3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

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How Do I Treat High Risk DLBCL in the Frontline?

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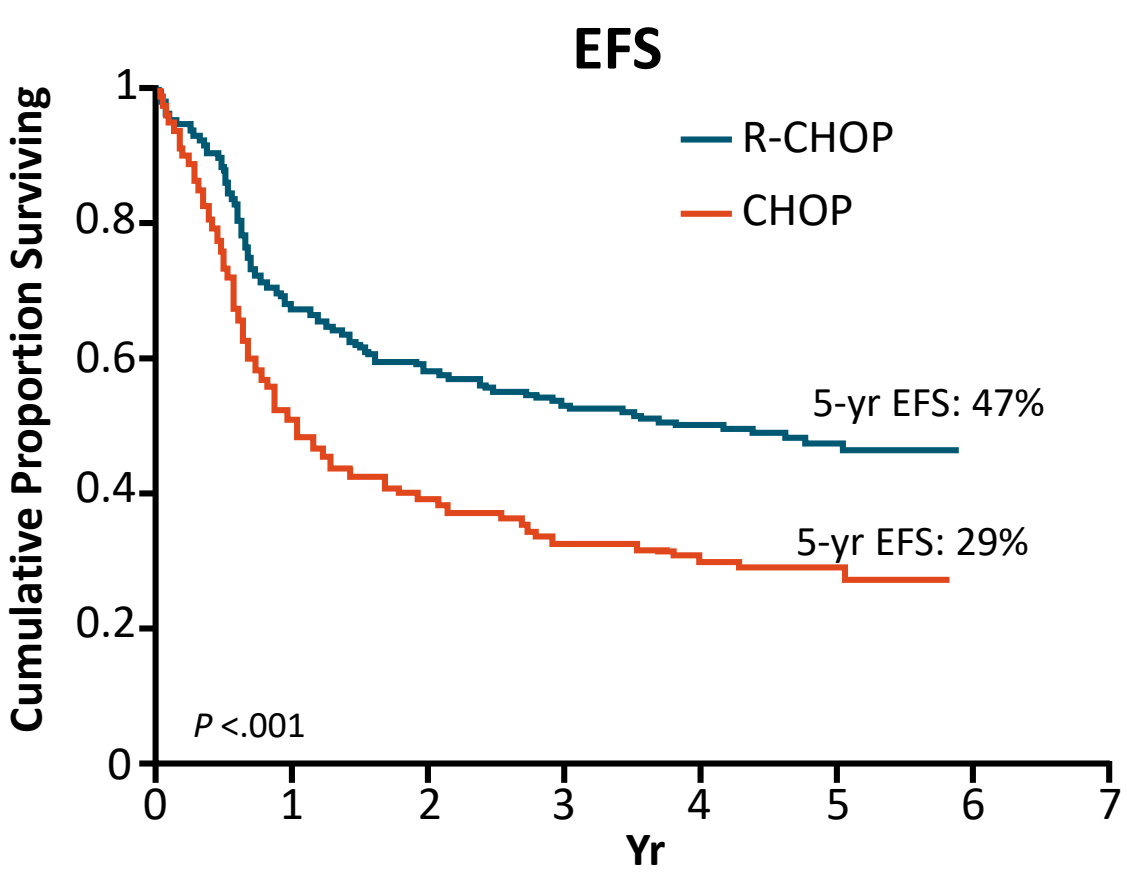
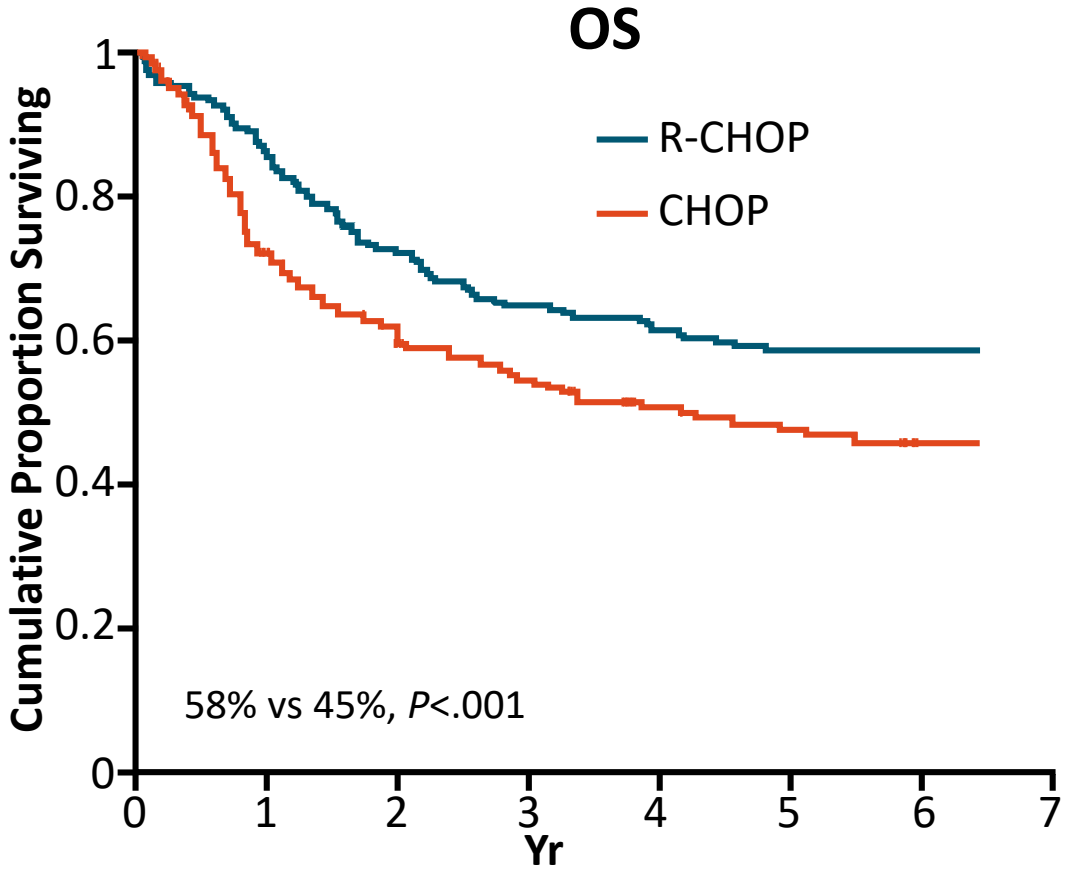
Speaker	Disclosures
Grzegorz S. Nowakowski, MD	**Employment: None** **Consultancy:** AbbVie, ADC Therapeutics, Bantam Pharmaceutical LLC, Blueprint Medicines, Bristol-Myers Squibb, Celgene Corporation, Curis, Debiopharm, F Hoffmann-La Roche Limited, Fate Therapeutics, Genentech, Incyte, Karyopharm Therapeutics, Kite Pharma, Kymera Therapeutics, MEI Pharma, MorphoSys AG, Ryvu Therapeutics, Seagen, Selvita Inc, TG Therapeutics, and Zai Lab Limited **Equity Ownership: None** **Research Funding:** Bristol-Myers Squibb, MporphoSys, **Honoraria: None** **Patents & Royalties: None** **Speakers Bureau: None** **Membership on an entity's Board of Directors or advisory committees:** MorphoSys, Karyopharm Therapeutics, Ryvu Therapeutics, Fate Therapeutics, Bristol-Myers Squibb

R-CHOP Has Been the Standard Initial Therapy for DLBCL for >20 Yr

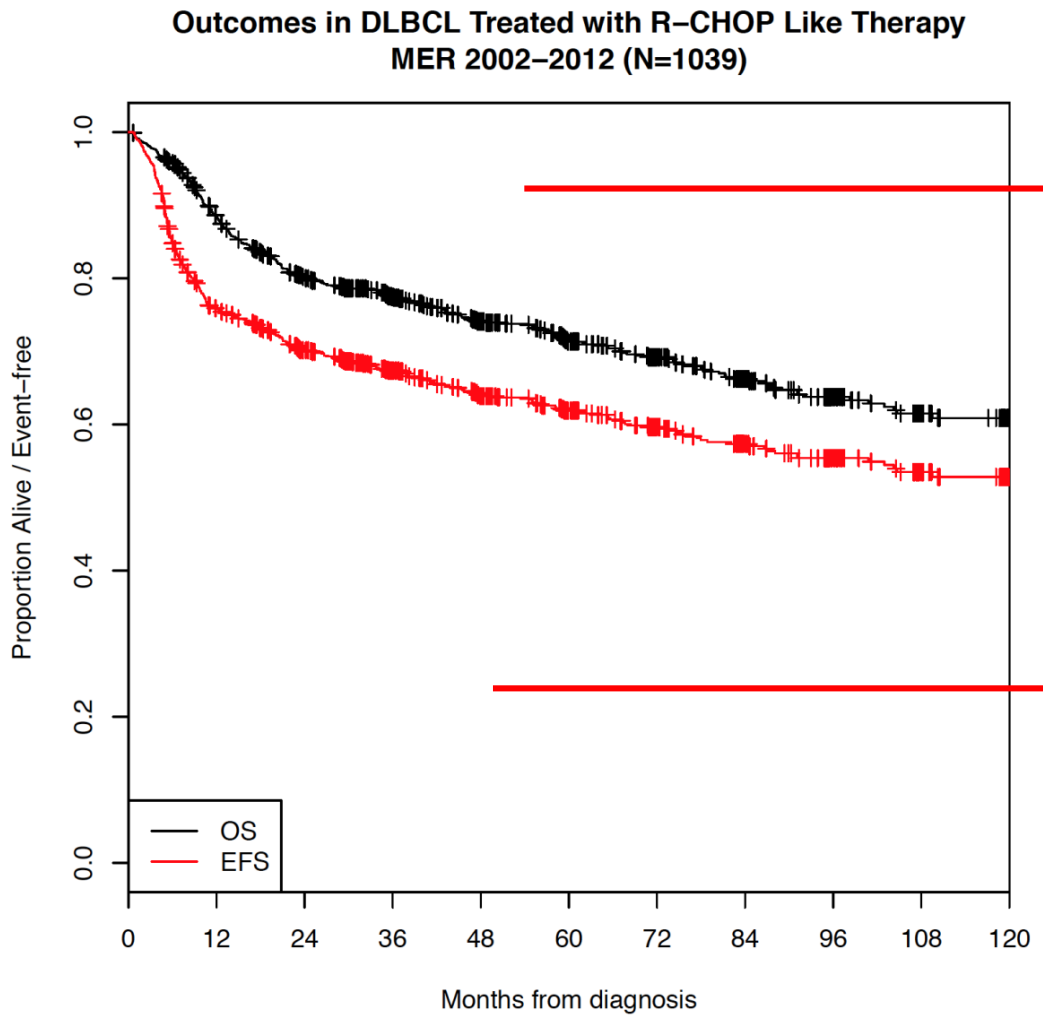
- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL





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

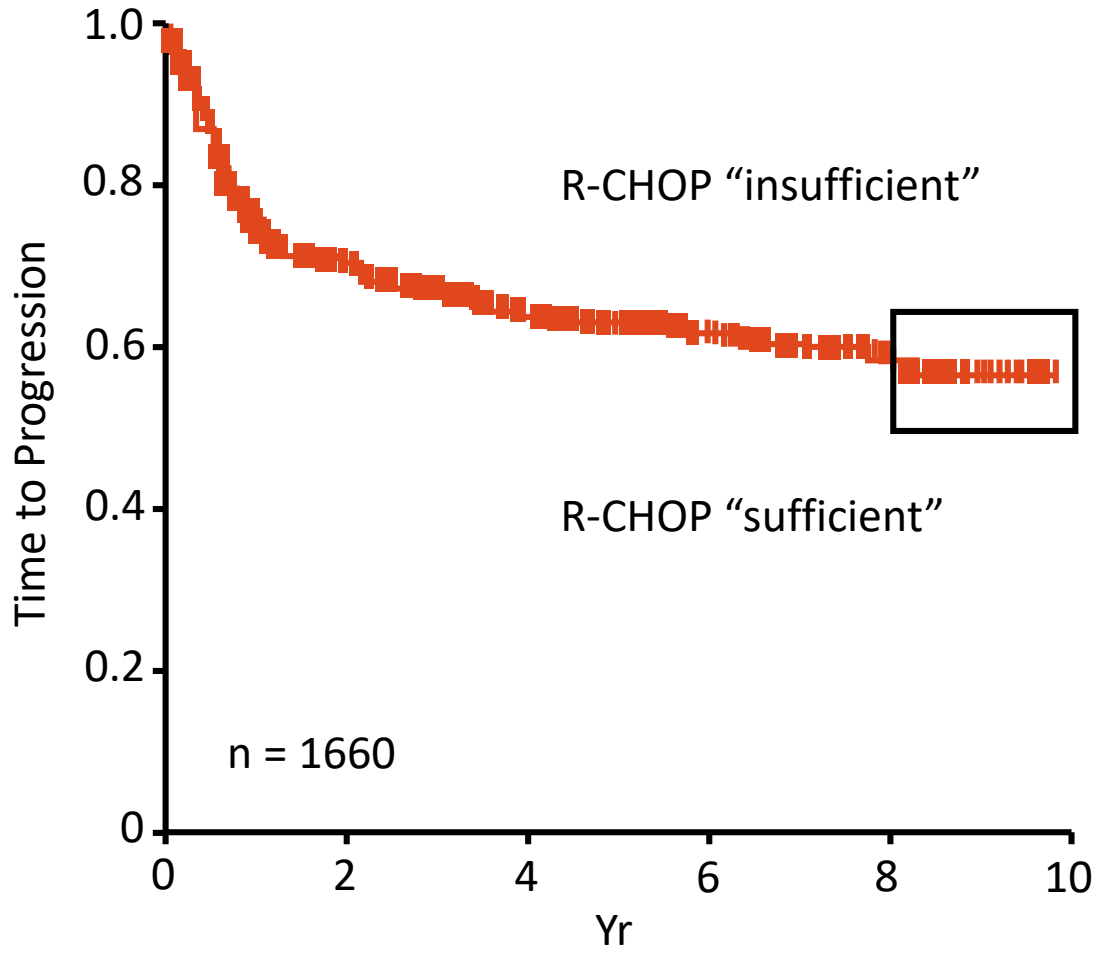
DLBCL Outcomes in Mayo Clinic Lymphoma SPORE Database



Failing RCHOP

Cured with RCHOP

Heterogeneity of Outcomes in Patients With DLBCL Receiving R-CHOP



Differences in clinical outcomes are driven by clinical and biological heterogeneity

Sehn. Blood. 2015;125:22.

Prognostic Factors in Newly Diagnosed DLBCL

Clinical

- IPI, R-IPI, and aaIPI
- Disease bulk/metabolic tumor volume
- Time from diagnosis to therapy
- Metabolic tumor heterogenicity

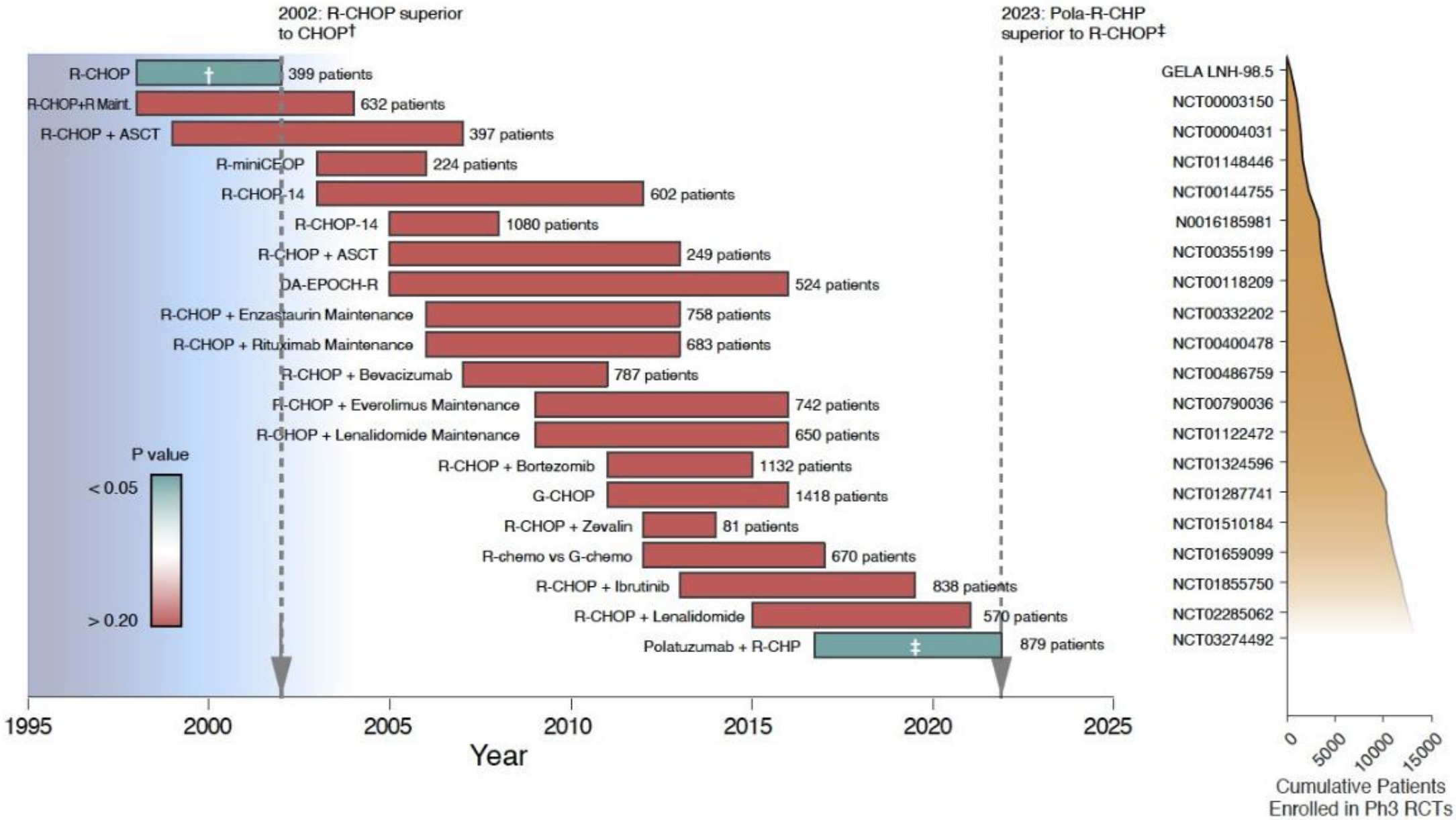
Response Based

- End of therapy PET CR
- Interim PET (PET2 or PET 3)
- MRD

Molecular

- Cell of origin
- Translocations in *MYC*, *BCL2*/*BCL6*
- *BCL2* and *MYC* expression
- Molecular clusters (aided by somatic mutation analysis)

Chapuy. Nat Med. 2018;24:679. Kubuschok. Cancer Treat Res. 2015;165:271. Vaidya. Ann Oncol. 2014;25:2124.

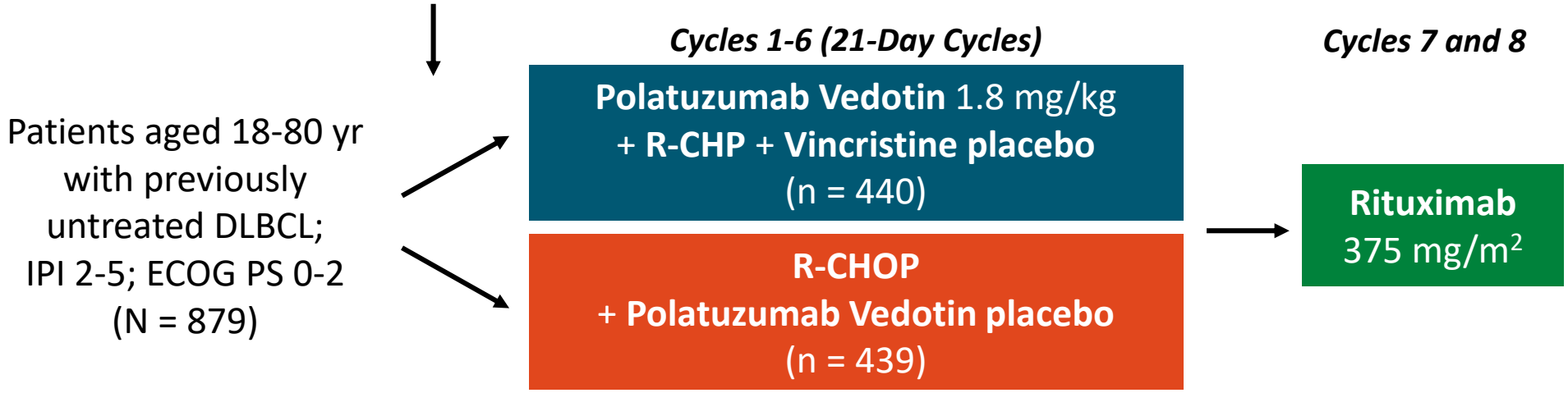


Alizadeh and Kurtz; Twitter/X

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)

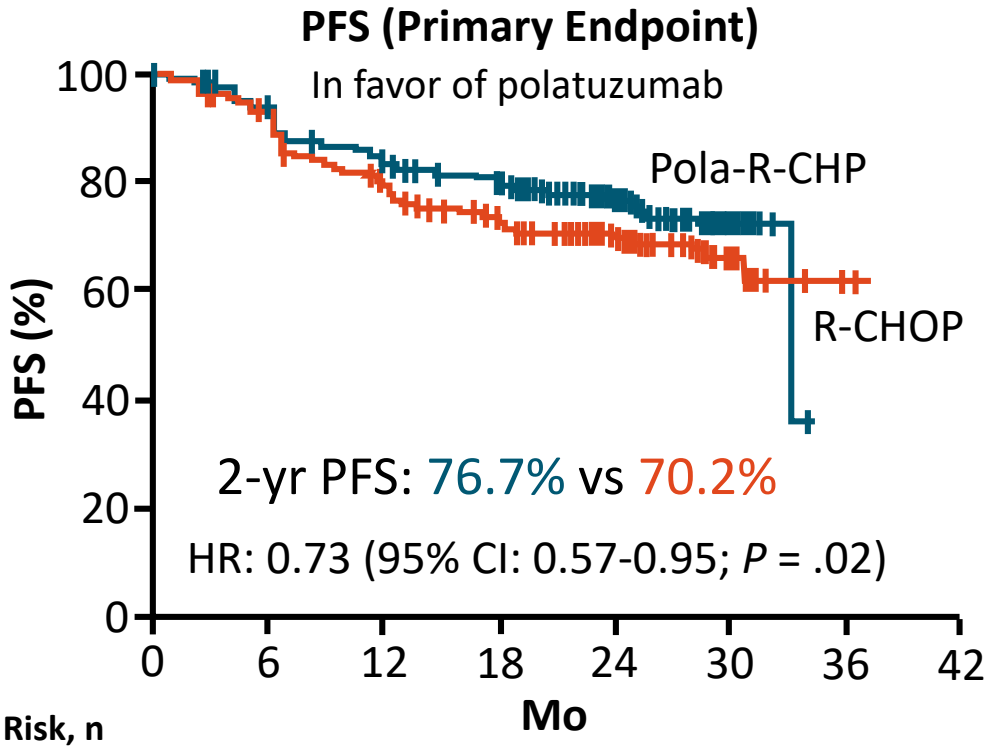


R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

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

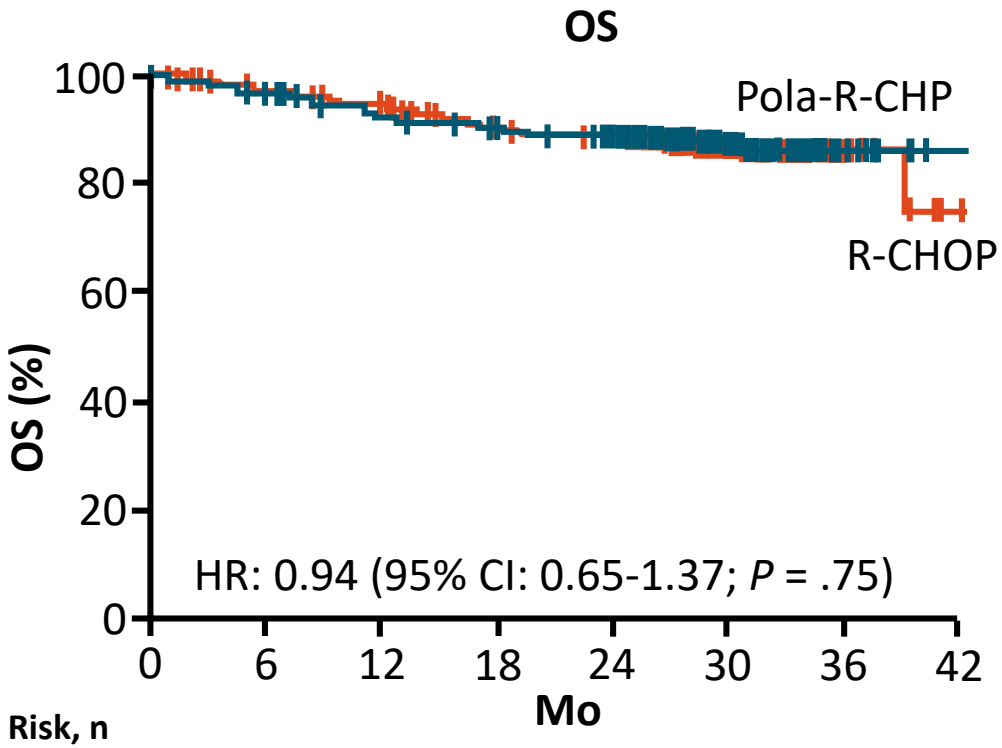
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

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

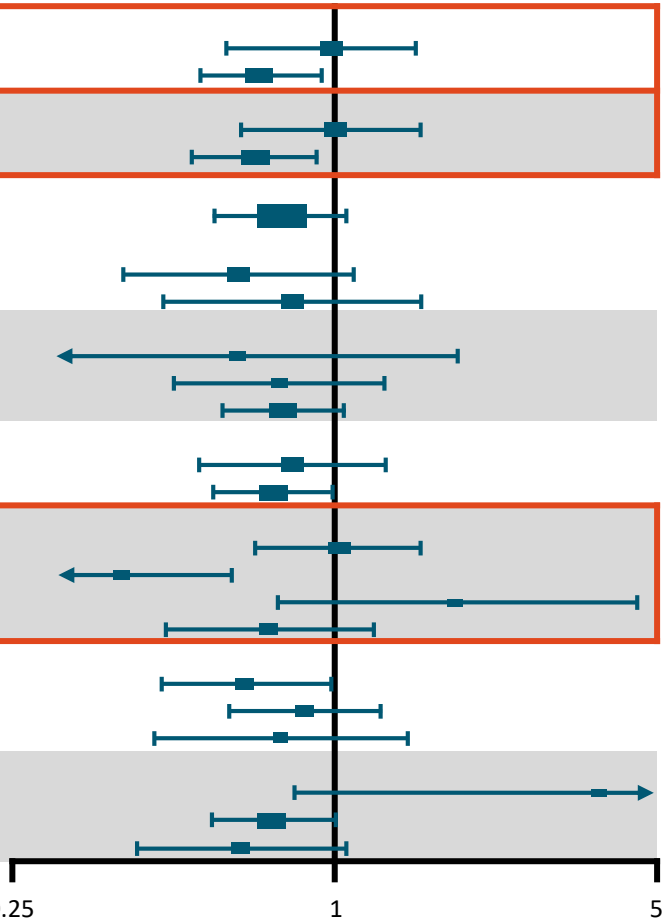
AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	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.

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.

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

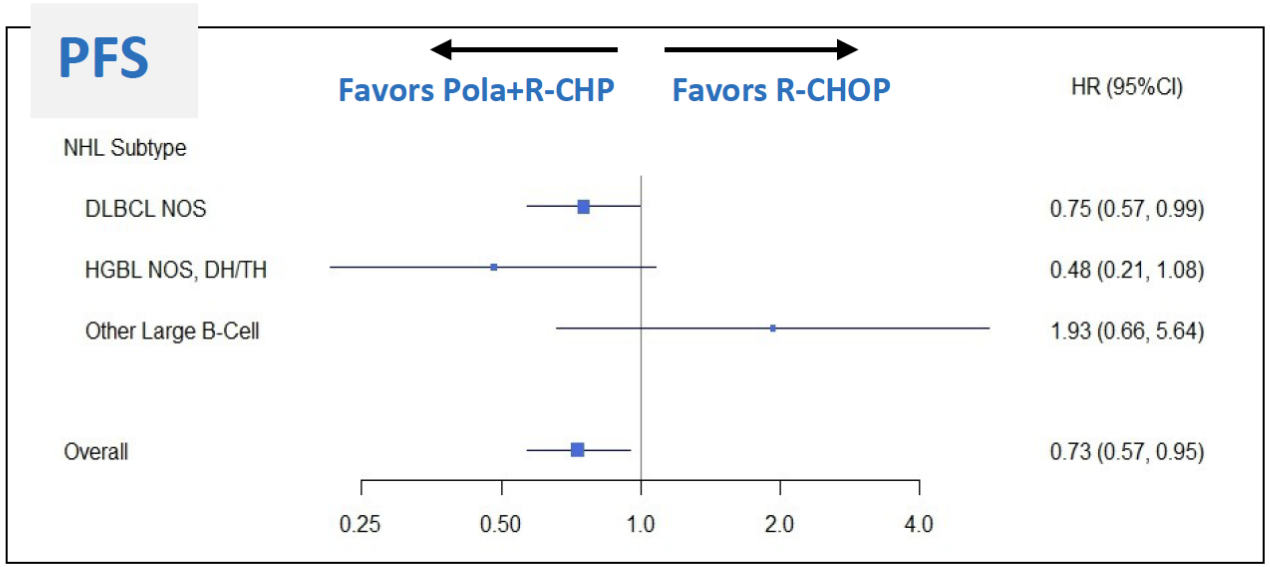
	Pola+R-CHP (N=422)	R-CHOP (N=413)
2-year DOR rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
Difference (95% CI)	4.0% (-2.5, 10.5)	

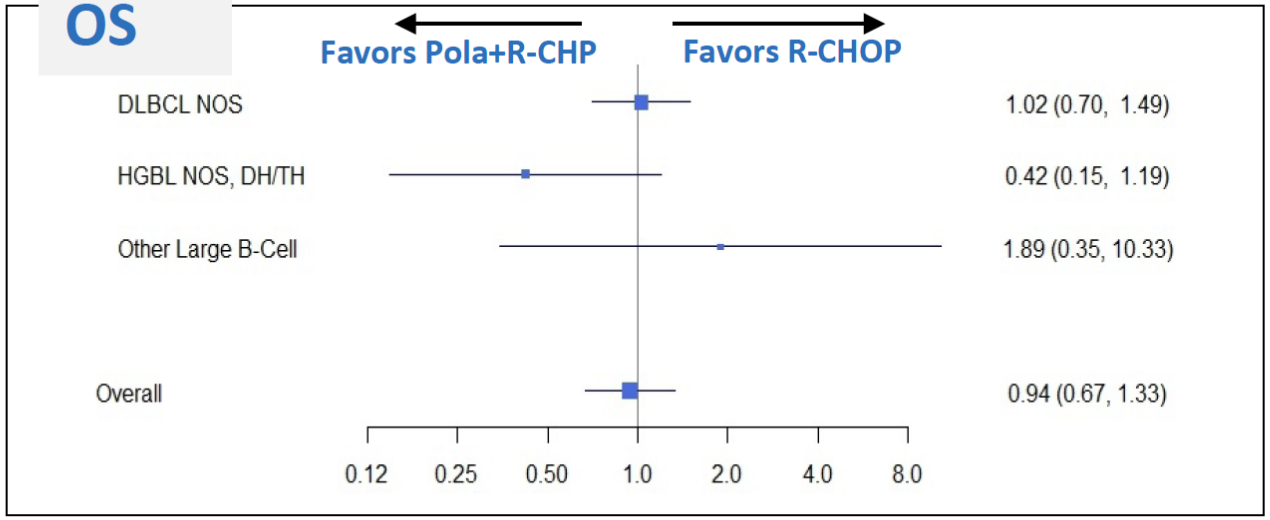
Disease-free survival

	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

ODAC on March 9th

OS bar is where it was 20 years ago….

We have 2 backbones to build on…

Benefit of Pola-RCHP in high risk LBCL (IPI >3) in subset analysis….? population to treat in the clinic

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

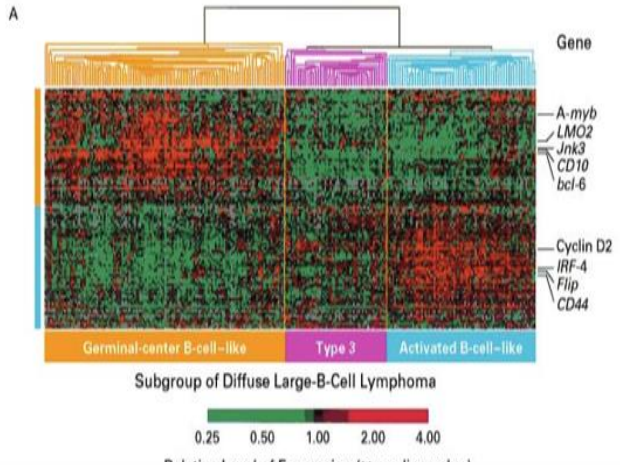
> I would like to note, however, that I would consider this regimen to be an option rather than a standard, in a setting of lack of overall survival difference from R-CHOP. I would consider them equivalent, including in ongoing clinical trials. I would not hesitate to randomize patients still to R-CHOP 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

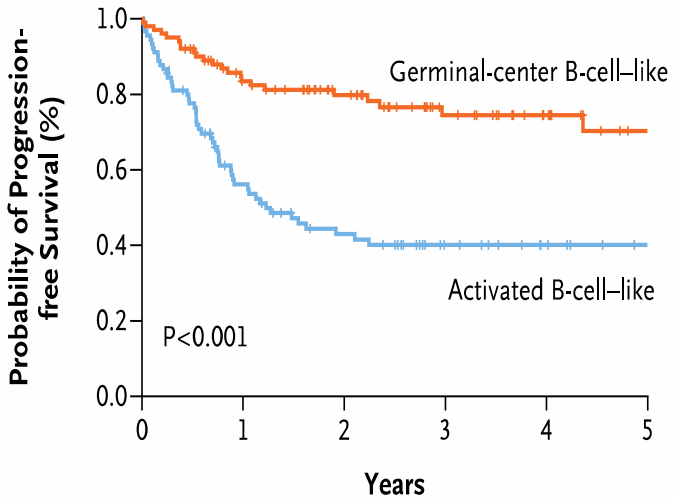
Cancer Letter, ODAC March 9th, 2023

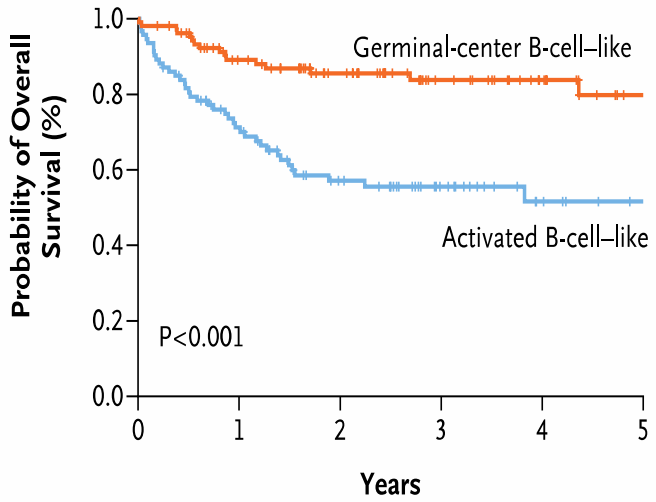
Cell of Origin Subtypes in DLBCL – Nearly 25 Years in Making



Two major molecular subtypes:

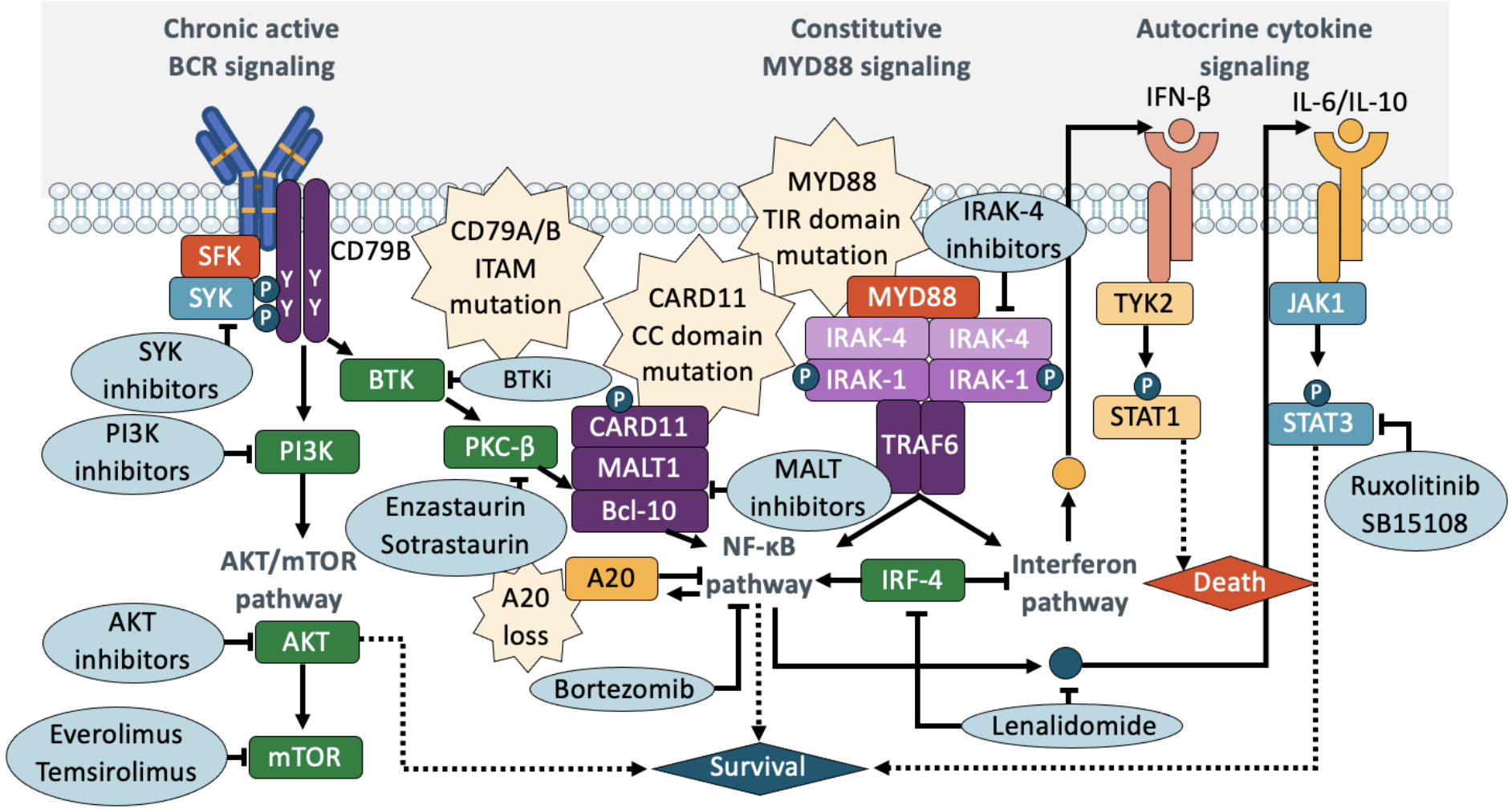
- Activated B-cell like (ABC)
  - B-cell receptor driven
- Germinal center B-cell like (GCB)





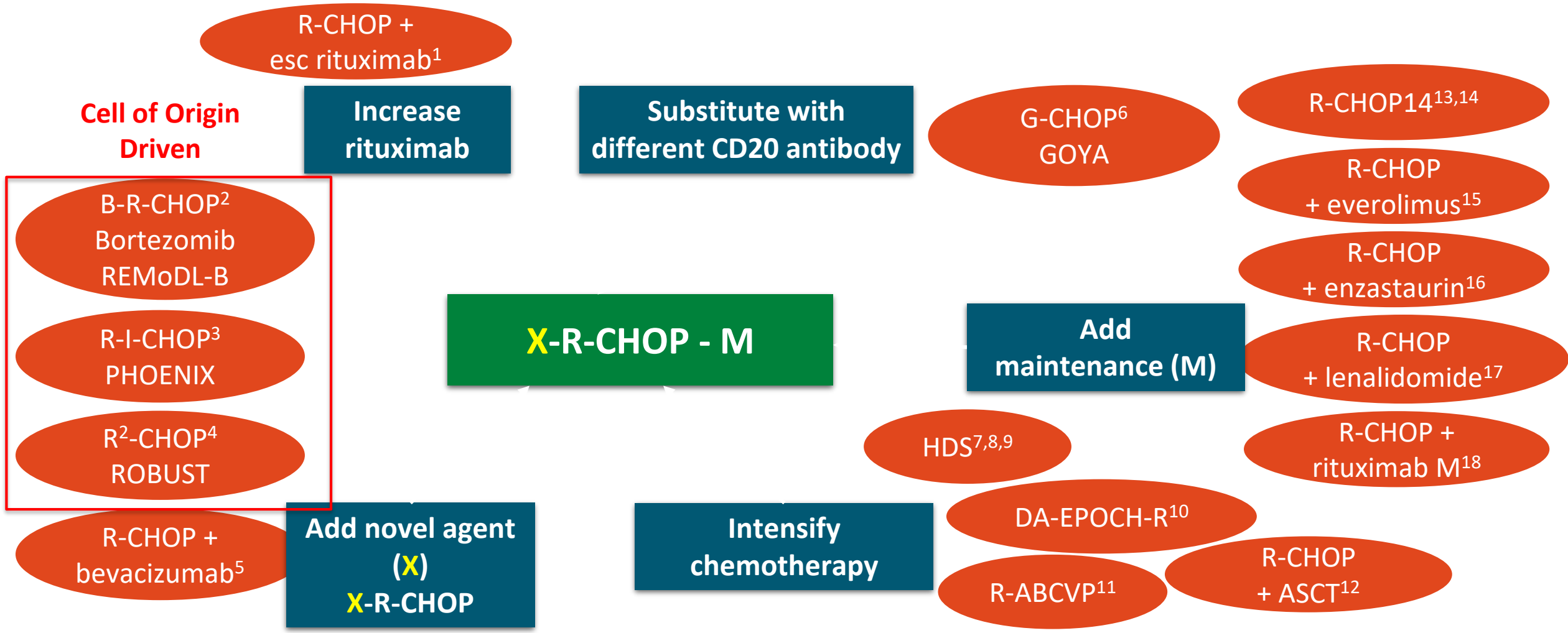
Lenz et al. N Engl J Med 2008;359:2313–2323.

Pathways With Therapeutic Potential in ABC DLBCL



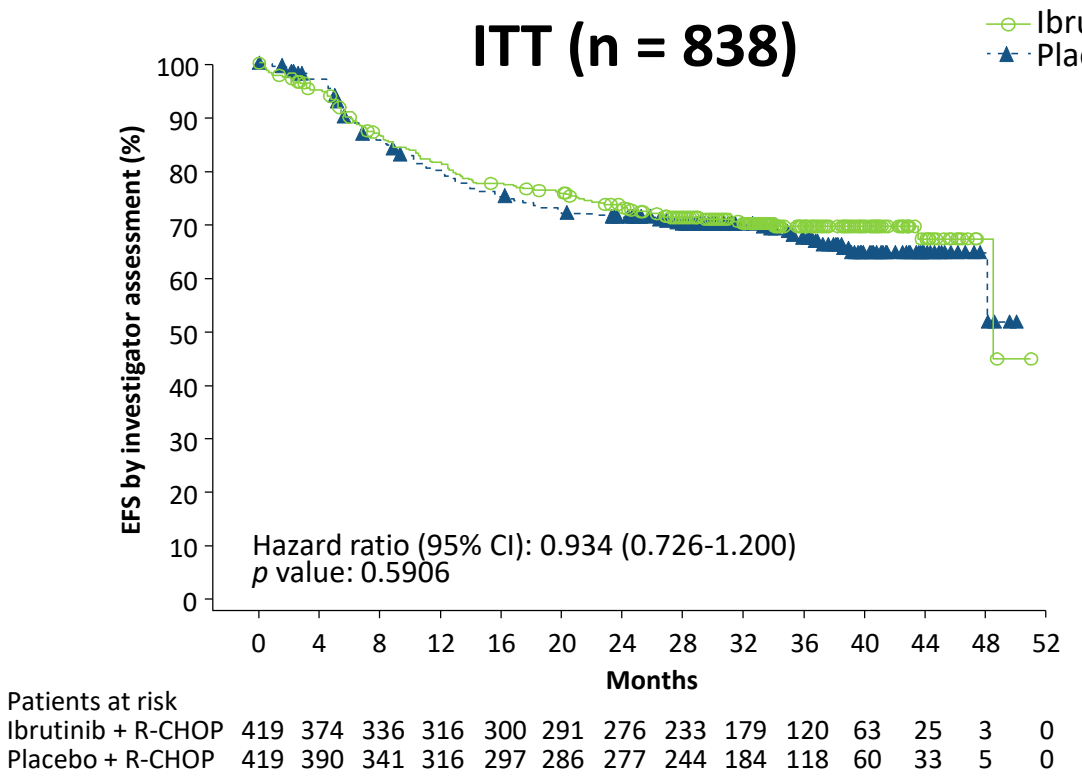
Roschewski. Nat Rev Clin Oncol. 2014;11:12.

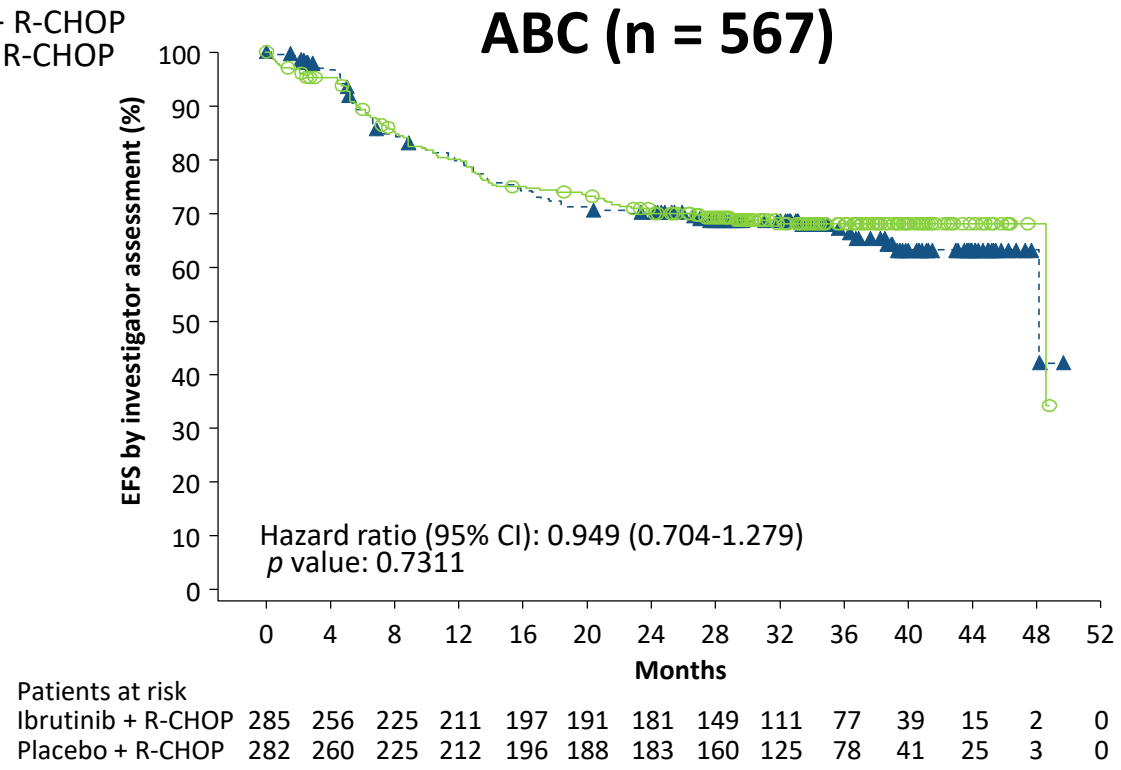
Improving on R-CHOP in DLBCL



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

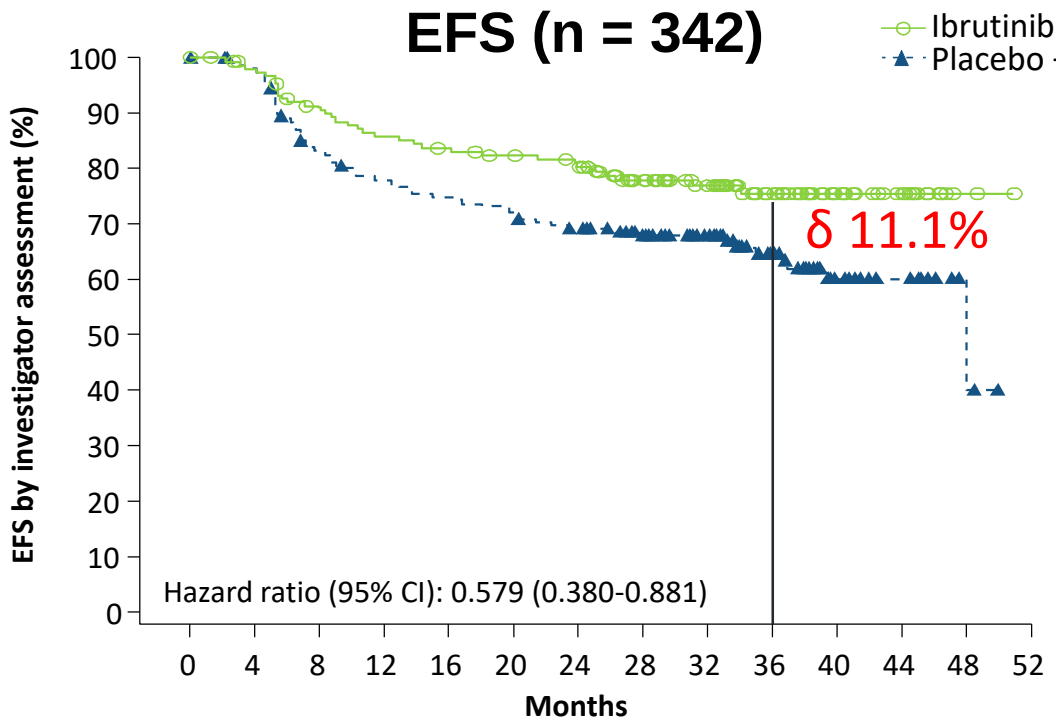


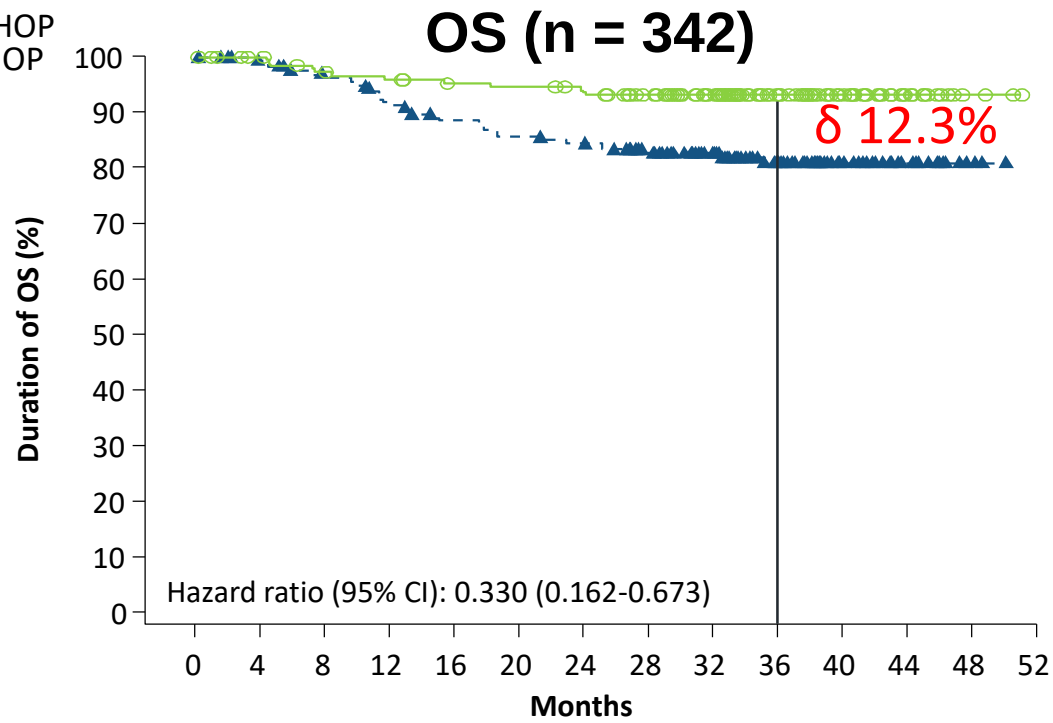


- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

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

EFS and OS in Patients < 60 Years





Patients at risk

Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0

Patients at risk

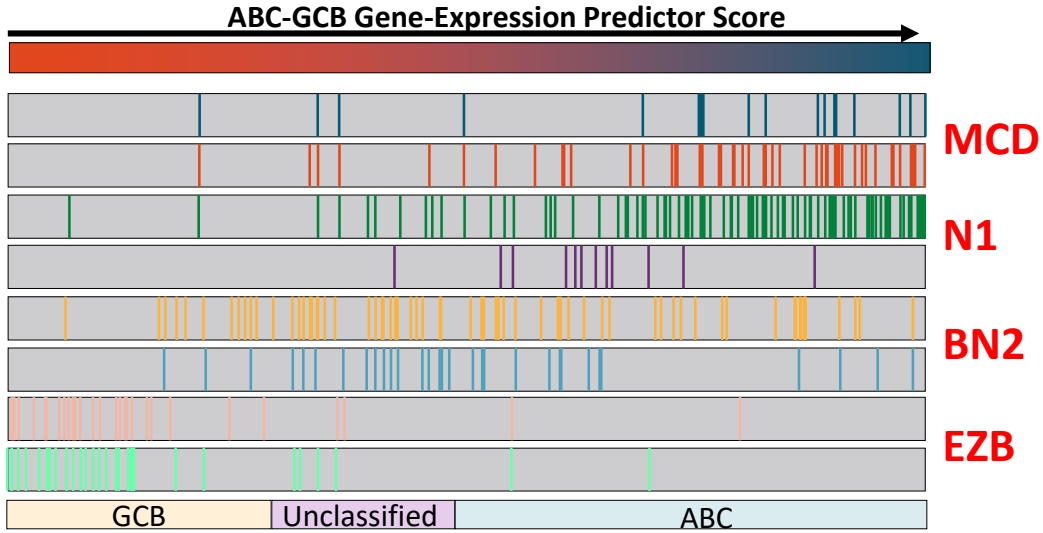
Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

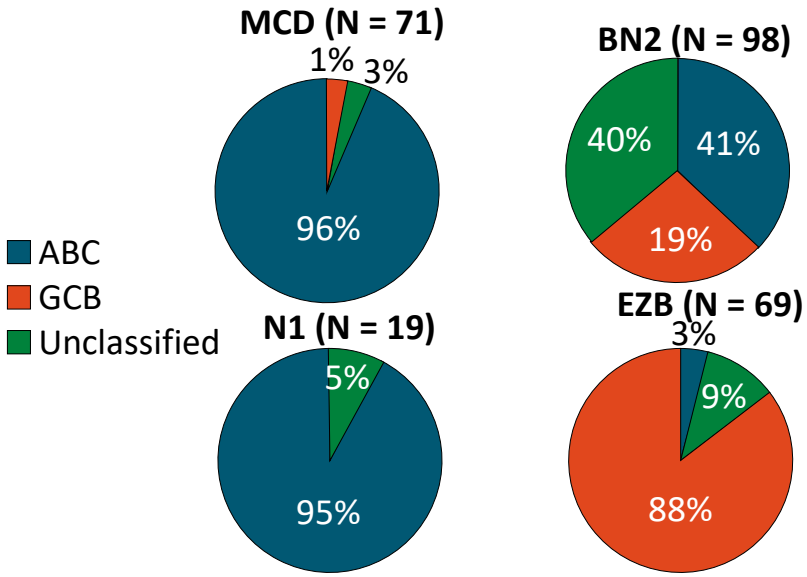
- **Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age**
- **Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors**
- **A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922]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

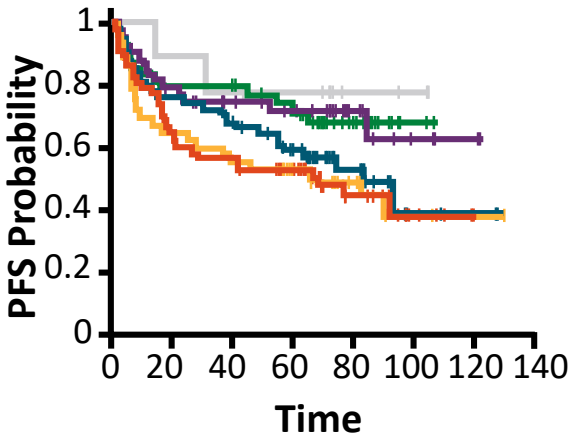
Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

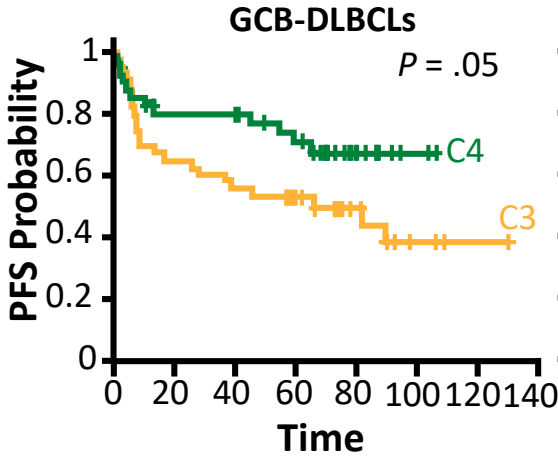
Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

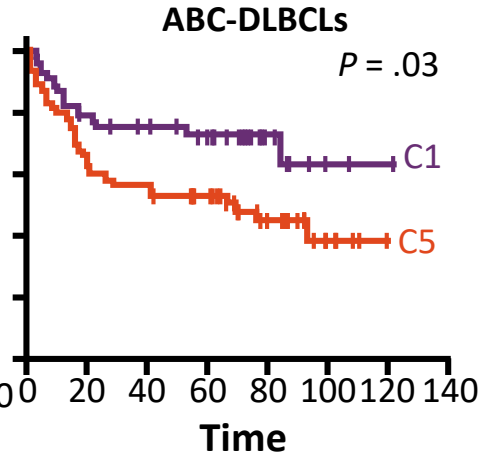
Genetic Feature	Log_{10} *P* Value	GCB	Unclassified	ABC
		Prevalence (%)		
CD79B+MYD88^{L265P} Double mutation	-6.4	0.6	1.7	11.5
CD79B mutation	-13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	-17.0	1.2	7.8	28.8
NOTCH1 mutation	-3.8	0.0	0.9	6.1
BCL6 fusion	-4.1	11.6	33.0	18.6
NOTCH2 mutation	-5.3	3.0	20.0	6.4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





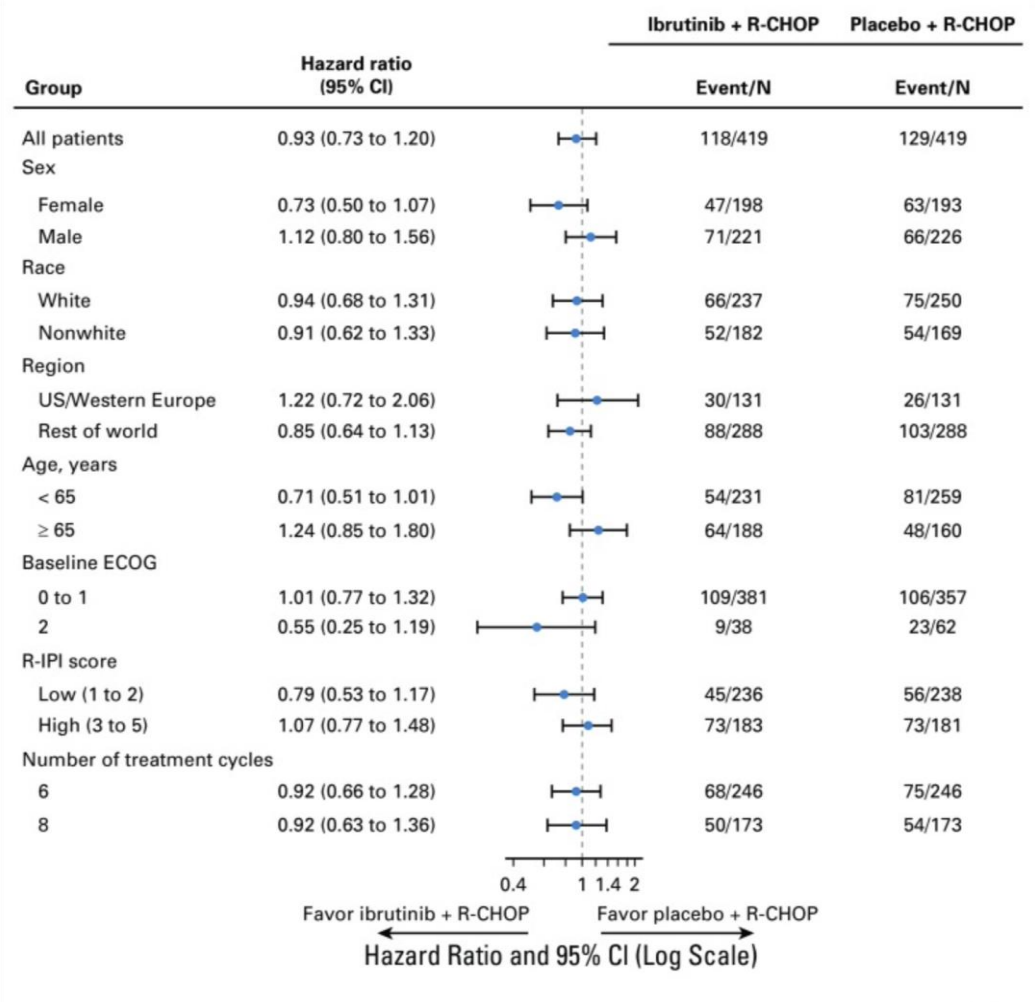






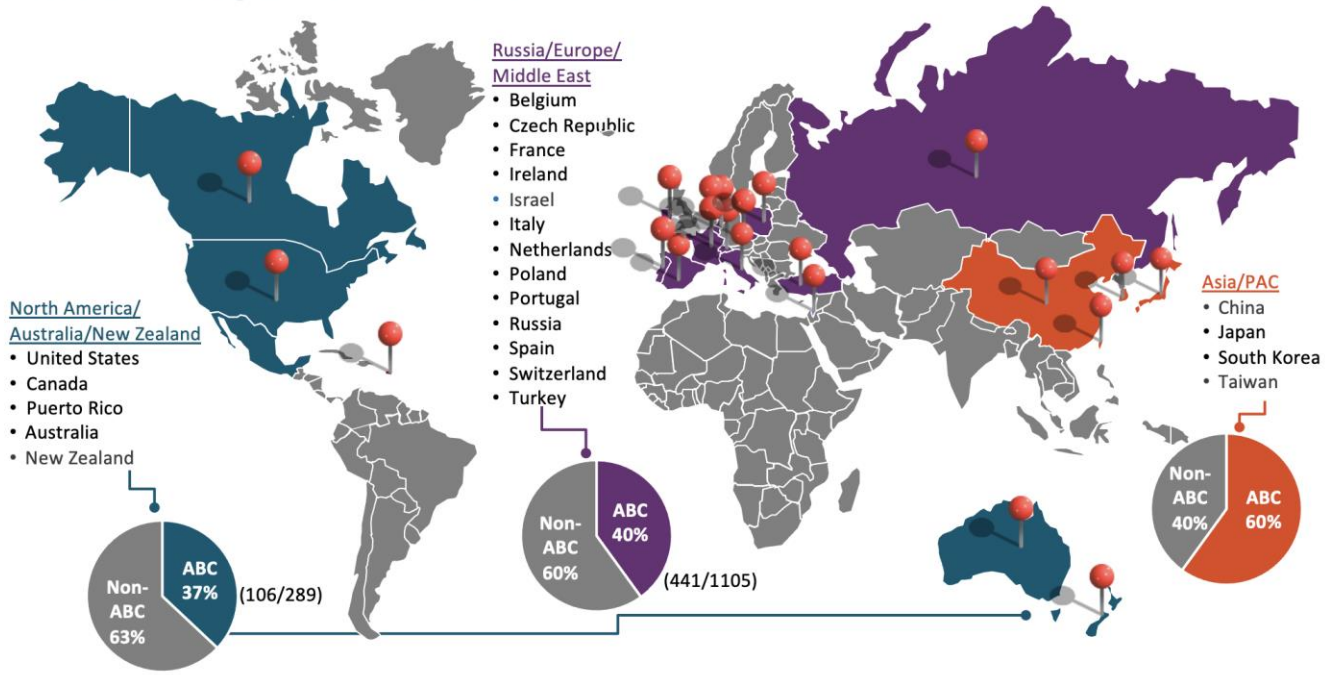
Chapuy. Nat Med. 2018;24:679. Schmitz. NEJM. 2018;378:1396.

Phoenix trial subgroup analysis



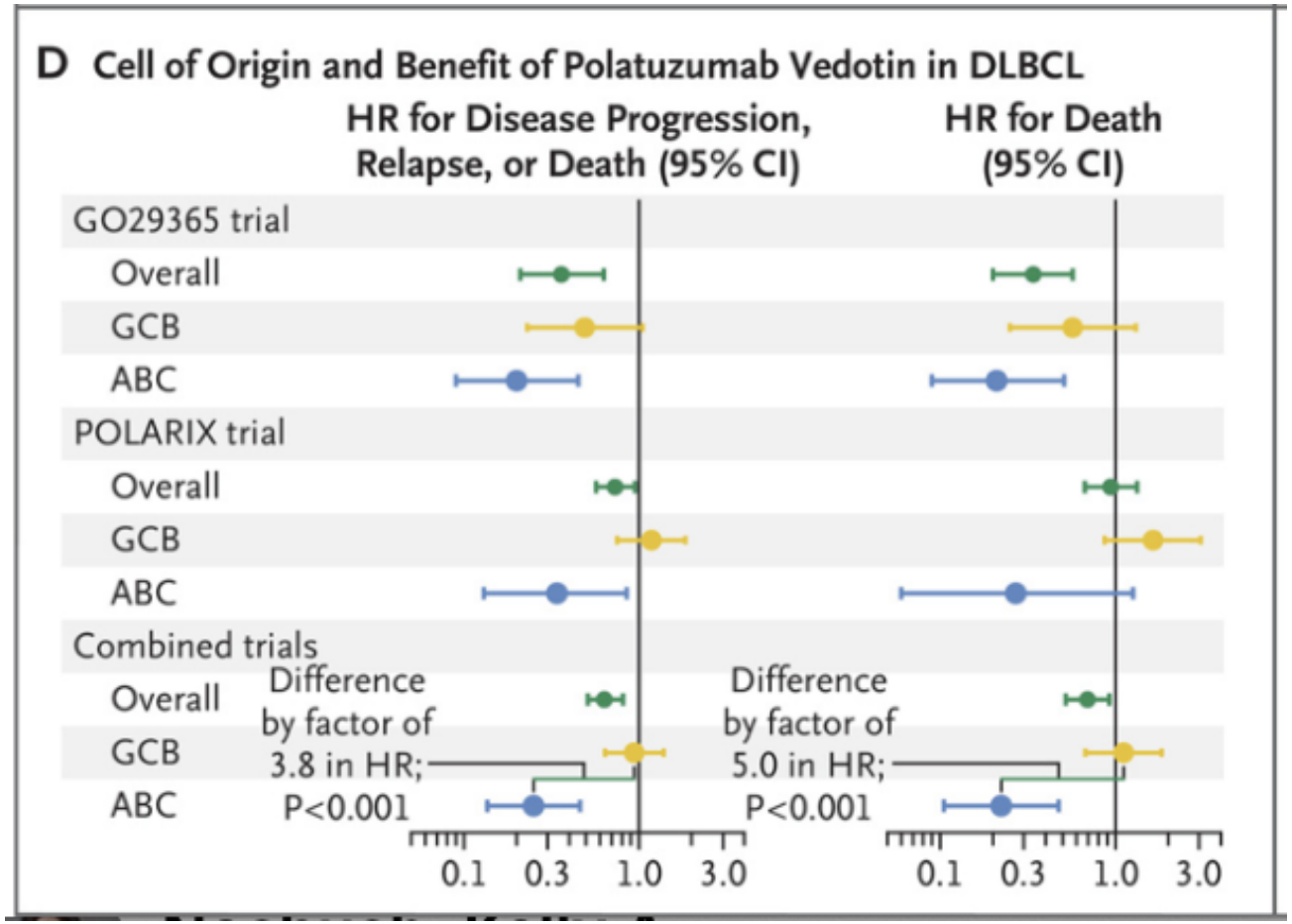
Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

ROBUST Trial: Geographical Distribution of Cell of Origin in DLBCL



Chiappella et al. EHA 2018 , Haematologica. 2020;105:e72.

COO and Benefit of Polatuzumab Vedotin

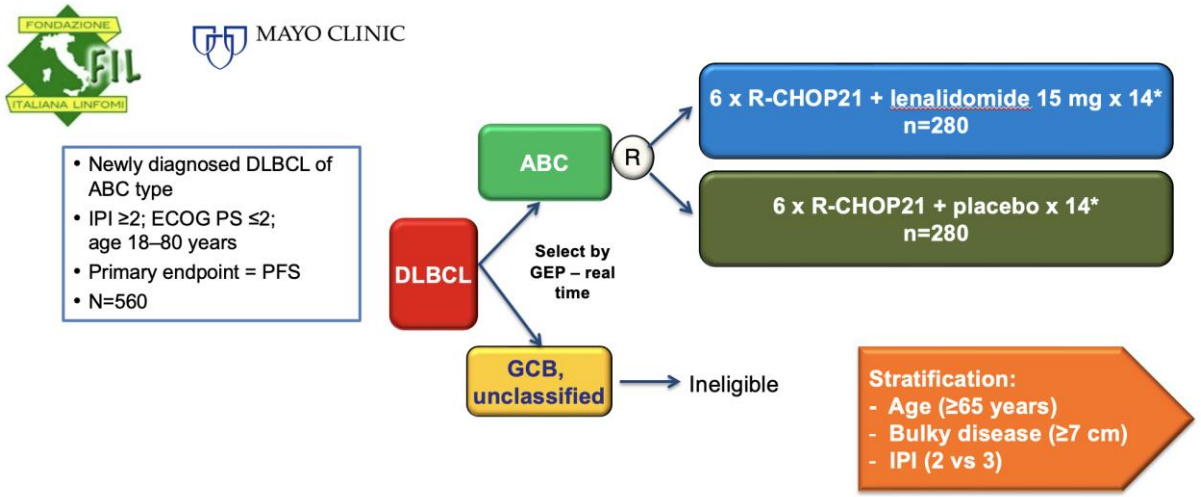


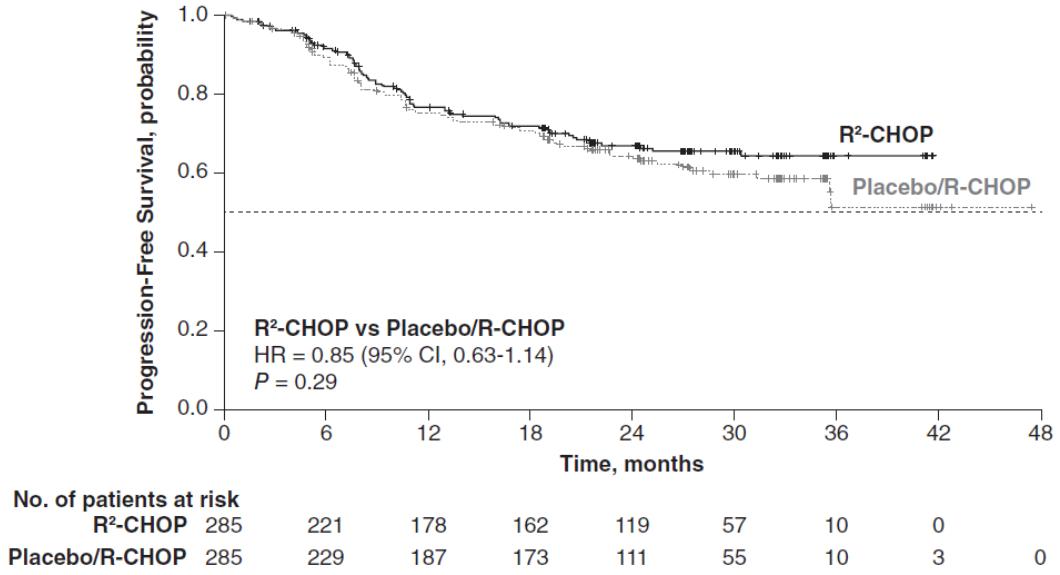
How do we interpret subset analysis in trials ?

Should PV RCHP be used only in ABC/non-GCB DLBCL?

Palmer, A. N Engl J Med 2023; 389:764-766

ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type DLBCL

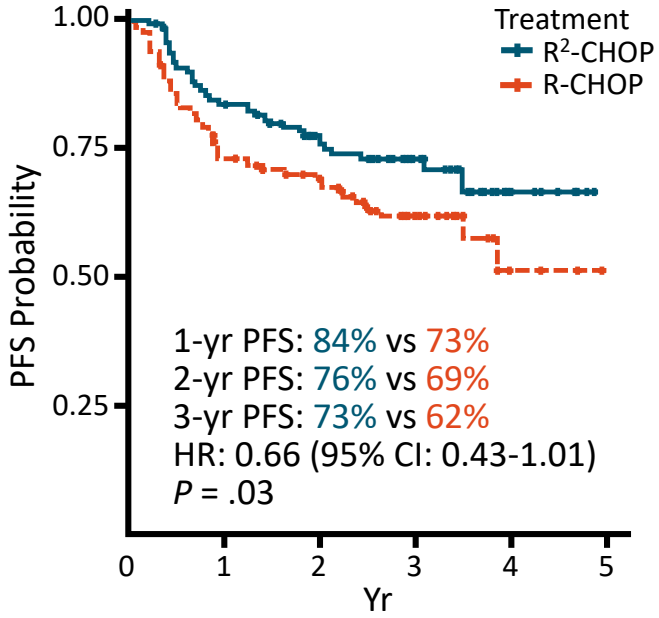




Vitolo U et al. 2019 International Conference on Malignant Lymphoma. Abstract 005.

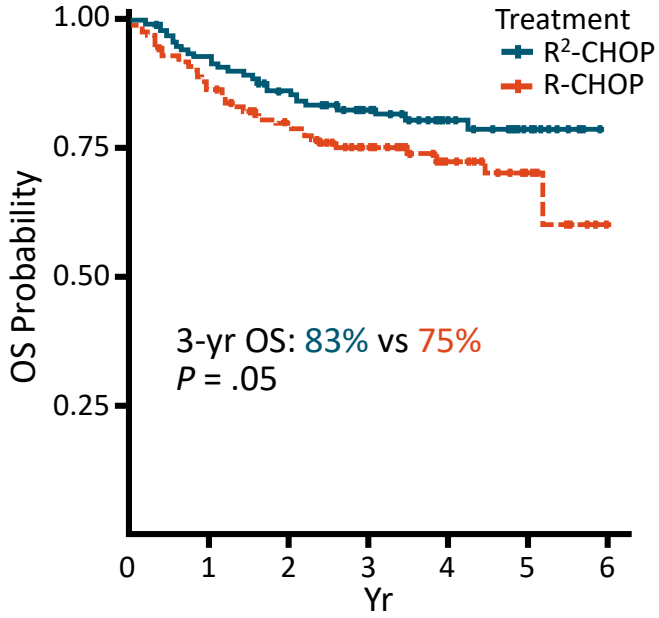
ECOG-ACRIN 1412: Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed DLBCL

- With a median follow-up of 3.0 yr
  - R^2-CHOP associated with a 34% decrease in the risk of progression or death
  - 3-yr OS was 83% (R^2-CHOP) vs 75% (R-CHOP)
- The addition of lenalidomide to R-CHOP prolonged survival



Patients at Risk, n

R^2-CHOP	145	113	85	46	7	0
R-CHOP	135	95	80	42	7	1



Patients at Risk, n

R^2-CHOP	145	129	116	95	55	21	0
R-CHOP	135	116	104	81	44	19	2

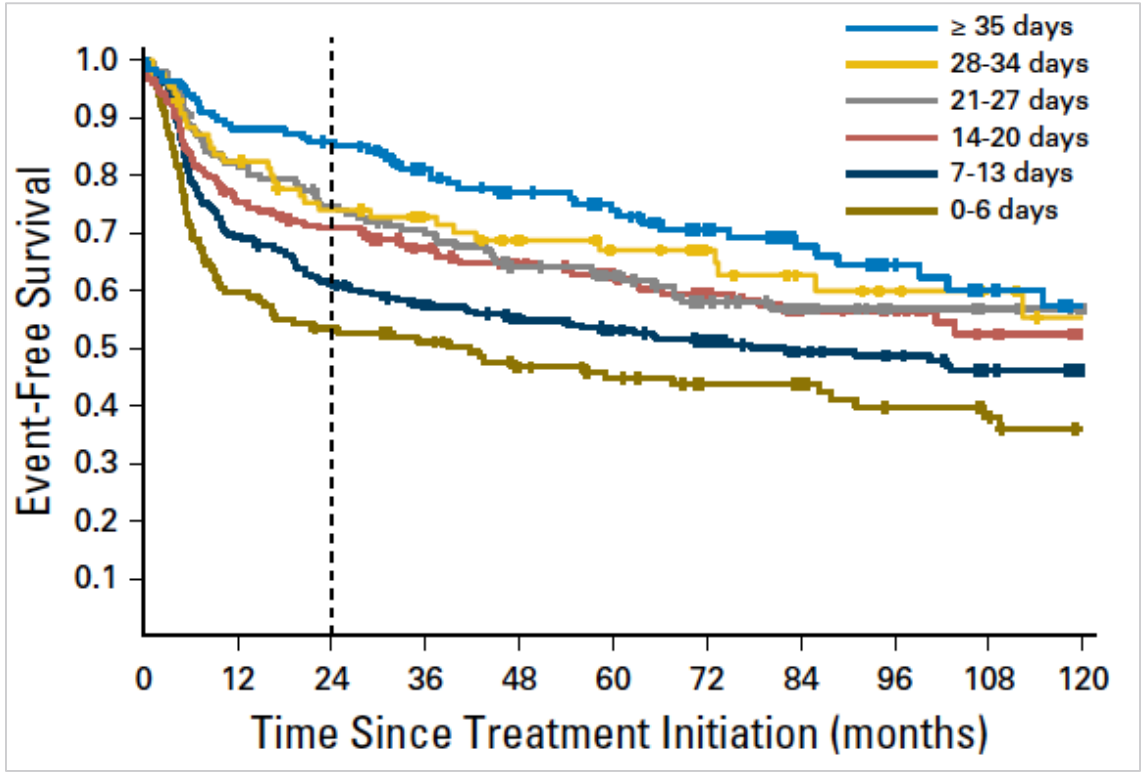
NowakowskI. JCO. 2021;39:1329.

Comparison of ROBUST and ECOG-ACRIN 1412

		ROBUST (N = 570)		E1412 (N = 280)	
Study design		Global, Phase 3, Double-blinded w/ placebo		US, Phase 2, Open-label	
COO by Nanostring		ABC Only		GCB, ABC, and Unclassified	
Len and prednisone dose		Len 15 mg days 1-14; Pred 100 mg flat		Len 25 mg days 1-10; Pred 100 mg/m^2	
		R^2-CHOP (n = 285)	**Placebo/R-CHOP (n = 285)**	**R^2-CHOP (n = 145)**	**R-CHOP (n = 135)**
Median age		65 (21-82)	65 (28-83)	67 (24-88)	66 (37-92)
IPI risk score	2	42%	42%	33%	34%
	≥3	58%	58%	66%	66%
Disease stage III/IV		87%	88%	97%	96%
ECOG	0-1	82%	80%	39%	35%
	2	18%	20%	61%	65%
Median time dx to tx, days		31	31	21	19
ORR (CR)		91% (69%)	91% (65%)	97% (72%)	91% (67%)
2-Year PFS		67%	64%	76%	70%
Median follow-up		27.1 mo (range, 0-47)		2.5 years	
2-Year OS		79%	80%	86%	80%
Safety		Most common grade 3/4 AEs were hematologic: neutropenia, leukopenia, and anemia		Grade 3/4 AEs with R^2-CHOP vs R-CHOP: anemia (30% vs 20%), thrombocytopenia (36% vs 12%)	

Possible reasons for equivalent outcomes

- Unexpectedly good outcomes for the control arm
- Enrollment bias on trial ie sickest pts don't go on trial due to path central review related delays



Maurer MJ et al. *J Clin Oncol*. 2018;36(16):1603-1610.

frontMIND: Tafasitamab + R^2-CHOP in Untreated DLBCL

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

Stratification by IPI score 3/aaIPI score 2 vs IPI 4-5/aaIPI 3 and and geographic region (Western Europe, US, Canada, and Australia vs Asia vs rest of world)

Patients aged 18-80 yr with previously untreated DLBCL or HGBL; IPI 3-5; ECOG PS 0-2; diagnosis to treatment interval ≤28 days; eligible for R-CHOP (N = 880)

Cycles 1-6 (21-day cycles)

Tafasitamab 12 mg/kg (D1, 8, 15) + **Lenalidomide** + **R-CHOP** (n = 440)

Tafasitamab placebo (D1, 8, 15) + **Lenalidomide** placebo + **R-CHOP** (n = 440)

EoT → Follow-up for up to 60 mo

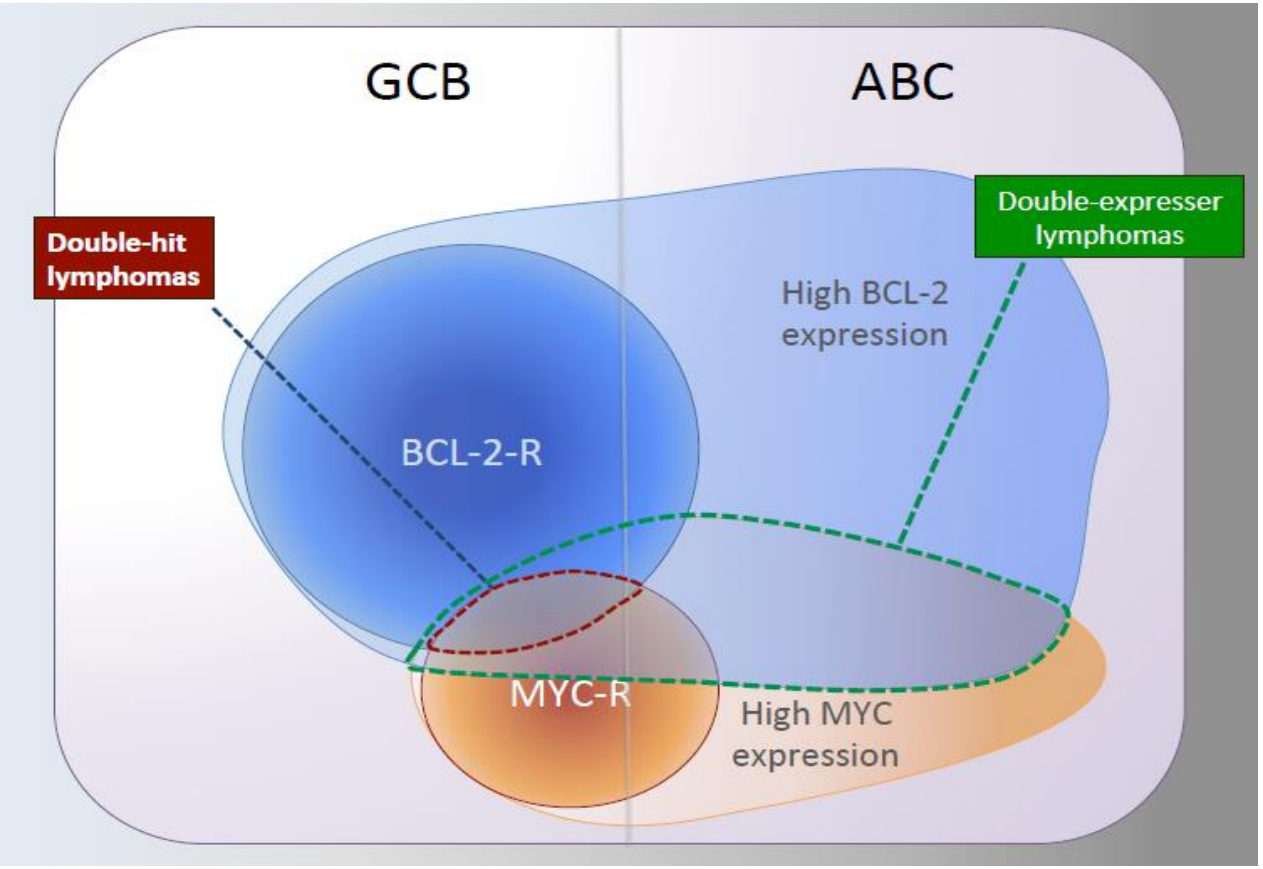
R-CHOP: IV rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 administered on D1 + oral prednisone 100 mg QD D1-5; lenalidomide: 25 mg/day on D1-10.

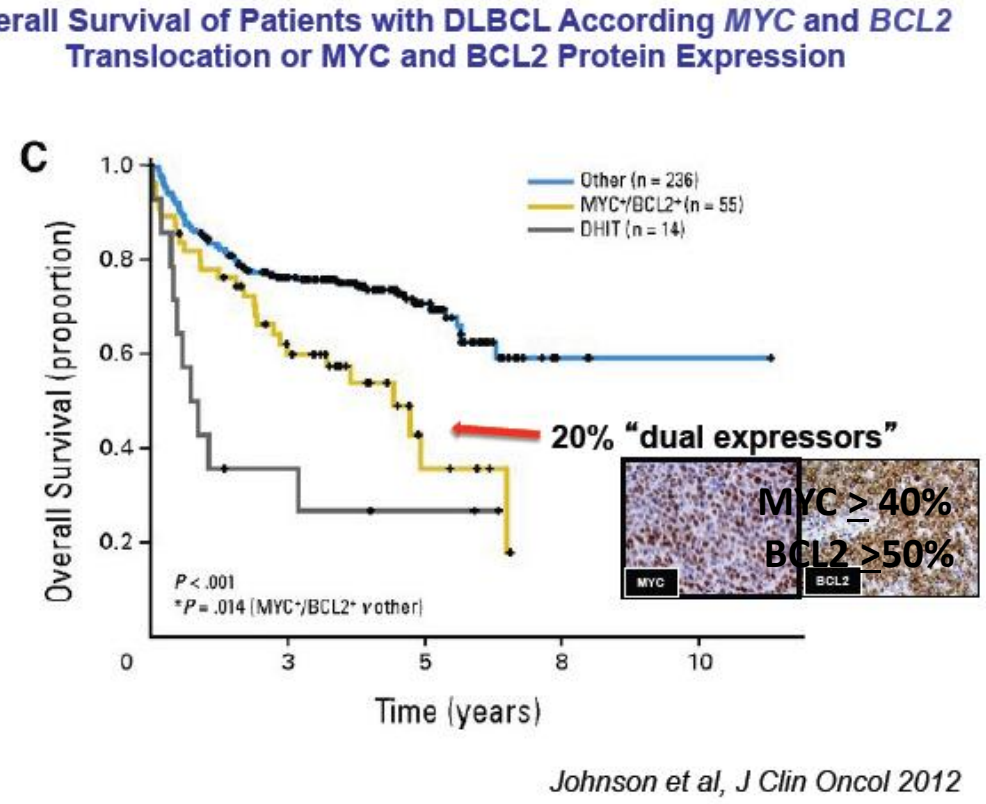
- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** EFS, OS, ORR, metabolic PET-negative CR rate EoT by BIRC and INV, MRD status at EoT

*Trial was initiated based on the results from the phase Ib first-MIND trial of tafasitamab + R-CHOP ± lenalidomide.

Vitolo. EHA 2021. Abstr PB1451.

Tumor Heterogeneity in DLBCL Subsets
Double Hit/Expresser DLBCL (myc and DLBCL)

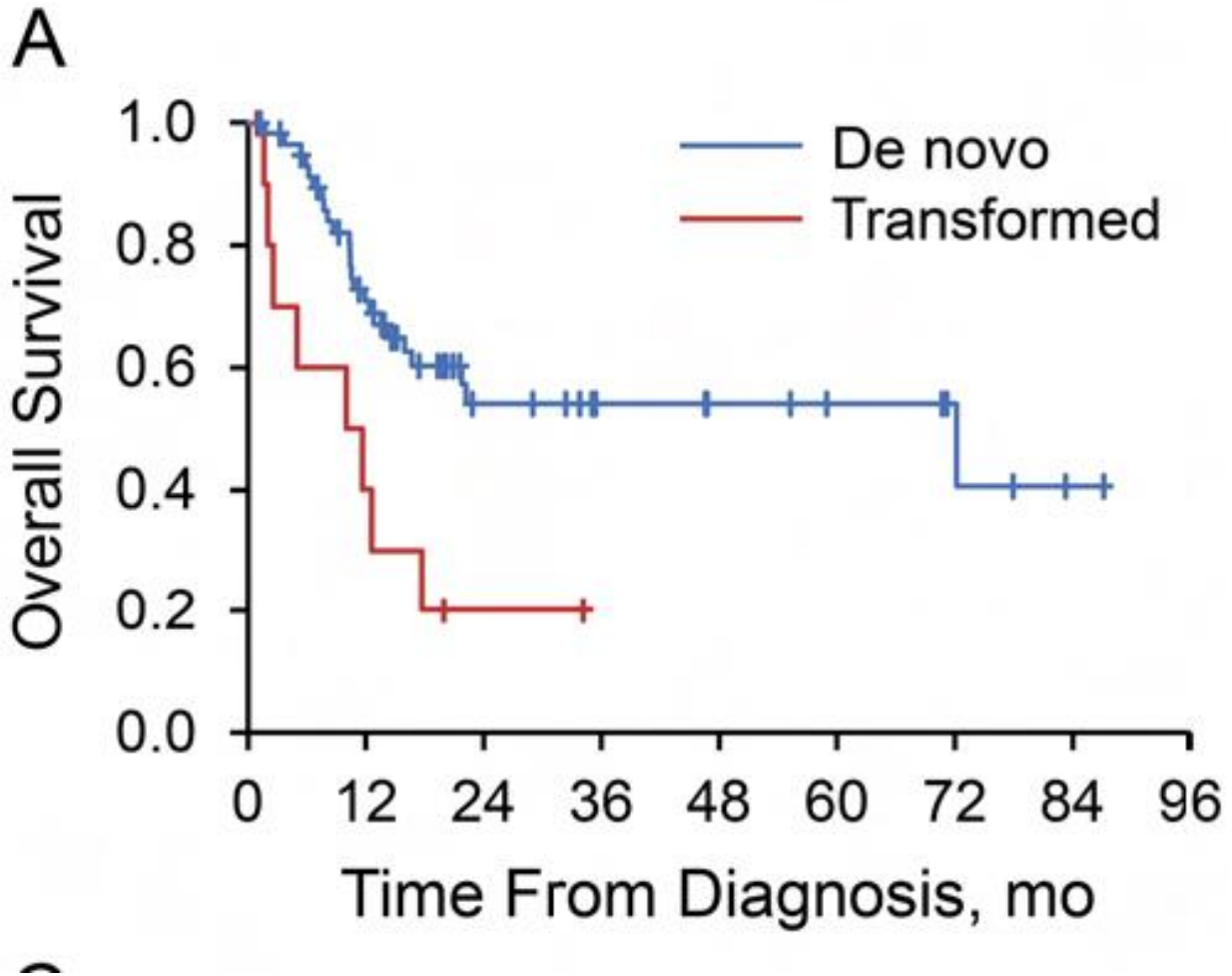




Dunleavey K. ASH. 2015.

Not All DH/THL Are Created Equal

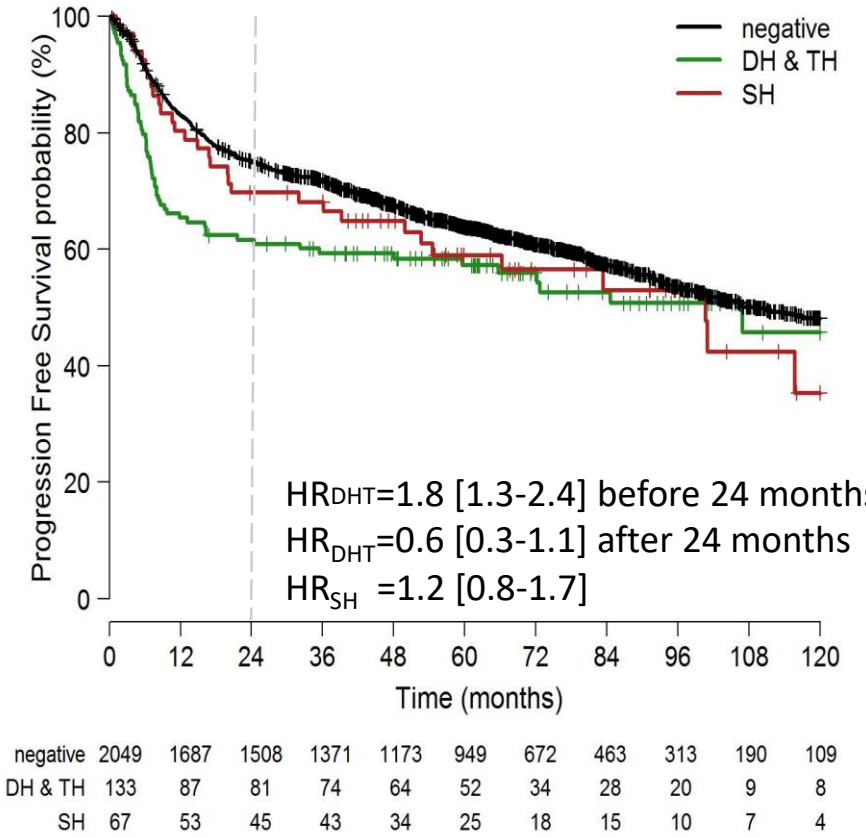
Event Free Survival (EFS) of Newly Diagnosed vs. Transformation Patients



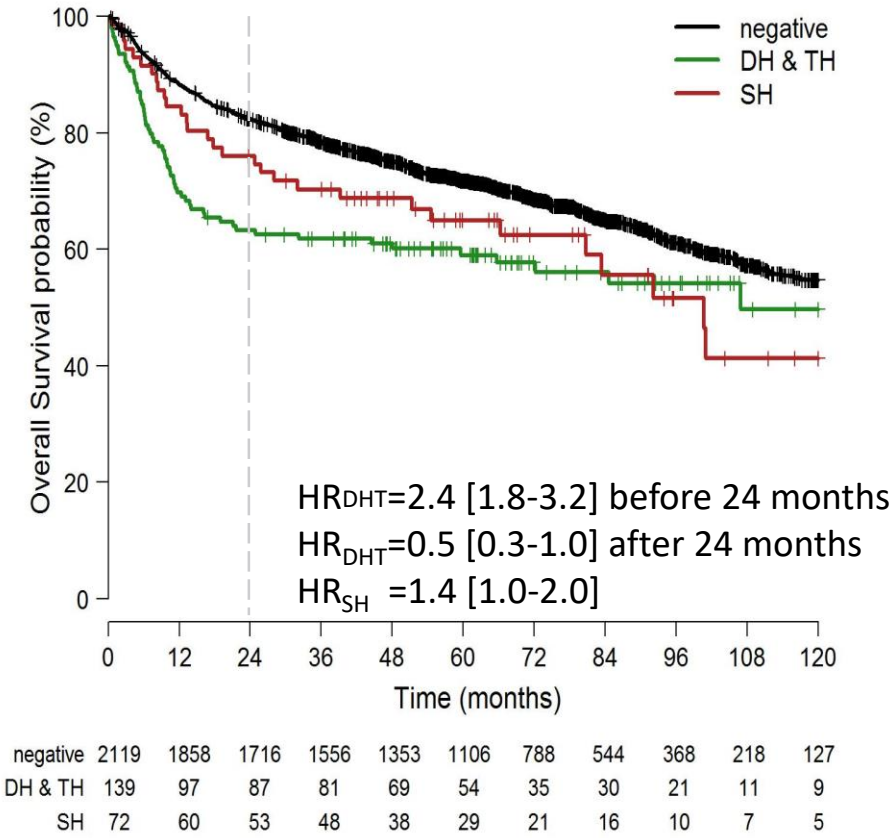
Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

LLBC: MYC Double-hit and Triple-hit predict inferior outcome
SH *MYC* no impact on PFS (Outcomes better than expected)
DHL and THL inferior PFS and OS

PFS

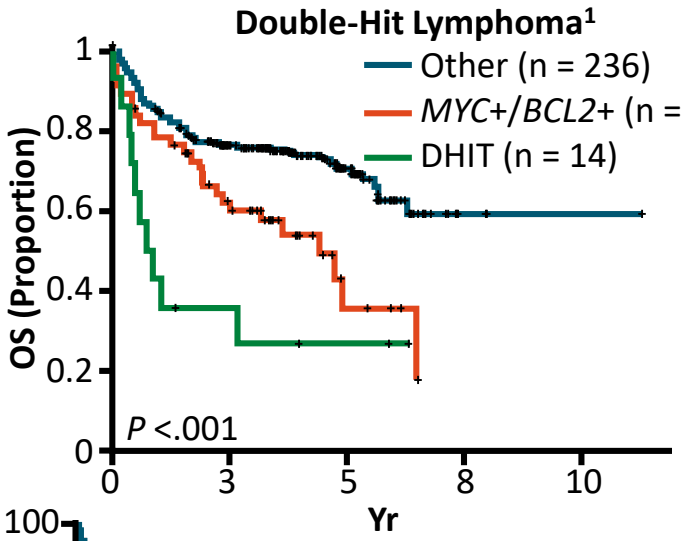


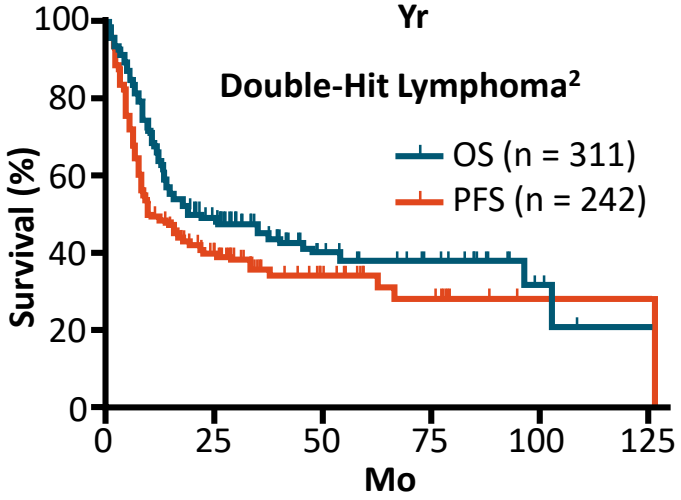
OS

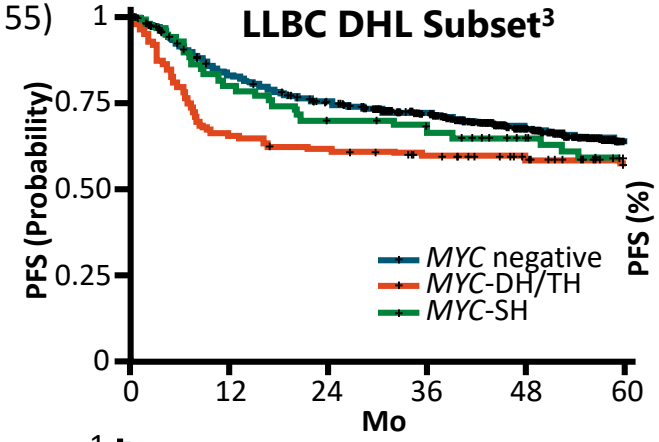


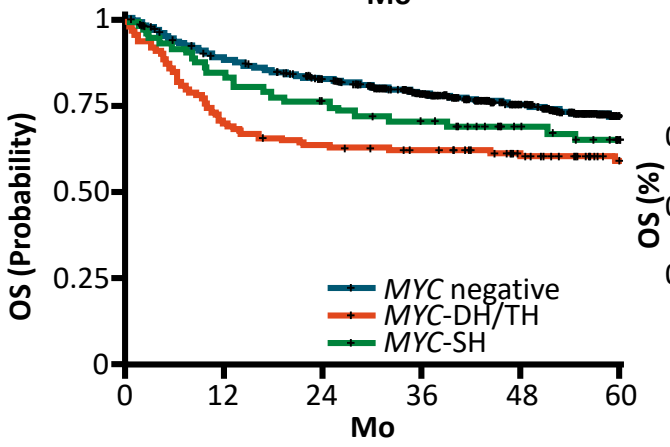
Rosenwald A et al. *J Clin Oncol*. 2019;37(35):3359-3368.

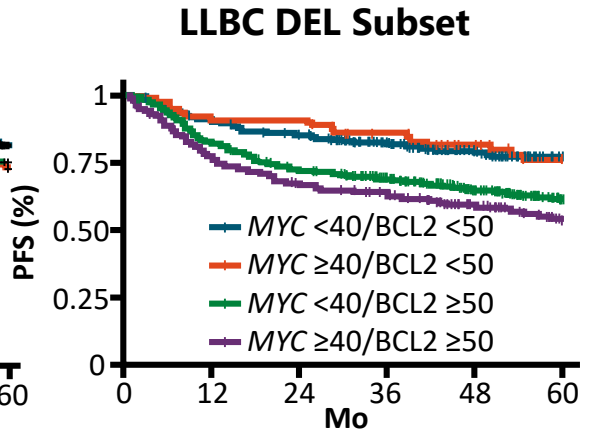
"Double Hits" and "Double Expressers": Impact of *MYC* and *BCL2* Translocations and Expression on Outcome

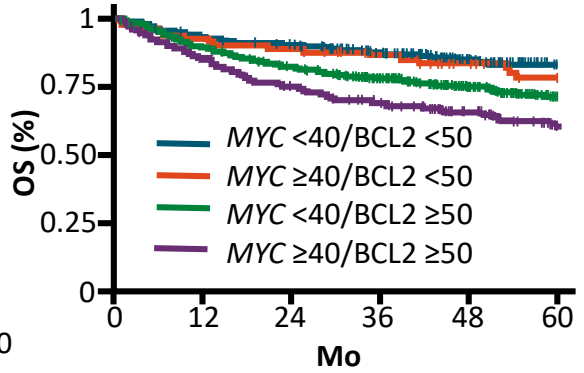


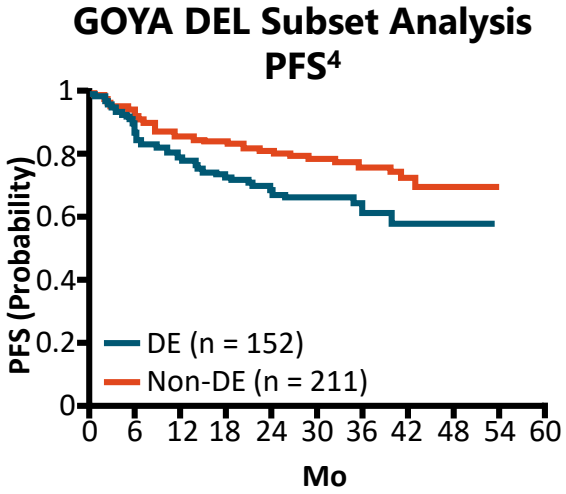






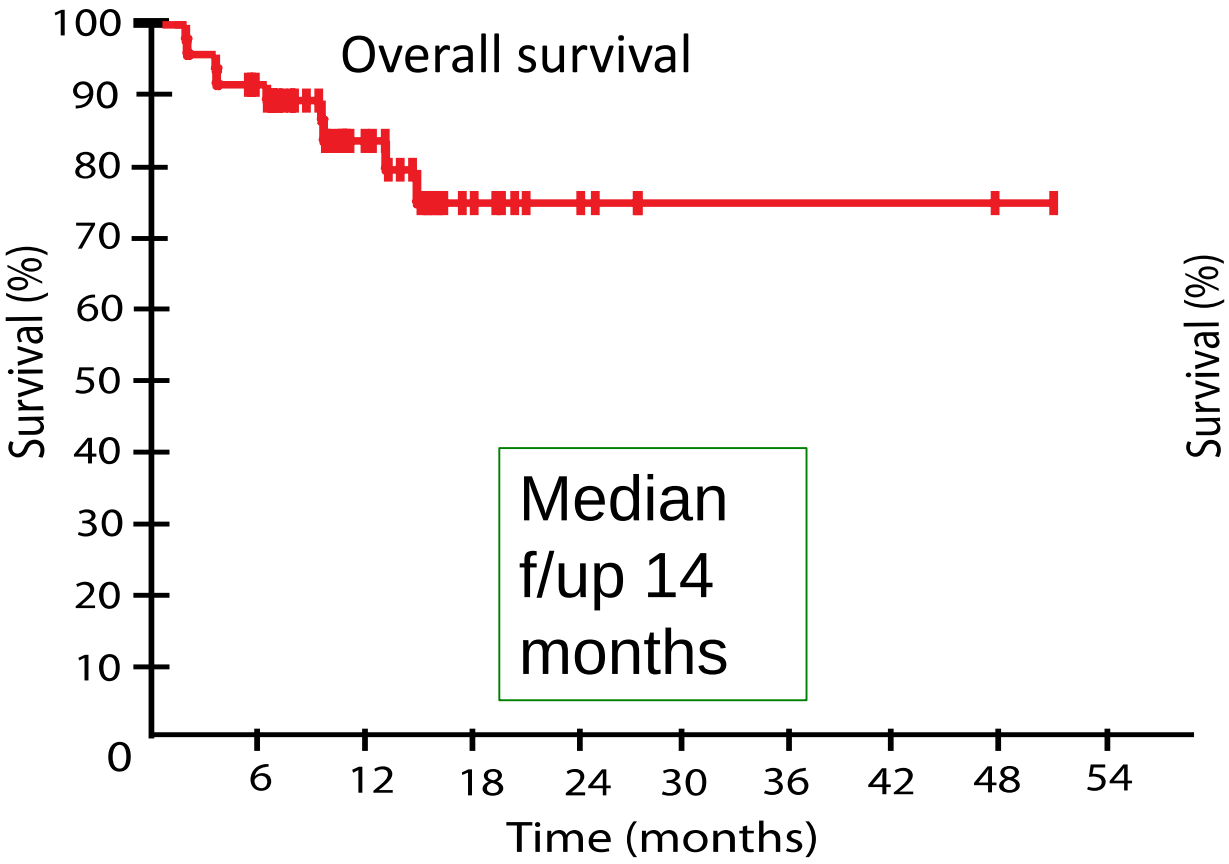




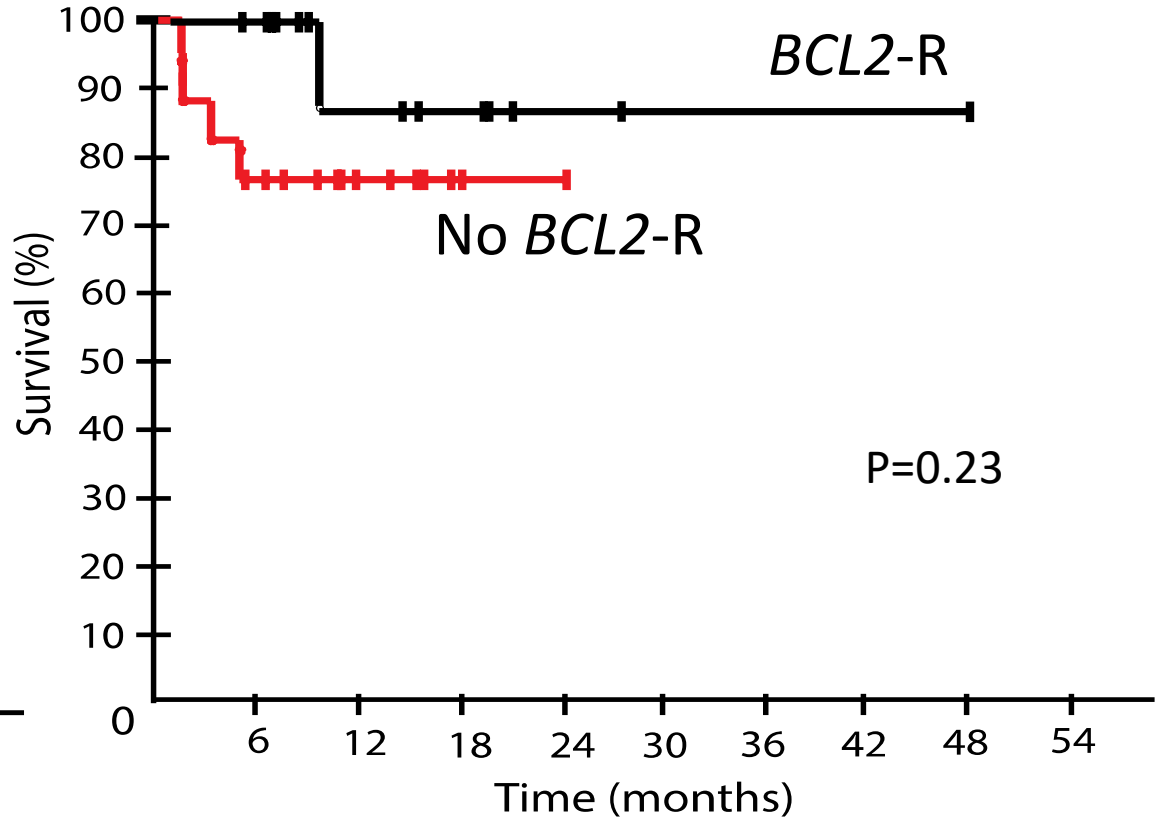


1. Johnson. JCO. 2012;30:3452. 2. Petrich. Blood. 2014;124:2354.
3. Rosenwald. JCO. 2019;37:3359. 4. Sehn. ICML. 2017.

Prospective Study
DA-EPOCH-R in *MYC* Rearranged DLBCL



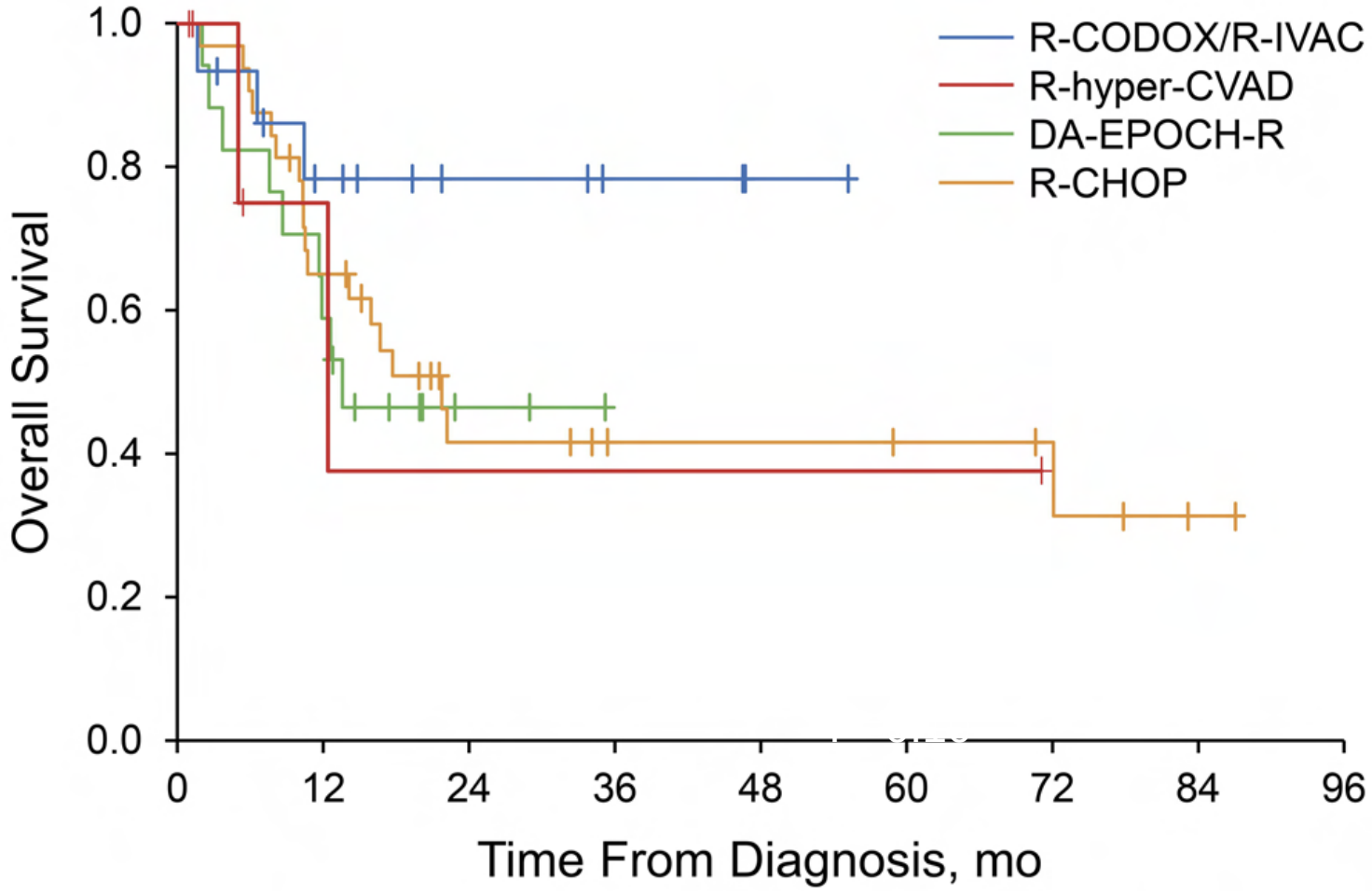
Double Hit vs. single *MYC* rearrangement



Results are preliminary and longer follow-up is needed
Central Path review for FISH pending

K. Dunleavy ASH 2014

EFS by Treatment

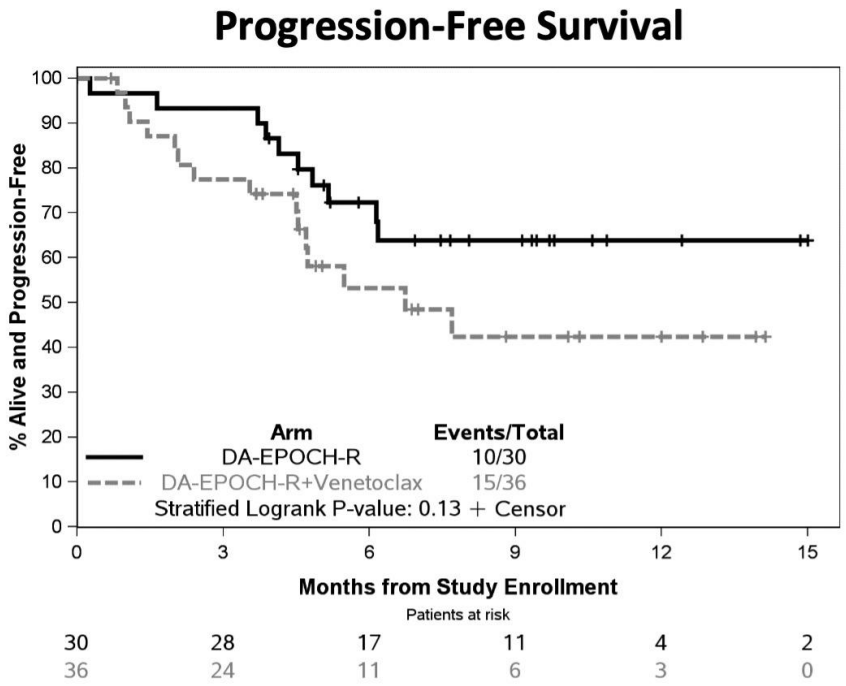


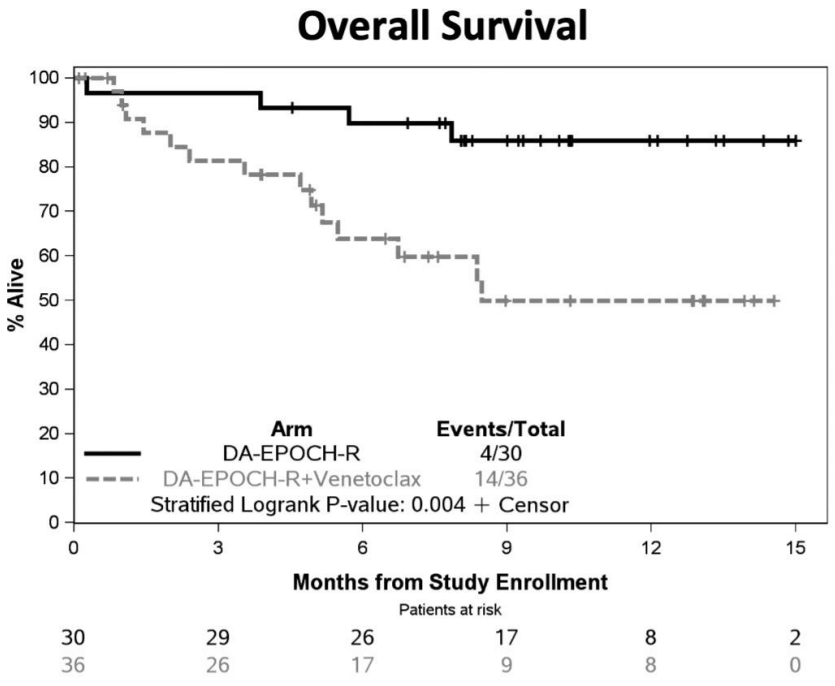
Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

How do I treat DHL frontline?

- Patients ≤60 yo R-CODOX-M/IVAC
- > 60 DAEPOCH-R (RCHOP/mini RCHOP elderly)

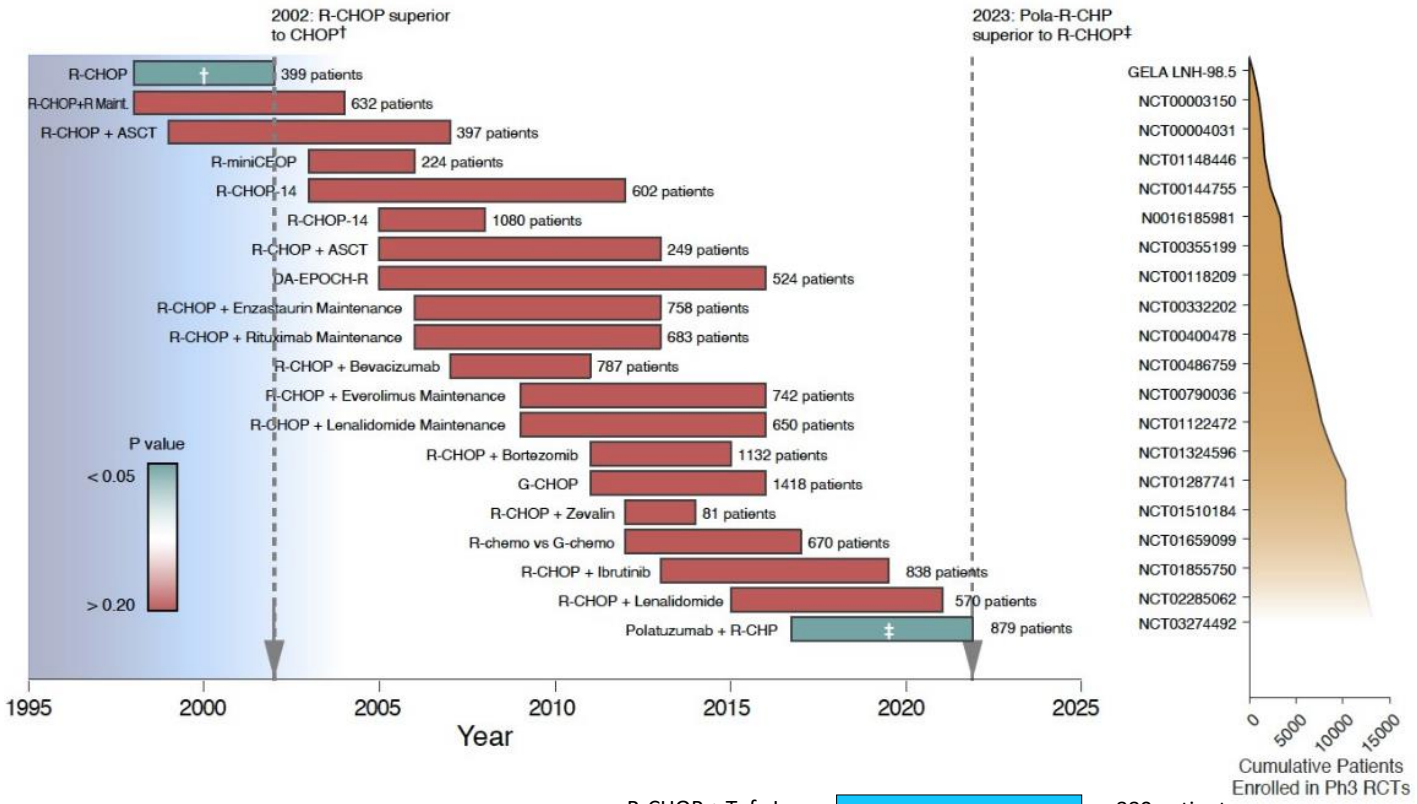
US Intergroup Study NCT03036904 – excess toxicity and worse outcome with addition of venetoclax to DA-EPOCH-R

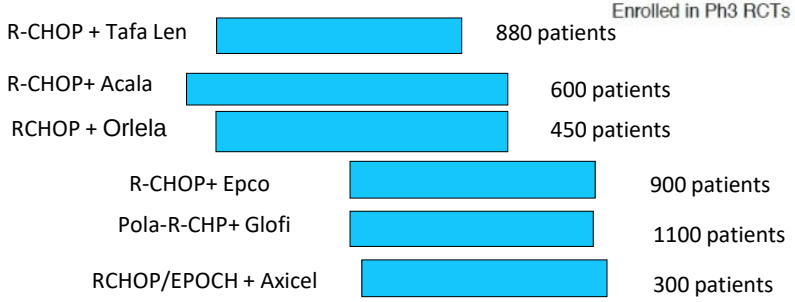


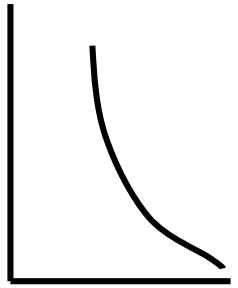


Blood (2021) 138 (Supplement 1): 523.

Beyond RCHOP – Molecularly Driven or Agnostic?







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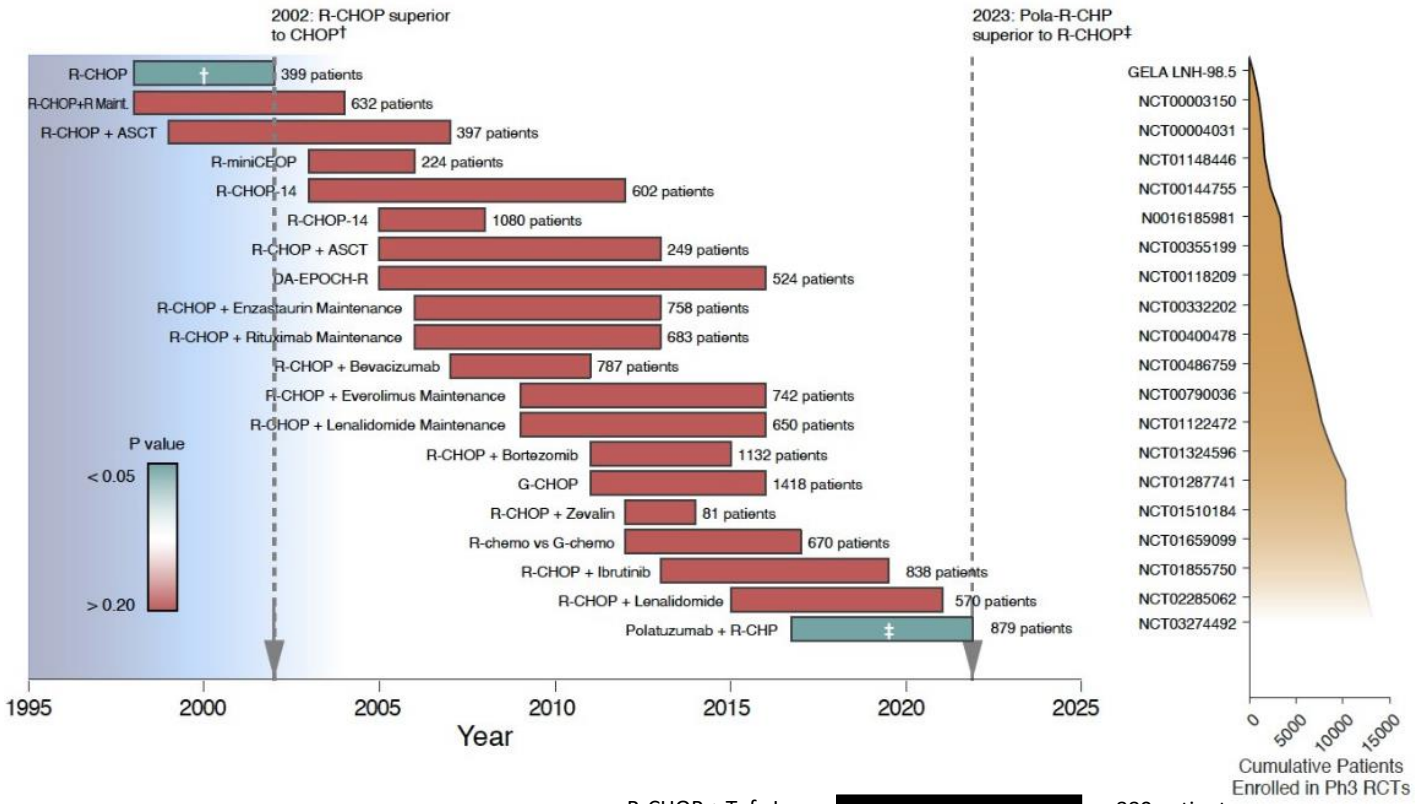
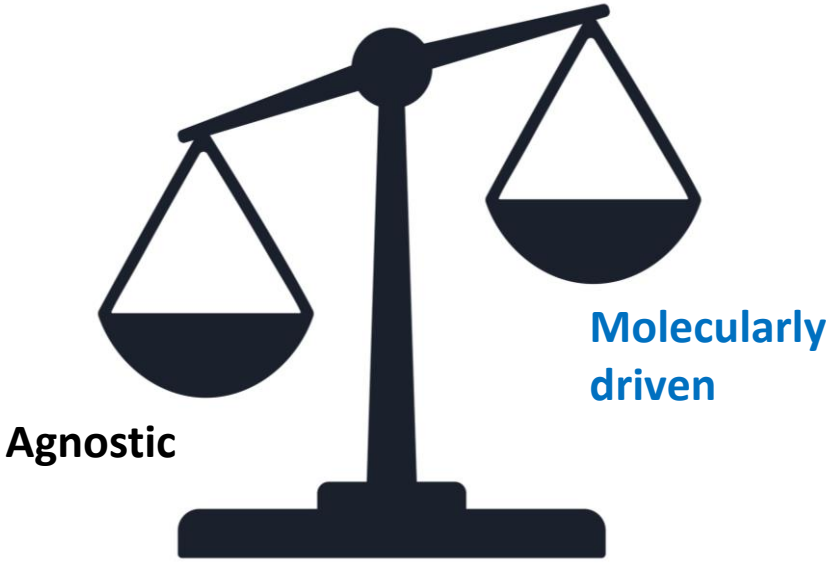
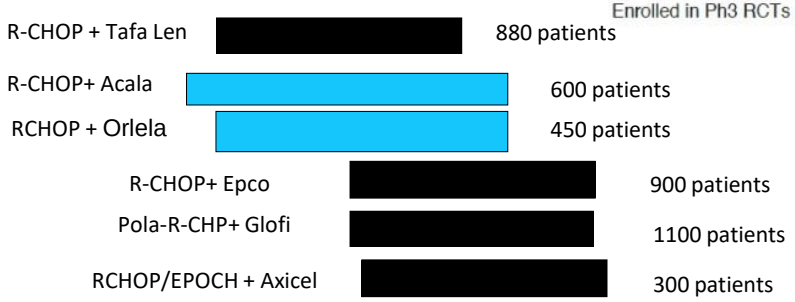
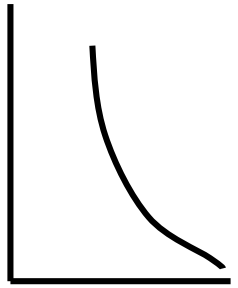
Beyond RCHOP – Molecularly Driven or Agnostic?









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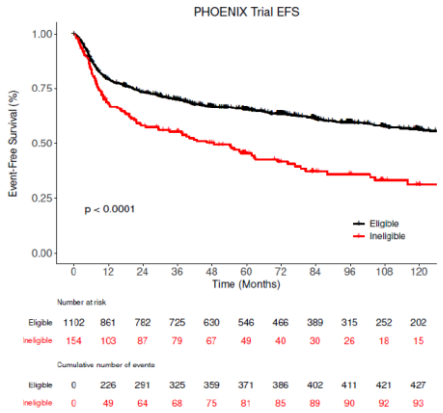
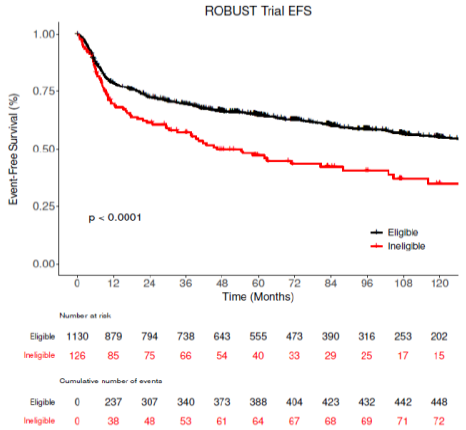
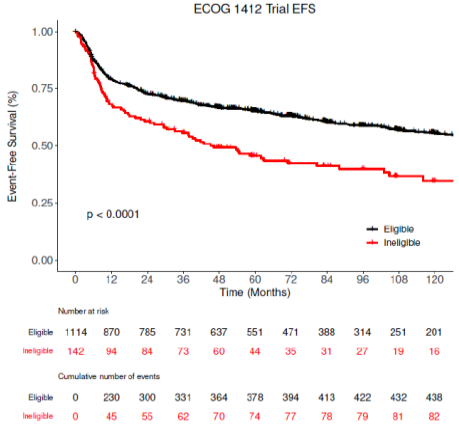
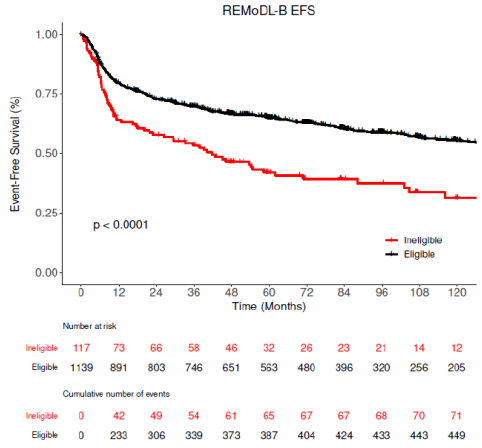
Who is left behind – eligibility criteria to clinical trials

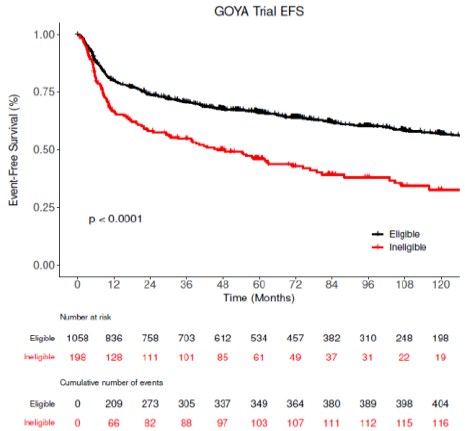
PARAMETER	PHOENIX	ROBUST	ECOG 1412	REMoDL-B	GOYA	ENGINE	CALGB 50303
Total	**12.3%**	**10.0%**	**11.3%**	**9.2%**	**15.9%**	**24.1%**	**17.2%**
ANC	1.3%	2.5%	2.5%	1.3%	2.5%	2.5%	1.3%
Platelets	3.2%	3.2%	4.7%	4.7%	3.2%	3.2%	4.7%
Hepatic	3.8%	3.8%	3.8%	1.5%	3.8%	3.8%	3.2%
Renal	5.2%	2.0%	2.0%	2.0%	5.2%	10.5%	10.5%
Hemoglobin	0.0%	1.3%	0.0%	0.0%	6.3%	12.7%	0.0%

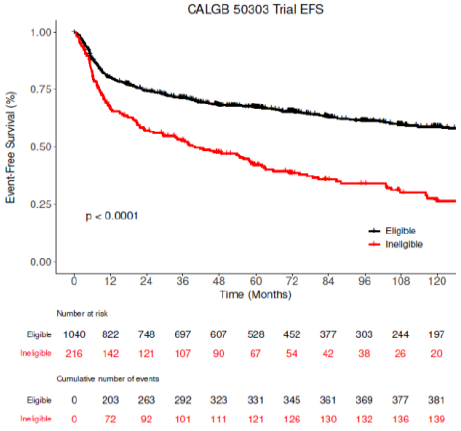












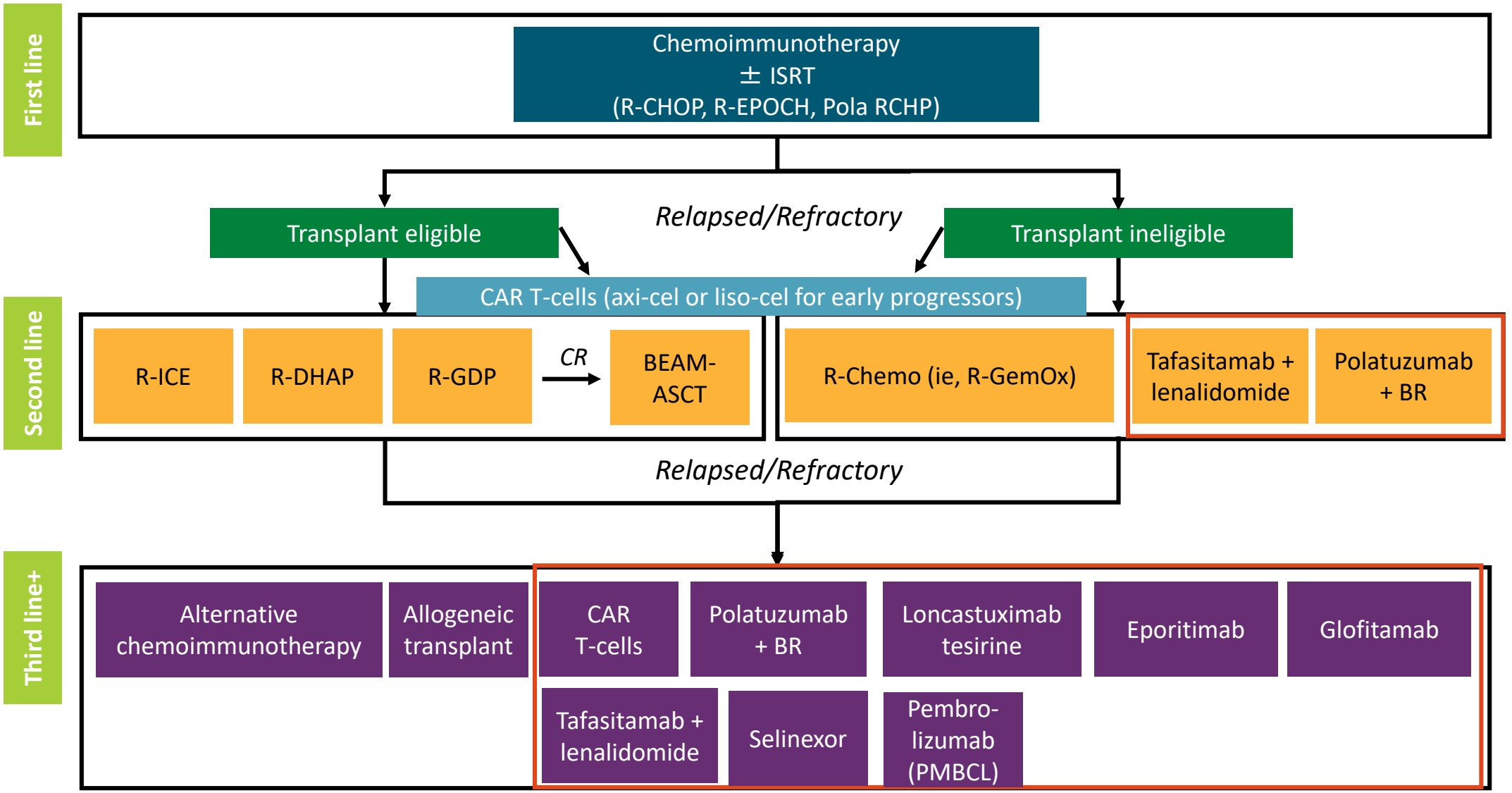
9.2-24.1% MER patients would be excluded

Khurana et al, JCO 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
  - Appears to benefit patents with high IPI
  - Benefit primary in ABC subtype
- DHL/THL may benefit from escalated chemotherapy
- There is a need to improve on RCHOP or PV-R-CHP
  - Molecularly agnostic approach is gaining traction
  - Need studies capturing patients “left behind”

The Current DLBCL Treatment Landscape



Thank You

nowakowski.grzegorz@mayo.edu