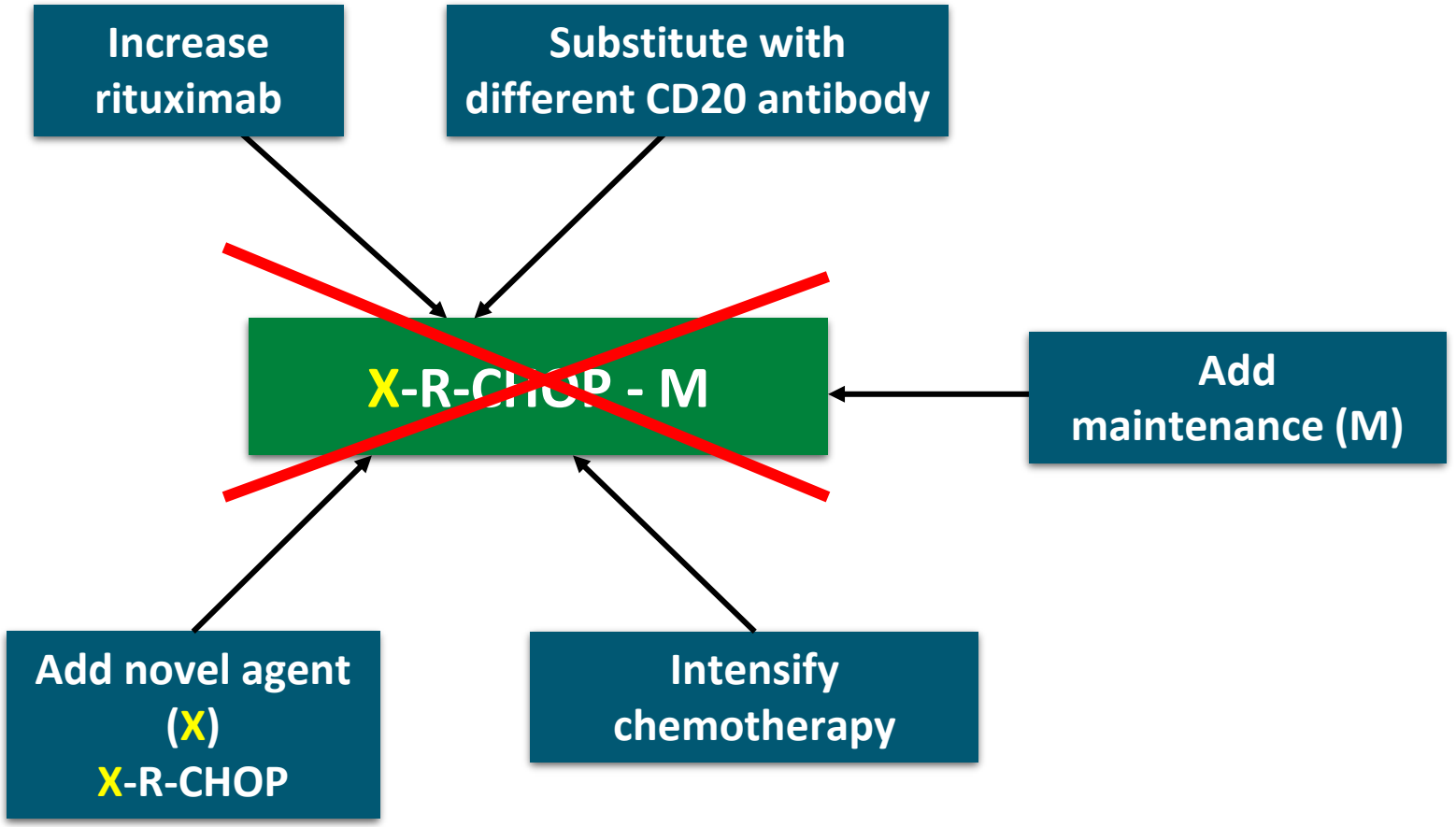


Coiffier. NEJM. 2002;346:235. Feugier. JCO. 2005;23:4117.

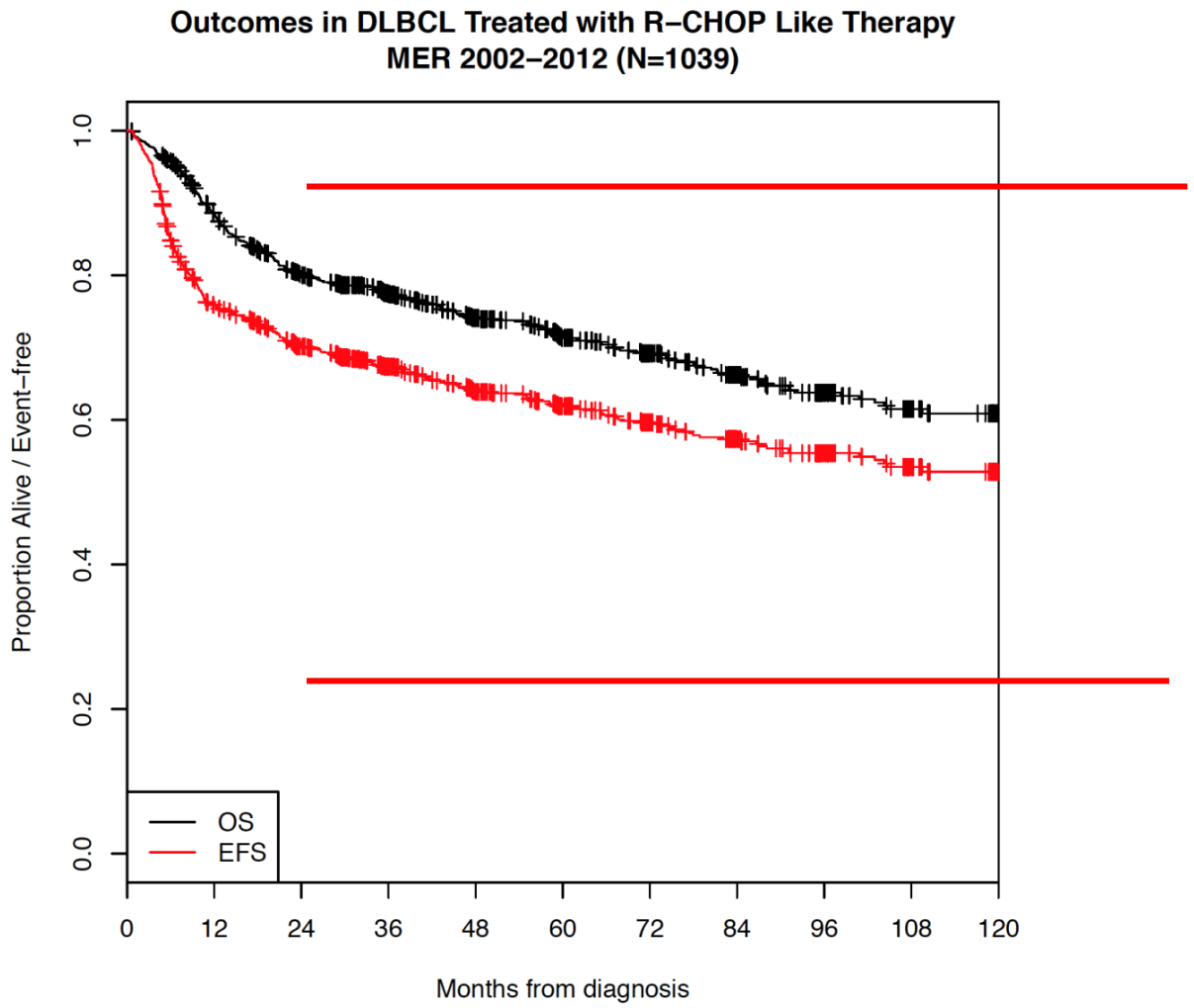
How to Improve on R-CHOP



How to Improve on R-CHOP



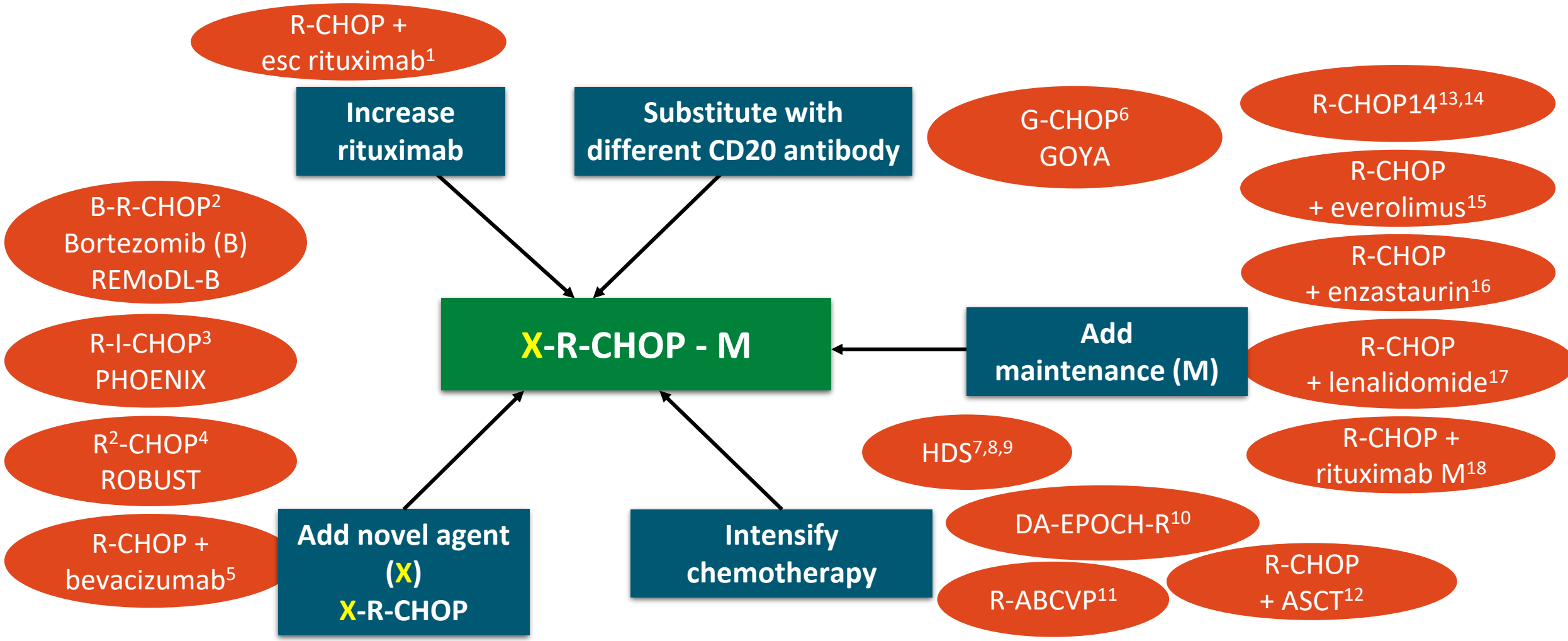
DLBCL Outcomes in Mayo Clinic Lymphoma SPORE Database



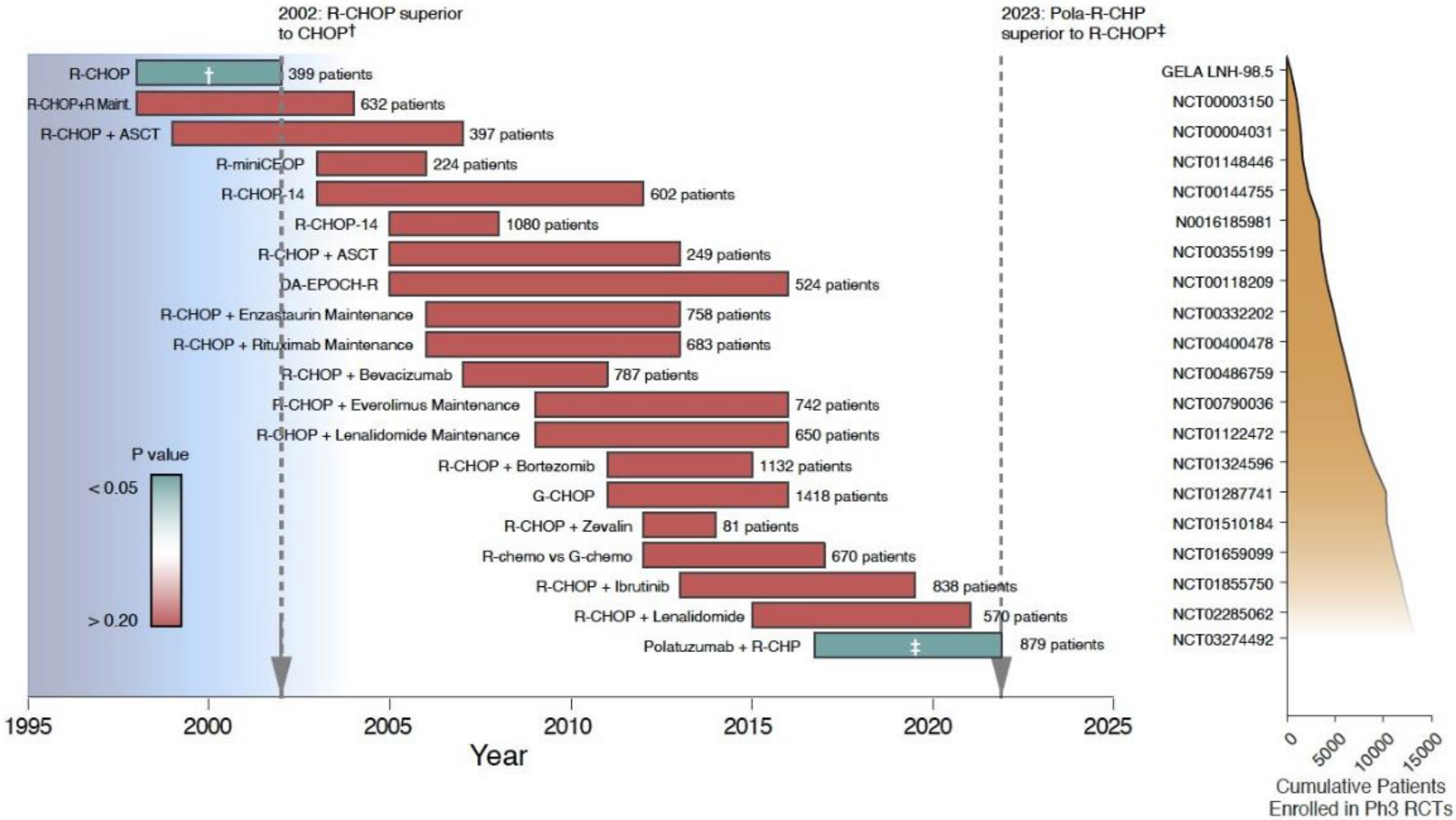
De-escalation

Completely different backbone

Improving on R-CHOP in DLBCL



1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955.



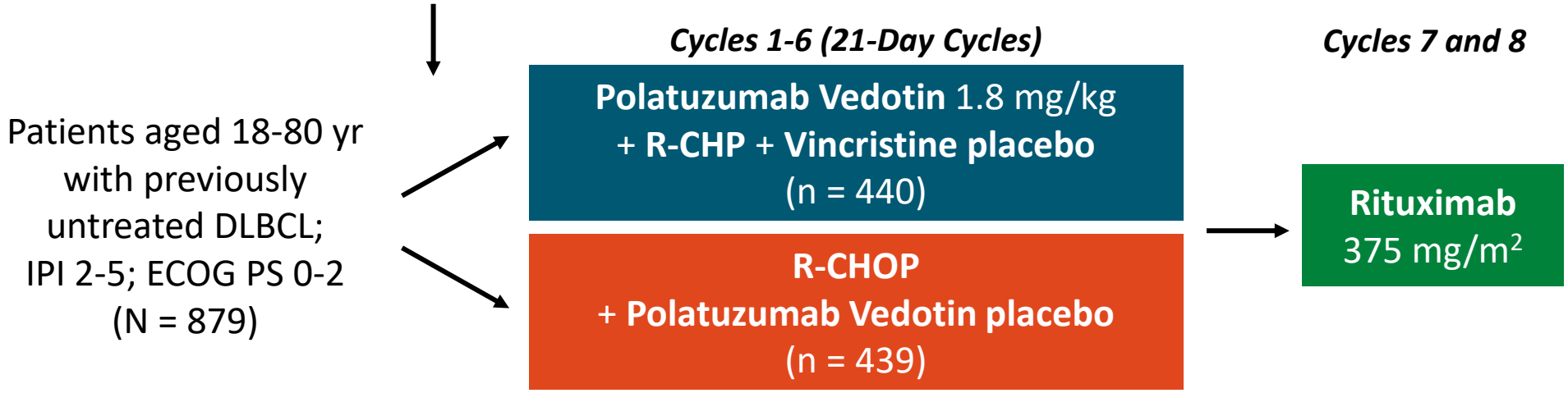
After Alizadeh and Kurtz; Twitter

Is RCHOP still a standard and a reasonable control arm and backbone ?

POLARIX: Polatuzumab + R-CHP vs R-CHOP in Previously Untreated DLBCL

- Multicenter, double-blind, placebo-controlled phase III trial

Stratification by IPI score (2 vs 3-5), bulky disease (<7.5 vs ≥7.5 cm), and geographic region (Western Europe, US, Canada, and Australia vs Asia vs rest of world)

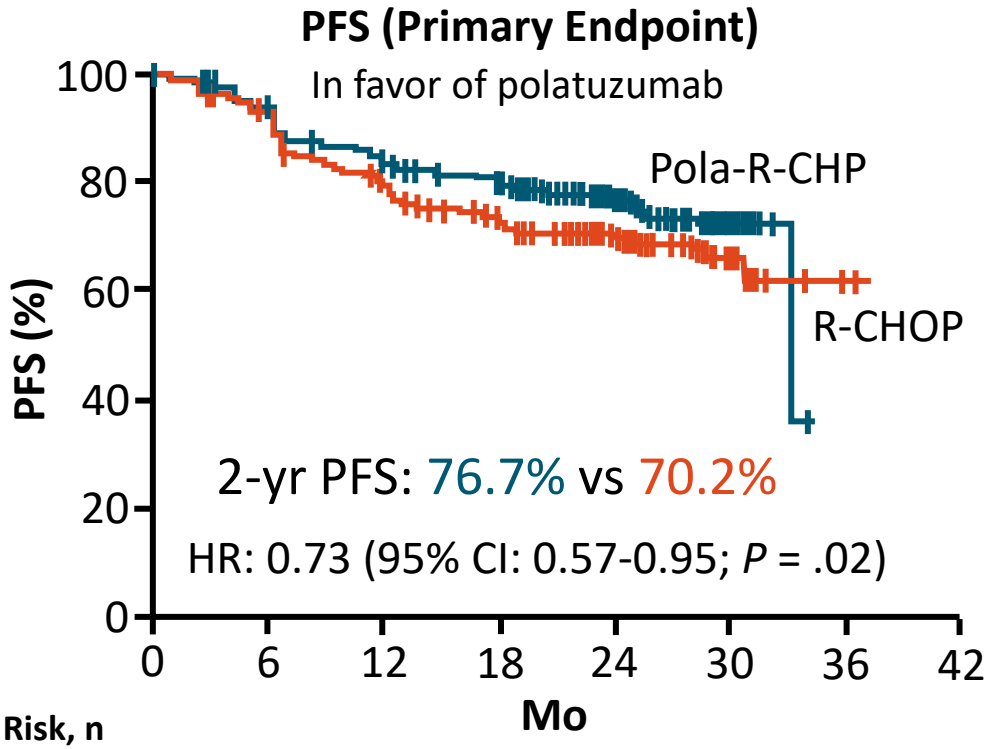


R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** EFS, CRR at end of treatment, DFS, OS, safety

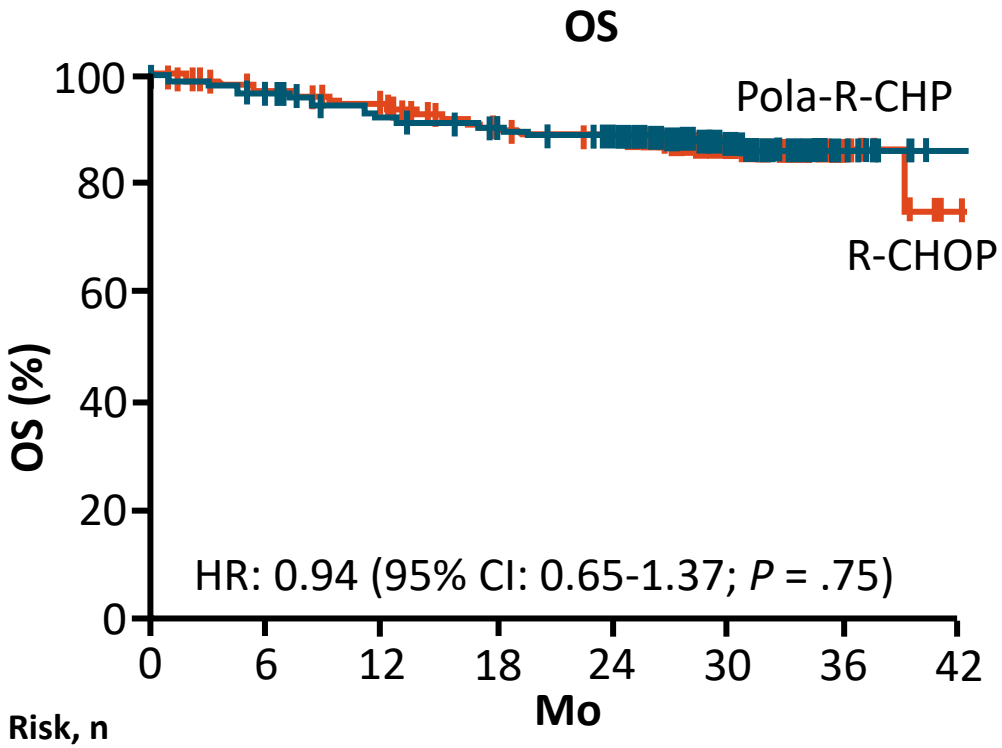
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP



Patients at Risk, n

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE



Patients at Risk, n

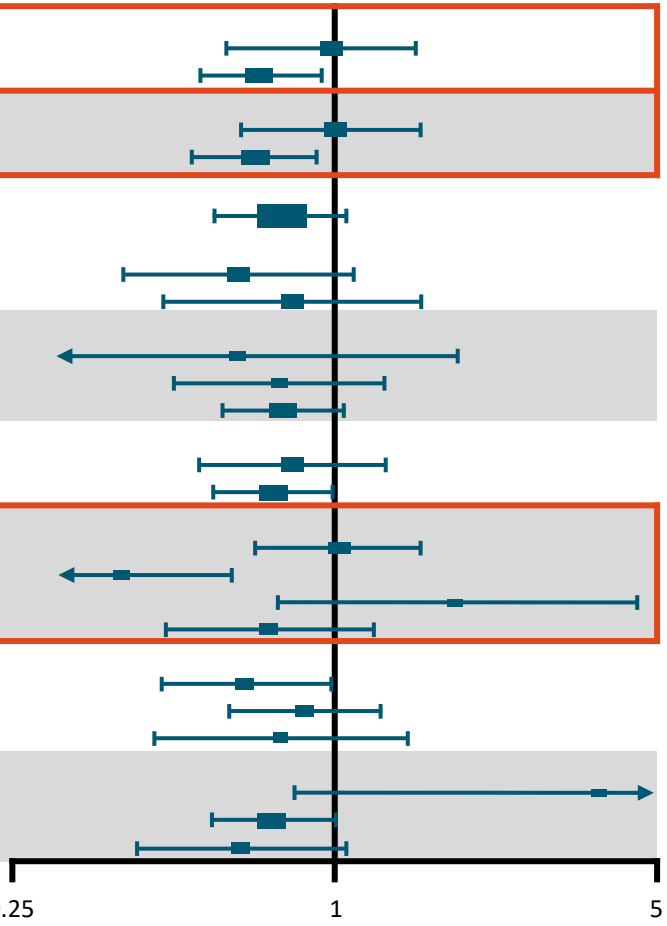
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	2

- Best overall response rate: **95.9 %** vs **94.1%**
  - Complete response rate: **86.6%** vs **82.7%**

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

POLARIX: Subgroup Analysis of PFS

Baseline Risk Factors	Total N	Pola-R-CHP (N = 440) n	Pola-R-CHP (N = 440) 2-Yr Rate	R-CHOP (N = 439) n	R-CHOP (N = 439) 2-Yr Rate	HR	95% Wald CI
Age group, yr							
≤60	271	140	74.1	131	71.9	0.9	(0.6-1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5-0.9)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6-1.6)
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5-0.9)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0.6-1.1)
Asia	160	81	74.3	79	65.6	0.6	(0.4-1.5)
Rest of world	116	57	70.8	59	67.3	0.9	(0.6-1.5)
Ann Arbor stage							
I-II	99	47	89.1	52	85.5	0.6	(0.2-1.8)
III	232	124	80.7	108	73.6	0.8	(0.5-1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6-1.1)
Baseline LDH							
≤ ULN	300	146	78.9	154	75.6	0.8	(0.5-1.3)
> ULN	575	291	75.4	284	67.2	0.7	(0.5-1.0)
Cell of origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7-1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2-0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8-4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4-1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4-1.0)
Non-DEL	438	223	77.7	215	75.7	0.9	(0.6-1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4-1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8-17.6)
No	620	305	76.8	315	70.3	0.7	(0.5-1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4-1.1)



Tilly. NEJM. 2022;386:351.

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP AEs

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
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	24.4	0	24.0	0.2
Dec appetite	16.3	1.1	14.2	0.7

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
Headache	12.9	0.2	13.0	0.9
Cough	12.9	0	12.1	0
Dec weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13.0	0

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

Main topics

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. Other efficacy endpoints
4. Heterogeneity of study population

Other secondary endpoints: modest differences

Modified EFS

HR 0.75 (95% CI: 0.58, 0.96); p = 0.0244*

2-year difference: 6.2%

* alpha allocation = 0.05

Duration of response

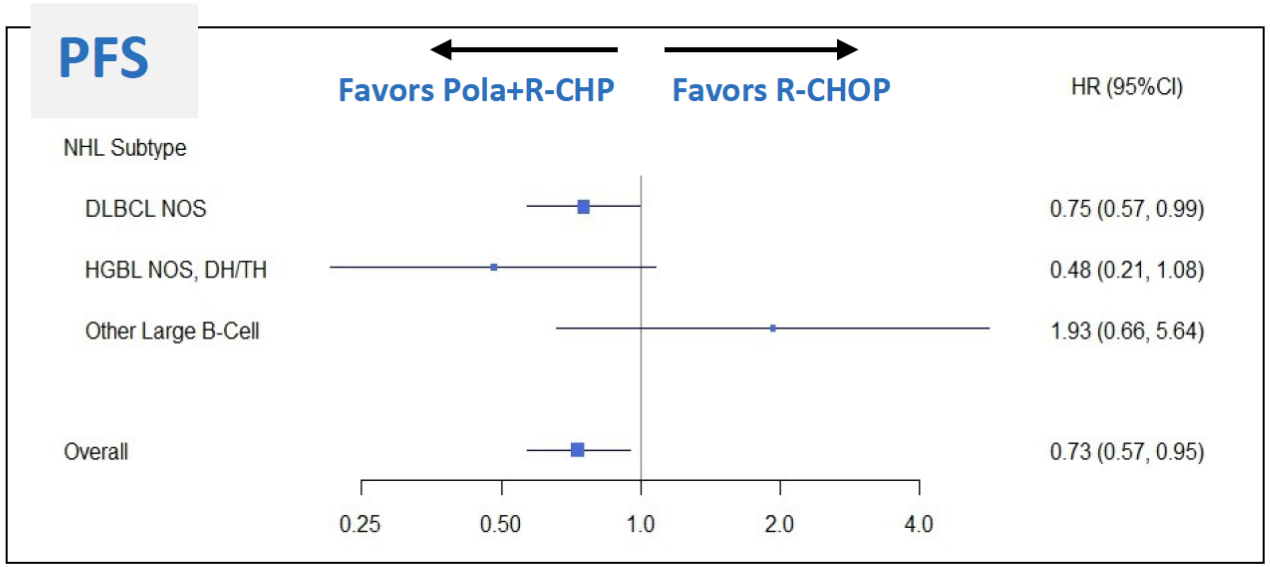
	Pola+R-CHP (N=422)	R-CHOP (N=413)
2-year DOR rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
Difference (95% CI)	4.0% (-2.5, 10.5)	

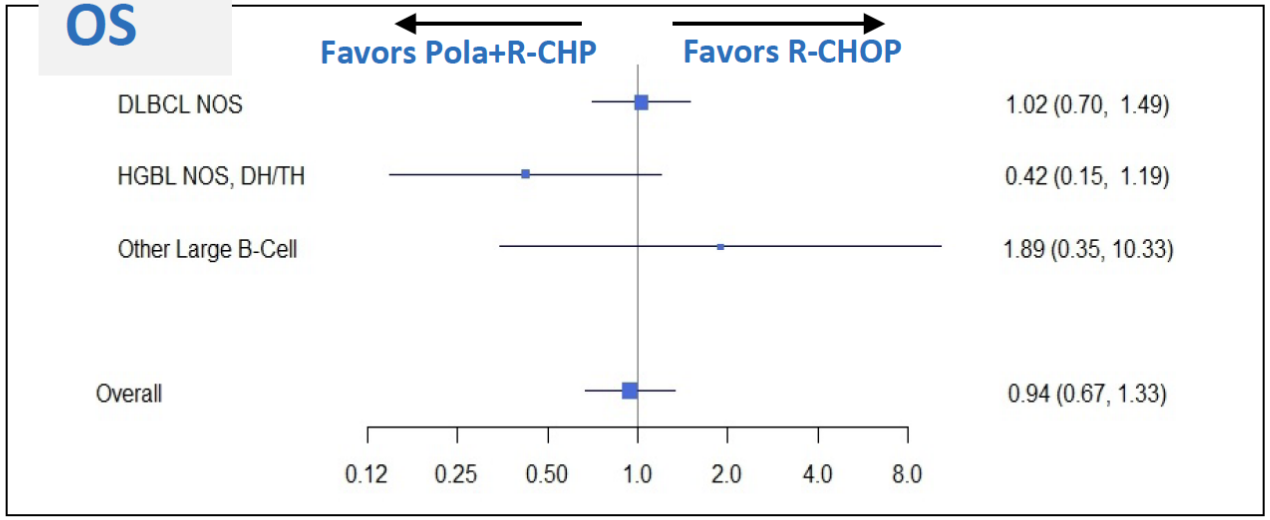
Disease-free survival

	Pola+R-CHP (N=381)	R-CHOP (N=363)
2-year DFS rate (95% CI)	81.8% (77.4, 86.2)	77.4% (72.7, 82.0)
Difference (95% CI)	4.4% (-1.9, 10.8)	

DOR, disease-free survival; DFS, disease-free survival

Heterogenous population and outcomes

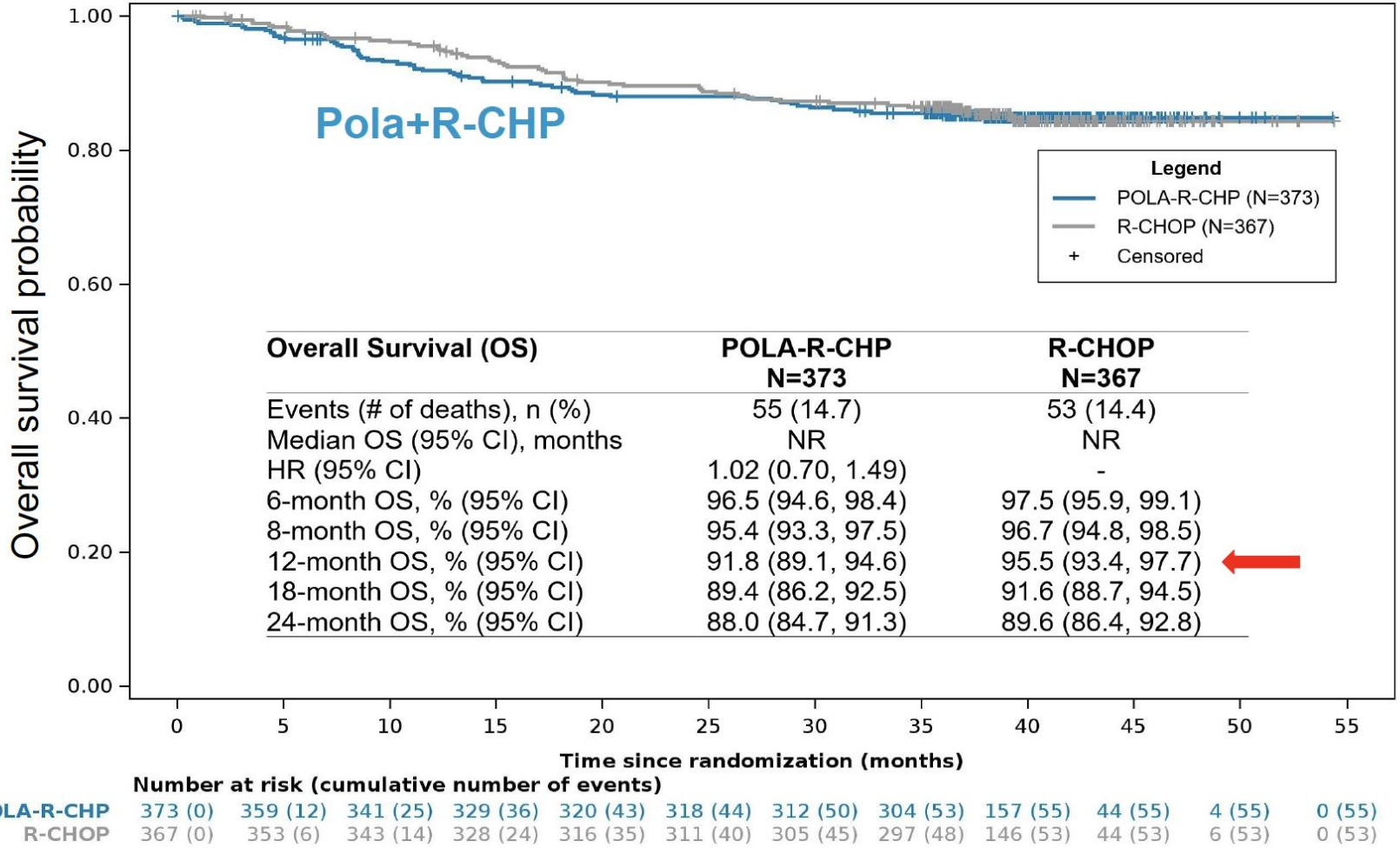




	Pola+R-CHP	R-CHOP
DLBCL NOS (n=740)		
CR rate	76.7%	74.9%
Difference	**1.7%**	
HGBL (n=93)		
CR rate	88.4%	64.0%
Difference	**24.4%**	
Other large B-cell lymphomas (n=46)		
CR rate	79.2%	81.8%
Difference	**-2.7%**	

NHL, non-Hodgkin lymphoma; DH/TH, double-hit/triple-hit
Source: FDA review

Heterogenous outcomes: Overall survival in DLBCL NOS



Overall Survival (OS)	POLA-R-CHP N=373	R-CHOP N=367
Events (# of deaths), n (%)	55 (14.7)	53 (14.4)
Median OS (95% CI), months	NR	NR
HR (95% CI)	1.02 (0.70, 1.49)	-
6-month OS, % (95% CI)	96.5 (94.6, 98.4)	97.5 (95.9, 99.1)
8-month OS, % (95% CI)	95.4 (93.3, 97.5)	96.7 (94.8, 98.5)
12-month OS, % (95% CI)	91.8 (89.1, 94.6)	95.5 (93.4, 97.7)
18-month OS, % (95% CI)	89.4 (86.2, 92.5)	91.6 (88.7, 94.5)
24-month OS, % (95% CI)	88.0 (84.7, 91.3)	89.6 (86.4, 92.8)

NR, not reached
Source: FDA review

ODAC on March 9th

The bar is where it was 20 years ago….but we have 2 backbones to build on…

Christopher S. Coffey, PhD, MS
Professor, Department of Biostatistics; Director, Clinical Trials Statistical & Data Management Center, University of Iowa

Yes, essentially for the reasons that the prior two stated.

Grzegorz (Greg) S. Nowakowski MD
Professor of medicine and oncology; Deputy director for clinical research, Mayo Clinic Comprehensive Cancer Center

> I would like to note, however, that I would consider this regimen to be an option rather than a standard, in a setting of lack of overall survival difference from R-CHOP. I would consider them equivalent, including in ongoing clinical trials. I would not hesitate to randomize patients still to R-CHOP control, because there's no overall survival difference.
>
> – *Grzegorz S. Nowakowski*

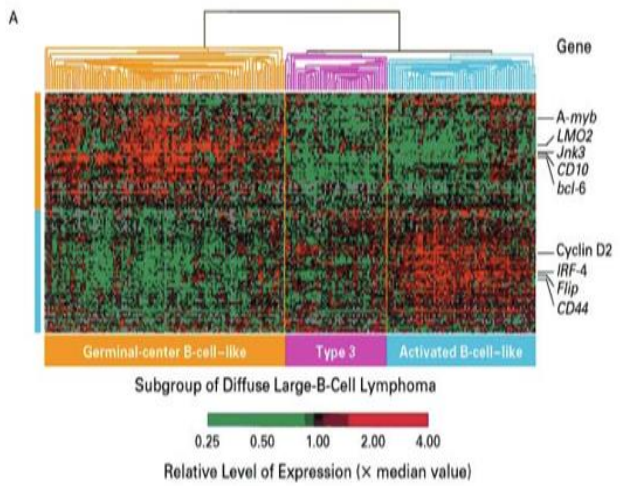
I voted yes, because I do believe that this gain in progression-free survival is clinically meaningful for patients, and also leads to reduction in the need of subsequent therapies, and there was no major toxicity signals, which would be detrimental in this study.

I would like to note, however, that I would consider this regimen to be an option rather than a standard, in a setting of lack of overall survival difference from R-CHOP. I would consider them equivalent, including

Why is RCHOP so difficult to improve on?

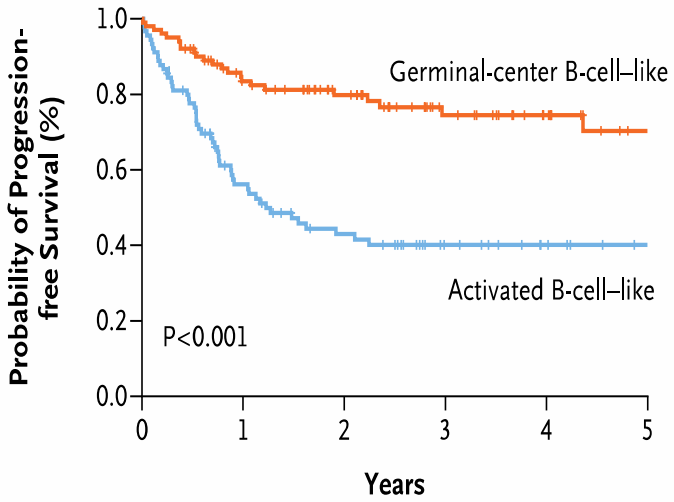
- Too broad population of patients?
  - Too many low risk
  - Too many excluded
- Agents with low efficacy
  - Added one at the time
- Novel endpoints

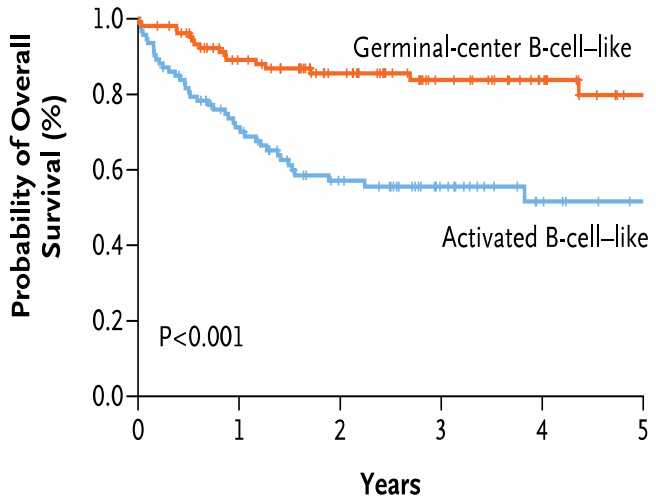
Cell of Origin Subtypes in DLBCL



Two major molecular subtypes:

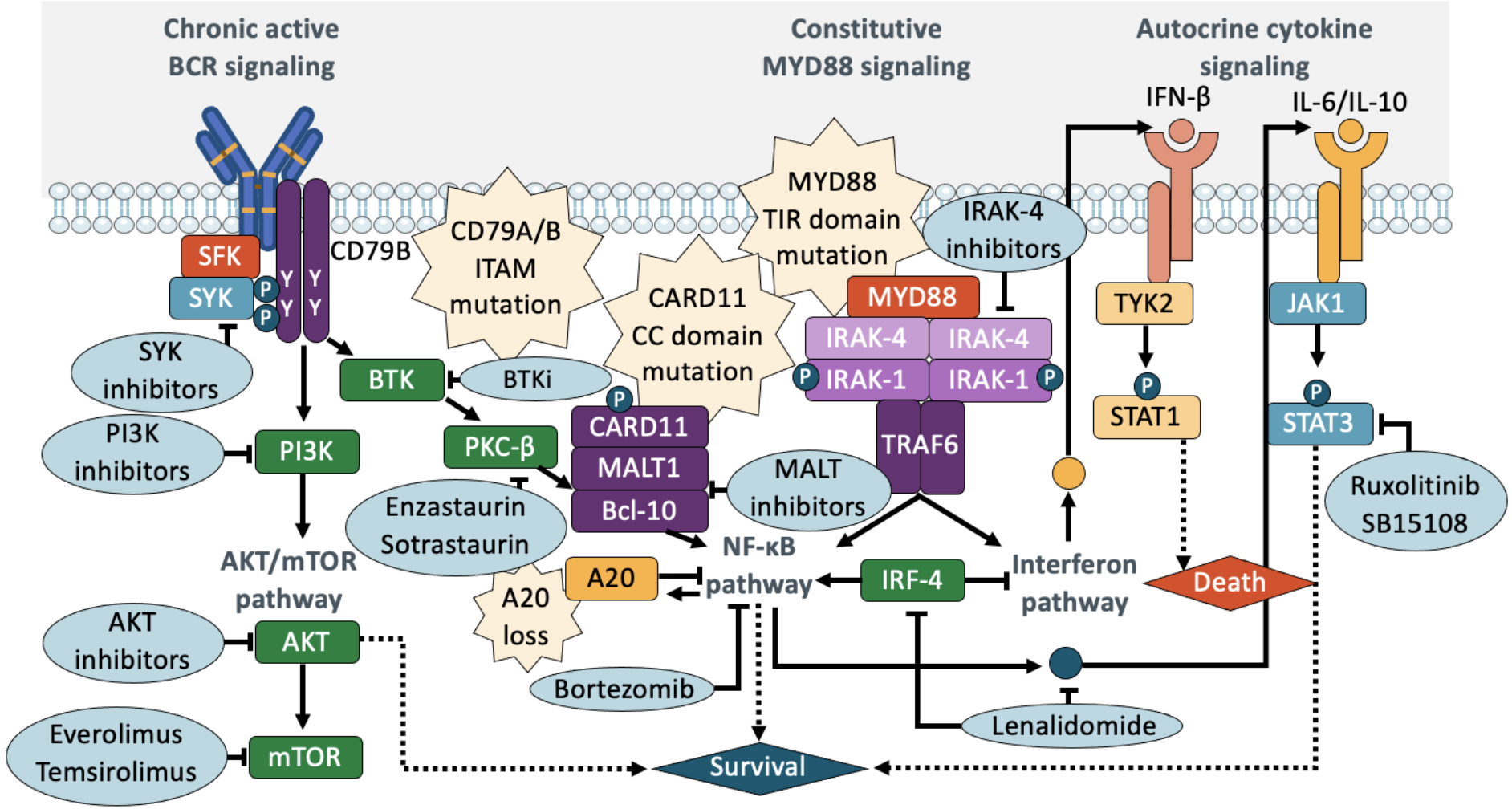
- Activated B-cell like (ABC)
  - B-cell receptor driven
- Germinal center B-cell like (GCB)





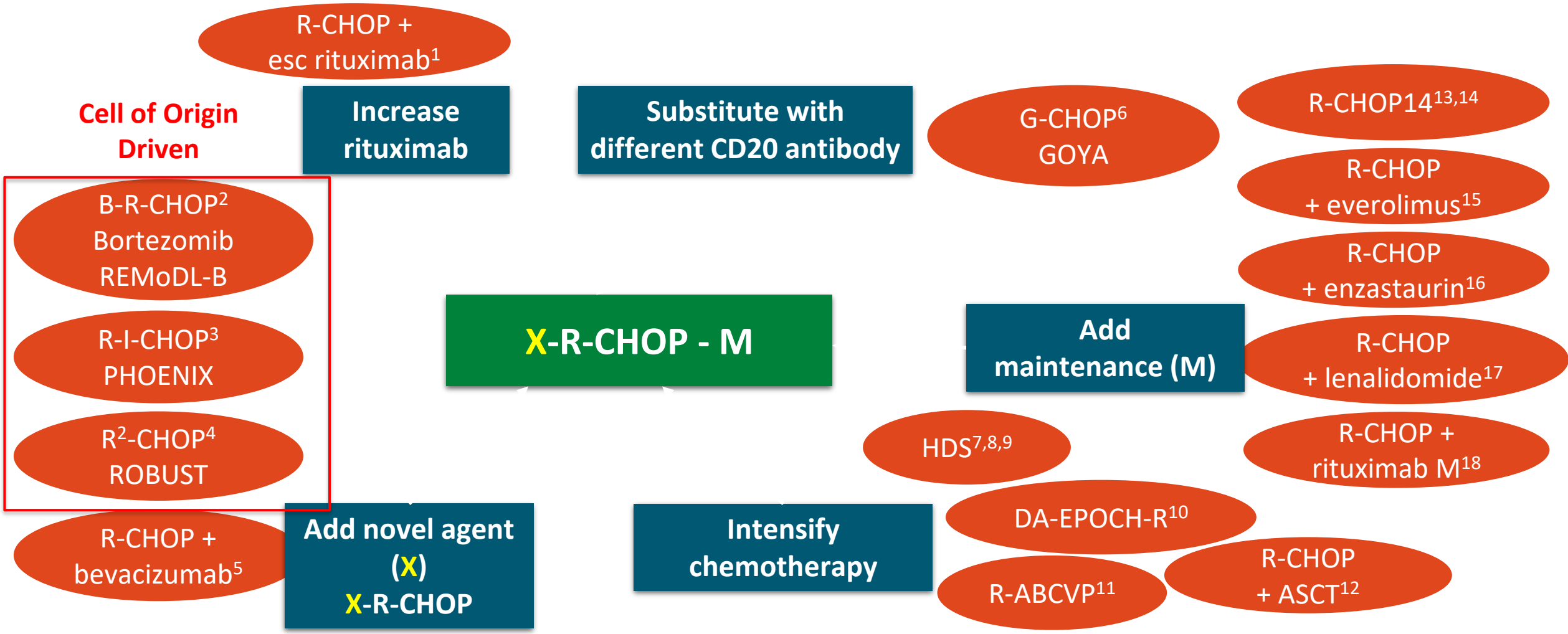
Lenz et al. N Engl J Med 2008;359:2313–2323.

Pathways With Therapeutic Potential in ABC DLBCL



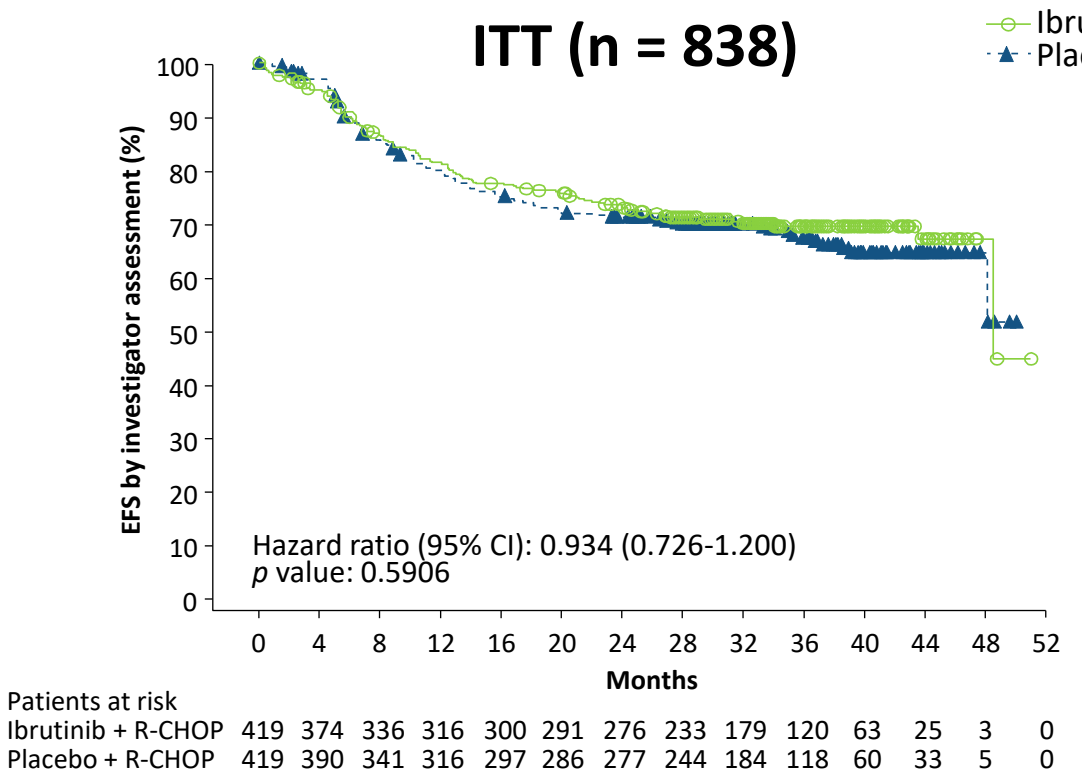
Roschewski. Nat Rev Clin Oncol. 2014;11:12.

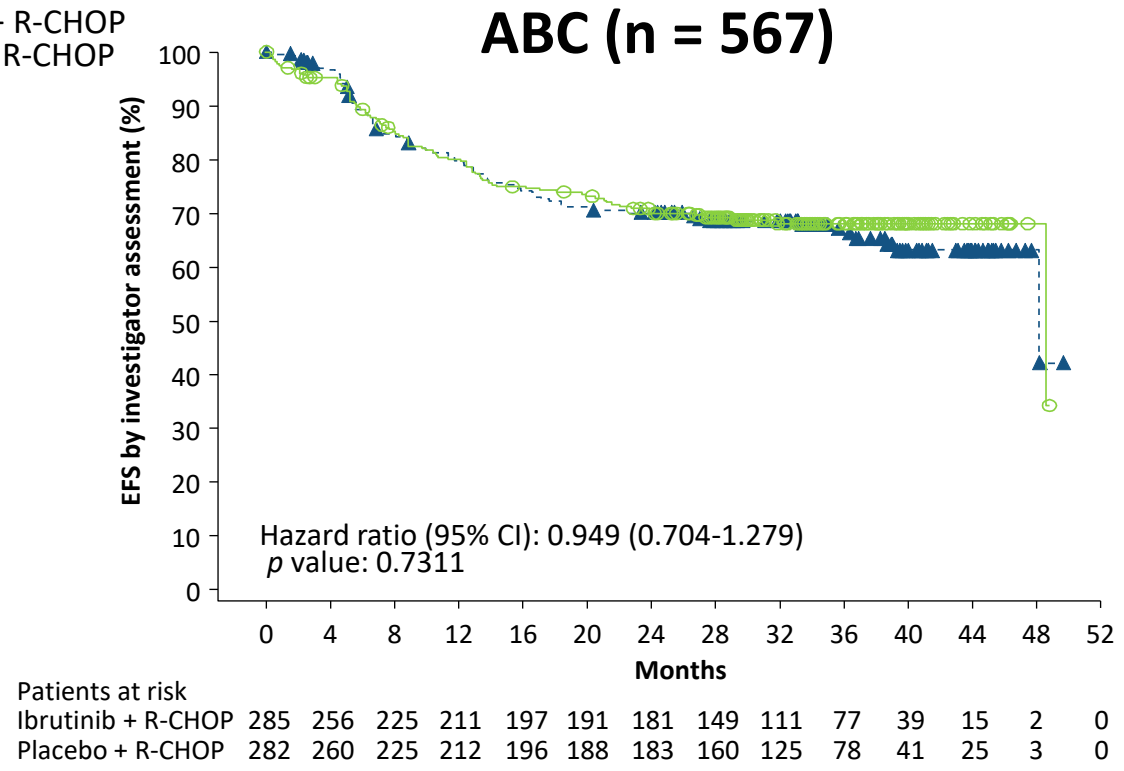
Improving on R-CHOP in DLBCL



1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955.

PHOENIX: R-CHOP +/- Ibrutinib in Newly Diagnosed Non-GCB DLBCL
Phase 3, double-blind, placebo-controlled

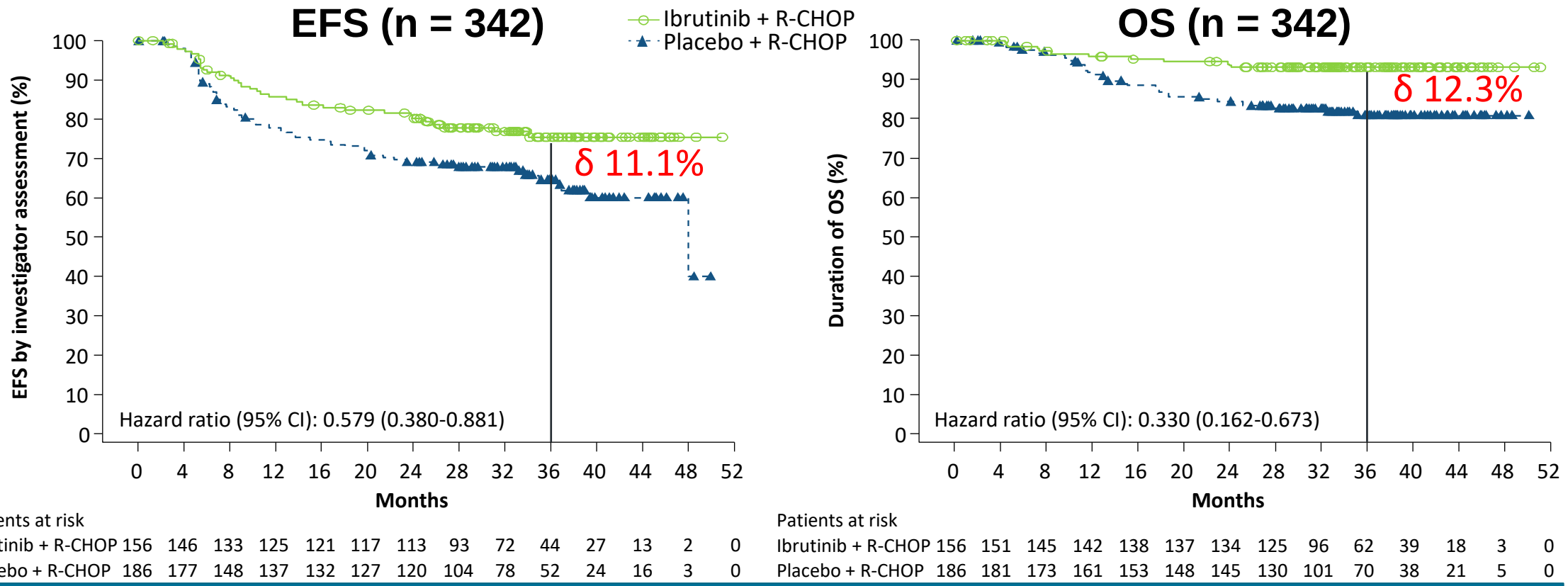




- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

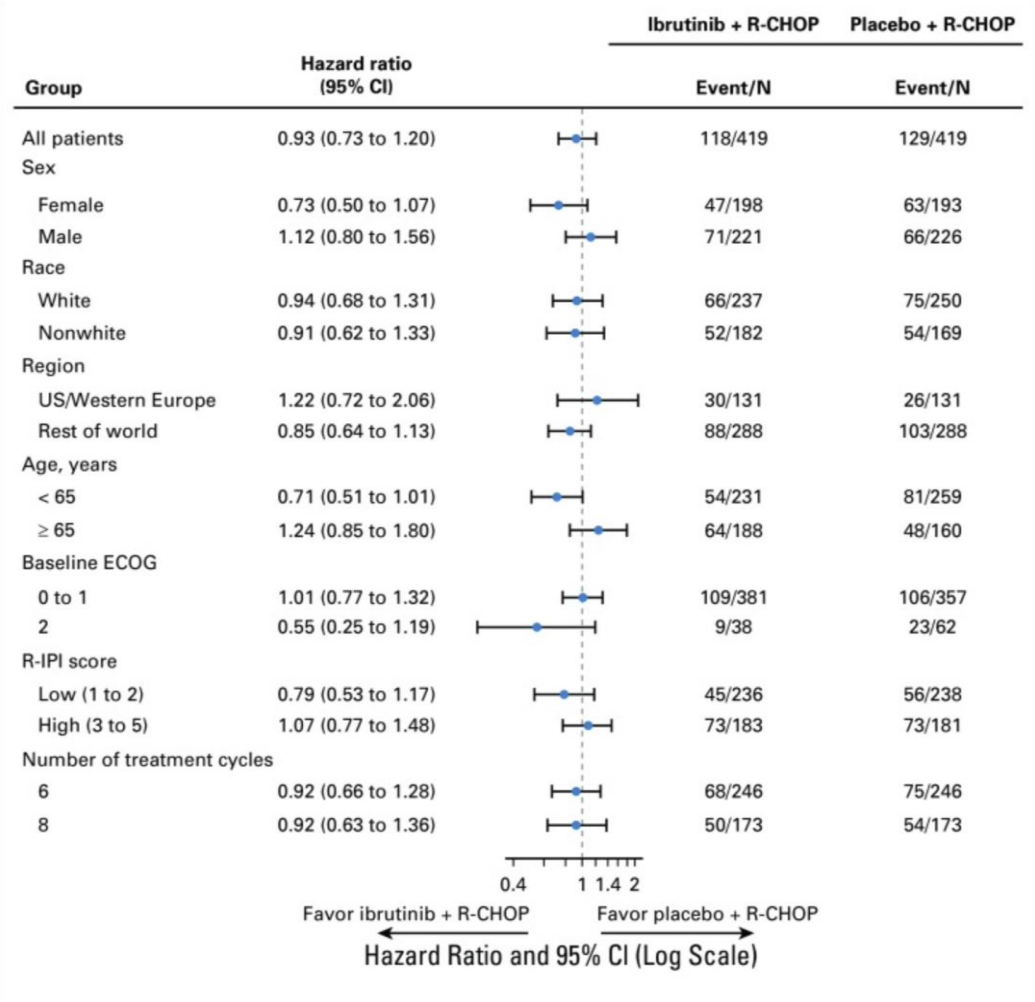
EFS and OS in Patients < 60 Years



- **Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age**
- **Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors**
- **A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS)**
- **More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (25.2% vs 33.5%)**

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

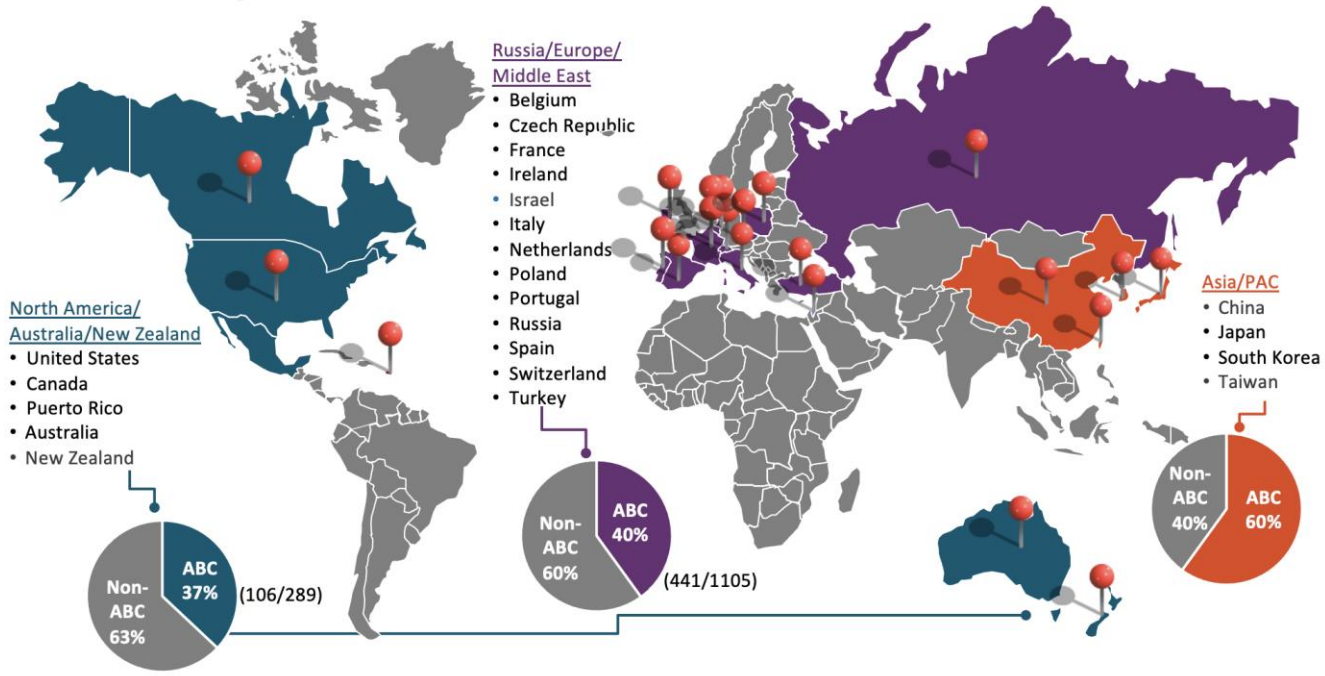
Phoenix trial subgroup analysis



Group	Hazard ratio (95% CI)	Ibrutinib + R-CHOP Event/N	Placebo + R-CHOP Event/N
All patients	0.93 (0.73 to 1.20)	118/419	129/419
Sex			
Female	0.73 (0.50 to 1.07)	47/198	63/193
Male	1.12 (0.80 to 1.56)	71/221	66/226
Race			
White	0.94 (0.68 to 1.31)	66/237	75/250
Nonwhite	0.91 (0.62 to 1.33)	52/182	54/169
Region			
US/Western Europe	1.22 (0.72 to 2.06)	30/131	26/131
Rest of world	0.85 (0.64 to 1.13)	88/288	103/288
Age, years			
< 65	0.71 (0.51 to 1.01)	54/231	81/259
≥ 65	1.24 (0.85 to 1.80)	64/188	48/160
Baseline ECOG			
0 to 1	1.01 (0.77 to 1.32)	109/381	106/357
2	0.55 (0.25 to 1.19)	9/38	23/62
R-IPI score			
Low (1 to 2)	0.79 (0.53 to 1.17)	45/236	56/238
High (3 to 5)	1.07 (0.77 to 1.48)	73/183	73/181
Number of treatment cycles			
6	0.92 (0.66 to 1.28)	68/246	75/246
8	0.92 (0.63 to 1.36)	50/173	54/173

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

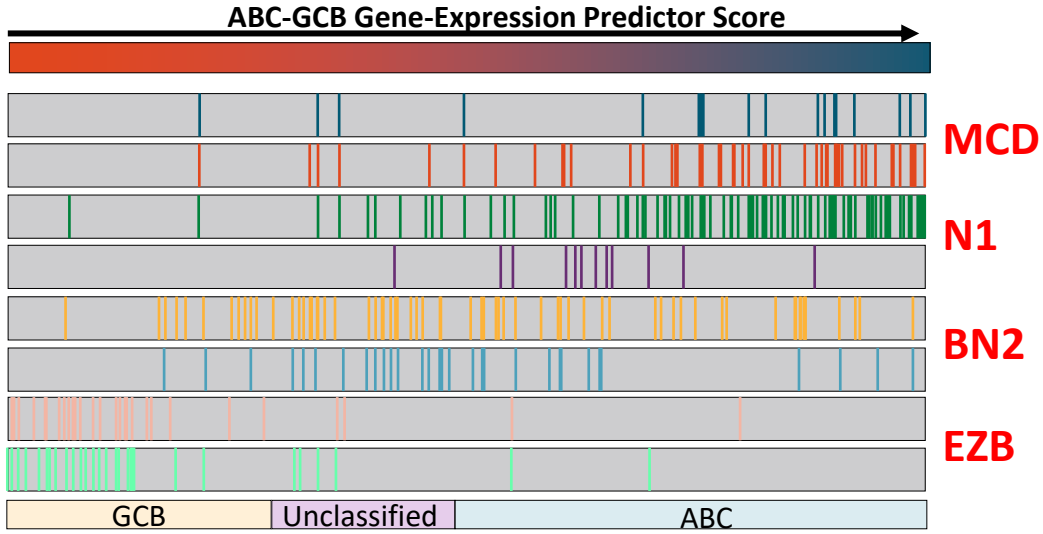
ROBUST Trial: Geographical Distribution of Cell of Origin in DLBCL

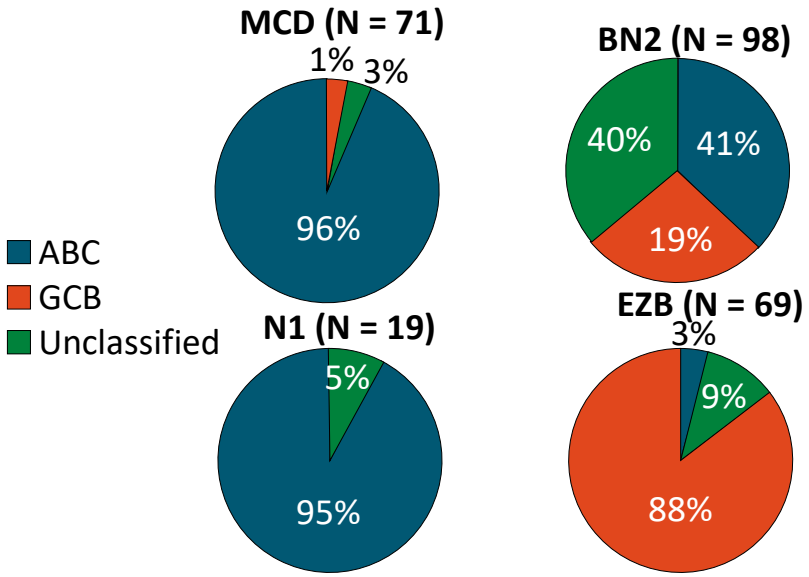


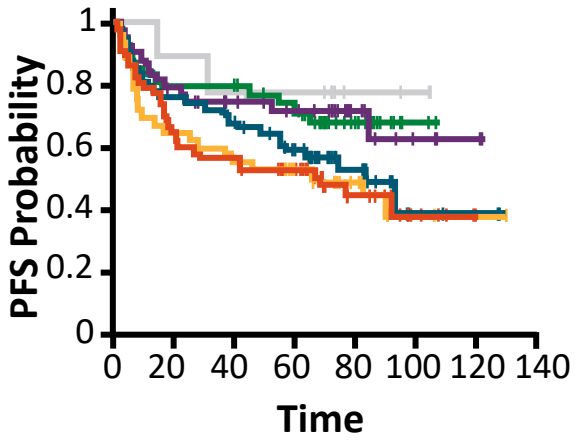
Nowakowski. Haematologica. 2020;105:e72.

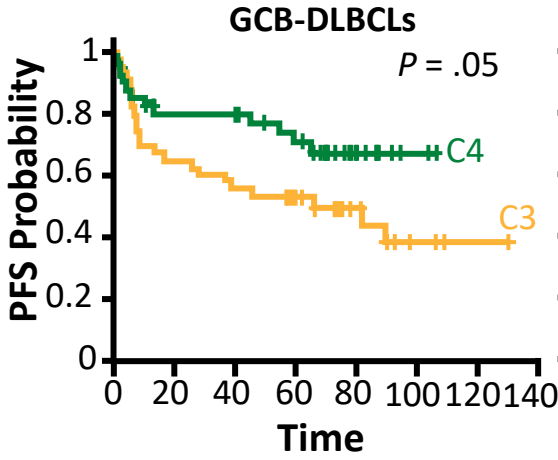
Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

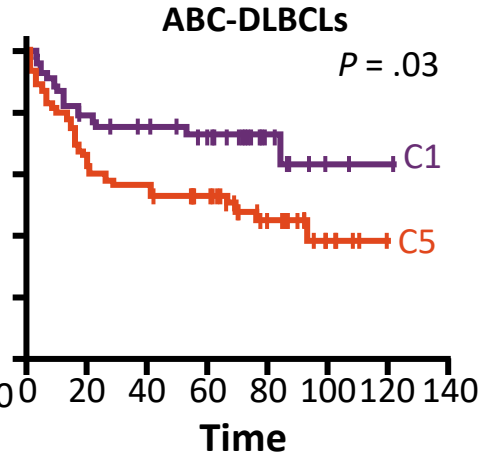
Genetic Feature	Log_{10} *P* Value	GCB	Unclass-ified	ABC
		Prevalence (%)		
CD79B+MYD88^{L265P} Double mutation	-6.4	0.6	1.7	11.5
CD79B mutation	-13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	-17.0	1.2	7.8	28.8
NOTCH1 mutation	-3.8	0.0	0.9	6.1
BCL6 fusion	-4.1	11.6	33.0	18.6
NOTCH2 mutation	-5.3	3.0	20.0	6.4
BCL2 translocation	-20.4	28.0	5.2	0.7
EZH2 mutation	-12.1	22.0	5.2	1.7









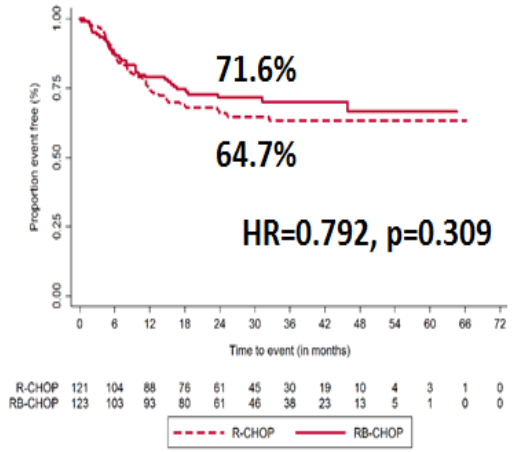


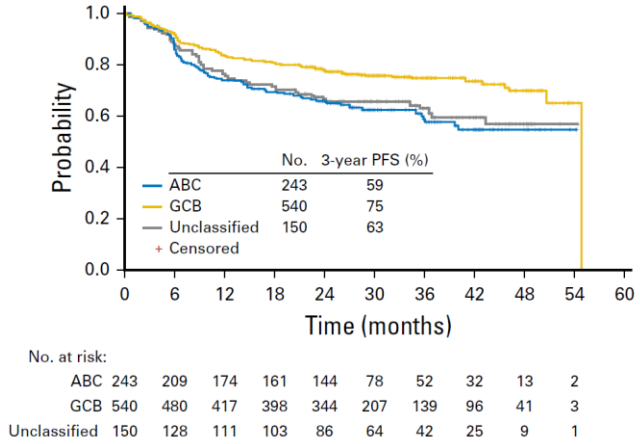
Chapuy. Nat Med. 2018;24:679. Schmitz. NEJM. 2018;378:1396.

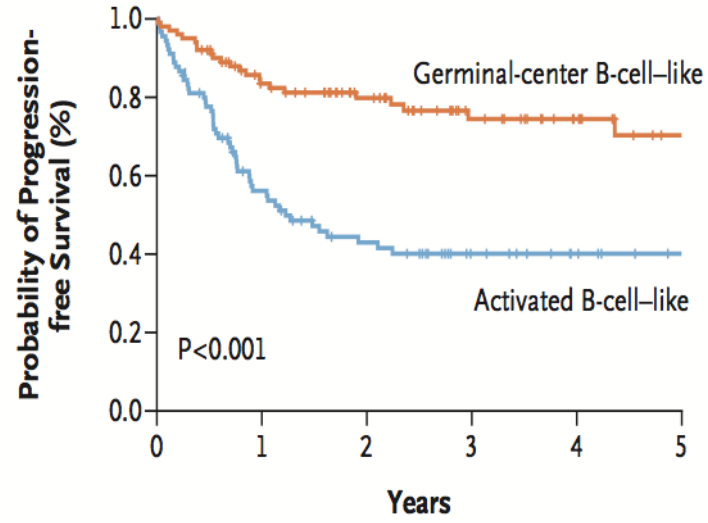
BTK inhibitors plus RCHOP approaches

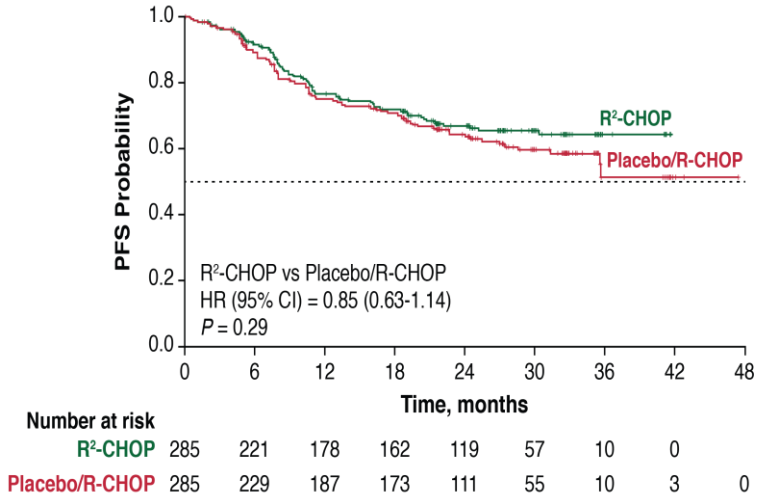
- **Younger patients**
  - Phase 3 study**, <65 (now 70) yo, non-GCB** : Acalabrutinib (A)R-CHOP vs RCHOP (Escalade)
- **Deeper molecular profiling**
  - Phase 3 Orlelabrutinib plus RCHOP vs RCHOP in **MCD subtype** of DLBCL (Belive 01) (NCT05234684)
- **3rd generation BTKs all commers or non-GCB**
  - Zanubrutinib plus CIT (RCHOP, DAEPOCHR)
  - Orlelabutinib plus CIT (RCHOP, DAEPOCHR)
  - ECOG is planning multi arm molecularly driven study one of them BTK inh

Outcomes of Patients in CT Are Better



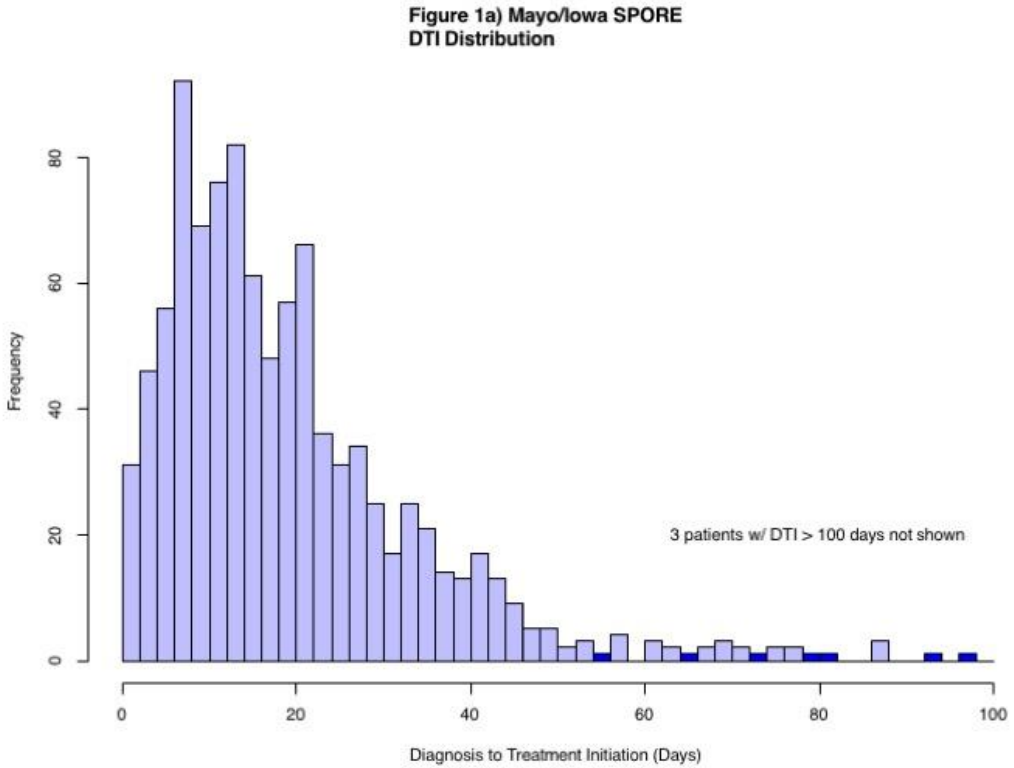


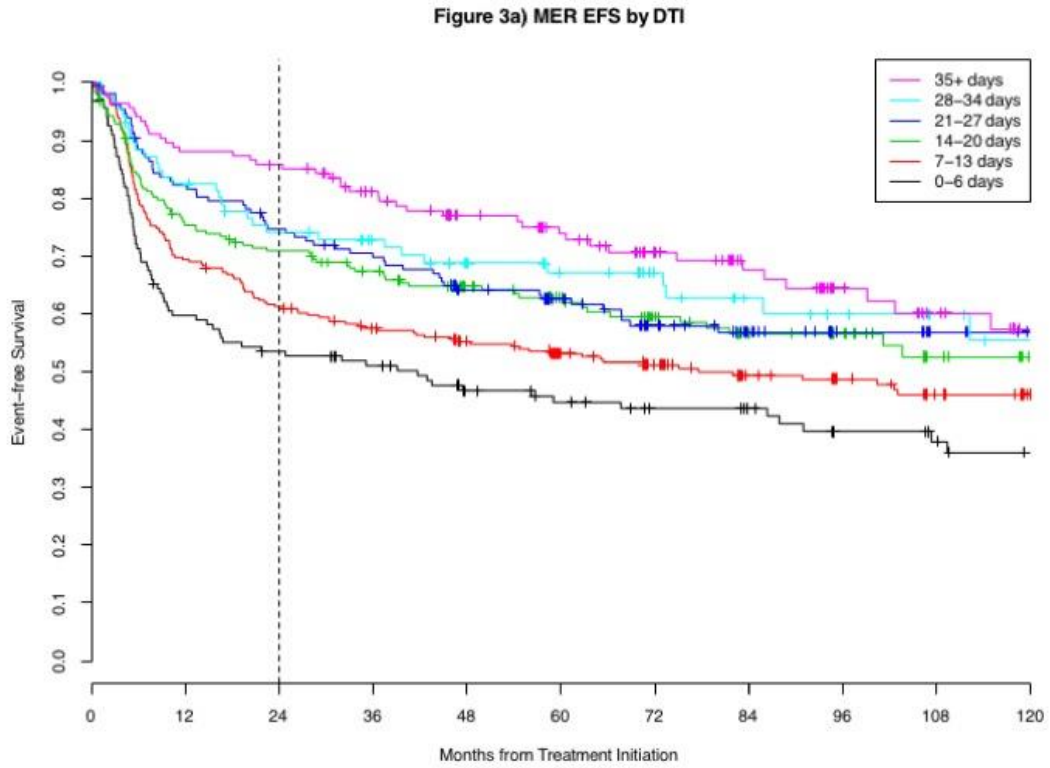




Davies AJ, et al. ICML 2017. Abstract 121. Updated data presented at ICML;
Vitolo U, et al. J Clin Oncol. 2017 Nov 1;35(31):3529-3537;
Nowakowski et al. J Clin Oncol 2021 Apr 20;39(12):1317-1328
Lenz et al. N Engl J Med 2008;359:2313–2323

Time from Diagnosis to Therapy and Outcome in DLBCL

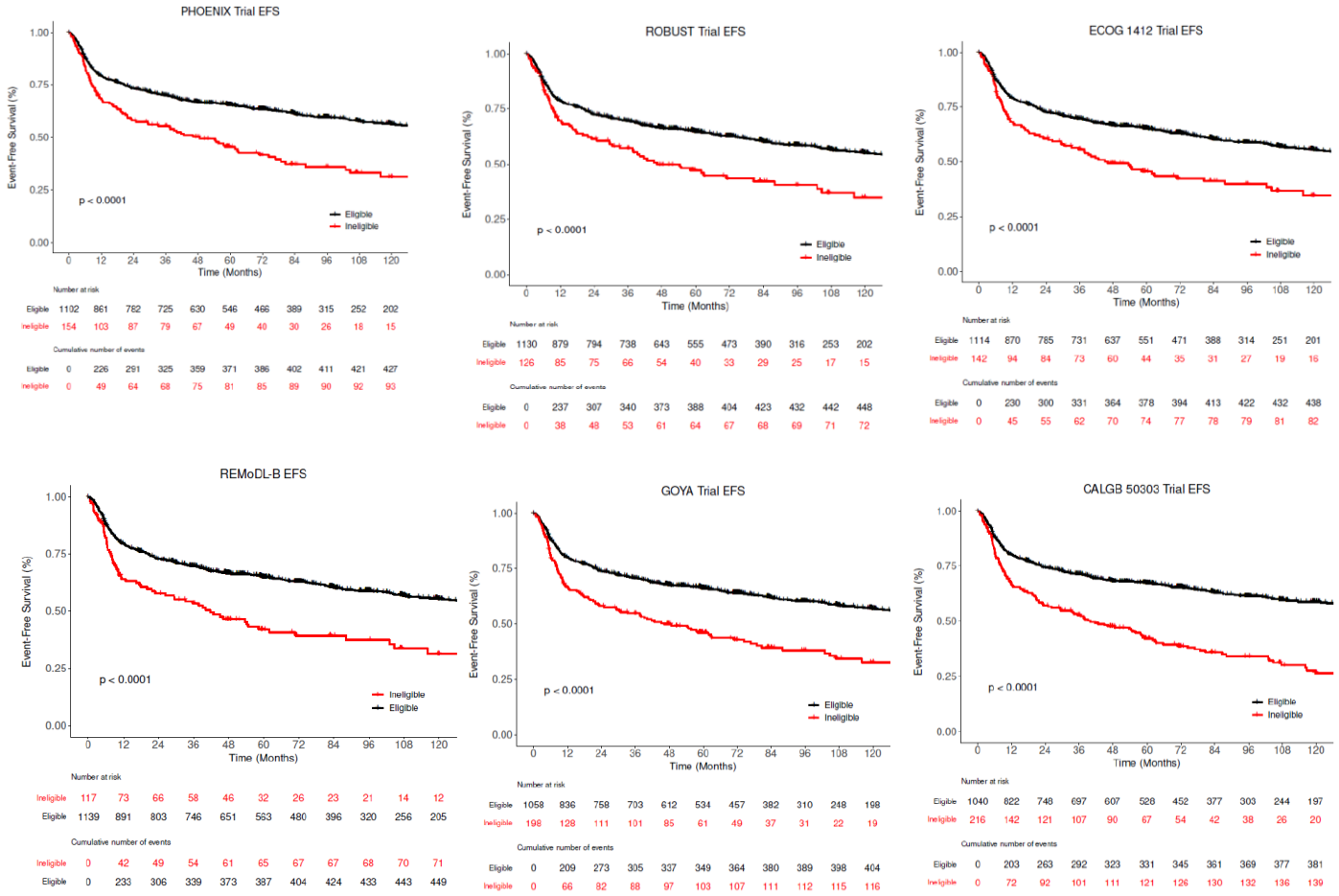




Maurer & Nowakowski J Clin Oncol. 2018 Jun 1;36(16):1603-1610.

Who is left behind – eligibility criteria to clinical trials

PARAMETER	PHOENIX	ROBUST	ECOG1412	REMoDL-B	GOYA	ENGINE	CALGB 50303
Total	**12.3%**	**10.0%**	**11.3%**	**9.2%**	**15.9%**	**24.1%**	**17.2%**
ANC	1.3%	2.5%	2.5%	1.3%	2.5%	2.5%	1.3%
Platelets	3.2%	3.2%	4.7%	4.7%	3.2%	3.2%	4.7%
Hepatic	3.8%	3.8%	3.8%	1.5%	3.8%	3.8%	3.2%
Renal	5.2%	2.0%	2.0%	2.0%	5.2%	10.5%	10.5%
Hemoglobin	0.0%	1.3%	0.0%	0.0%	6.3%	12.7%	0.0%



9.2-24.1% patients would be excluded from trials

Khurana A, JCO 2021

Adding more active agents or 2 or more agents at the time

Bispecific

CART

Tafa/len

Lonca

Len

BTKi

Pola

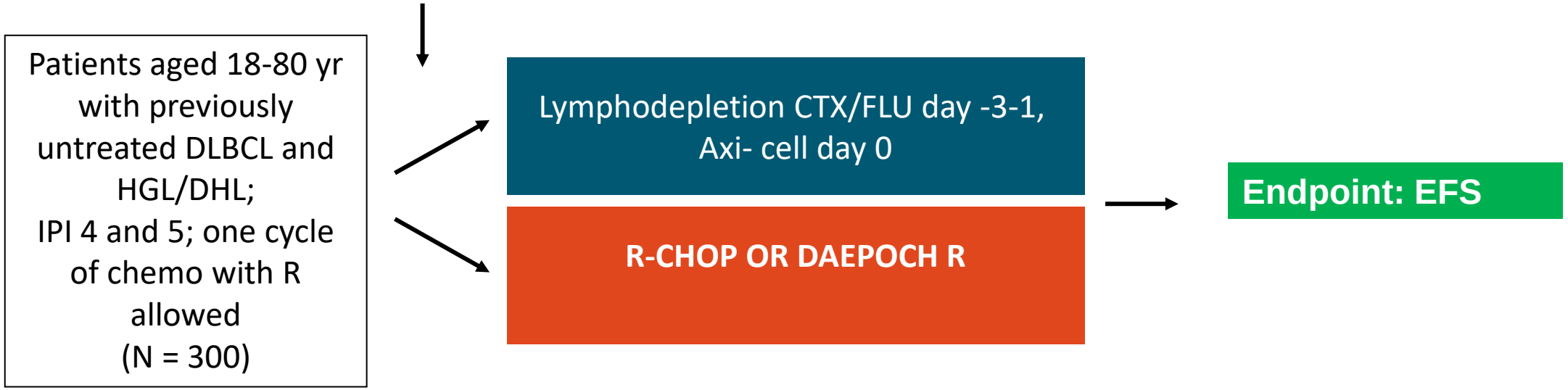
Beva

Enza

Bort

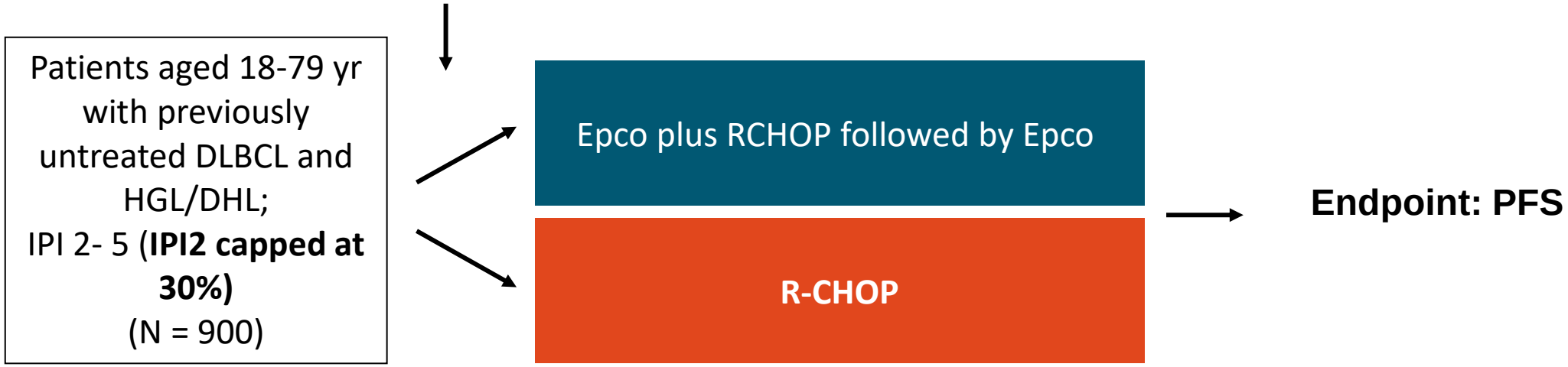
Evero

Axicabtagene Ciloleucel vs CIT as First-line Treatment in Participants With High-risk Large B-cell Lymphoma (ZUMA-23)



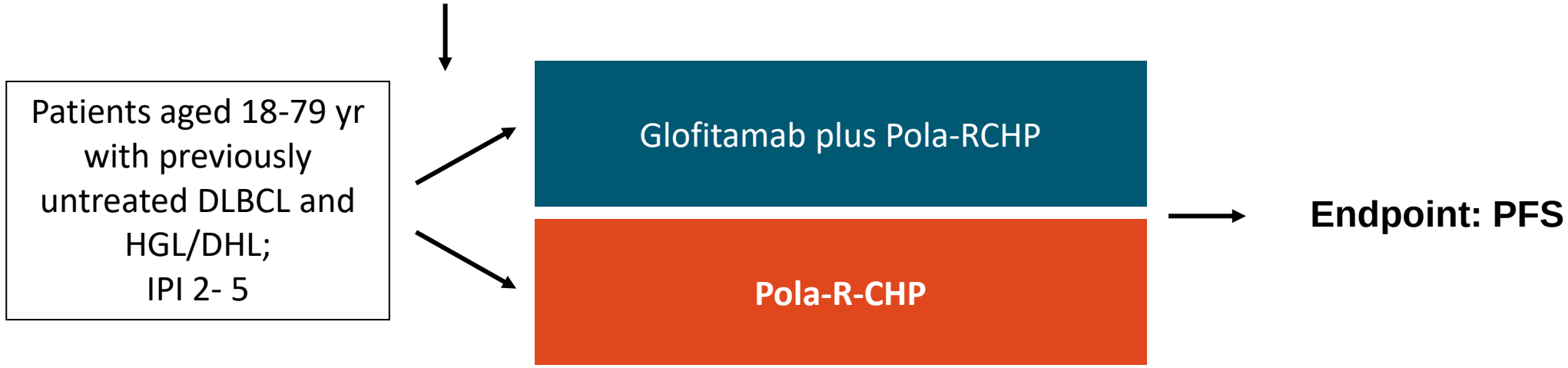
NCT05605899

Epcoritamab in Combination With R-CHOP vs R-CHOP in Newly Diagnosed DLBCL



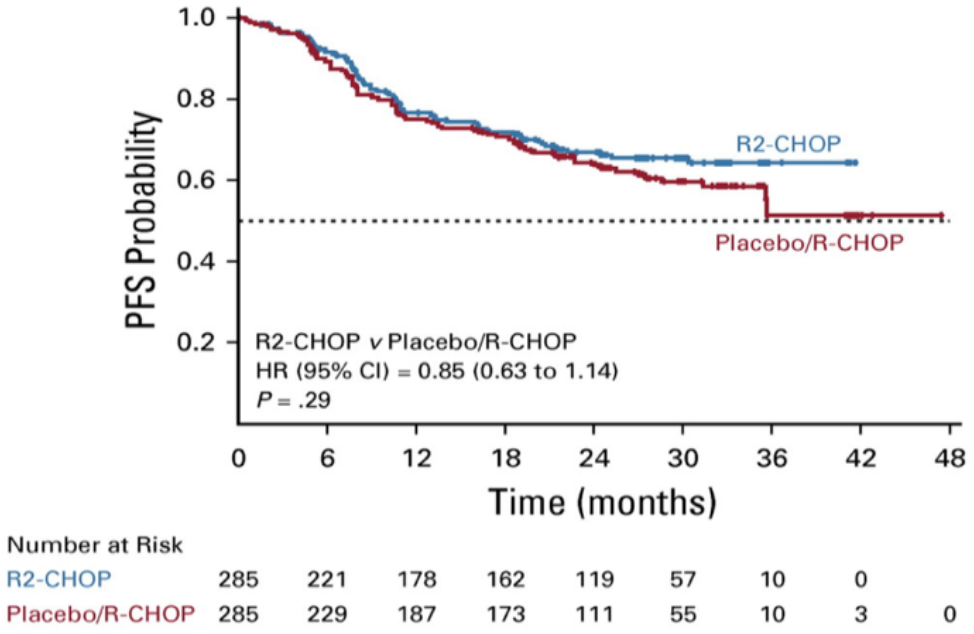
NCT05578976

Glofitamab R-CHP vs Pola-R-CHP in Newly Diagnosed DLBCL

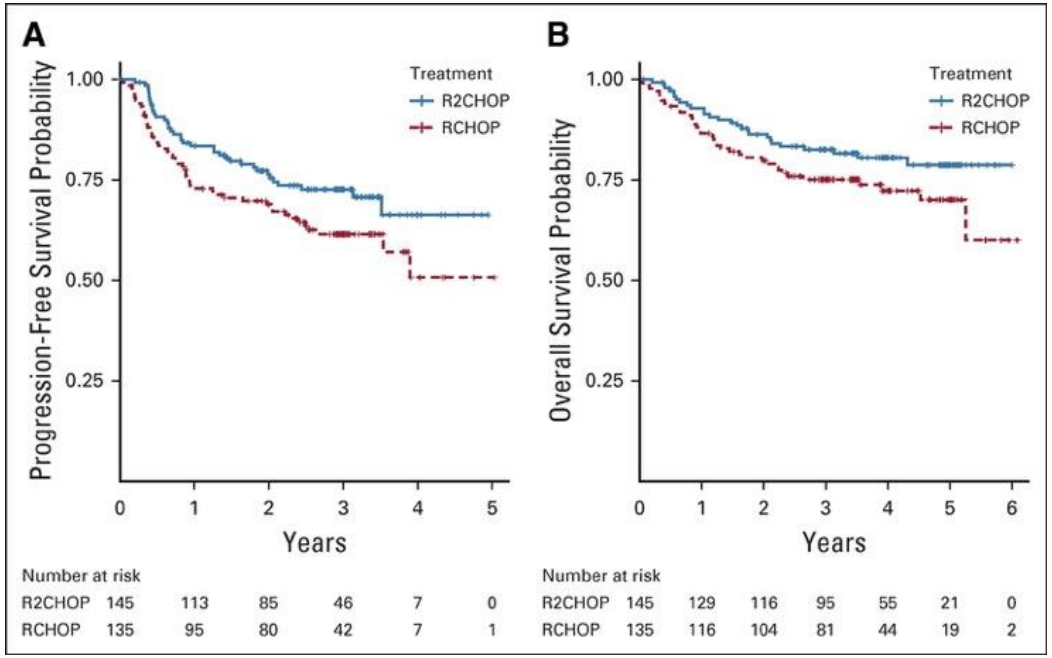


Results of Randomized Studies of Lenalidomide Plus RCHOP (R2CHOP) vs. RCHOP

Robust



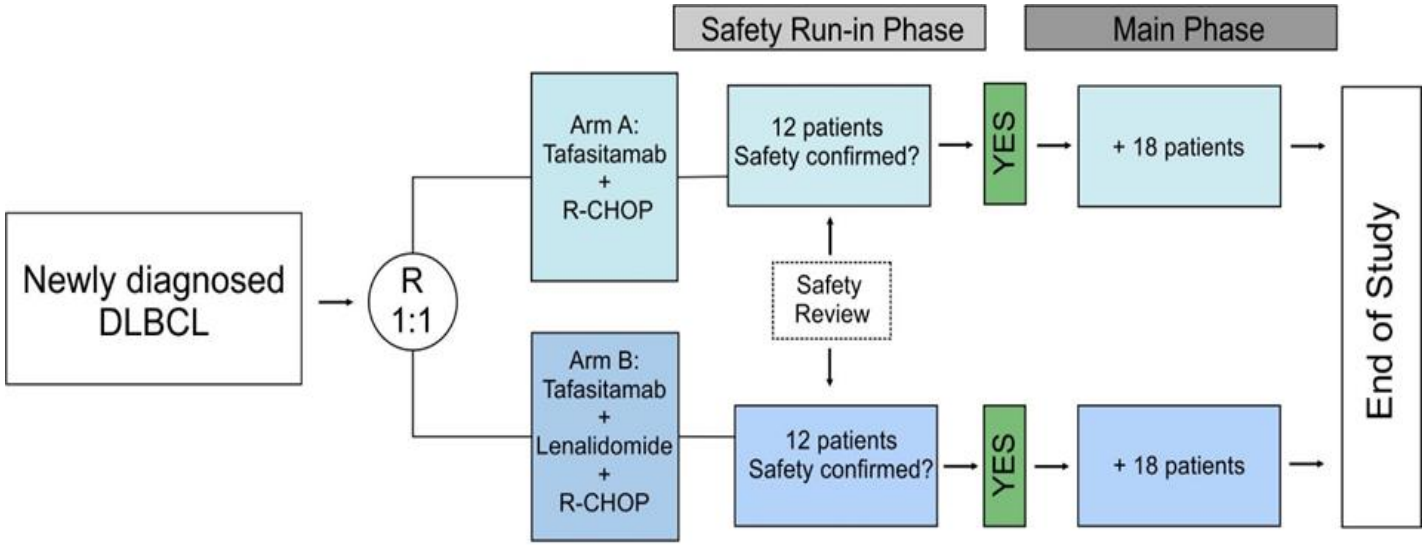
E1412



Nowakowski GS et al. *J Clin Oncol.* 2021Feb23;JCO2001366.

Nowakowski GS et al. *J Clin Oncol*. 2021 Feb 8:JCO2001375

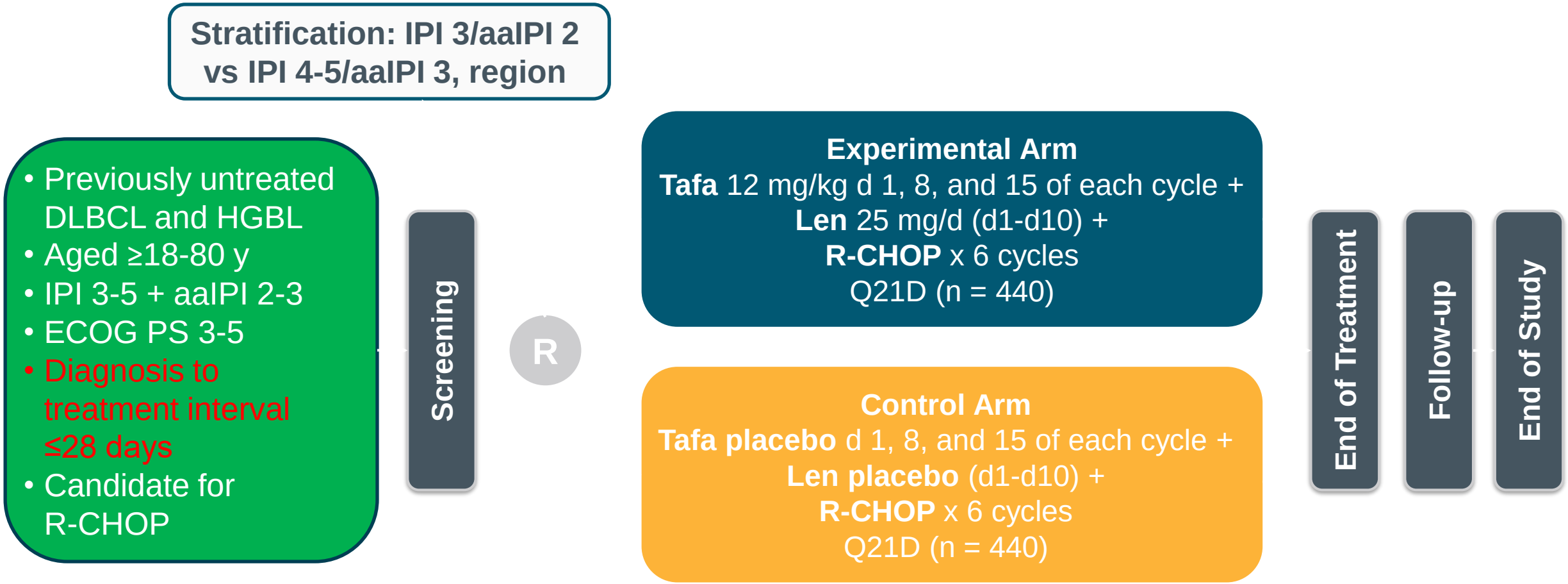
First-MIND Trial – RCHOP/R2CHOP (E1412 Dose) Plus Tafasitamab



- Neutropenia and thrombocytopenia more common in arm B but no increase in neutropenic fever/infections
- Discontinuations due to AEs rare and not different average relative dose intensity of R-CHOP
- ORR at EOT was 75.8% (arm a) vs 81.8% (arm B)

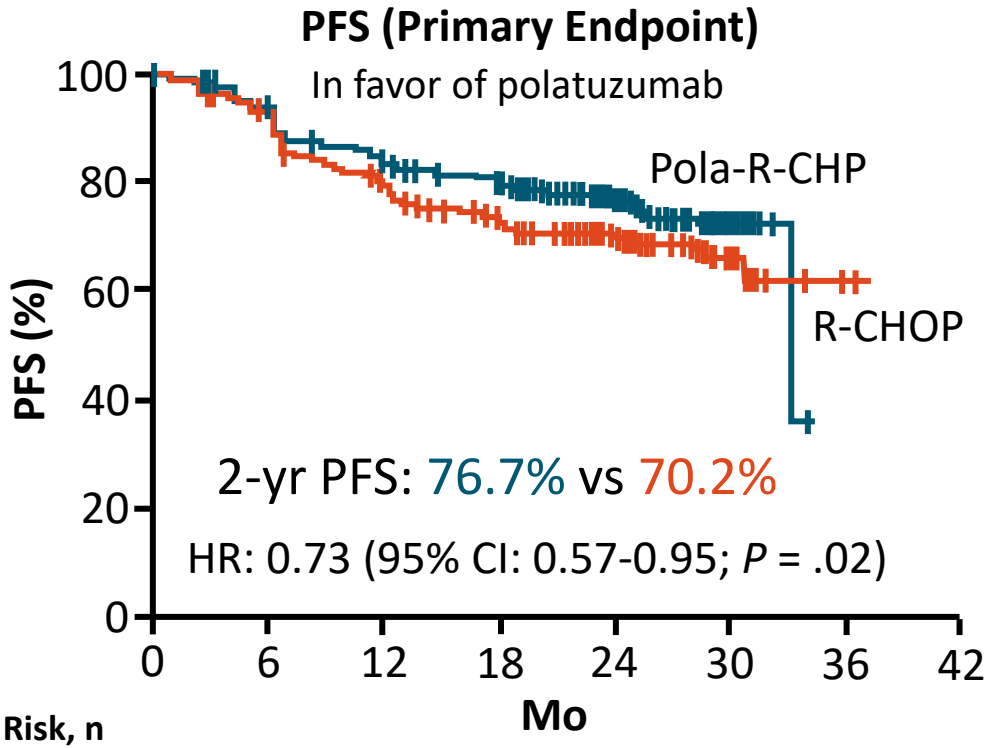
Figure 1: Grade ≥3 TEAEs by system organ class and toxicity grade

Front-MIND Newly Diagnosed DLBCL



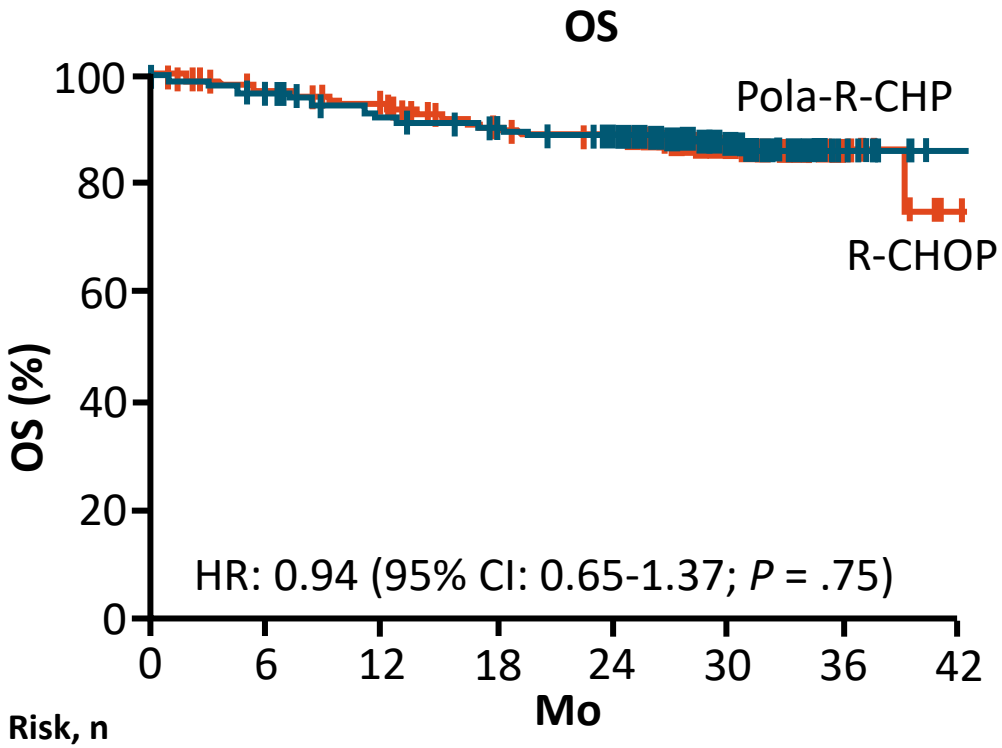
NCT04824092

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP



Patients at Risk, n

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE



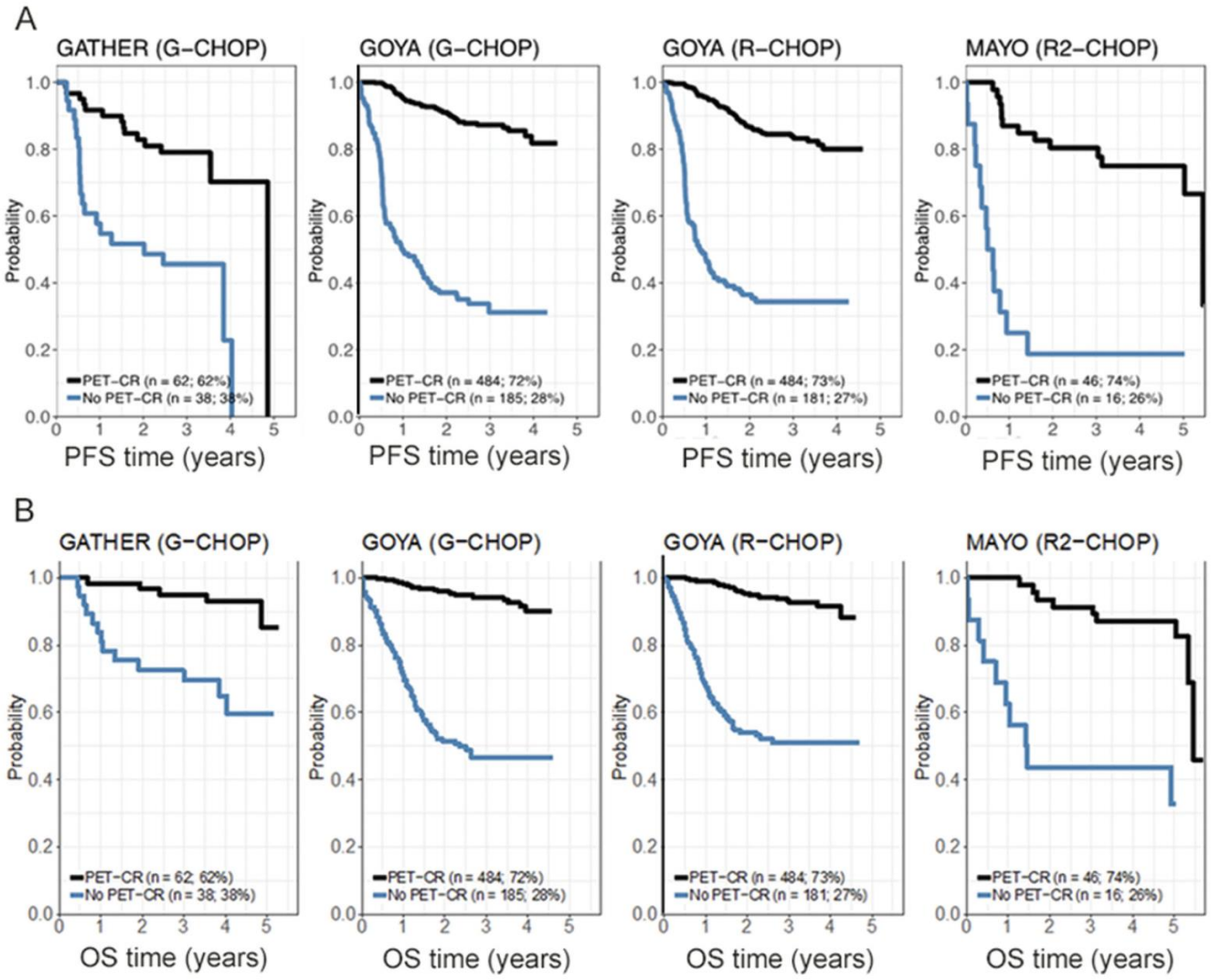
Patients at Risk, n

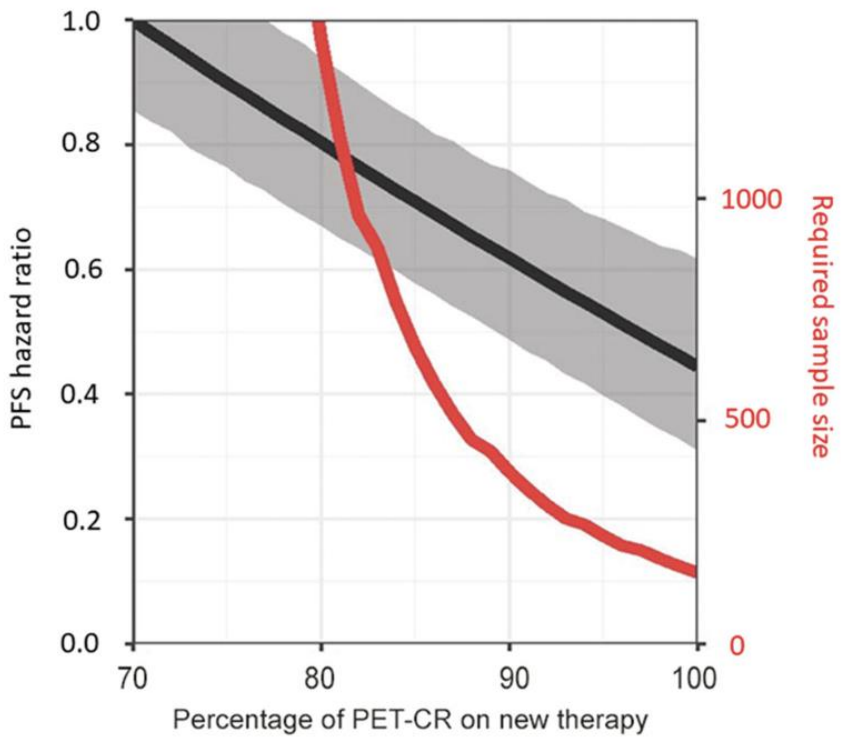
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	2

- Best overall response rate: **95.9 %** vs **94.1%**
  - Complete response rate: **86.6%** vs **82.7%**

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

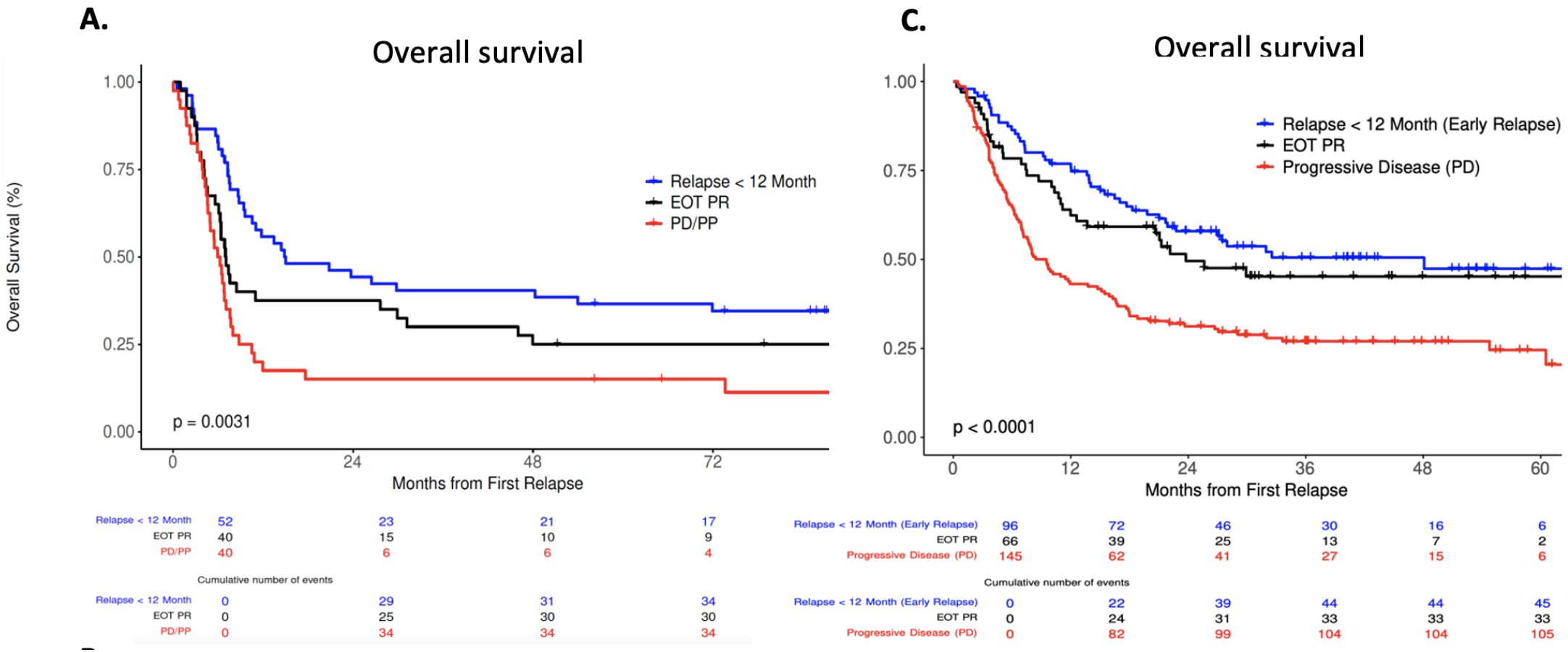
PET CR as Surrogate of PFS and OS





LEUKEMIA & LYMPHOMA 2022, VOL. 63, NO. 12, 2816–2831

Impact of disease progression on survival

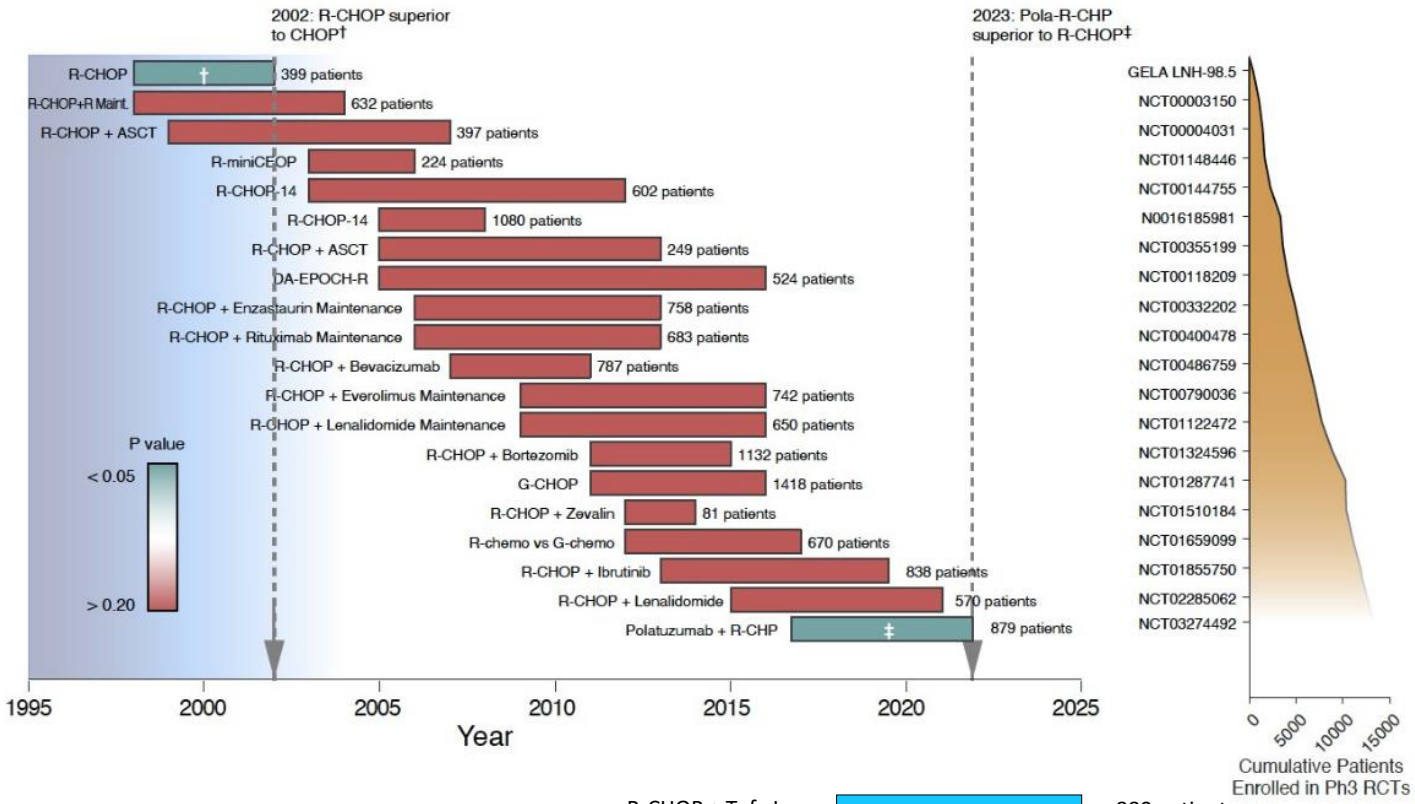


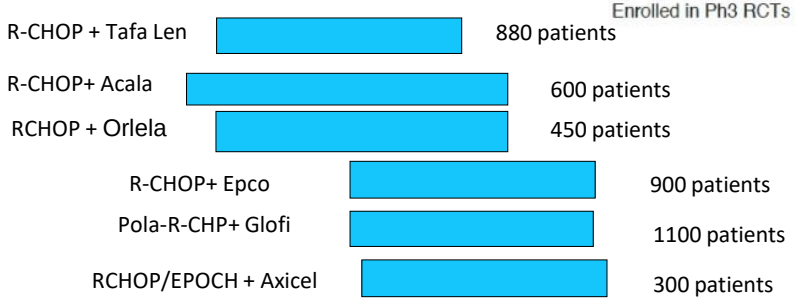
Khurana et al , ASH 2022

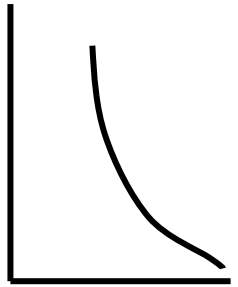
Summary

- RCHOP remains a standard for majority of patients with DLBCL
- New option - polatuzumab vedotin plus R-CHP associated with PFS benefit but not OS
- There is a need to improve on RCHOP or PV-R-CHP
  - Need studies capturing patients “left behind”

Beyond RCHOP







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