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Has the first-line standard truly changed in advanced stage DLBCL?

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Disclosures for Andrew D. Zelenetz, MD, PhD

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Major Stockholder	None
Speakers Bureau	None
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International Standard of Care: R-CHOP (2001-2023?)

Rituximab 375 mg/m² day 1

Cyclophosphamide 750 mg/m² day 1

Doxorubicin 50 mg/m² day 1

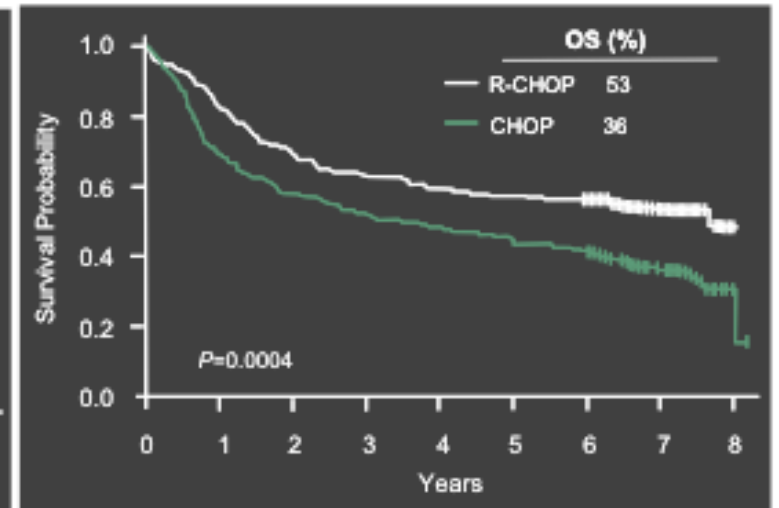
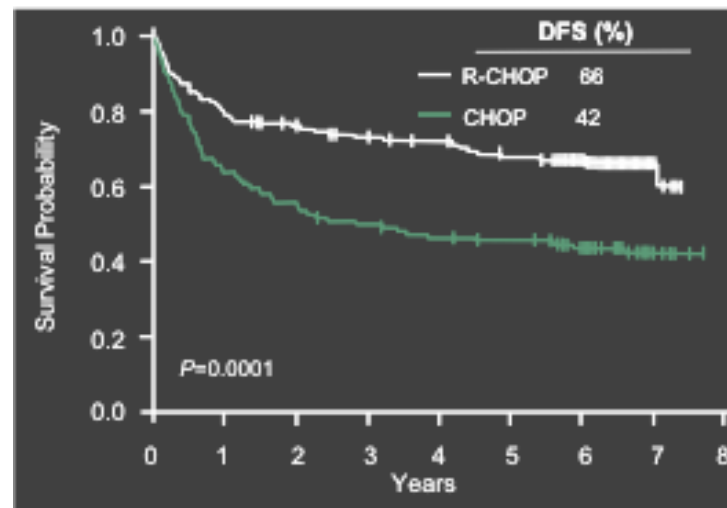
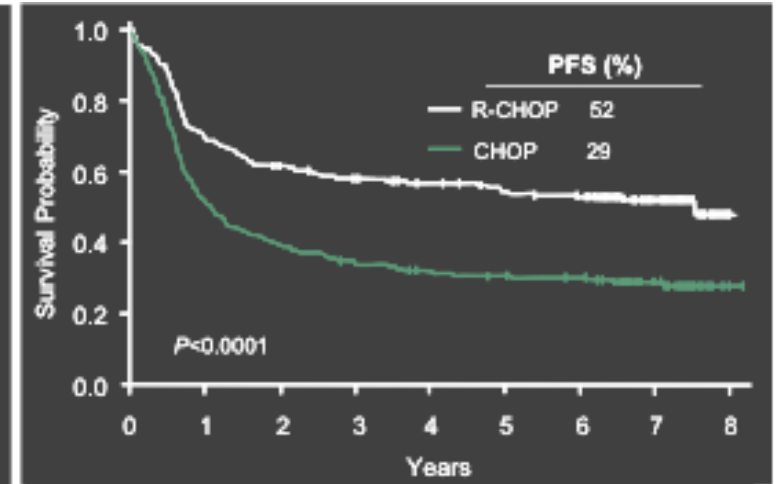
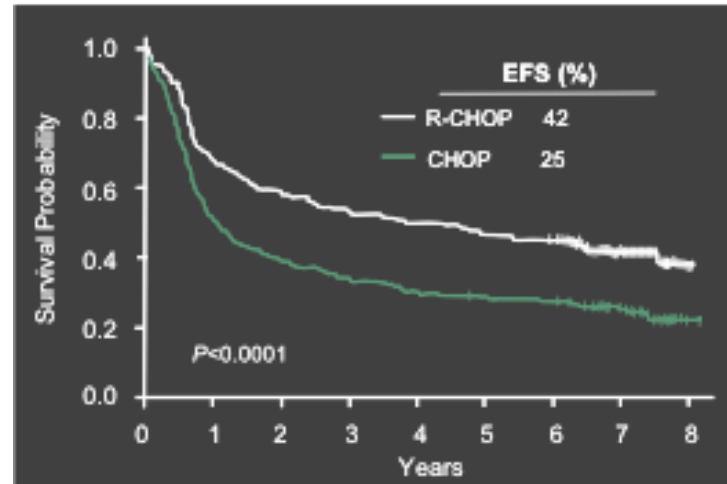
Vincristine 1.4 mg/m² day 1 (2 mg max)

Prednisone 40 mg/m² (or 100 mg) daily x 5

Age > 60 Pegfilgrastim 6 mg subcut day 2

Original Gela LNH 98-5 confirmed in multiple studies

- Caveat: this standard does not apply to
 - PMBL
 - HGL with translocation of MYC and BCL2 and/or BCL6
 - PCNS



Improving on R-CHOP-21: Alternative Dosing and Regimens

Investigational Arm	PFS HR (p-value)	OS HR (p-value)	Comments	Ref
R-CHOEP	NR (0.571)	NR (0.257), IPI 1±bulk		Pfreundschuh et al. Lancet Oncol 2011 12:1013-1022
R-ACVBP	0.48 (0.0015)	0.44 (0.0071)	Age 18-59, IPI 1	Récher et al. Lancet 2011 378:1858-1867
R-CHOP-14	0.99 (0.8983)	0.96 (0.7487)		Delarue et al. Lancet Oncol 2013 14:525-533
	0.94 (0.5907)	0.90 (0.3763)		Cunningham et al., Lancet 2013 381:1817-1826
G-CHOP	0.92 (0.3868)	1.00 (0.9982)		Vitolo et al. J Clin Oncol 2017 35:3529-3537
DA-EPOCH-R	0.93 (0.6519)	1.09 (0.6414)		Bartlett et al. J Clin Oncol 2019 DOI: 10.1200/JCO.18.01994



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Improving on R-CHOP-21: Maintenance After Induction with R- CHOP-like Therapy

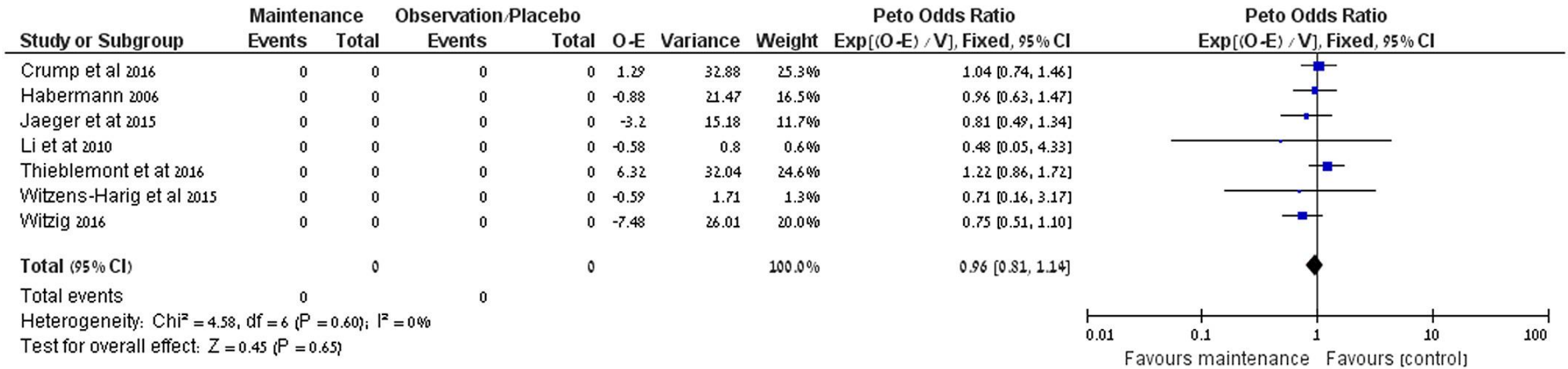


Improving on R-CHOP-21: Maintenance

Investigational Arm	PFS HR (p-value)	OS HR (p-value)	Comments	Ref
Rituximab	0.73 (0.27)	1.28 (0.48)	R-CHOP treated subset Age >60, PR/CR randomized	Habermann et al. J Clin Oncol 2006 24:3121-3127.
Rituximab	0.62 (0.0120)	0.81 (0.4145)	Age >18, CR or CRu	Jaeger et al., Haematologica 2015 100: 955-963
Enzastaurin	EFS 0.92 (NS)	1.04 (NS)	Stage II bulky, III/IV, IPI 3-5, CR or CRu	Crump et al., J Clin Oncol 2016 34:2484-2492.
Lenalidomide	0.708 (0.0135)	1.218 (0.2640)	Age 60-80; PR and CR patients randomized	Thieblemont et al. J Clin Oncol 2017 35:2473-2481
Everolimus	0.92 (0.276)	0.75 (NS)	Stage II bulky, III/IV, IPI 3-5, CR	Witzig et al., Ann Oncol 2018 29: 707-714



Improving on R-CHOP-21: Meta-analysis of maintenance after R-CHOP





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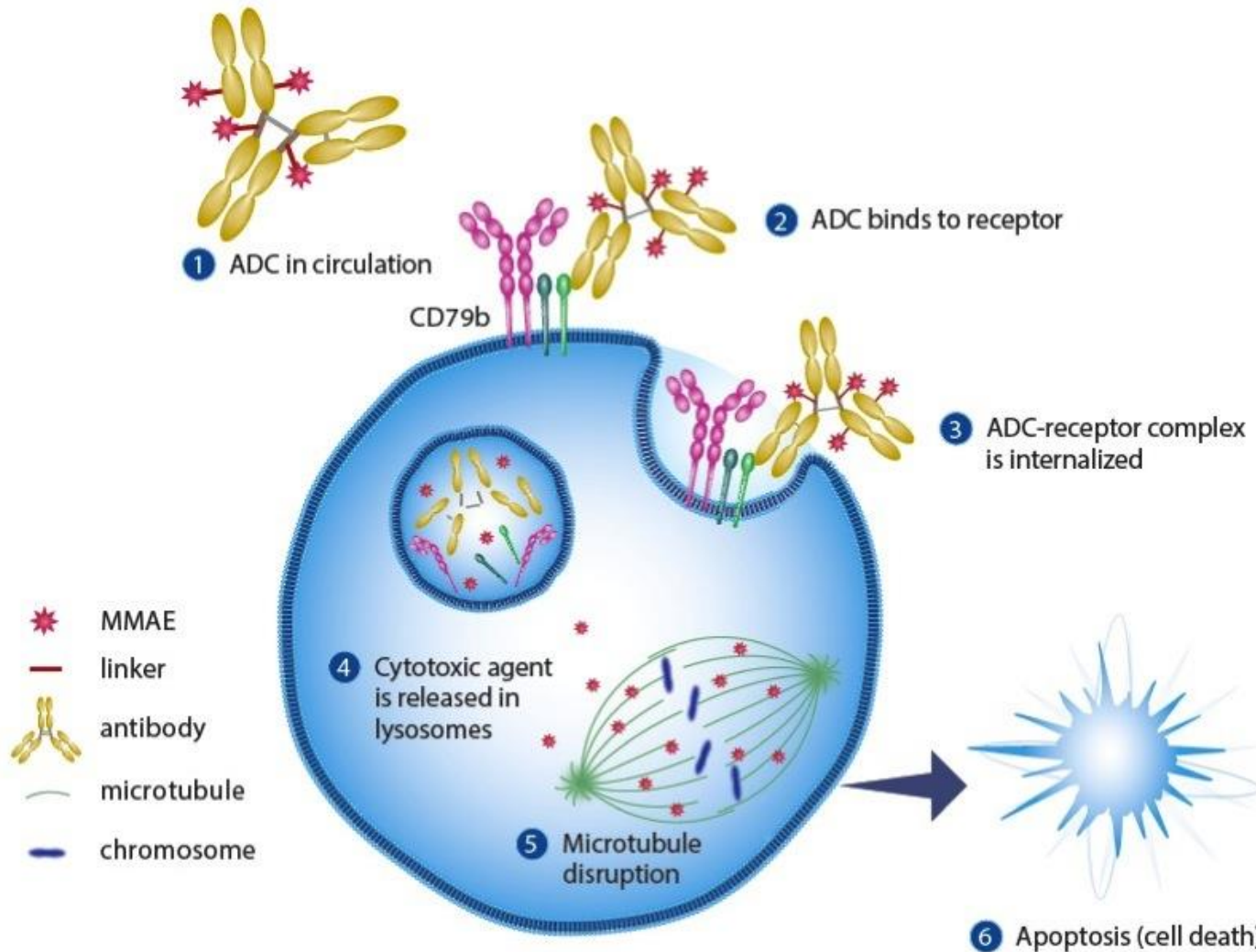
Improving on R-CHOP-21: R-CHOP + X



Improving on R-CHOP-21: R-CHOP + X

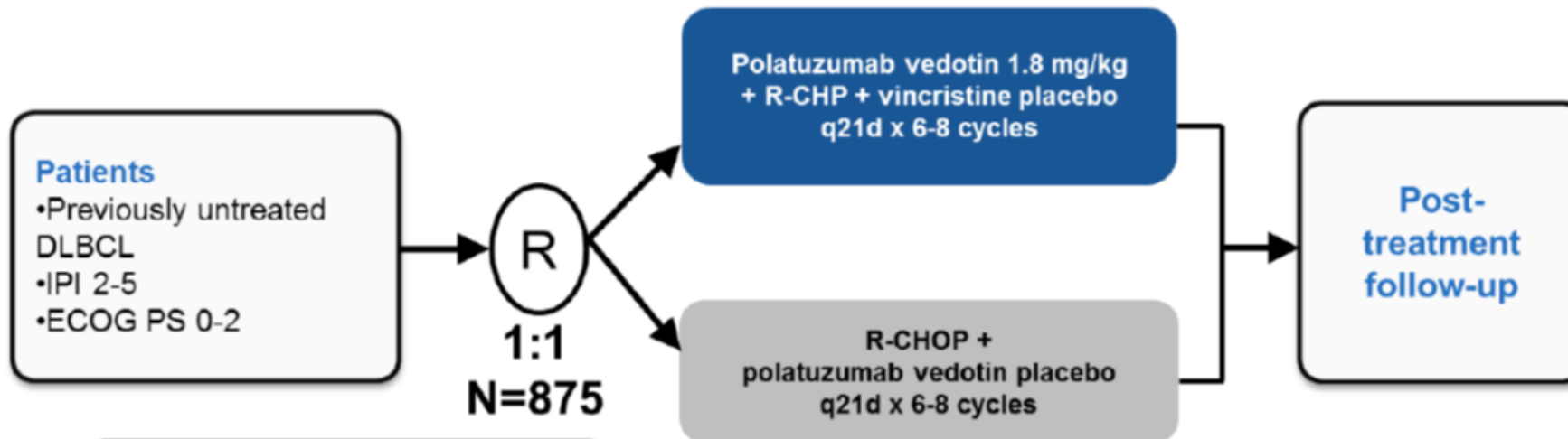
Investigational Arm (X)	PFS HR (p-value)	OS HR (p-value)	Comments	Ref
Bortezomib	0.81 (0.085)	0.86 (0.32)	Randomization after cycle 1 R-CHOP	Davies et al. Lancet Oncol 2019 doi.org/10.1016/S1470-2045(18)30935-5
	0.65 (0.041)	0.58 (0.032)	ABC Subset	Davies et al. J Clin Oncol (2023) doi.org/10.1200/JCO.23.00033
Iburtinib	0.934 (0.5906)	0.991 (0.9593)	OS benefit for patients <60	Younes et al. J Clin Oncol 2019 DOI: 10.1200/JCO.18.02403
Lenalidomide	NS	NR		Nowakowski et al. J Clin Oncol (2021) 39(12) 1317-1328
	0.66 (0.03 one-sided)	0.69 (0.08 one-sided)	ECOG 1412 Ph 2	ICML 2019
Polatuzumab	0.73 (0.02)	0.94 (0.75 one-sided)	POLARIX ~6% improvement in PFS @ 2y	Tilly et al. NEJM 2022 386:351-363
Venetoclax	0.61 (v matched GOYA)	0.72 (v matched GOYA)	Phase I/II Only	Zelenetz et al. Blood 2019 Morschauer et al. Blood 2021

Polatuzumab vedotin is an antibody drug conjugate targeting CD79b



POLARIX: R-CHOP v R-CHP+ Polatuzumab vedotin in 1st line DLBCL

Randomized and double-blind international phase 3 trial



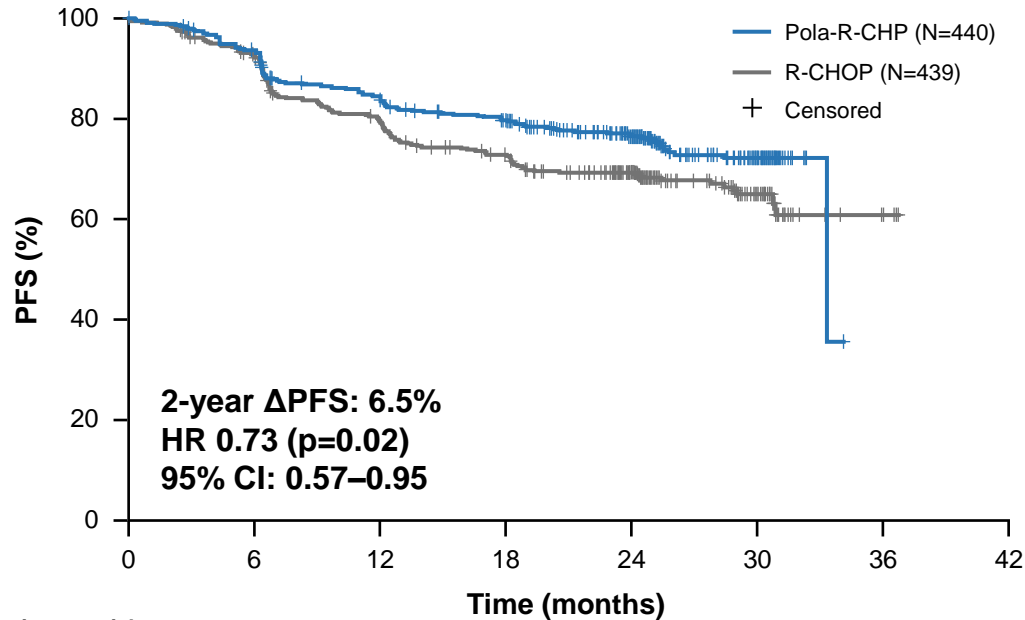
Stratification factors:

- IPI score (2 vs. 3-5)
- Chemotherapy cycles (6 vs. 8)
- Region (Western Europe, U.S., Canada and Australia vs. Rest of World)

- N = 879 (440/439)
- Well balanced
- Med FU = 28.2 m
- **Primary endpoint:** Investigator-assessed PFS

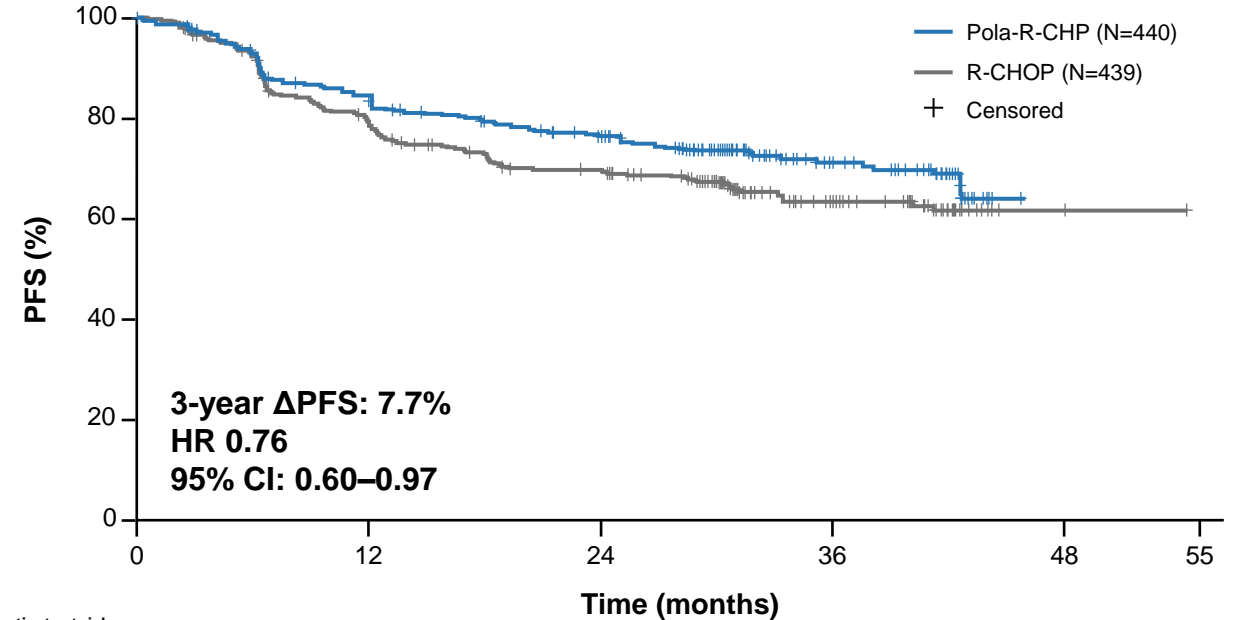
POLARIX: PFS benefit with Pola-R-CHP vs R-CHOP was maintained with longer follow-up

Primary analysis (CCOD: June 28, 2021)¹
Median follow-up: 28.2 months



No. of patients at risk	0	6	12	18	24	30	36	42
Pola-R-CHP	440	404	353	327	246	78	0	0
R-CHOP	439	389	330	296	220	78	3	0

Updated results (CCOD: June 15, 2022)²
Median follow-up: 39.7 months



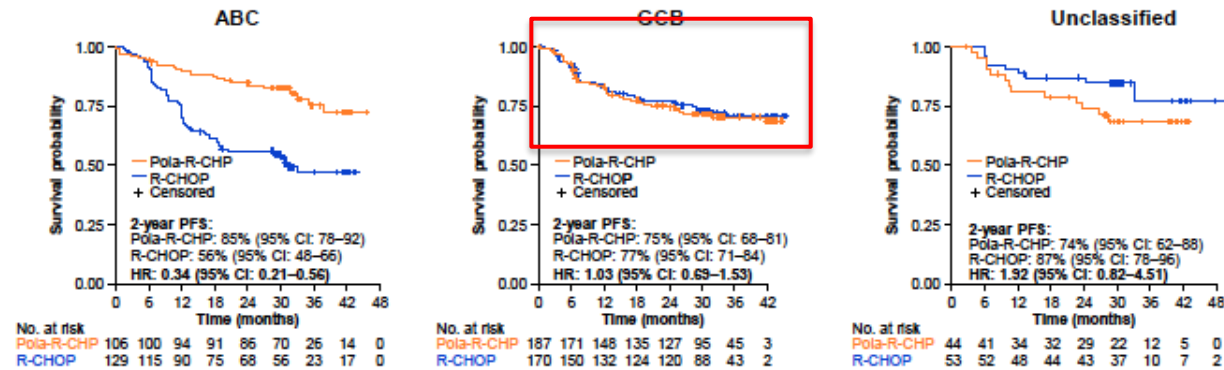
No. of patients at risk	0	6	12	18	24	30	36	42	48	55
Pola-R-CHP	440	405	354	331	313	242	103	66	0	0
R-CHOP	439	390	331	300	284	222	94	59	2	1

Analysis based on the ITT population.

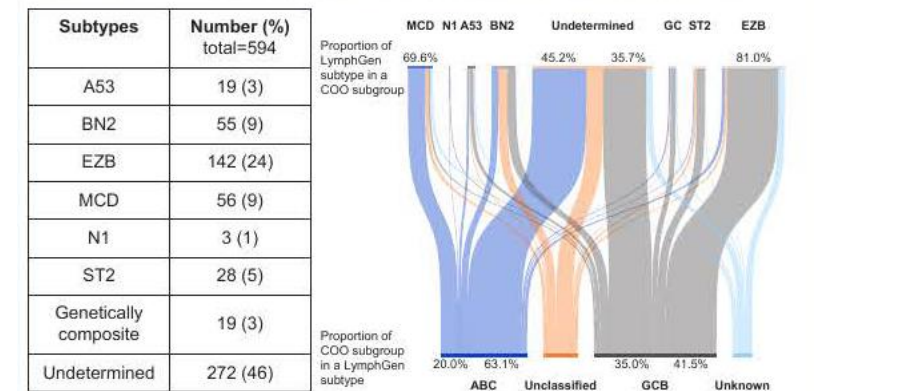
ITT, intention-to-treat; NE, not evaluable; no., number.

POLARIX: Outcome by genetic subtypes

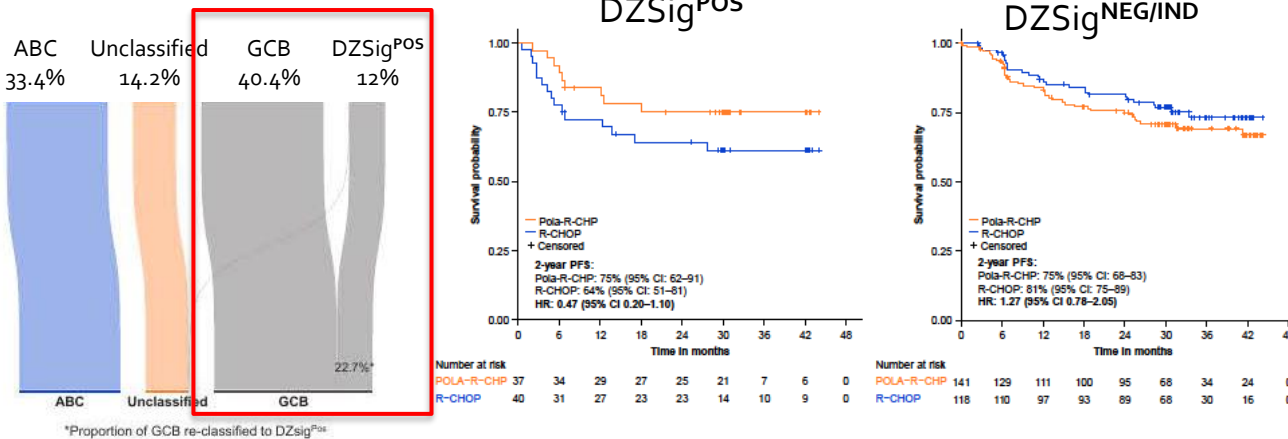
PFS by Cell of Origin (Lymph2Cx)¹



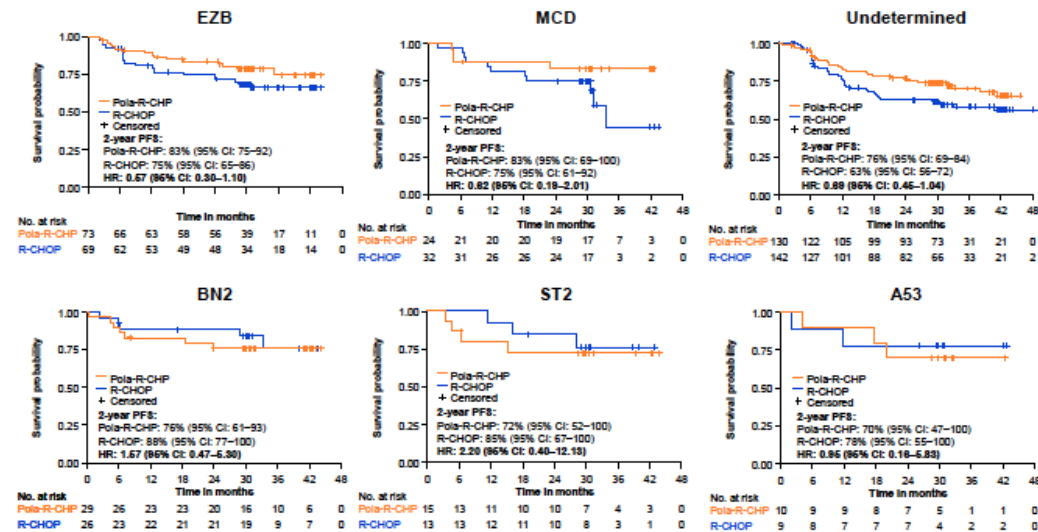
PFS by LymphGen Subtypes³



PFS Dark Zone Signature²



*Proportion of GCB re-classified to DZSig^{POS}



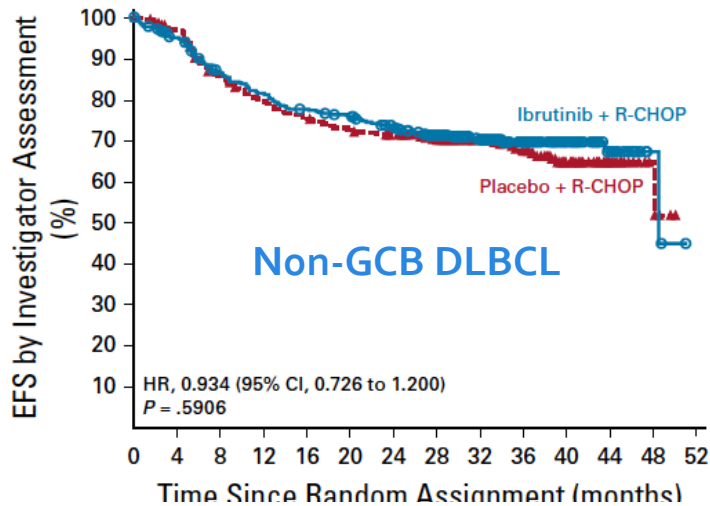
How I apply POLARIX

- I do not have access to cell of origin by gene expression or the dark zone signature. At MSK, we use the Hans algorithm as an approximation of the cell of origin
 - Non-GCB: I use R-CHOP-Pola
 - GCB: I use R-CHOP
- MSK IMPACT (460 gene targeted gene panel) can be used to approximate the LymphGen classification
 - However, turn around time (4-6 weeks) is insufficient for use in clinic decision making regarding 1L therapy

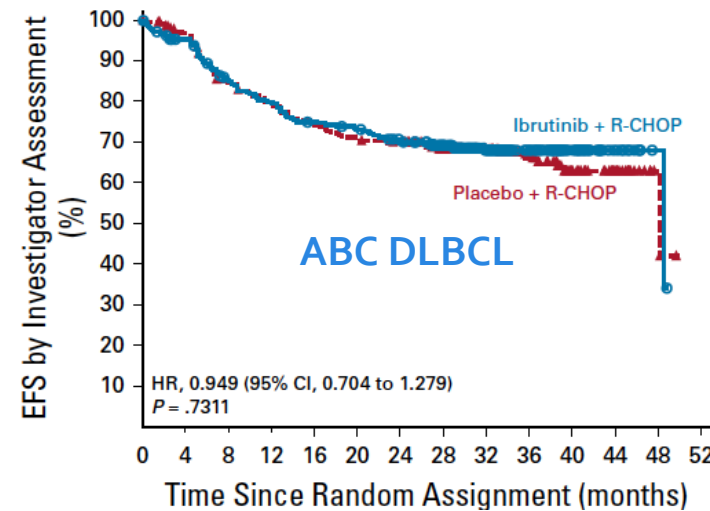


PHOENIX: R-CHOP ± Ibrutinib for non-GCB DLBCL

Primary Endpoint

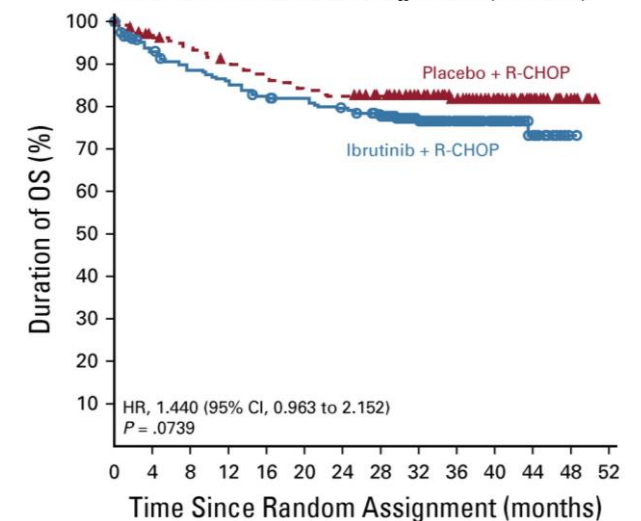
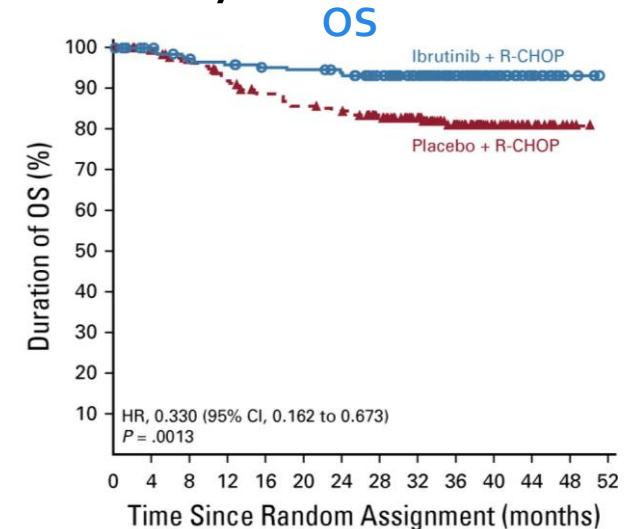
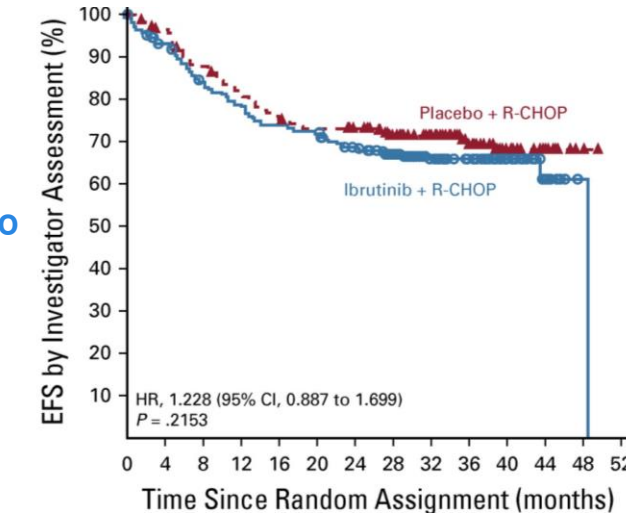
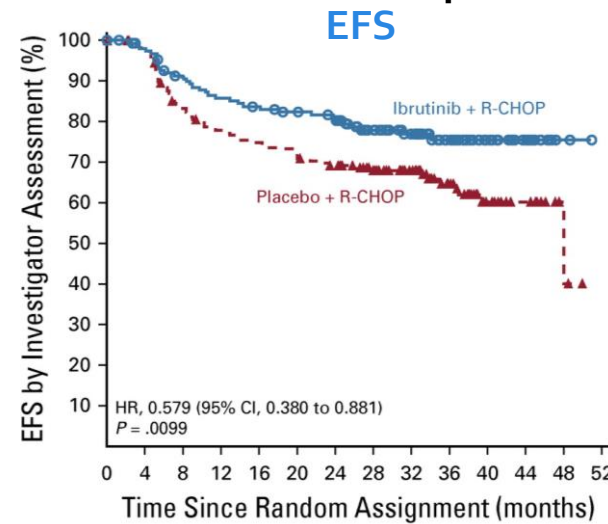


Age <60



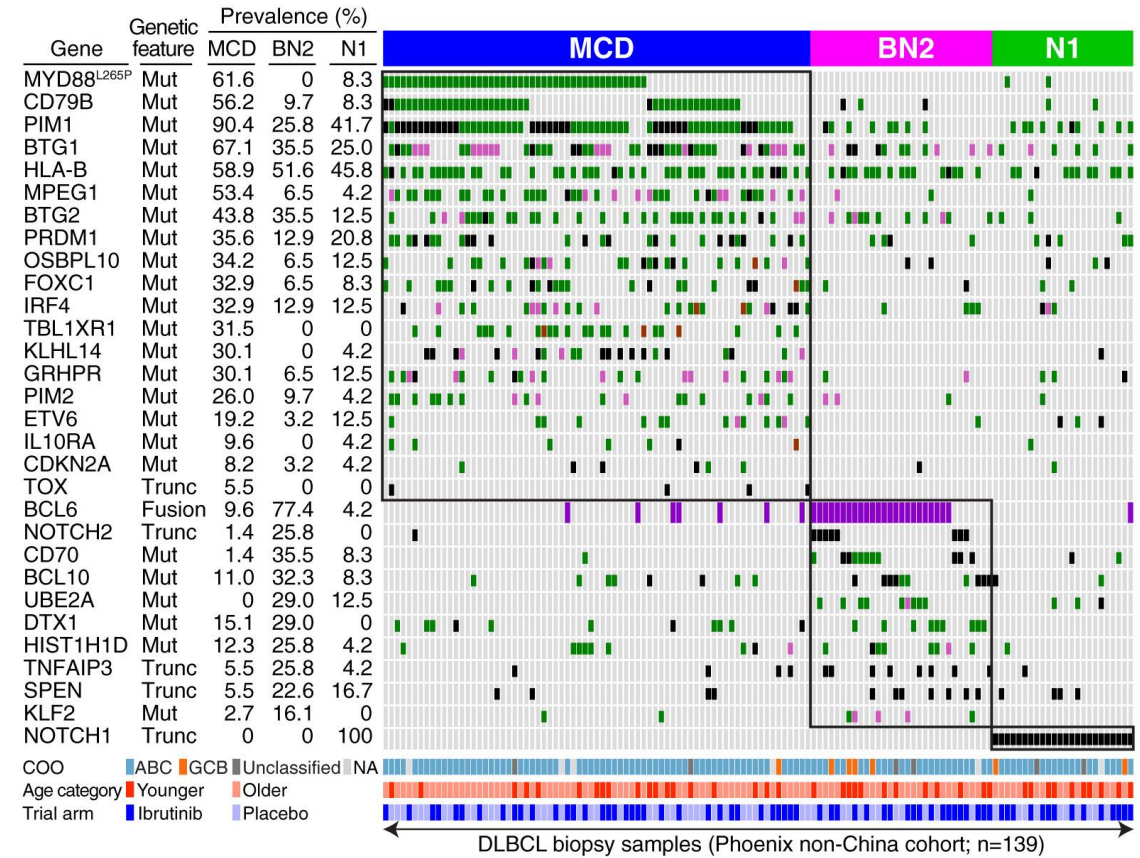
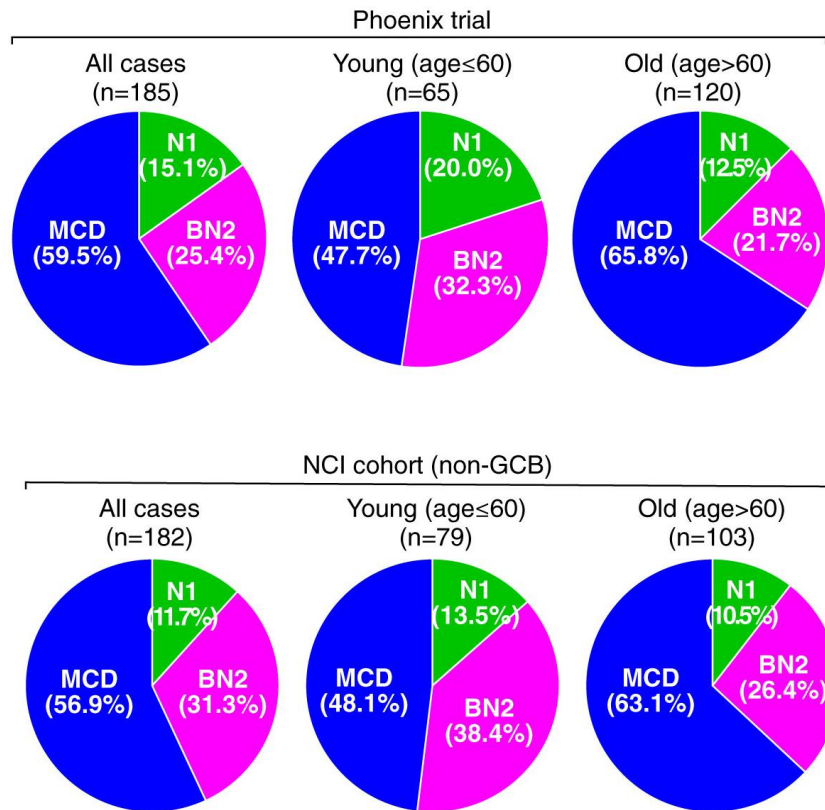
Age ≥60

Unplanned Subset Analysis

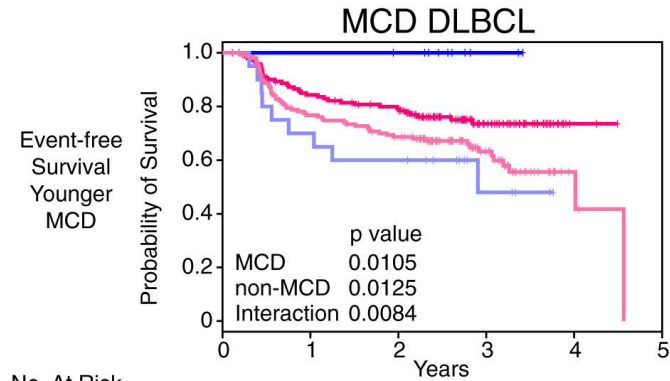


PHOENIX: DLBCL Subtypes

Differential Distribution of Subtype by Age

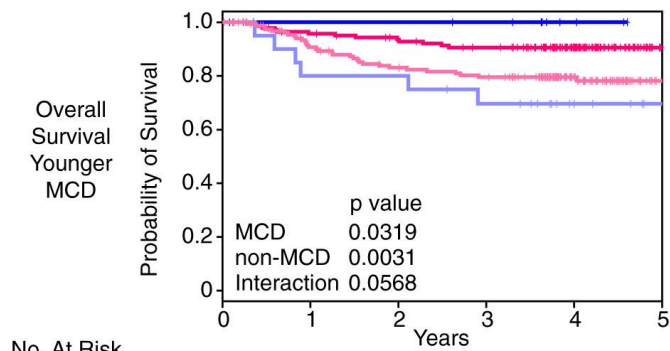


Benefit of ibrutinib in younger patients is subtype specific



No. At Risk

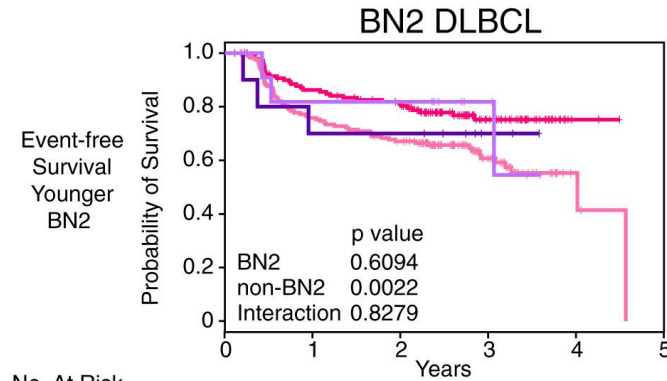
MCD Ibrutinib	11	10	9	2	0	0
Non-MCD Ibrutinib	147	117	106	43	2	0
MCD Placebo	20	14	12	4	0	0
Non-MCD Placebo	157	114	100	41	4	0



No. At Risk

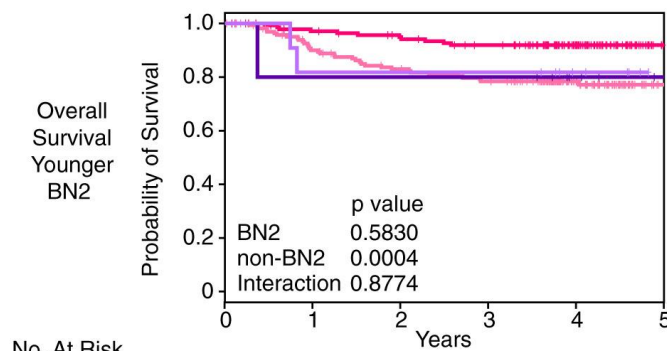
MCD Ibrutinib	11	10	10	9	3	0
Non-MCD Ibrutinib	147	134	127	120	77	12
MCD Placebo	20	16	16	13	6	1
Non-MCD Placebo	157	134	119	113	62	9

■ MCD Ibrutinib ■ Non-MCD Ibrutinib
■ MCD Placebo ■ Non-MCD Placebo



No. At Risk

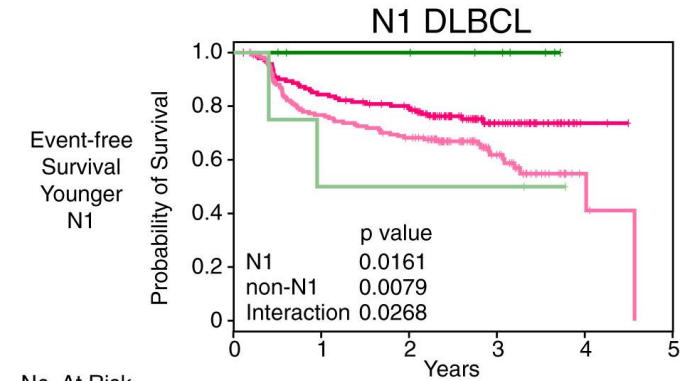
BN2 Ibrutinib	10	7	7	2	0	0
Non-BN2 Ibrutinib	146	118	106	43	2	0
BN2 Placebo	11	9	9	4	0	0
Non-BN2 Placebo	168	121	105	43	4	0



No. At Risk

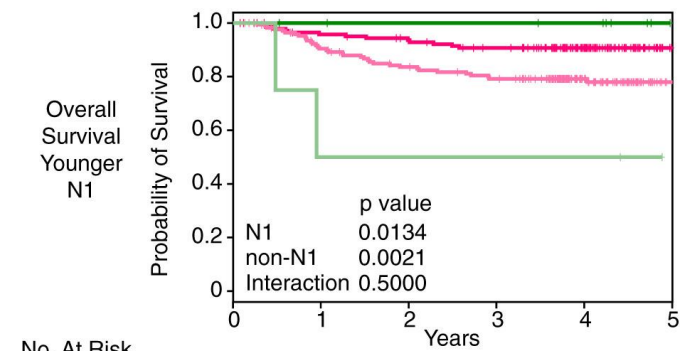
BN2 Ibrutinib	10	8	8	8	4	1
Non-BN2 Ibrutinib	146	134	127	119	75	11
BN2 Placebo	11	9	9	9	5	0
Non-BN2 Placebo	168	143	128	119	65	10

■ BN2 Ibrutinib ■ Non-BN2 Ibrutinib
■ BN2 Placebo ■ Non-BN2 Placebo



No. At Risk

N1 Ibrutinib	9	7	7	5	0	0
Non-N1 Ibrutinib	148	119	107	41	2	0
N1 Placebo	4	2	2	2	0	0
Non-N1 Placebo	174	127	111	43	4	0



No. At Risk

N1 Ibrutinib	9	8	7	7	6	0
Non-N1 Ibrutinib	148	135	129	121	74	12
N1 Placebo	4	2	2	2	2	0
Non-N1 Placebo	174	149	134	125	66	10

■ N1 Ibrutinib ■ Non-N1 Ibrutinib
■ N1 Placebo ■ Non-N1 Placebo





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Future Directions:



Completed (not reported), ongoing, and planned 1L Phase 3 trials in DLBCL

R-CHOP + X

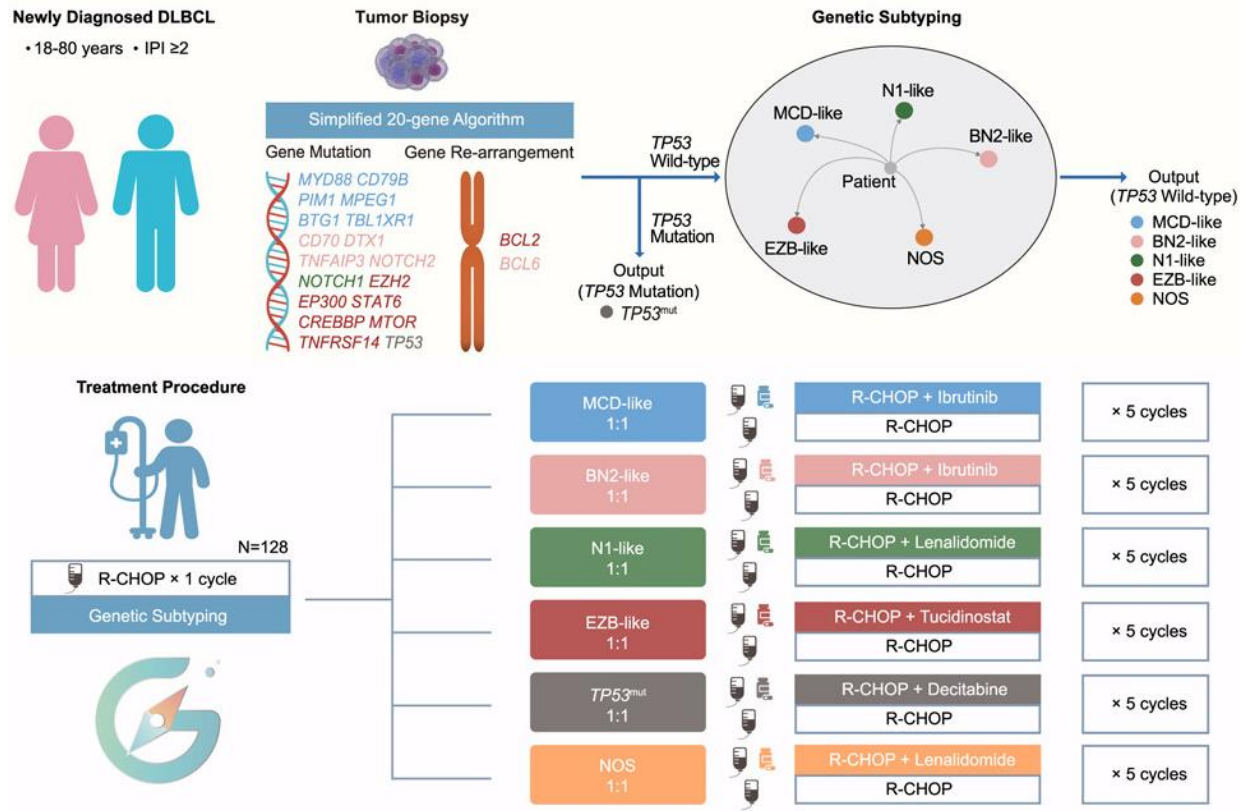
- R-CHOP ± acalabrutinib (ABC DLBCL)
- R-CHOP ± orelabrutinib (MCD DLBCL)
- R-miniCHOP ± azacytidine (age ≥ 75)
- R-CHOP ± tucidinostat (MYC/BCL2 DEL)
- R-CHOP ± tafasitamab-lenalidomide
- R-CHOP ± epcoritamab

Altered Backbone

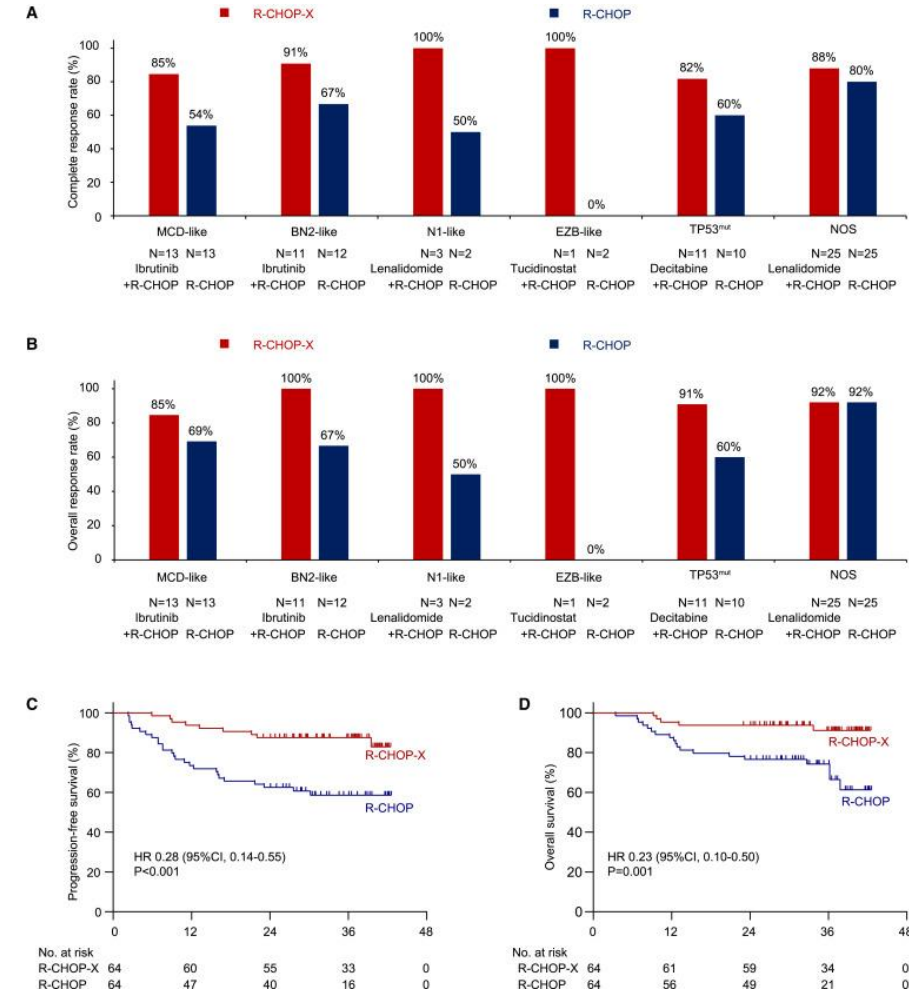
- R-CHOP/DA-EPOCH-R x 1 then randomization between axicabtagene ciloleucel vs 5 additional cycles of R-chemotherapy
- R-CHOP v odronextamab-CHOP
- R-miniCHOP v R-miniCHP-Pola (age ≥ 75)

Fully enrolled; Recruiting; Not yet recruiting

GUIDANCE-01: Rational approach to R-CHOP + X



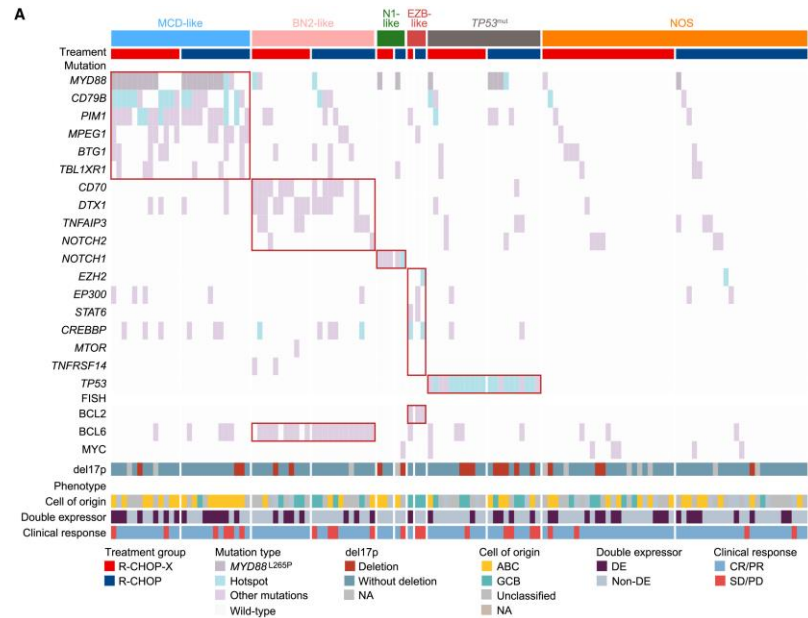
- This was a first attempt at a genetics-based treatment adaptation:
 - Some of the assigned treatments may have been suboptimal.
- However, the treatment schema could provide for changes an assigned treatment if a Bayesian analysis suggests lack of efficacy



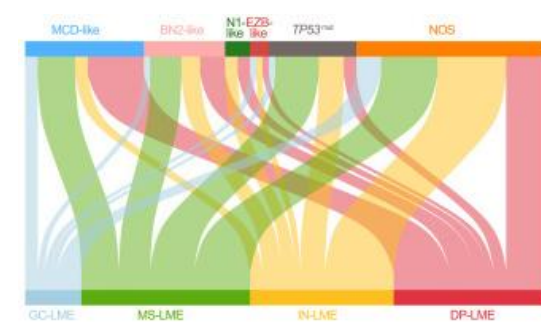
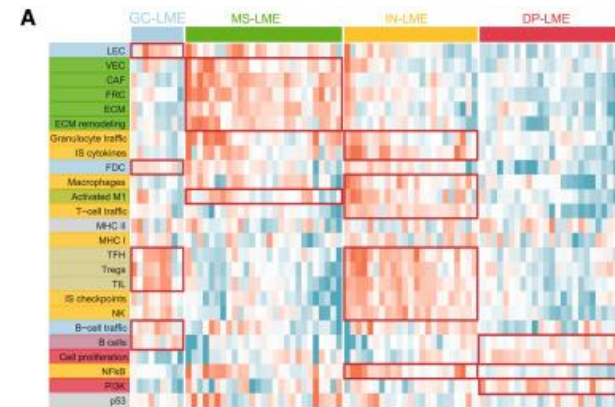
R-CHOP ORR and CR are lower than would be expected from historical data.

GUIDANCE-01: Fit the treatment to the disease

Determination of Molecular Subtypes

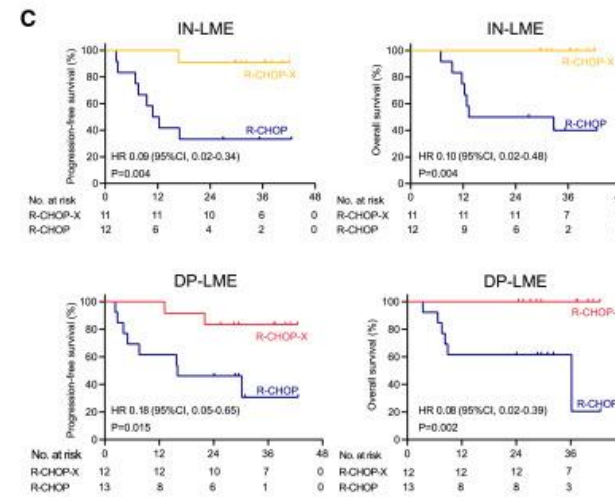
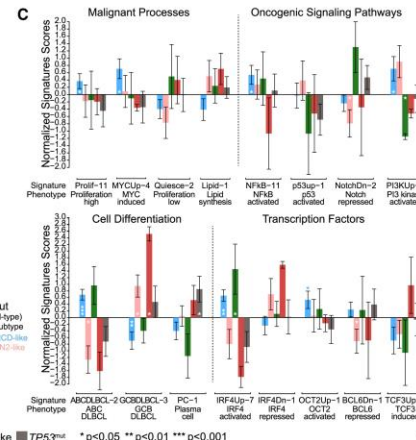
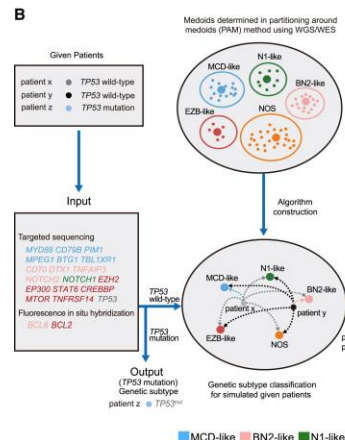


Molecular Subtypes Associated with Various TME Signatures



Microenvironments:

- GC:** germinal center-like (cell types commonly found in GCs)
- MS:** mesenchymal (abundance of stromal cells and extracellular matrix pathways)
- IN:** inflammatory (presence of inflammatory cells and pathways)
- DP:** depleted (overall lower presence of microenvironment-derived gene expression)





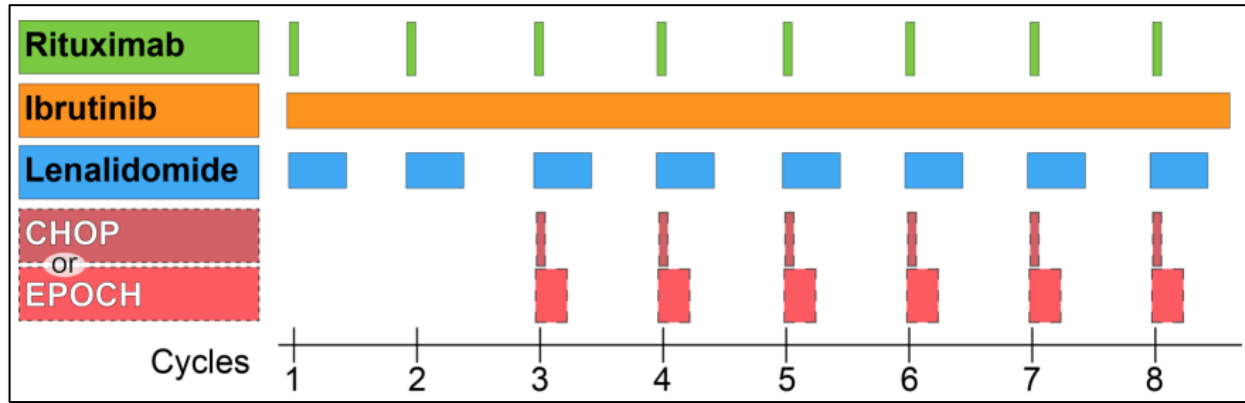
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Break the mold to improve outcomes

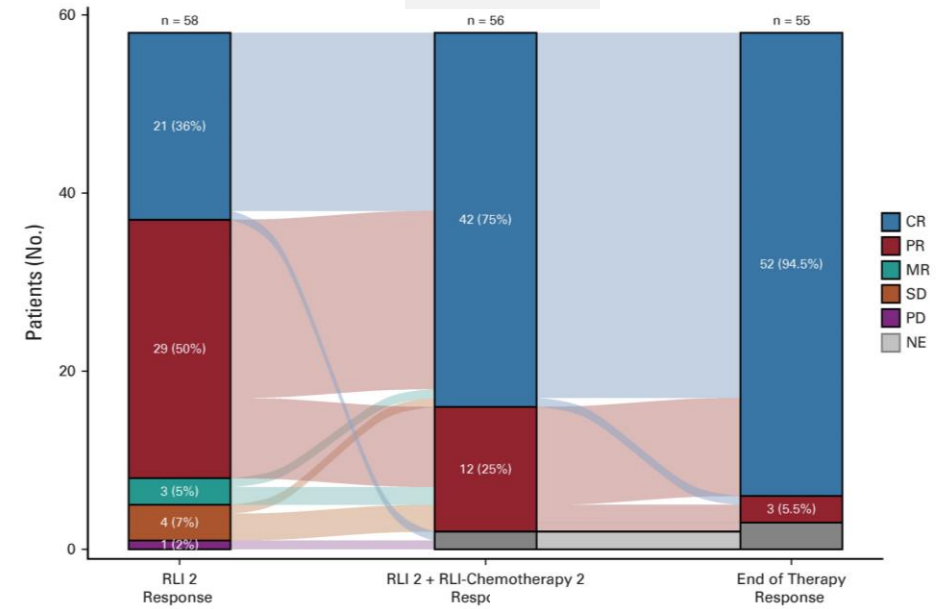


Window Study: Rituximab, lenalidomide, ibrutinib for 1L DLBCL (Smart Start)

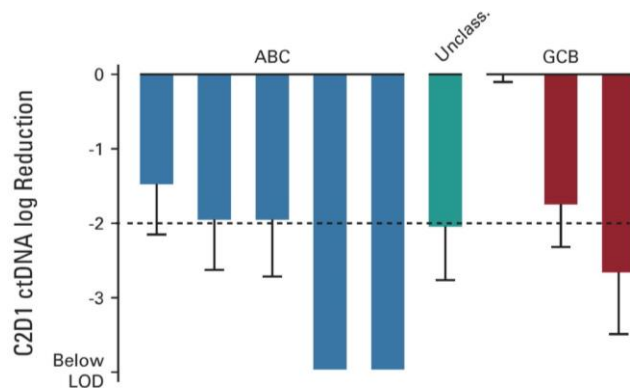
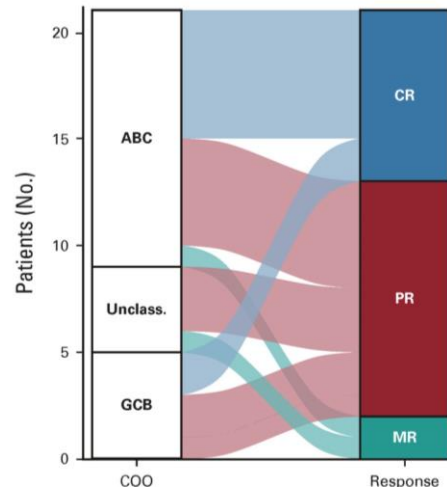
Schema



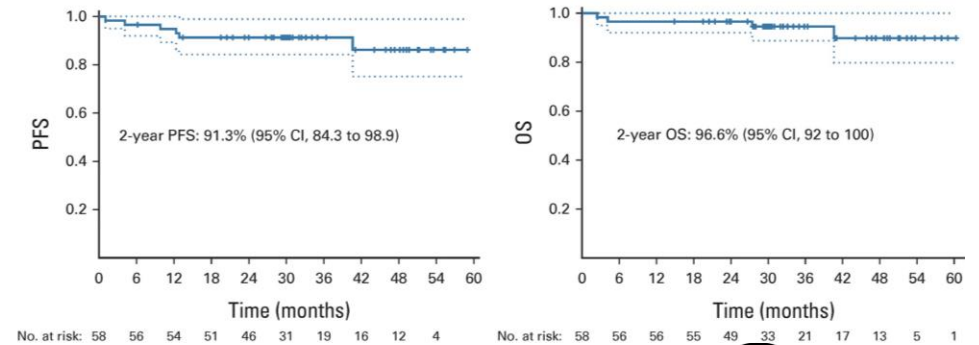
Response



ctDNA Response by Cell of Origin

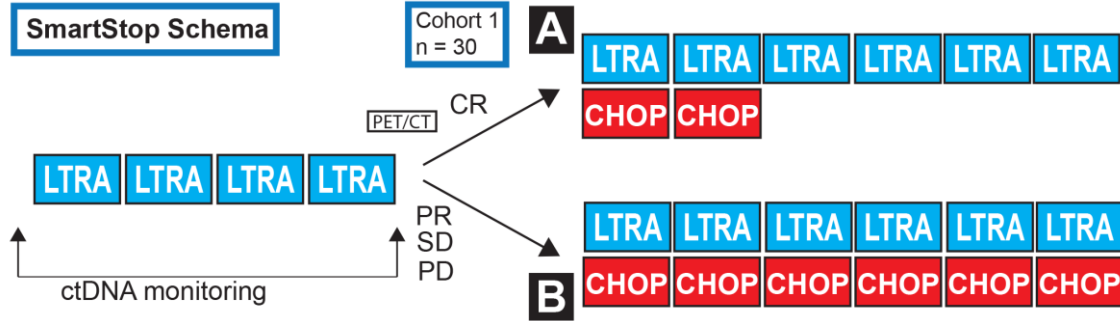


PFS and OS



Smart Stop: Is Len-Tafa-Ritux-Acal (LTRA) enough therapy?

SmartStop Schema



Drug Name	Dose	Route	Dosing/cycle	Days
Lenalidomide (L)	25 mg	PO	Daily	1-10
Tafasitamab (T)	12 mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375 mg/m ²	IV	Once	1
Acalabrutinib (A)	100 mg	PO	BID	1-21

Response to LTRA x 4 Lead In

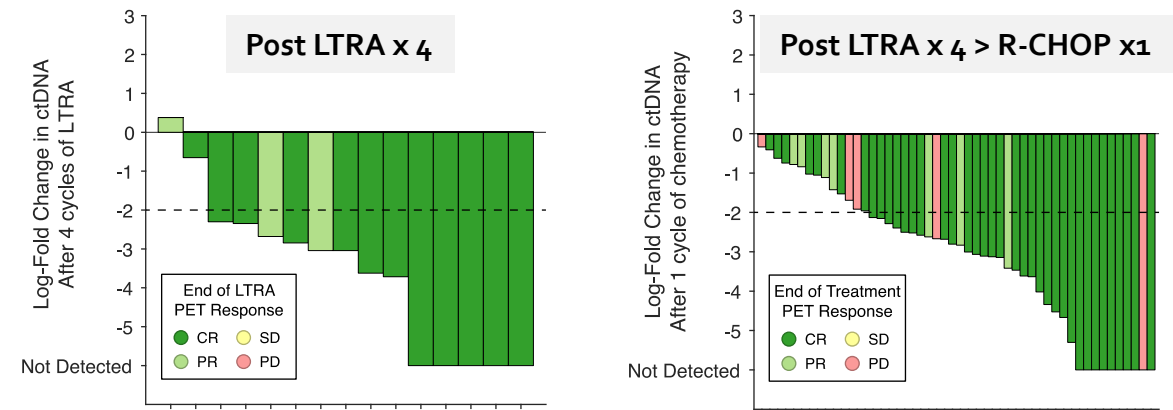
	All (N=30)	GCB (N=5)
CR	19 (63.3%) (95% CI: 50.0 ~ 75.2%)	4 (80%)
PR	11 (36.7%)	1 (20%)
SD	0	0
PD	0	0
ORR	30 (100%) (95% CI: 92.6 ~ 100%).	

EOT Response

N = 22		Group A (2 CHOP, N=19)	Group B (6 CHOP, N=11)
CR	22 (100%)* (95% CI: 90.1 ~ 100%)	19 (100%)	11 (100%)*
PR	0*	0	0*
SD	0	0	0
PD	0	0	0
On Treatment	8	5	3

*FDG avid lesion biopsied with benign inflammatory response without lymphoma cells

MRD by PhasED-seq



In the next two cohorts, patient in CR after LTRA x 4 will continue with additional LTRA x6 and those with PD, SD, PR will get CHOP + LTRA x 6



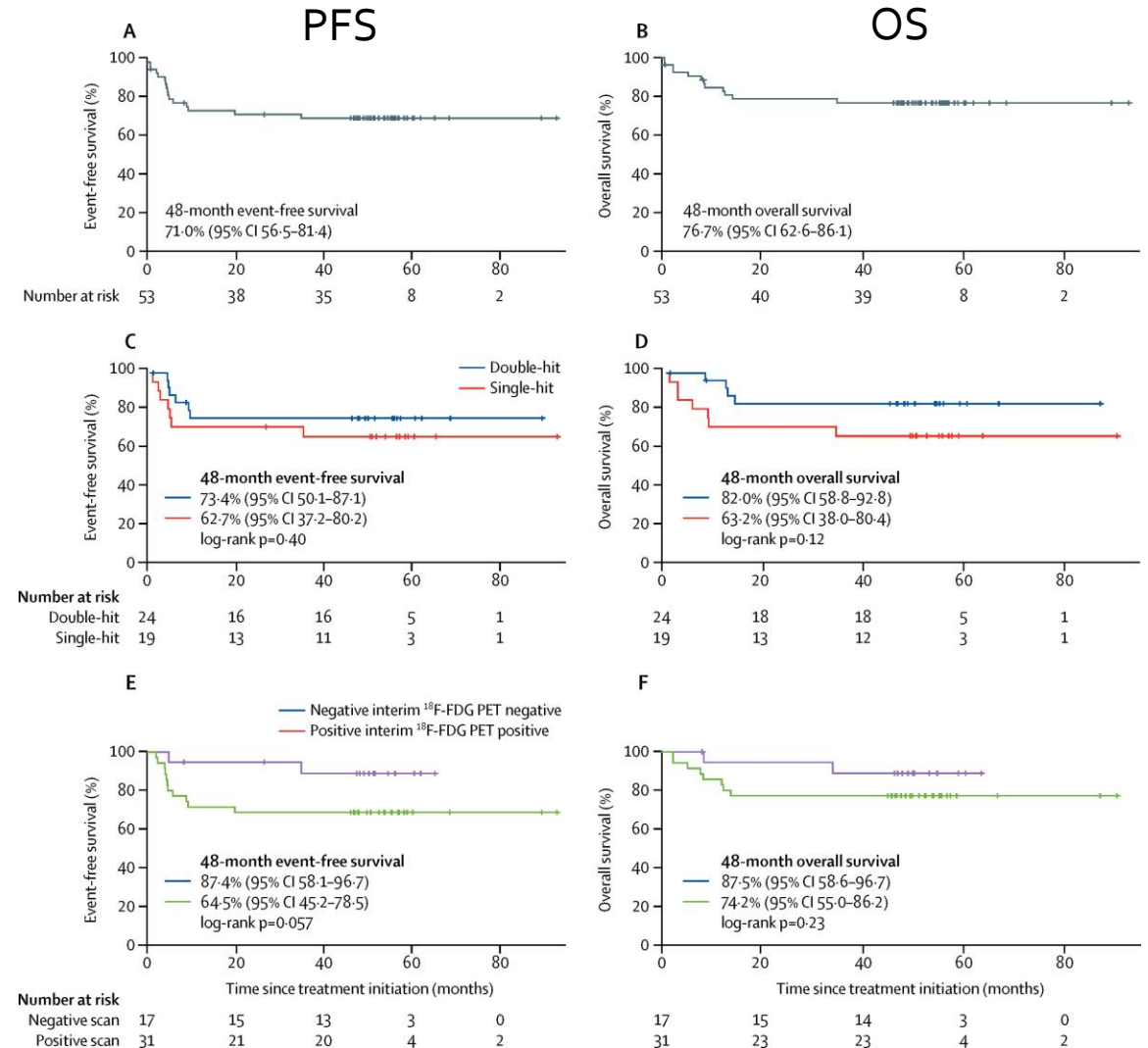
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When is other therapy appropriate? (not including CNS disease)

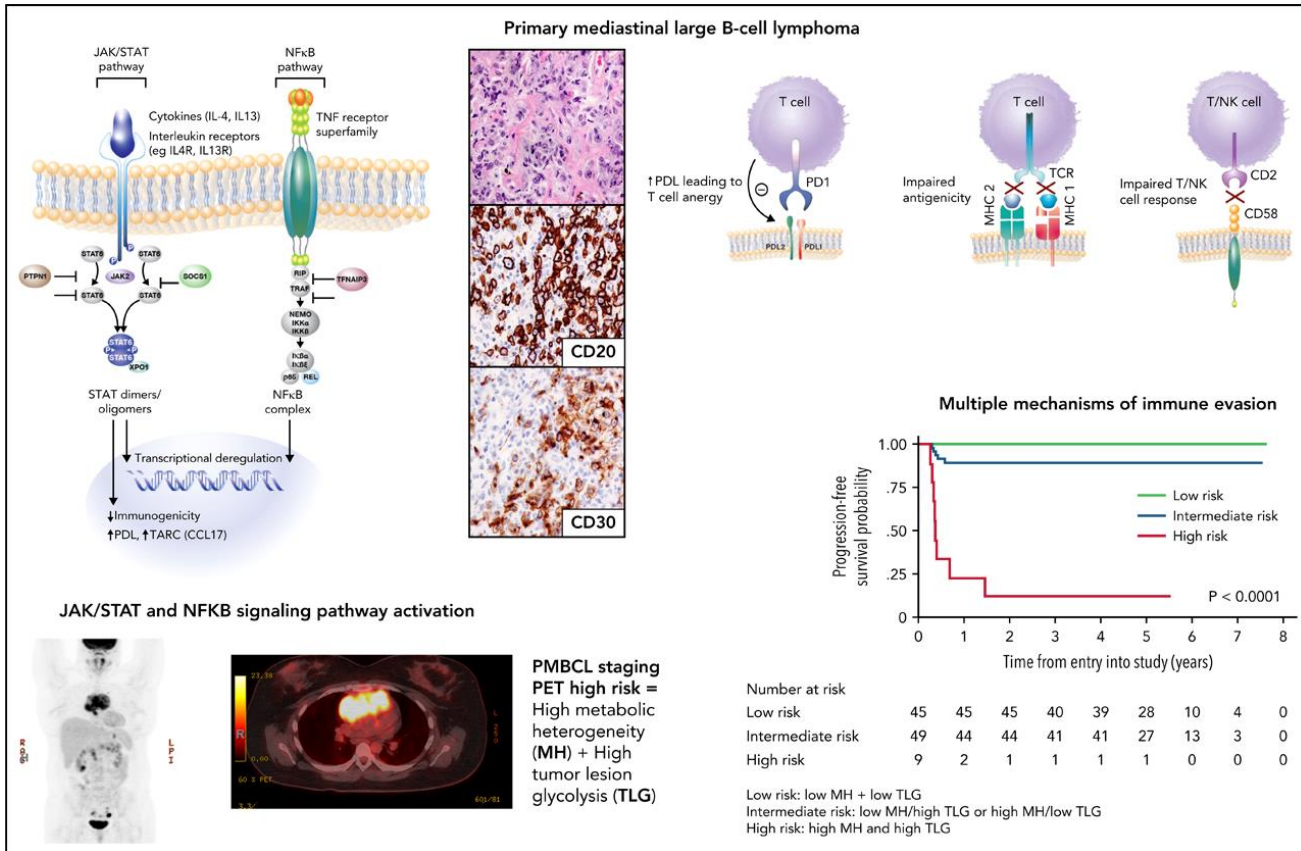


MYC Rearranged DLBCL: with or without BCL₂R/BCL6R

	All MYCR (n=53)	MYCR only (n=19)	MYCR with BCL ₂ R and/or BCL6R (n=24)
Total	53	19/32	24/52
HGBL, DH	24/53	0	24/24
HGBL, NOD	10/53	6/19	0
DLBCL	18/53	13/19	0
Plasmablastic	1/53	0	0
MYCR	53/53	19/19	24/24
BCL ₂ R	22/53	0	22/24
BCL6R	5/32	0	5/24



PMBL: Opt for regimens without RT



PMBCL studies R-chemotherapy	Study size, n; Median age, y (range)	Study type	PFS/EFS, % (y)	OS, % (y)	% RT
R-CHOP ₁₄ /ICE±R (MSKCC 01-142) Moskowitz et al (abstract), 2010	54 34 (19-59)	Prospective + per protocol	78 (3)	88 (3)	0
R-CHOP/R-CHOEP (MINT study group), Rieger et al, 2011	44 36 (27-43)	Prospective subgroup	78 (3)	89 (3)	73
DA-EPOCHR (NCI) DA-EPOCHR (Stanford) Dunleavy et al, 2013	51 30 (23-51) 16 33 (23-68)	Prospective Retrospective	93 (5) 100	97 (5) 100	4 0
R-MACOPB/R-VACOPB (84%) or R-CHOP IELSG-26 Martelli et al, 2014	125 33 (range, NR)	Prospective observational	86 (5)	92 (5)	92
R-CHOP ₁₄ /21 (NCI) Gleeson et al, 2016	50 38.5 (22-78)	Prospective subgroup	80 (5)	84 (5)	58
DA-EPOCH-R (pediatric) Burke et al, 2021	47 15 (range NR)	Prospective	69 (2)	82 (2)	0
R-CHOP ₂₁ /14 (UNFOLDER trial) Held et al (abstract), 2020	131 34 (range NR)	Prospective subgroup	93 (3)	97 (3)	62.5

Conclusions

- R-CHOP, the international standard of care for advanced stage, may be replaced for certain patients
 - R-CHP-Pola for non-GCB DLBCL
 - DA-EPOCH-R for MYC rearranged lymphoma
 - Either DA-EPOCH-R or sequential R-CHOP/(R)ICE for PMBL (without mediastinal radiation)
- R-CHOP + X has not been a very successful strategy; however, if X is based on the molecular subtype, this may be a viable approach
- Completely rethinking first line therapy in DLBCL is challenging given the excellent outcomes
 - New emerging agents can be tested in a window study to test hypothesis
 - Stepwise studies to then test new regimens is a path towards new approaches in DLBCL





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Has the first-line standard truly changed in advanced stage DLBCL?

Yes, for some patients



It takes a village

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