6th POSTGRADUATE

Lymphoma Conference

Frontline treatments in DLBCL: what have we learned from the recent trials?

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VOI Donna Camilla Savelli Hotel

President:
P.L. Zinzani

Disclosures

Disclosures of Grzegorz S. Nowakowski

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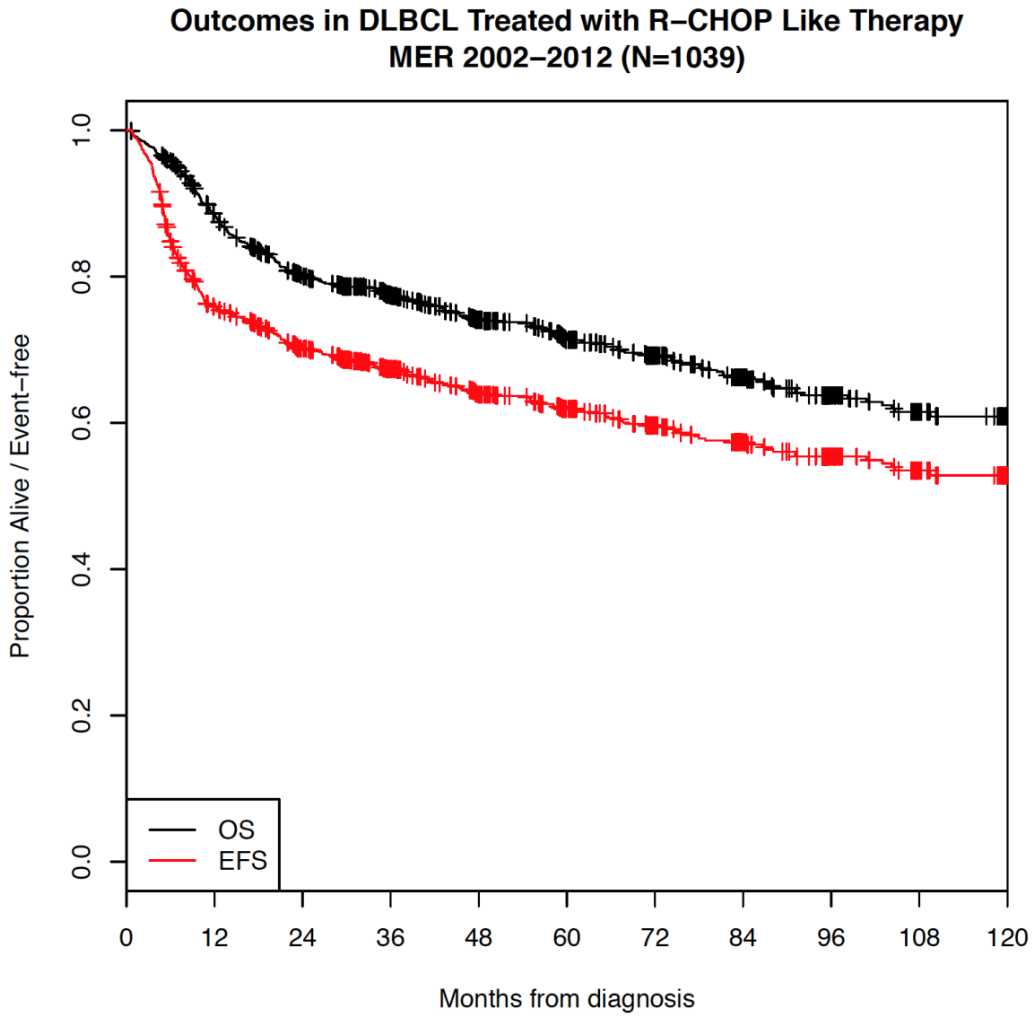
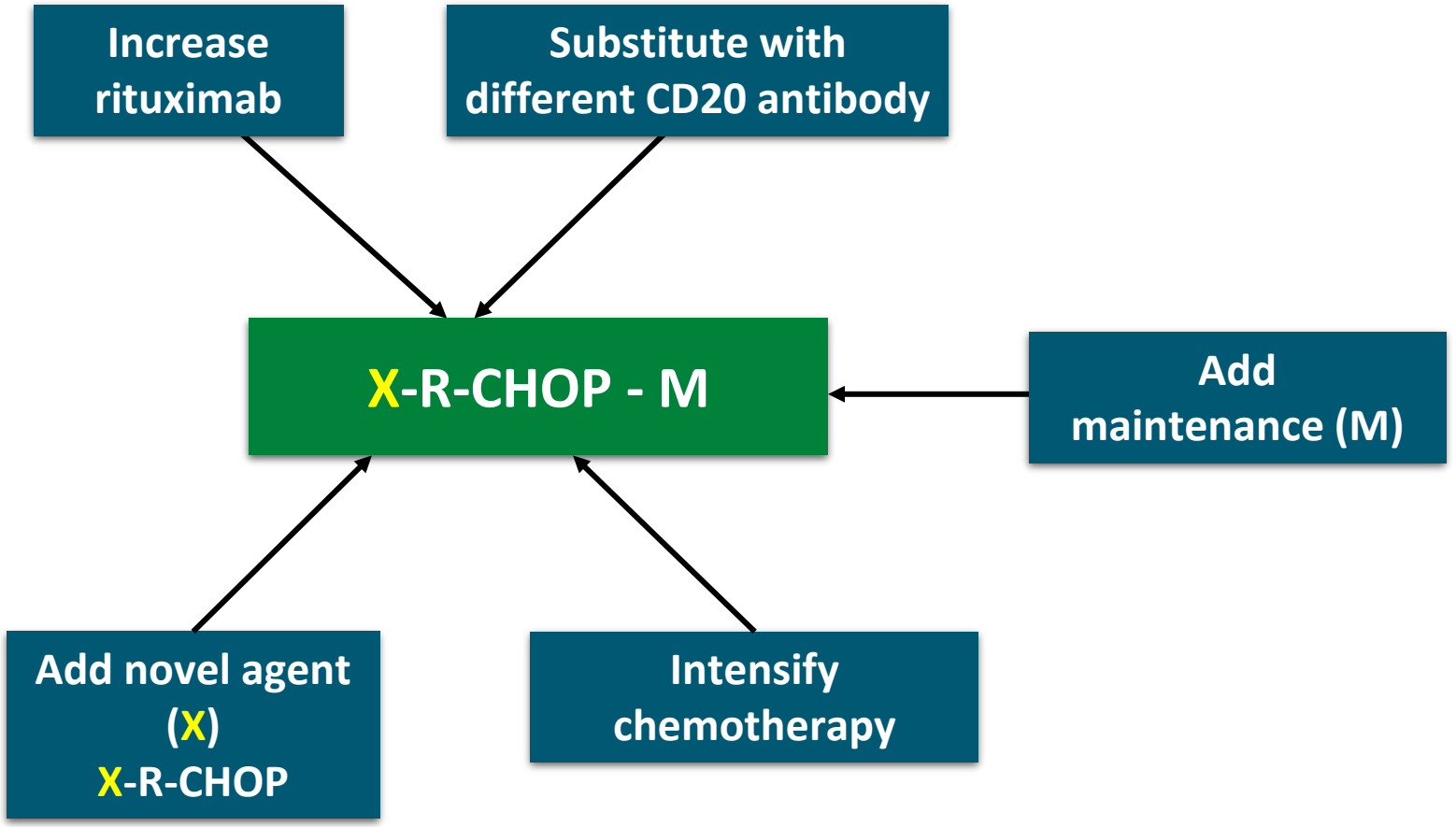
DLBCL Outcomes in Mayo Clinic/Iowa Lymphoma SPORE Database

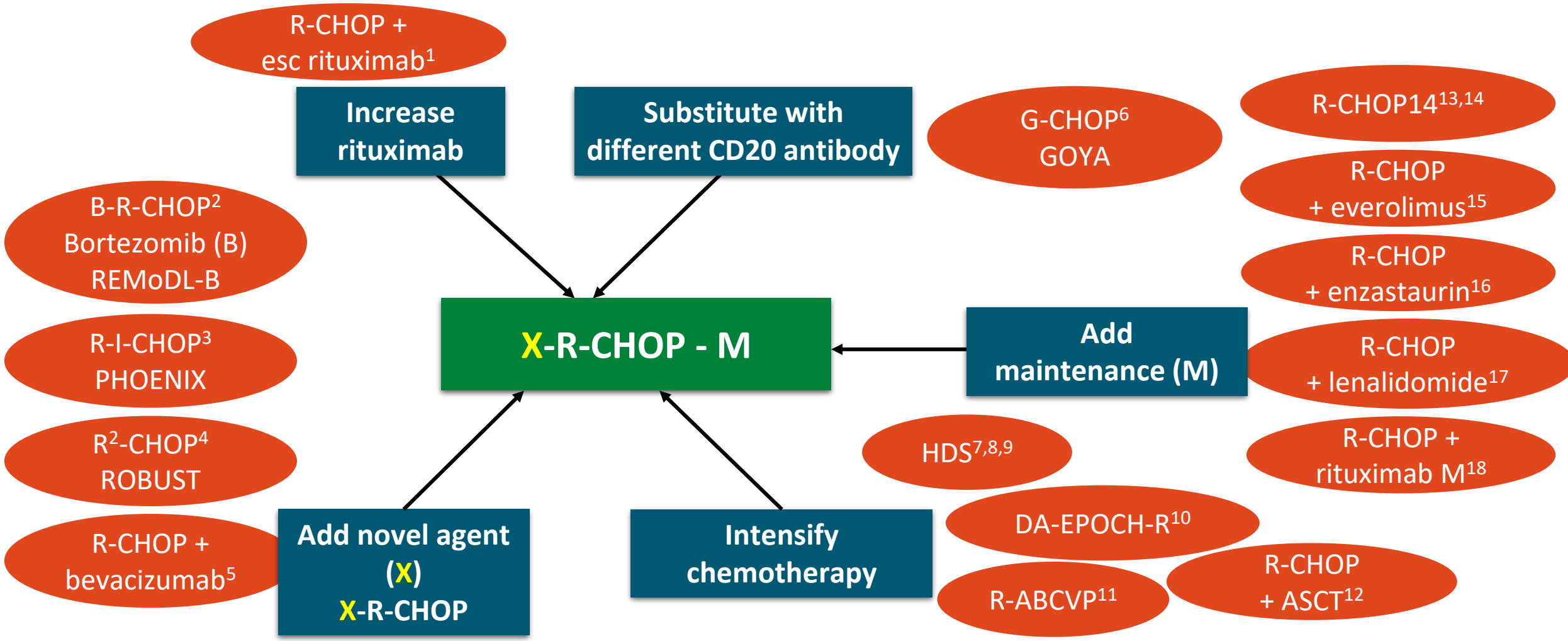


Improving on RCHOP has been difficult….

Improving on R-CHOP – Strategies



Improving on R-CHOP in DLBCL

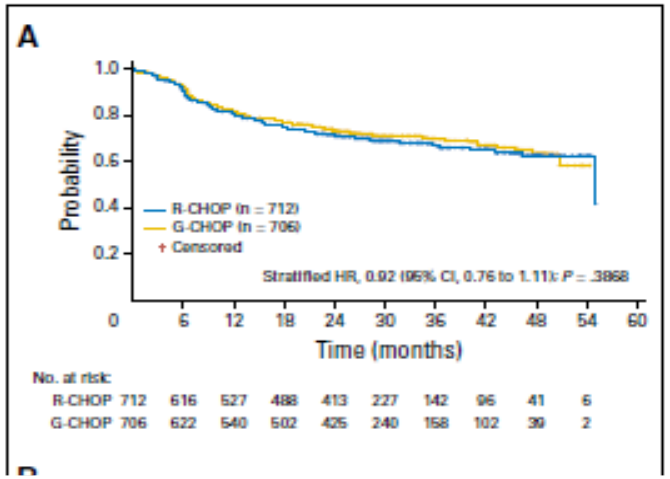


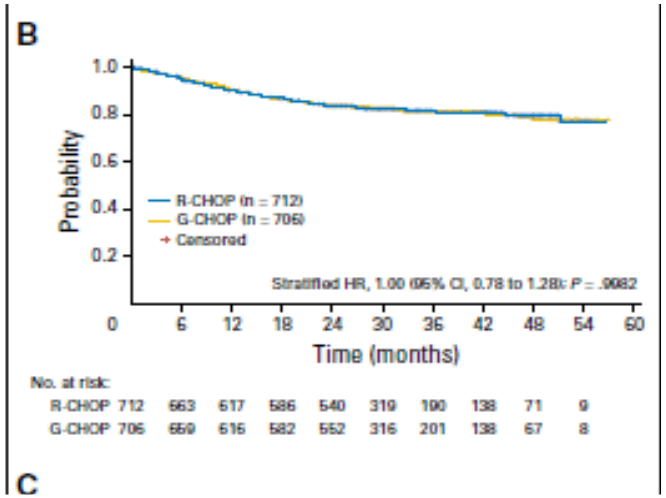
1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 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.

All trials are bias for patient selection… but frontline studies in DLBCL are particularly prone to it with impact on patents outcome…

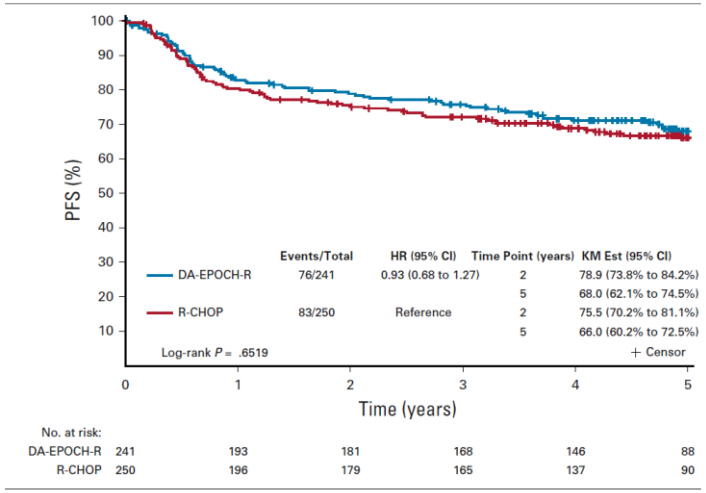
Outcomes in Phase 3 Trials Better Than Expected in Control Arms

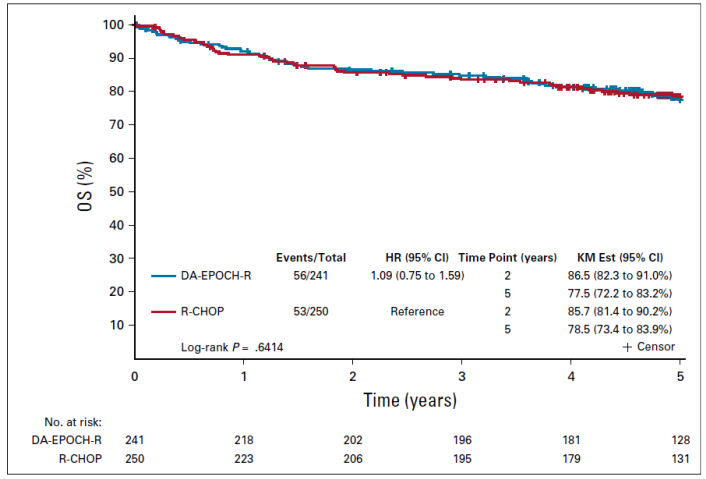
G-CHOP vs RCHOP P3 Study





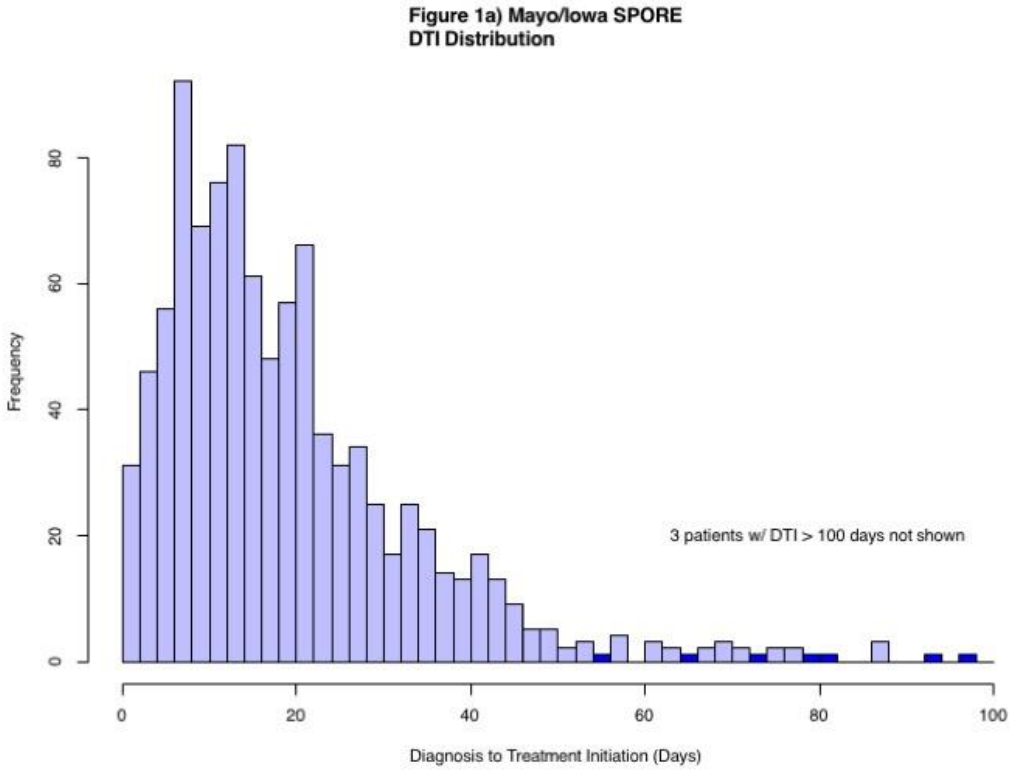
DAEPOCH-R vs RCHOP P3 Study

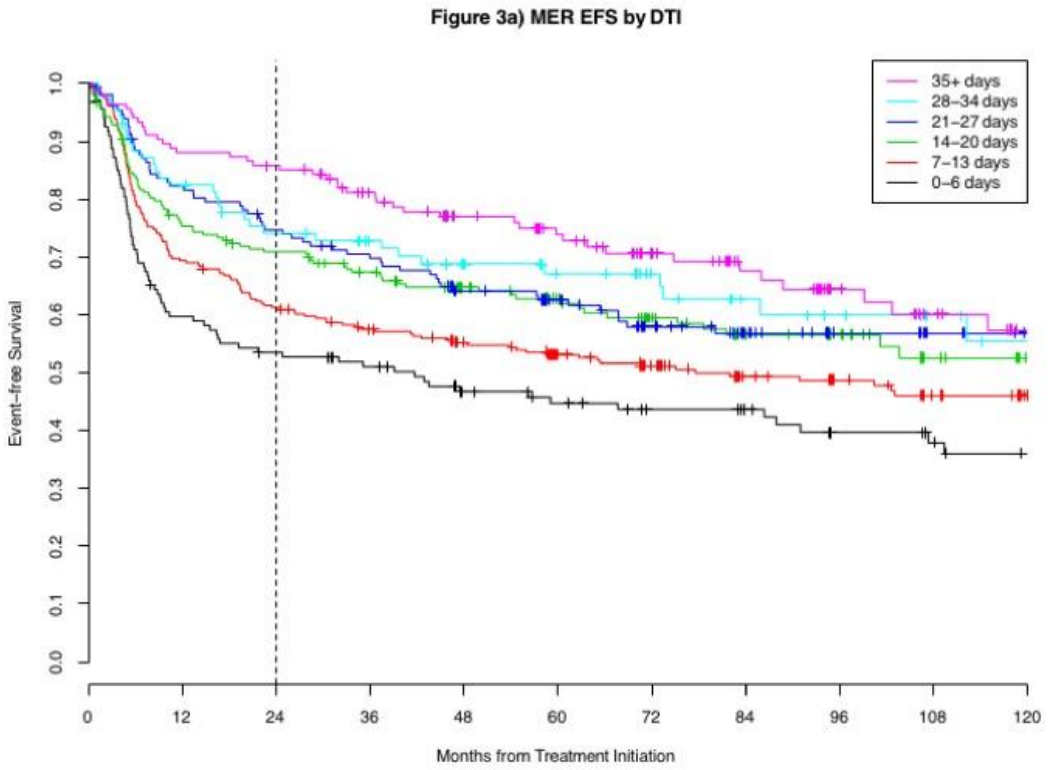




Vitolo U et al. *J Clin Oncol*. 2017;35(31):3529-3537. Bartlett NL et al. *J Clin Oncol*. 2019;37(21):1790-1799.

Time from Diagnosis to Treatment and Outcome in DLBCL



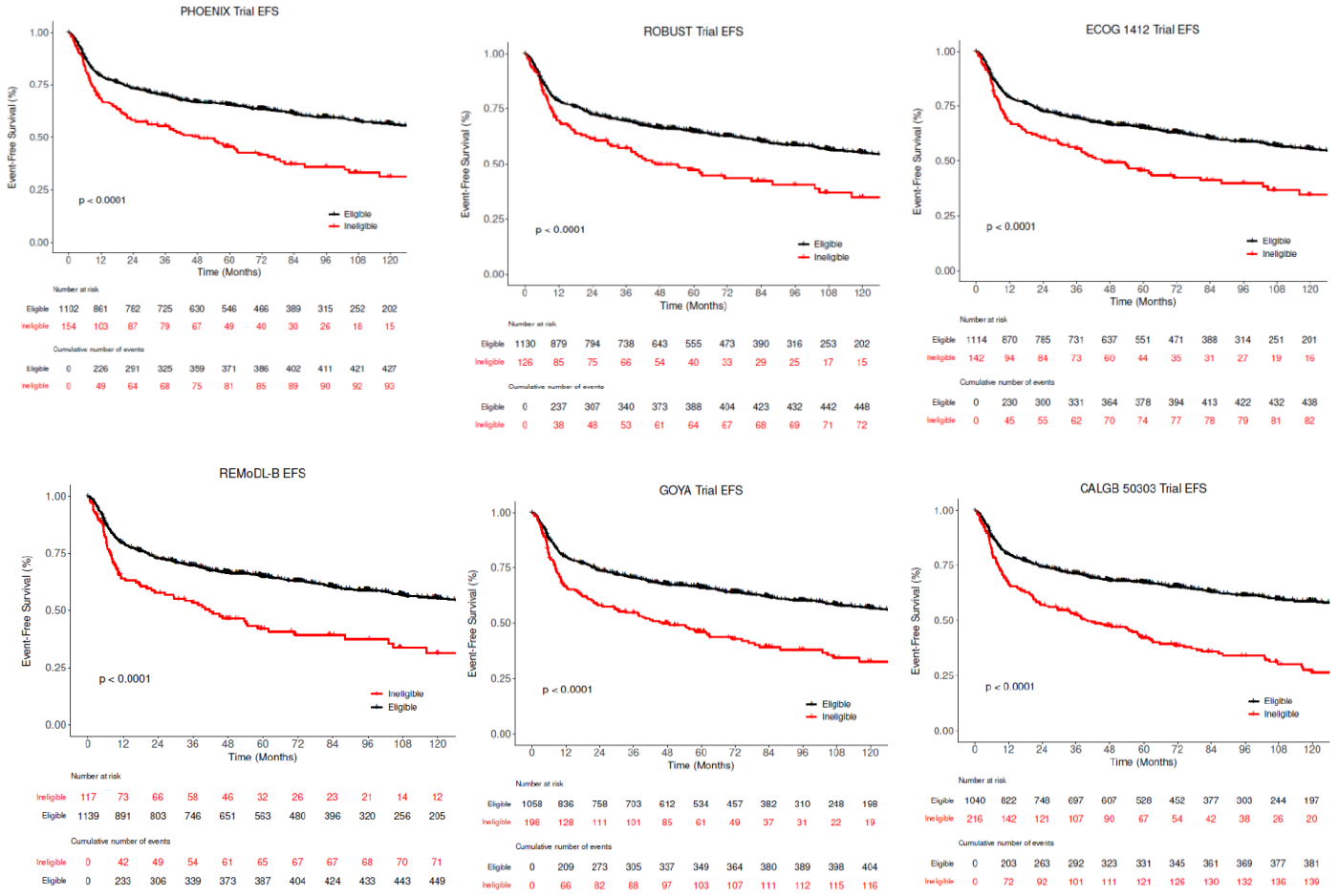


Maurer & Nowakowski J Clin Oncol. 2018 Jun 1;36(16):1603-1610.

Who is left behind – applying clinical trials eligibility criteria to real patients

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%

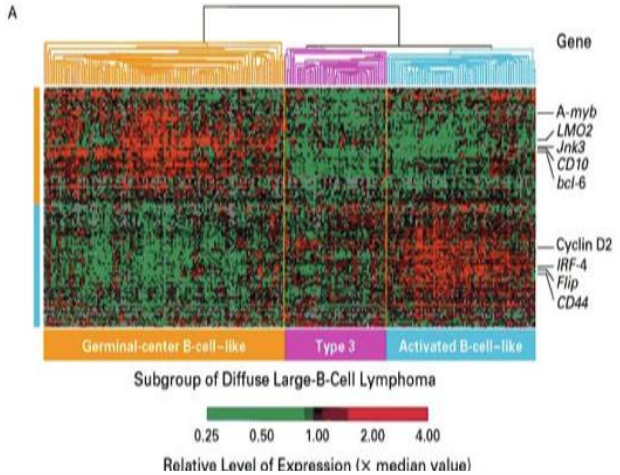
9.2-24.1% real world patients would be excluded

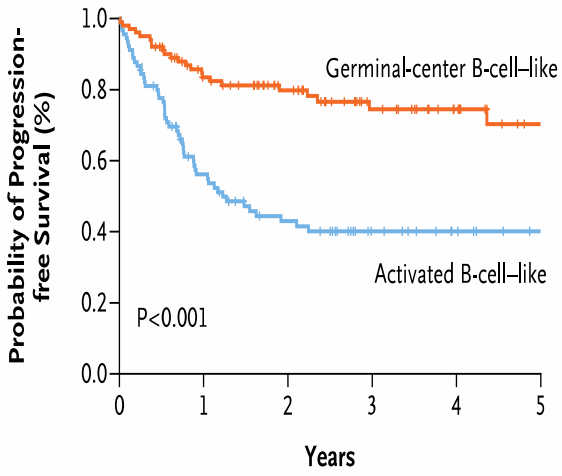


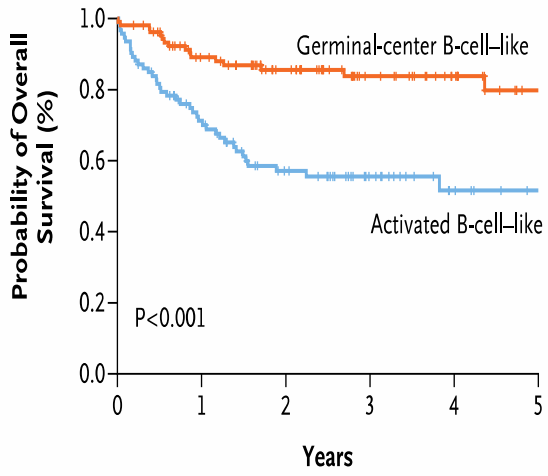
Khurana A, Nowakowski GS, Witzig TE et al JCO 2021

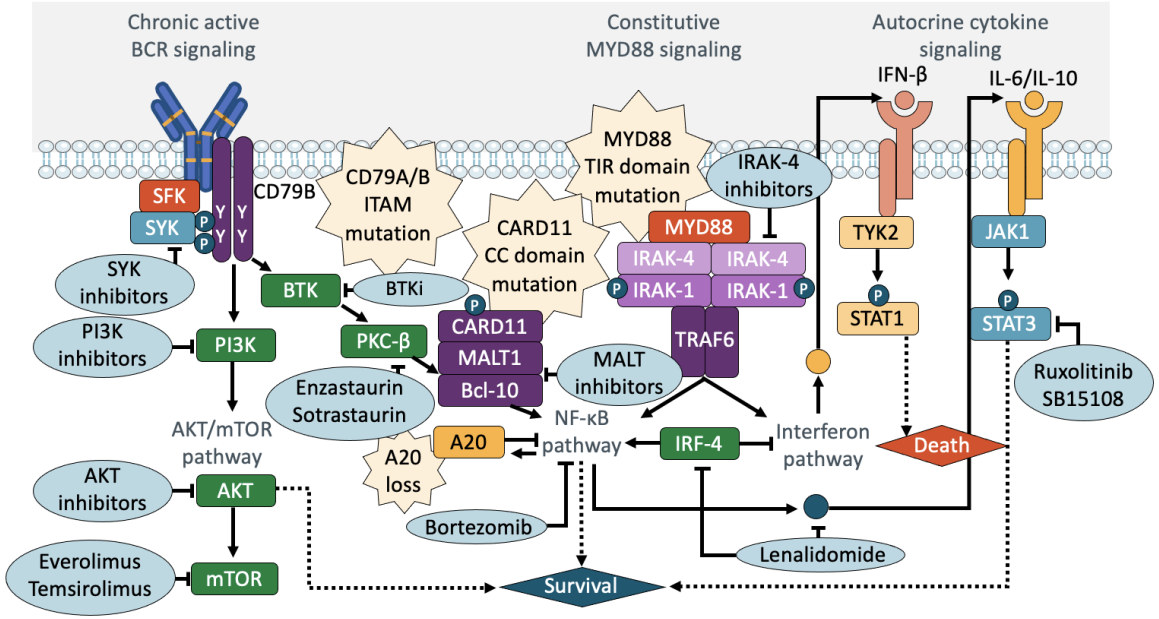
Building on molecular markers to select patents for clinical trials has been even harder…

Cell of Origin Subtypes in DLBCL and Therapeutic Potential in ABC DLBCL



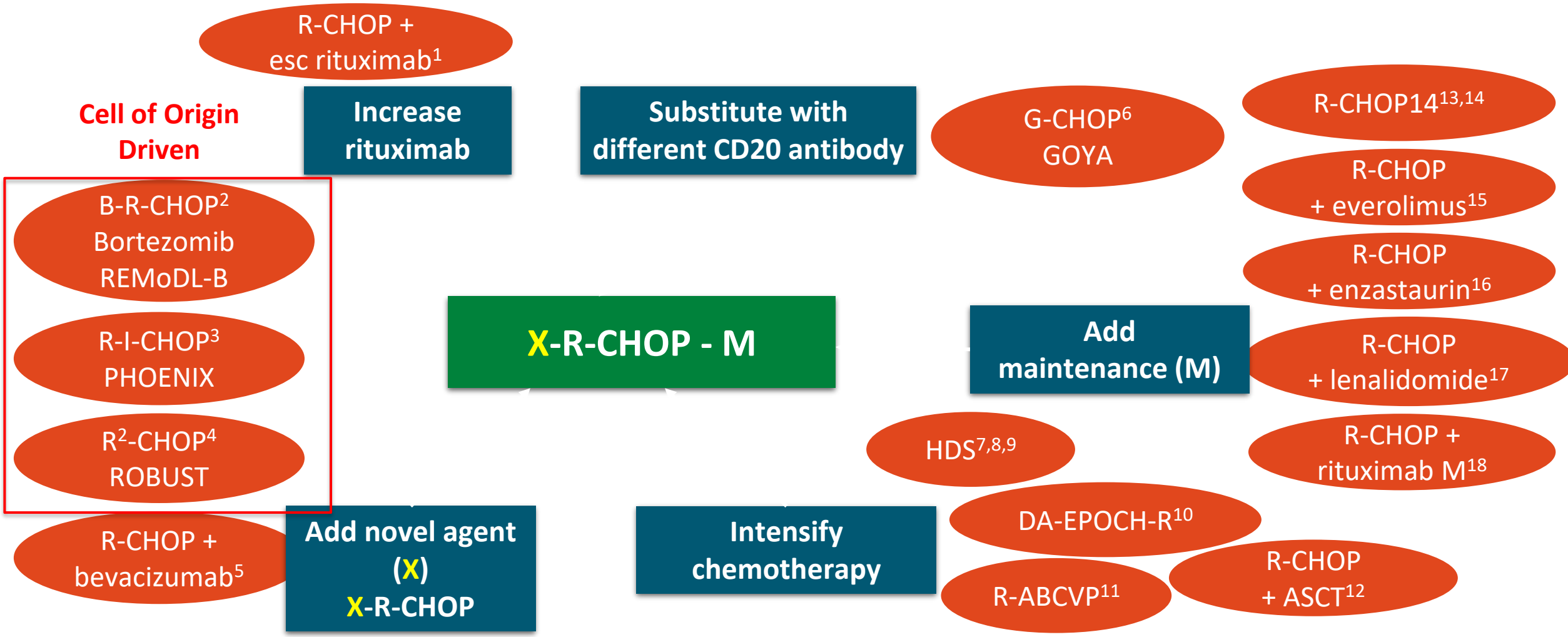






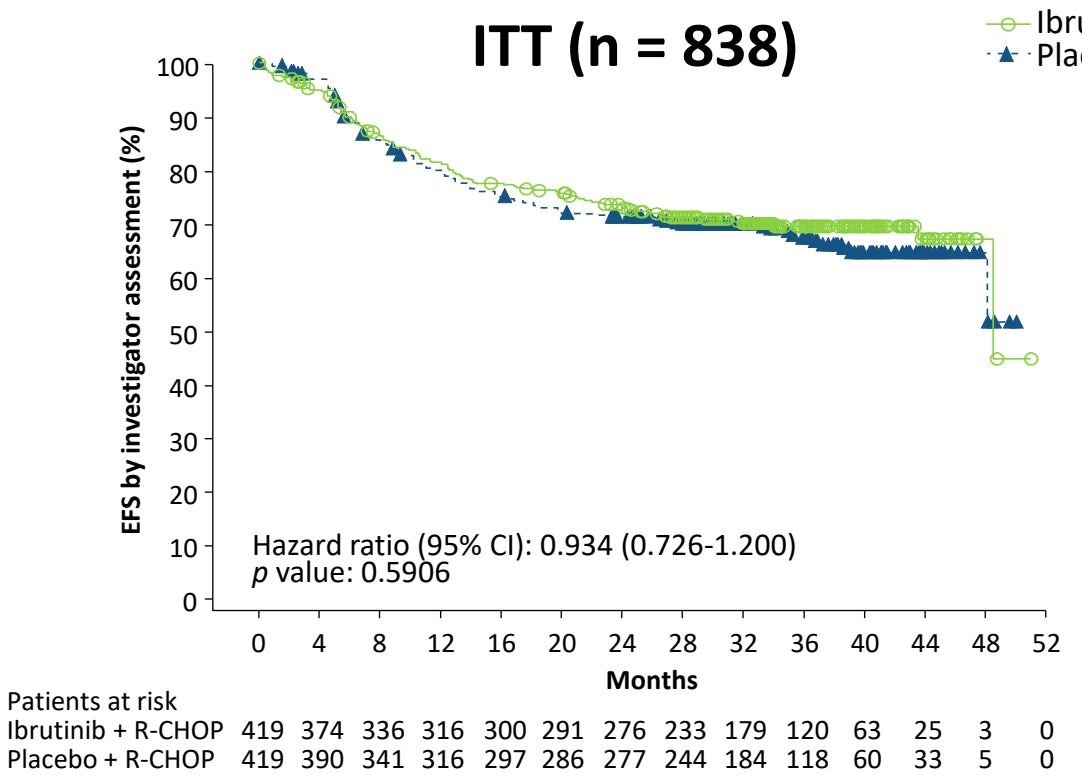
Lenz et al. N Engl J Med 2008;359:2313–2323, Roschewki. Nat Rev Clin Oncol. 2014;11:12.

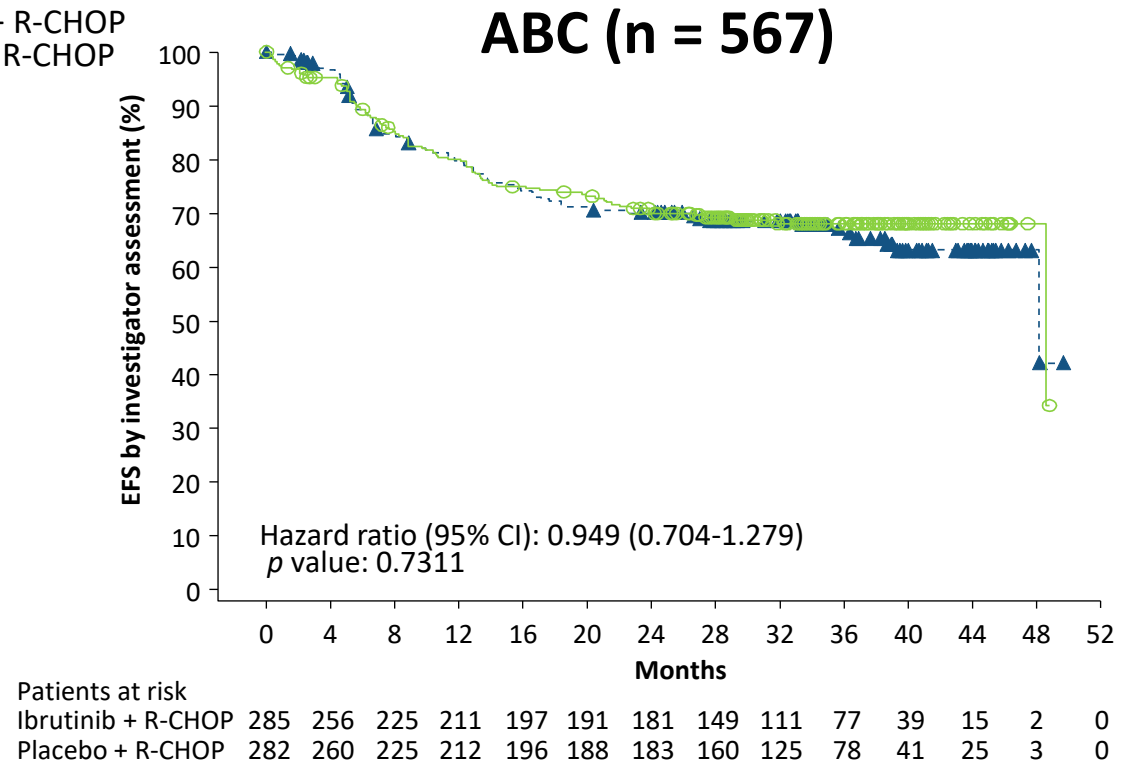
Improving on R-CHOP in DLBCL



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





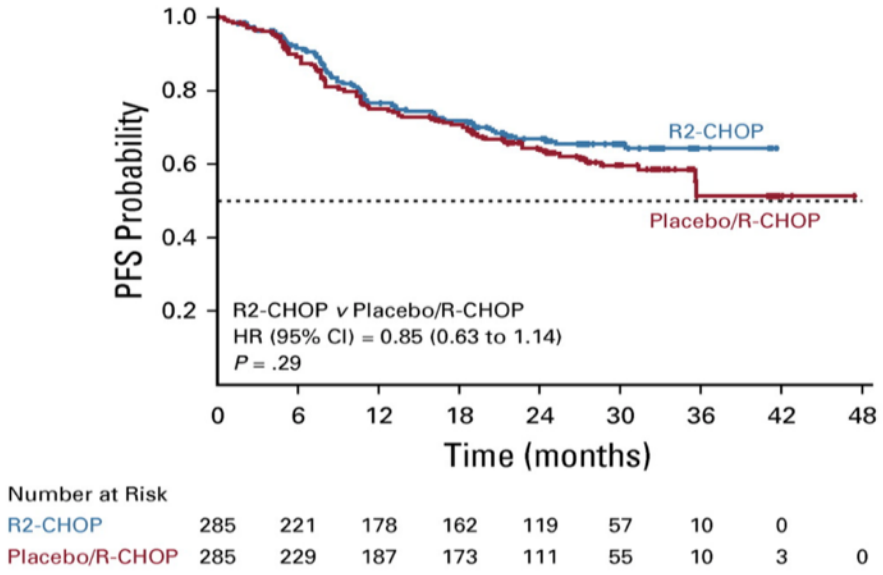
- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

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

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

Robust: Phase 3 for ABC DLBCL selected by GEP

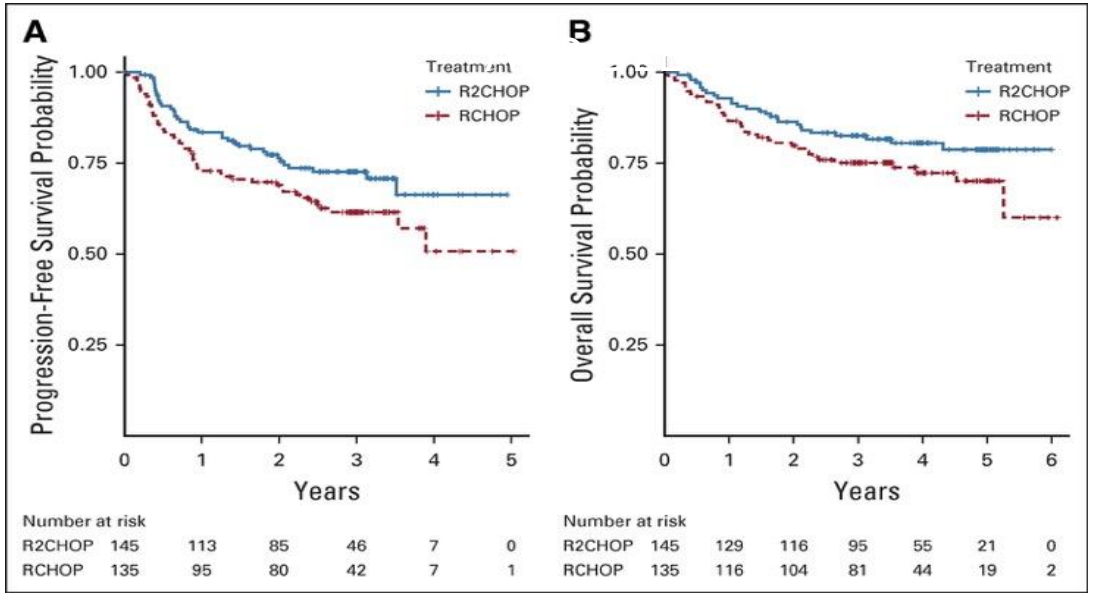
Median time to rx: 31



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

E1412: Phase 2, all Comers

Median time to rx: 20



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

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 25 mg x 10 days** + **R-CHOP** (n = 440)

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

EoT → Follow-up for up to 60 mo

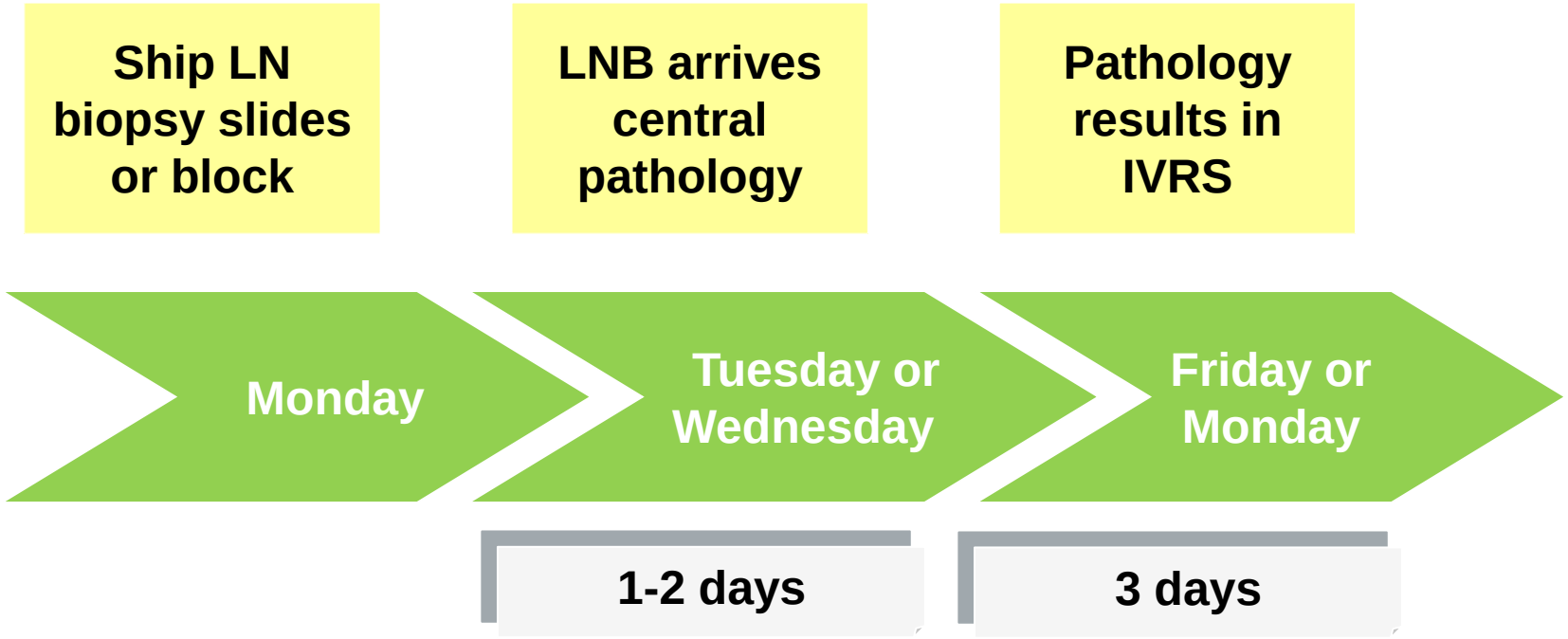
R-CHOP: IV rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 administered on D1 + oral prednisone 100 mg QD D1-5; lenalidomide: 25 mg/day on D1-10.

- **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.

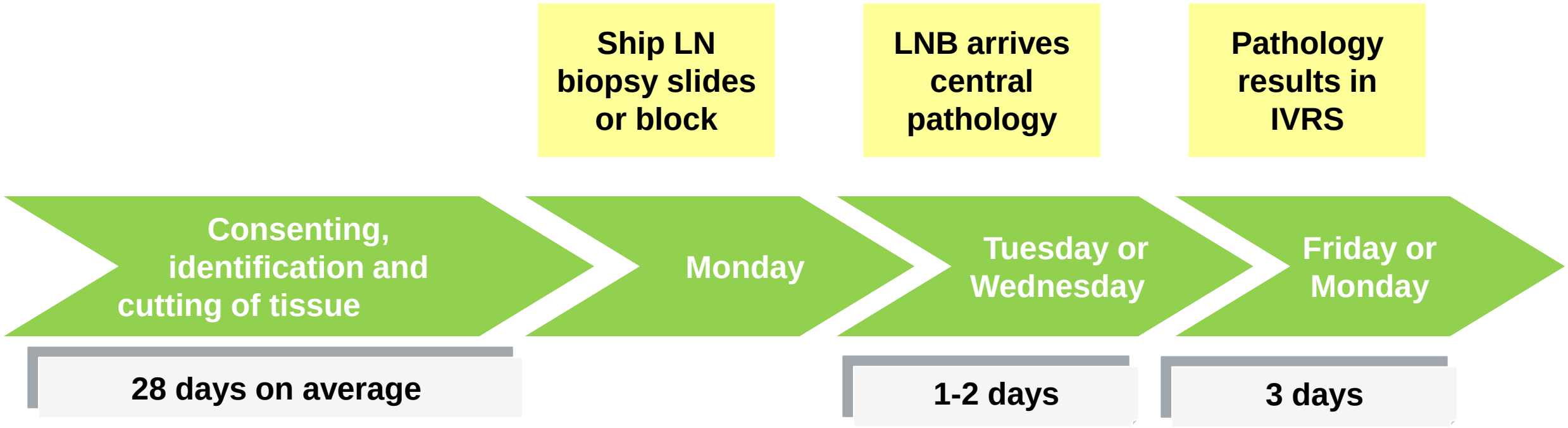
Vitolo. EHA 2021. Abstr PB1451.

Time for COO determination in Robust



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

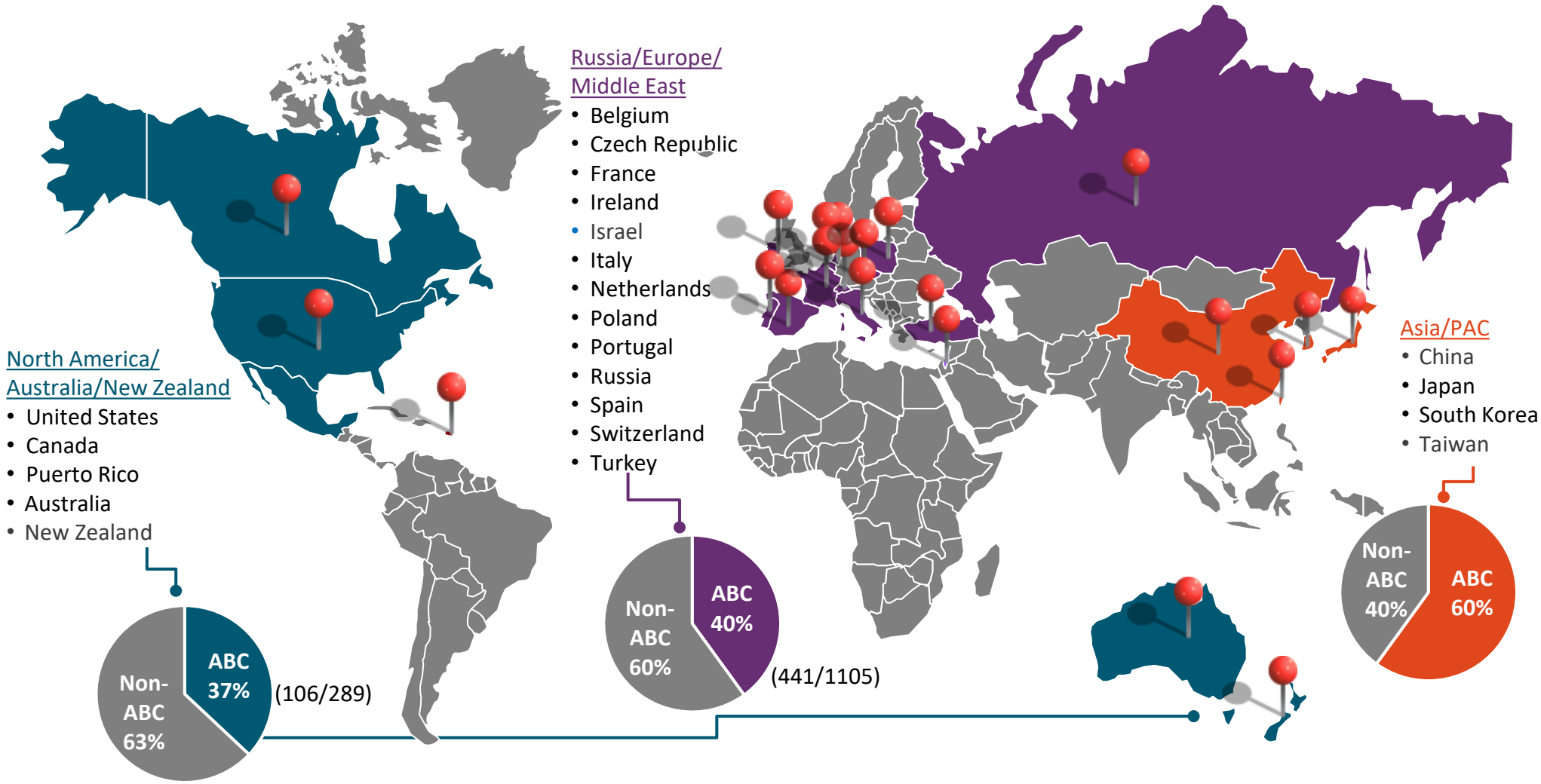
Time for COO determination in Robust



There is no way to accelerate this process

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

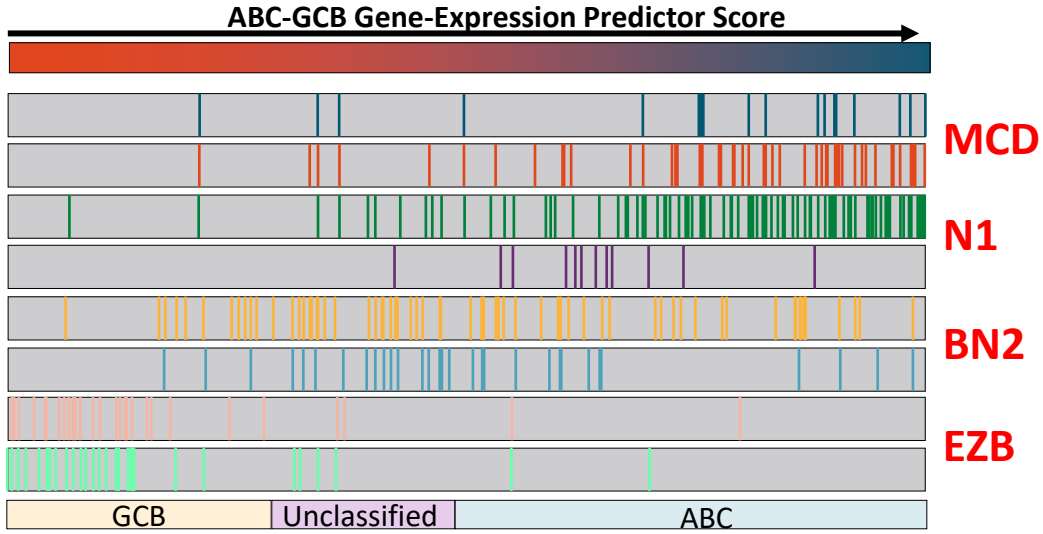
ROBUST Trial: Geographical Distribution of Cell of Origin in DLBCL

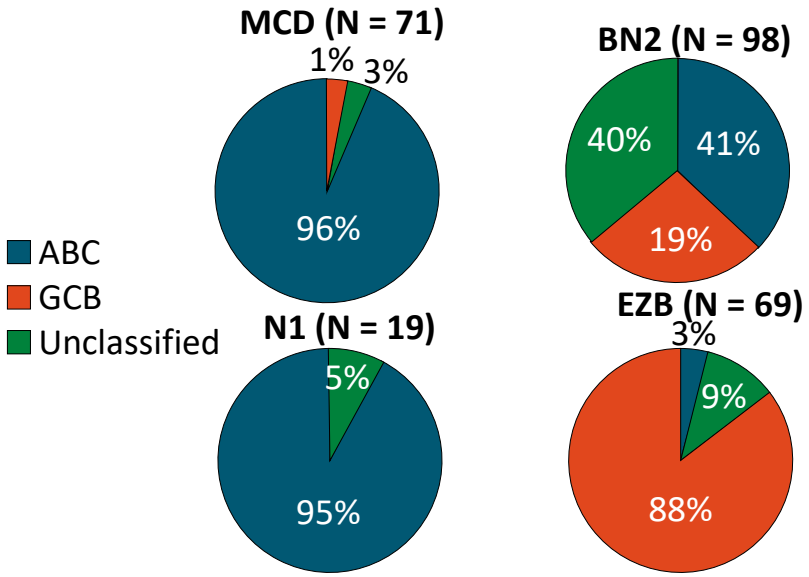


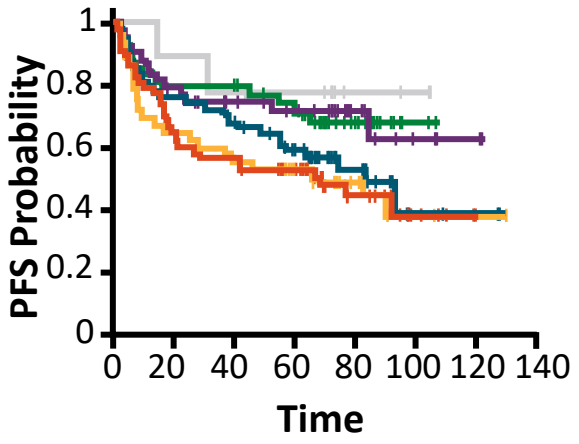
Nowakowski. Haematologica. 2020;105:e72.

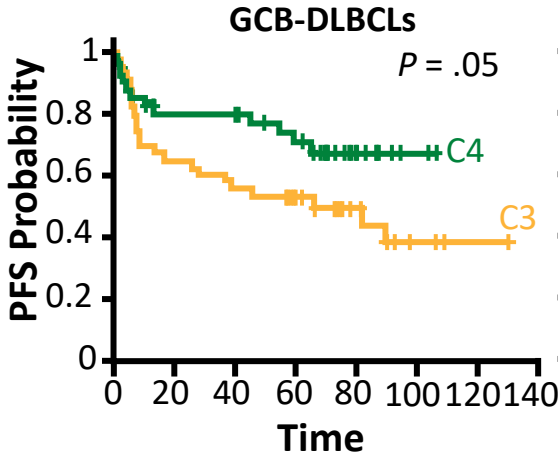
Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

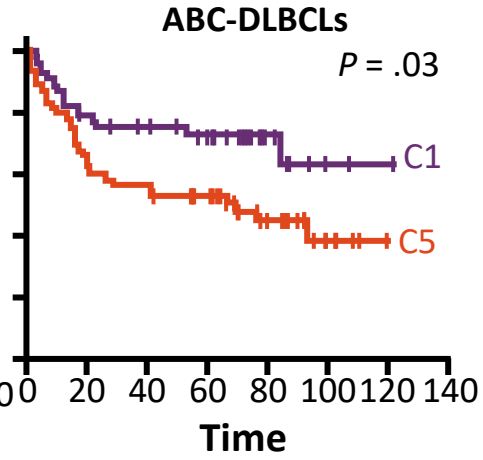
Genetic Feature	Log_{10} *P* Value	GCB	Unclass-ified	ABC
		Prevalence (%)		
CD79B+MYD88^{L265P} Double mutation	-6.4	0.6	1.7	11.5
CD79B mutation	-13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	-17.0	1.2	7.8	28.8
NOTCH1 mutation	-3.8	0.0	0.9	6.1
BCL6 fusion	-4.1	11.6	33.0	18.6
NOTCH2 mutation	-5.3	3.0	20.0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

Preliminary Results from a Phase II Trial of Frontline Acalabrutinib + DA-EPOCH-R or R-CHOP in DLBCL

Previously Untreated

Patients ≥18 yr and ECOG PS 0-2 DLBCL or HGBL, including ABC DLBCL, GCB DLBCL, unclassified DLBCL, and double-hit or triple-hit HGBL (n = 34)

Tx Window

Acalabrutinib 100 mg BID for 14 d

Tumor Size Reduction

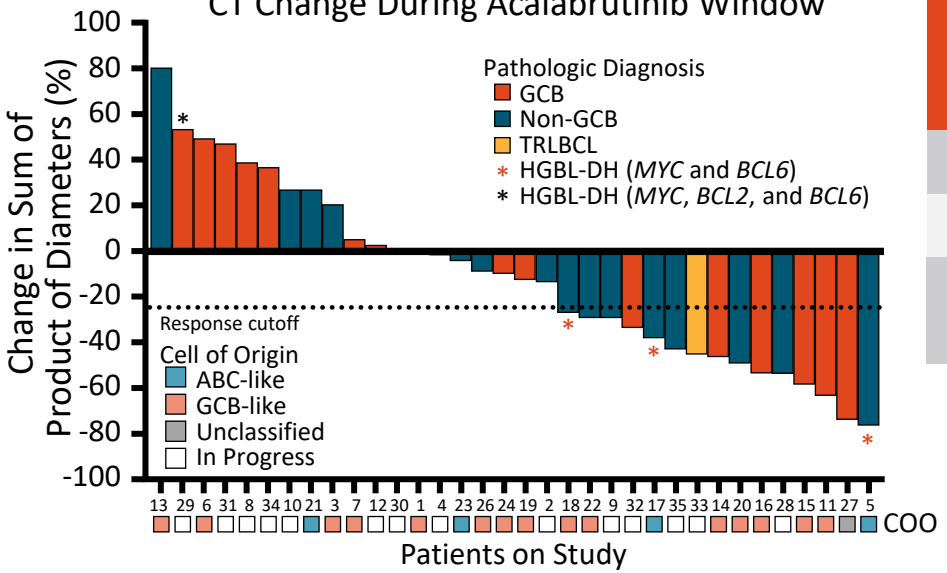
<25% → DA-EPOCH-R or R-CHOP for 4-6 cycles

≥25% → DA-EPOCH-R or R-CHOP for 4-6 cycles + Acalabrutinib for 10 days/cycle

Combination Tx

- Patients who completed tx: n = 27
  - Achieved a CR: 100%
  - Relapsed: n = 1
  - Deaths: n = 1
- After median follow-up of 9.2 mo, 1-yr PFS: 84.9%

CT Change During Acalabrutinib Window



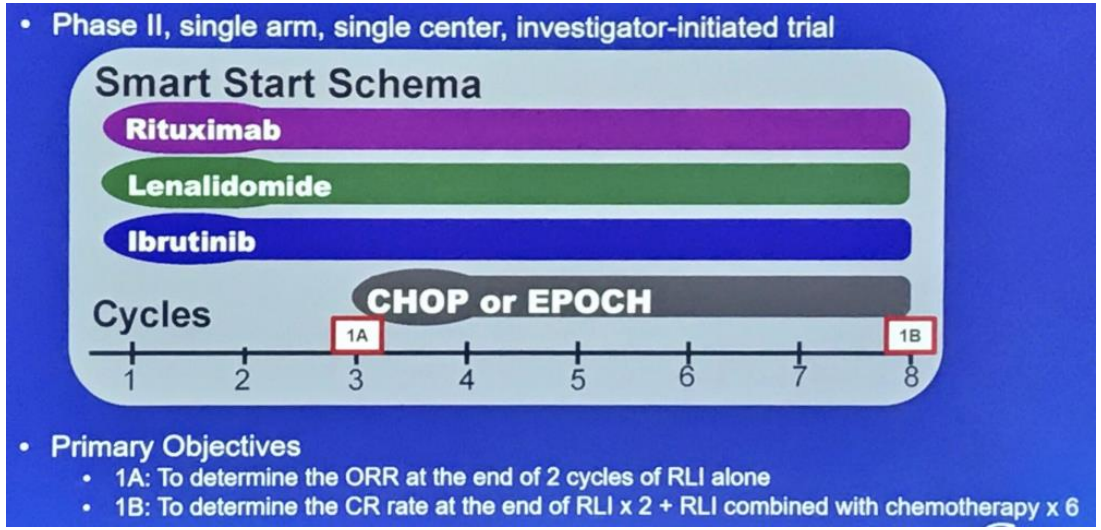
AEs Across 156 Cycles in 34 Patients, %	Acala + R-Chemo Gr 3	Gr 4
Neutropenia	50	38
Thrombocytopenia	22	12

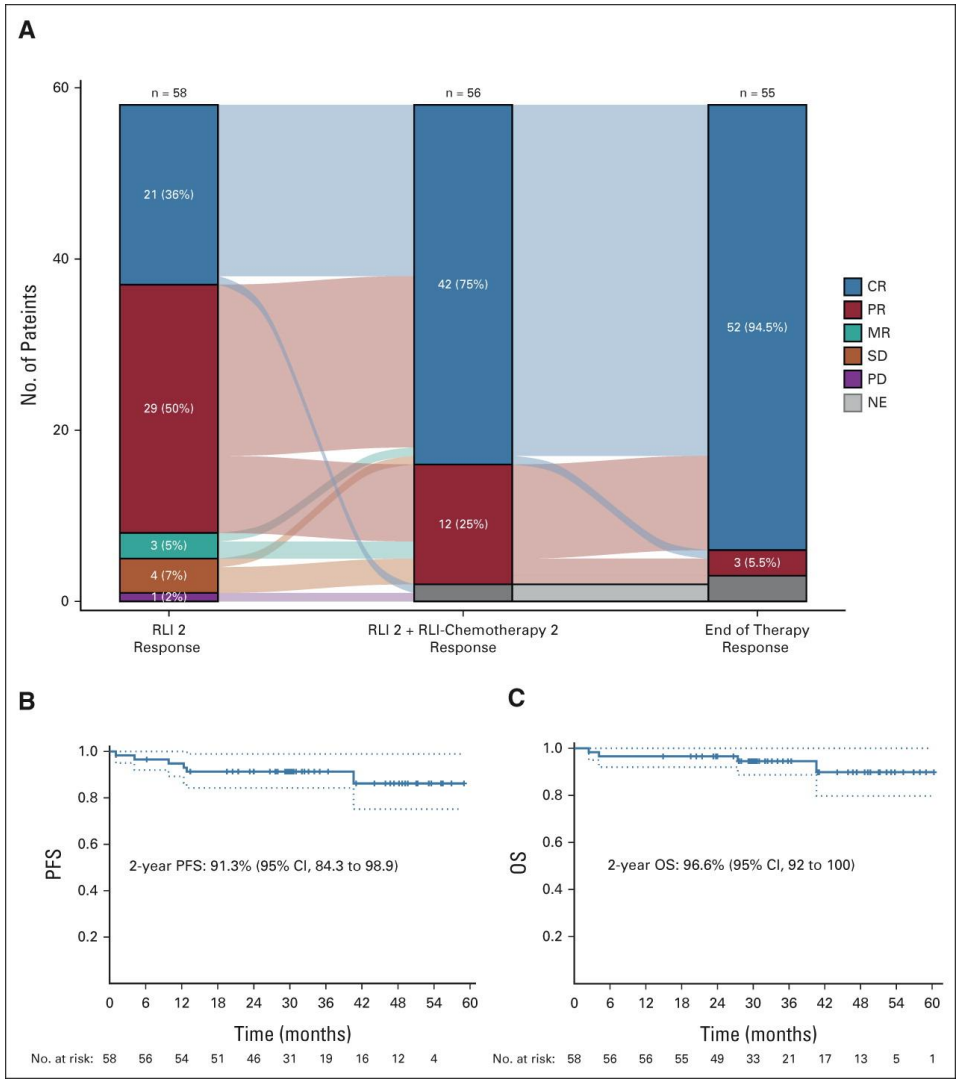
No increase in infections, atrial fibrillation, or bleeding with acalabrutinib

- Limited evidence that molecular subtypes drive responsiveness to BTK inhibitors in untreated DLBCL

Roschewski. ASH 2021. Abstr 524.

Targeted therapy with delayed chemotherapy in ABC DLBCL

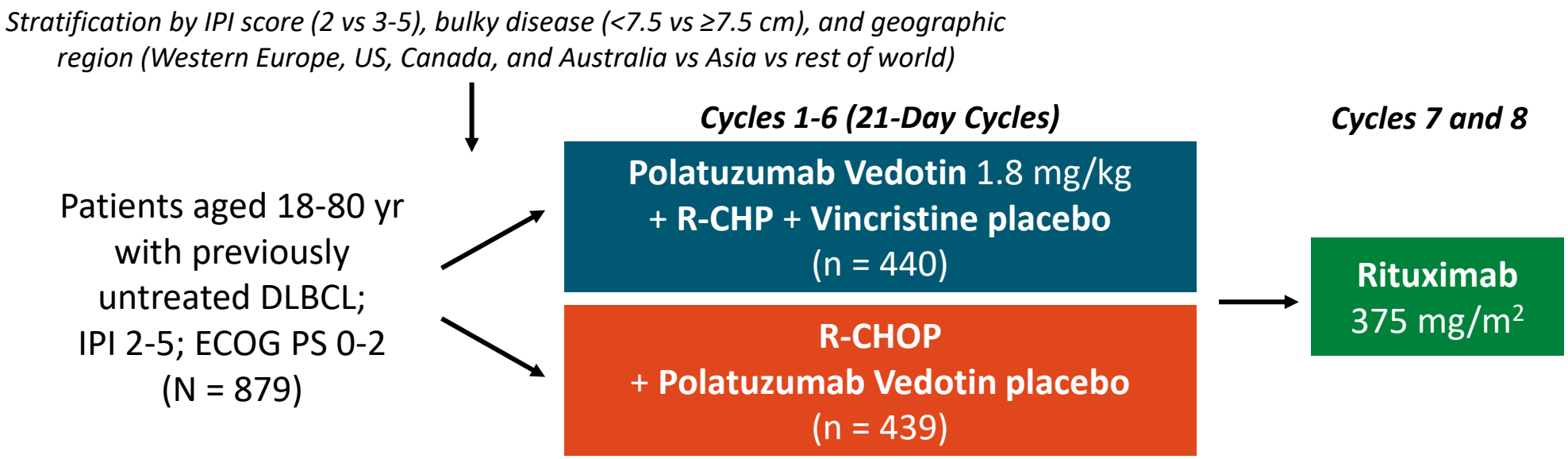




Westin, JCO 2022

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

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



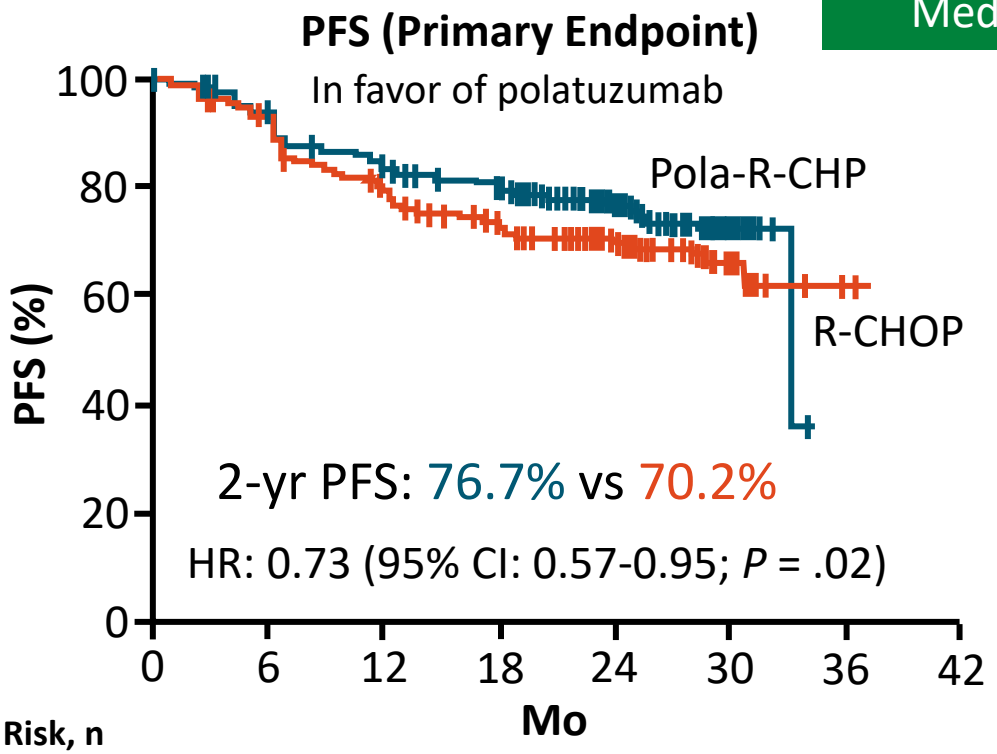
R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

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

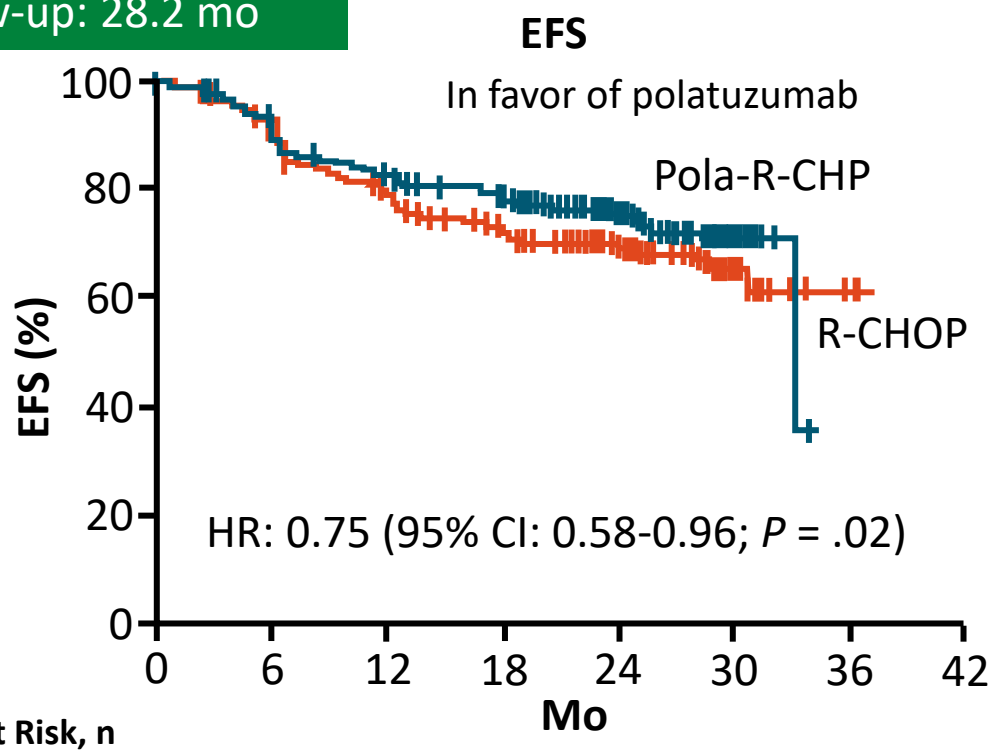
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP
PFS, EFS, and Response

Median follow-up: 28.2 mo



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



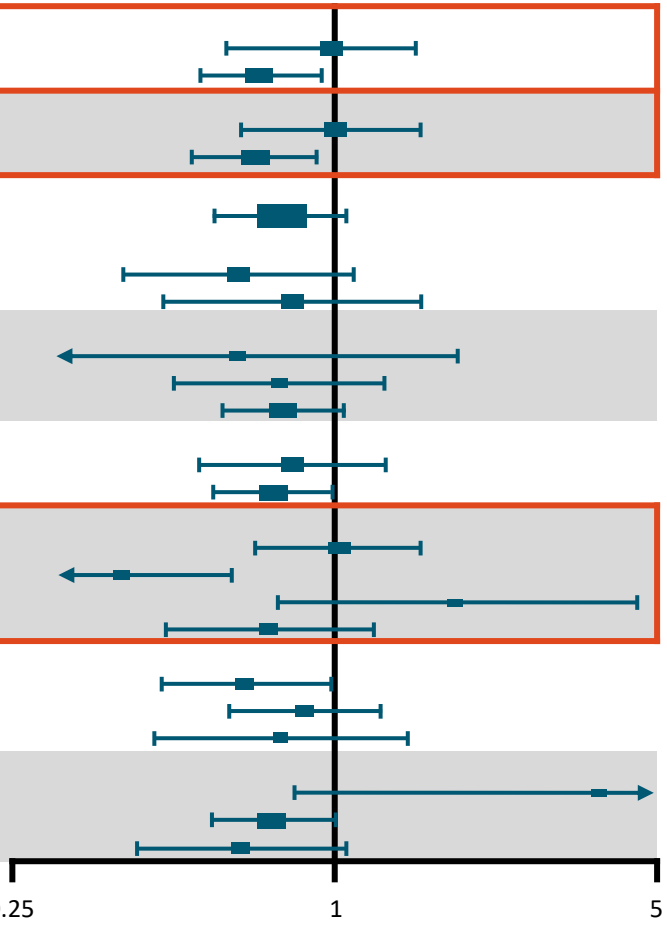
Patients at Risk, n								
Pola-R-CHP	440	402	348	323	243	78	NE	NE
R-CHOP	439	386	327	294	218	78	3	NE

- 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.

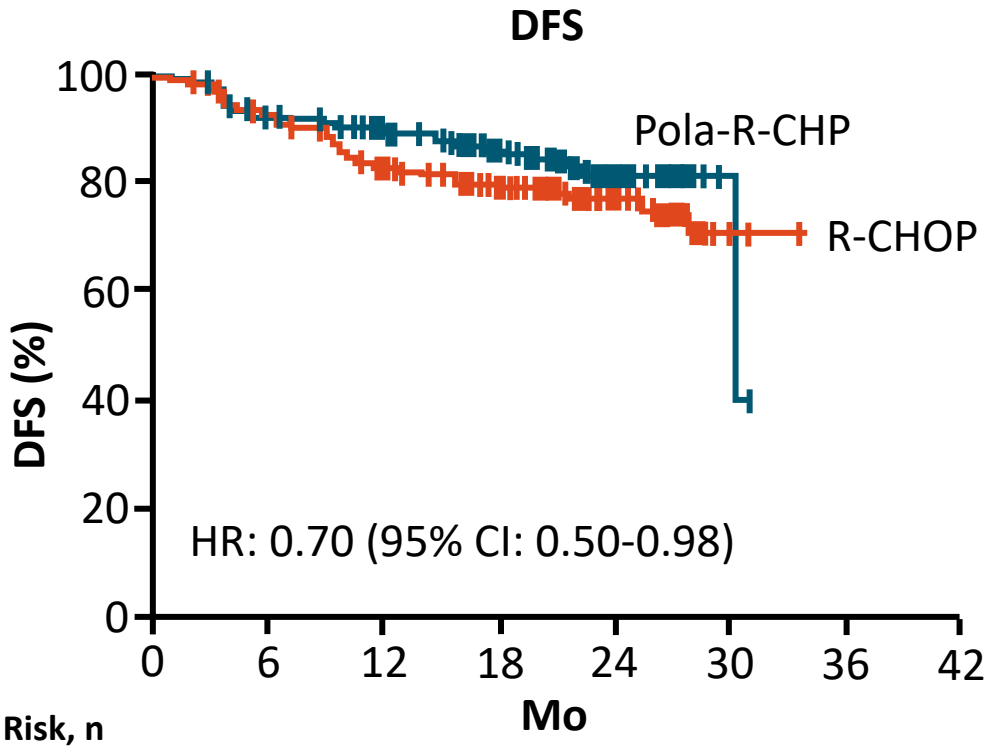
POLARIX: Subgroup Analysis of PFS

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)



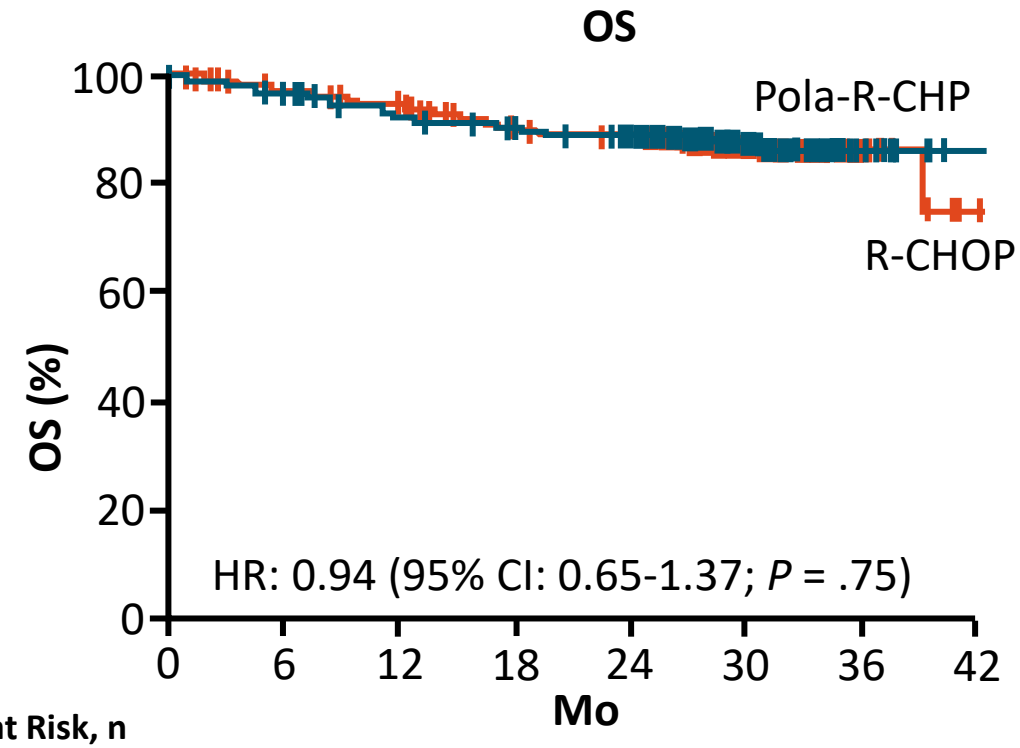
Tilly. NEJM. 2022;386:351.

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP DFS and OS



Patients at Risk, n

Pola-R-CHP	381	342	322	266	106	2	NE	NE
R-CHOP	363	326	282	238	96	5	NE	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

- DFS suggests that patients on polatuzumab who achieved CR were more likely to maintain remission
- No difference in OS between arms

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

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

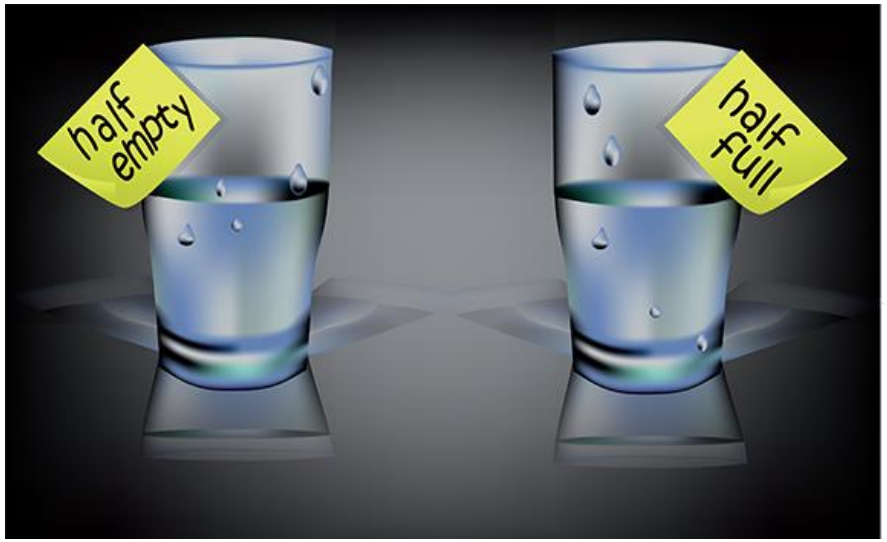
AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia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

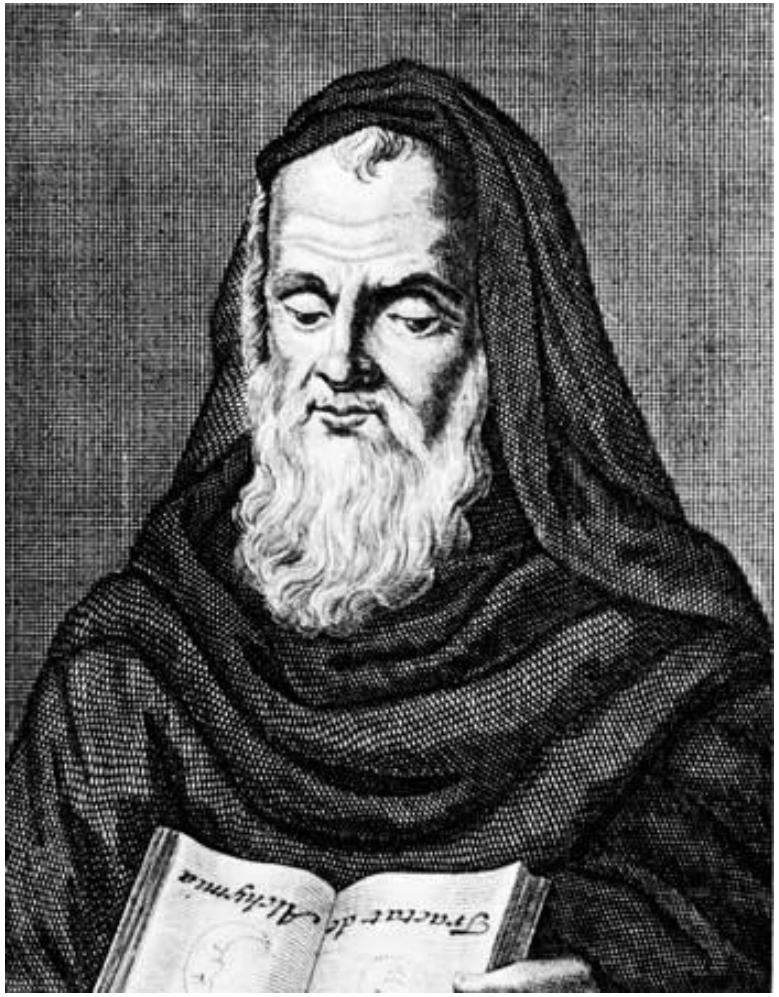
POLARIX: Analysis of PFS Outcomes

- The absolute difference in PFS is small
  - However, polatuzumab + R-CHP resulted in a relative reduction of 27%
- The late separation of the PFS curves is very interesting
  - **It is easier to impact patients with "less refractory" disease**
  - **Lack of OS difference puts PFS in question as a surrogate marker in of OS: early PFS separation yes, late no?**
- Signal in ABC DLBCL ? biology



POLARIX: Analysis of PFS Outcomes

- The absolute difference in PFS is small
  - However, polatuzumab + R-CHP resulted in a relative reduction of 27%
- The late separation of the PFS curves is very interesting
  - It is easier to impact patients with “less refractory” disease
- **R-CHOP can be improved upon !**



Roger Bacon

Select Key Strategies Under Investigation in Frontline DLBCL

Study	Patient Population	Treatment Arms	Estimated N	Trial Status	Primary Endpoint(s)
ESCALADE (NCT04529772)	Non-GCB DLBCL; 18-70 yr	Acalabrutinib + R-CHOP	600	Recruiting	**PFS** Per Lugano classification (up to 60 mo)
frontMIND (NCT04824092)	High-intermediate and high-risk DLBCL; 18-80 yr	R-CHOP ± tafasitamab and lenalidomide	880	Recruiting	**PFS** by investigator (up to 43 mo)
GO40515 (NCT03677141)	B-cell lymphoma; IPI 2-5; ≥18 yr	Mosunetuzumab + CHOP or polatuzumab vedotin-CHP	160	Active, not recruiting	Safety; CR rate (by PET)
M22-132 (NCT05283720)	Non-Hodgkin lymphoma; CD20+; ≥18 yr	Epcoritamab + antineoplastic agents	132	Not yet recruiting	Dose-limiting toxicities (up to 60 mo)
19-C-0116 (NCT04002947)	Aggressive B-cell lymphoma; HGBL; ≥18 yr	Acalabrutinib + DA-EPOCH-R or R-CHOP	132	Recruiting	**Response rate** (every 2 cycles)

Clinicaltrials.gov.

Novel and Emerging Combinations: Next Wave of R-CHOP "Plus"

- Bispecific antibodies plus:
  - R-CHOP
  - R-CHP/Polatuzumab vedotin
- R^2-CHOP + tafasitamab
- Loncastuximab tesirine + R-CHOP
- R-CHOP plus CART

Agnostic
- CAR T-cell therapy
- Tafasitamab/lenalidomide
- Loncastuximab tesirine
- Polatuzumab vedotin

- BTK inhibitors
- PI3K inhibitors
- BCL2 inhibitors
- IRAK4 inhibitors

Tilly. NEJM. 2022;386:351. Belada. ASH 2021. Abstr 1413. Belada. ASH 2021. Abstr 3556. Hamadani. ASCO 2021. Abstr TPS7574.

Lessons from recent trials

- RCHOP can and will be improved
- Studies capturing
  - real world patents and
  - using agents active across molecular spectrum of the disease more likely to succeed

Thank you

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