Recent Advances in the Frontline Treatment of DLBCL: Is there a new standard of care?

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Disclosures

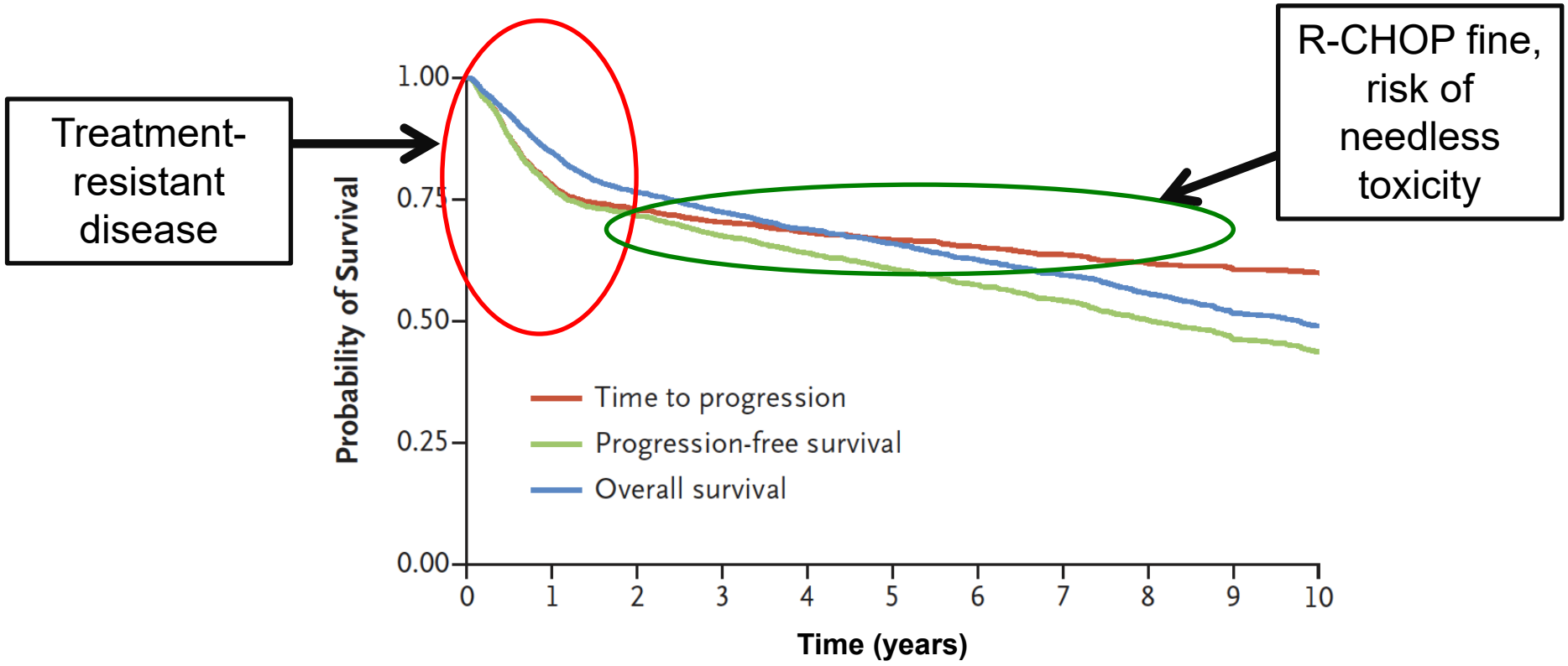
- **Consulting/Honoraria: Abbvie, Acerta, Amgen, Apobiologix, AstraZeneca, Celgene, Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, Morphosys, Roche/Genentech, Sandoz, Seattle Genetics, Servier, Teva, Takeda, TG Therapeutics, Verastem**

- **Research funding: Teva, Roche/Genentech**

Key Considerations

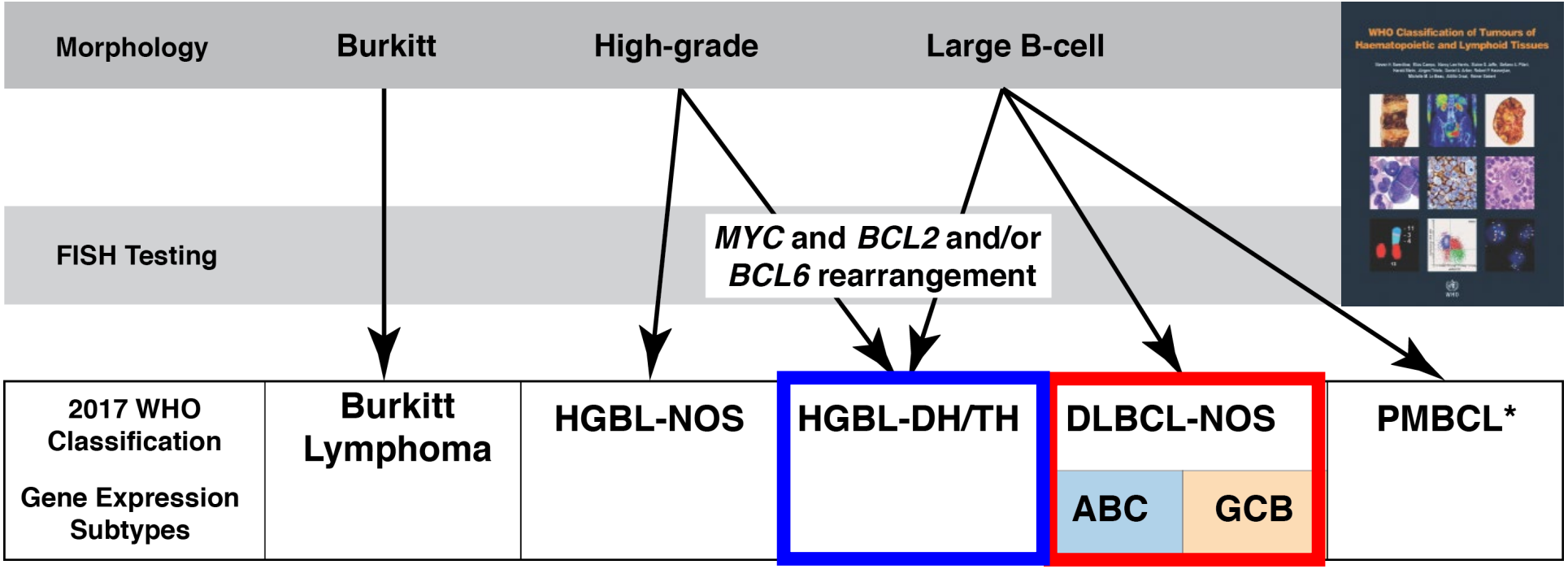
- What is standard of care and who do we treat differently now?
- Should we treat based on biology?
- Is the standard of care changing?
- What are the limitations to current trial design?
- How do we move the bar in the future?

Outcomes with R-CHOP in Untreated DLBCL



Sehn and Salles, NEJM 2021

WHO Classification – Aggressive B-cell Lymphoma

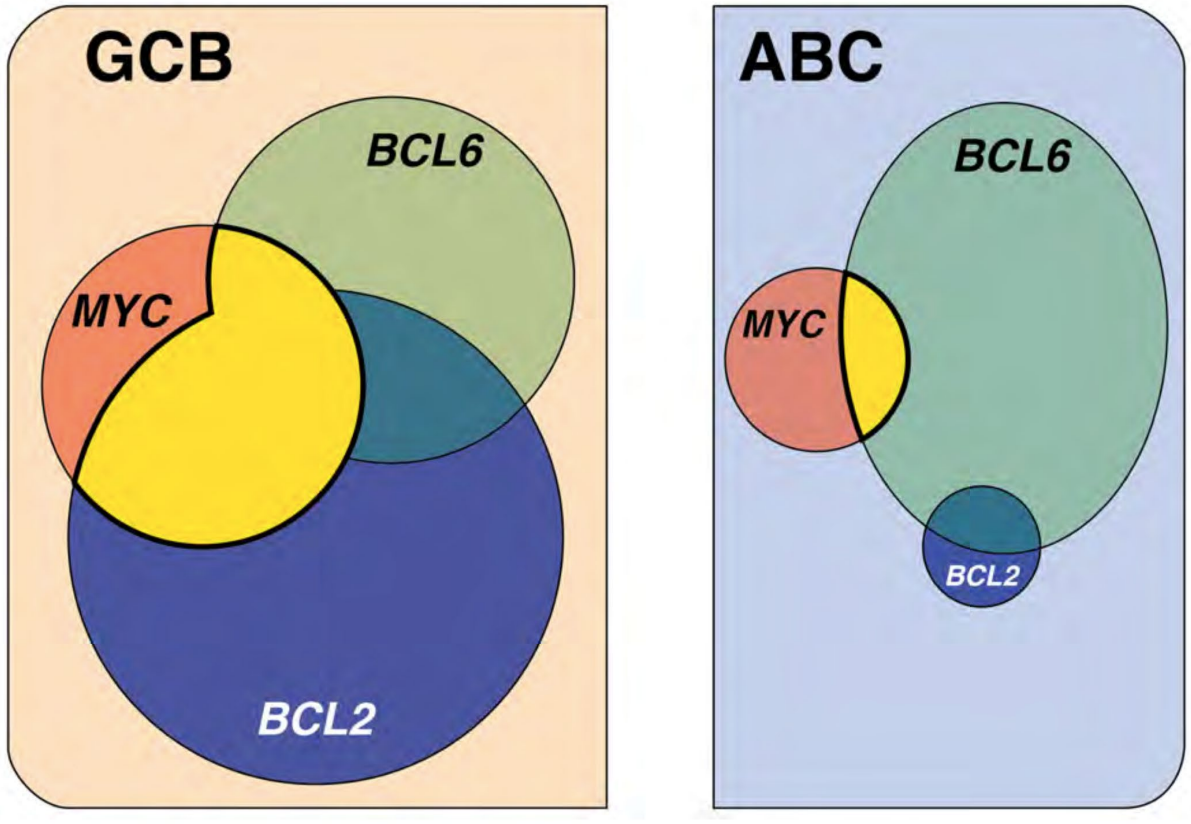


HGBL-NOS: high-grade B-cell lymphoma NOS
HGBL-DH/TH: high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
PMBCL: Primary mediastinal B-cell lymphoma

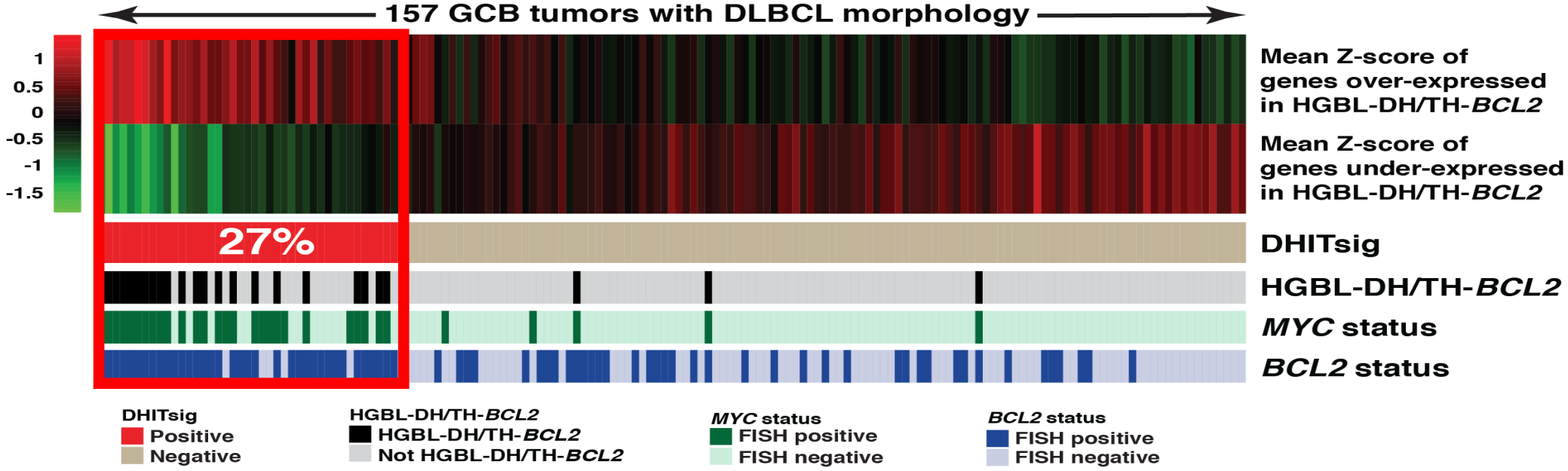
Swerdlow et al WHO revised 4th Edition 2017

Incidence of Double/Triple-Hit in DLBCL

- 12% harbour *MYC* rearrangements (> in GCB)
- **~7%** are *MYC/BCL2* DHIT or *MYC/BCL2/BCL6* THIT
  - All cases are GCB
- **~1-2%** are *MYC/BCL6*
  - GCB or ABC
- **~8% total incidence double/triple-hit**



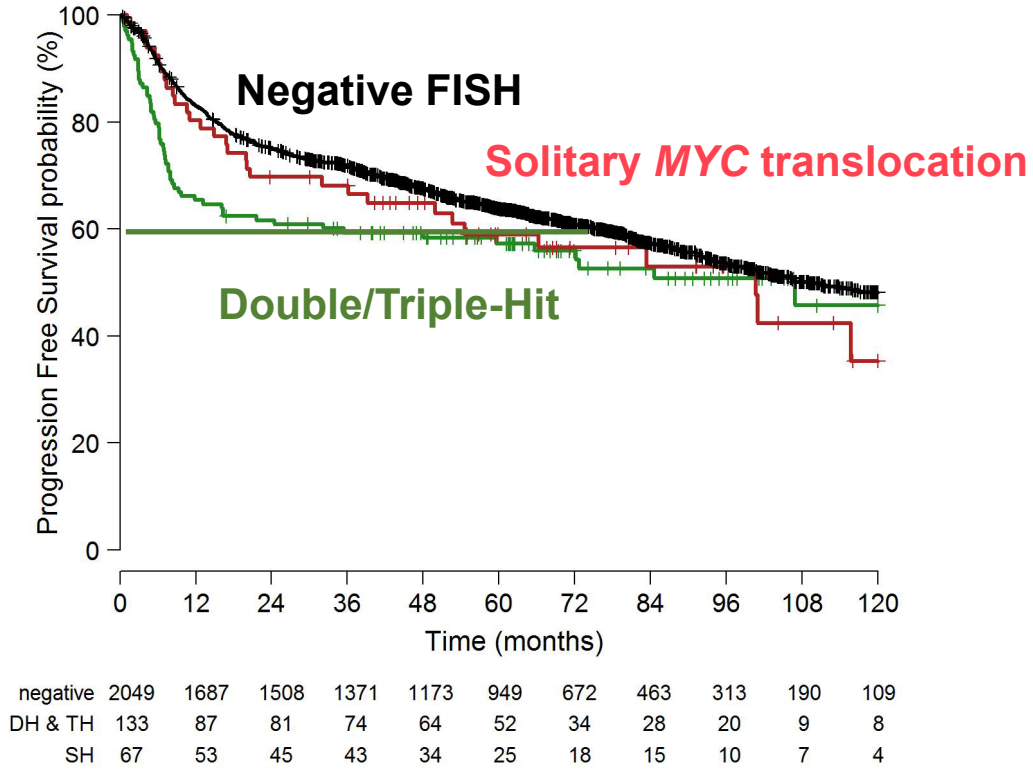
The “Double-Hit Gene Signature”



- **Unique gene-expression signature identifies Double/Triple-Hit DLBCL**
- **Identifies an additional subset not detected by FISH**

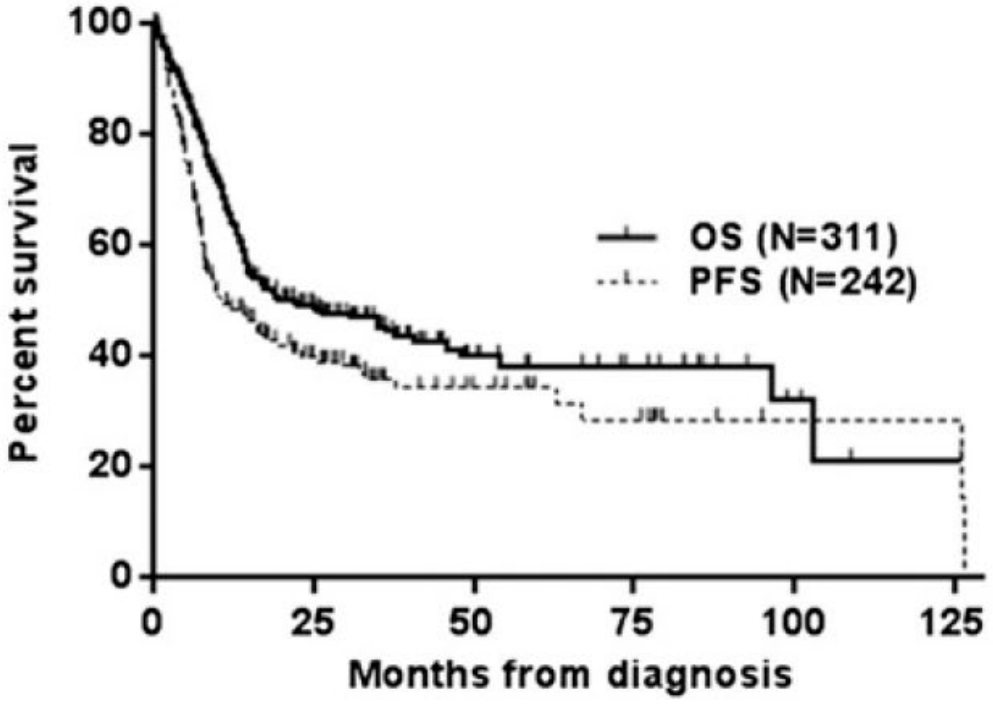
Ennishi et al J Clin Oncol 2019

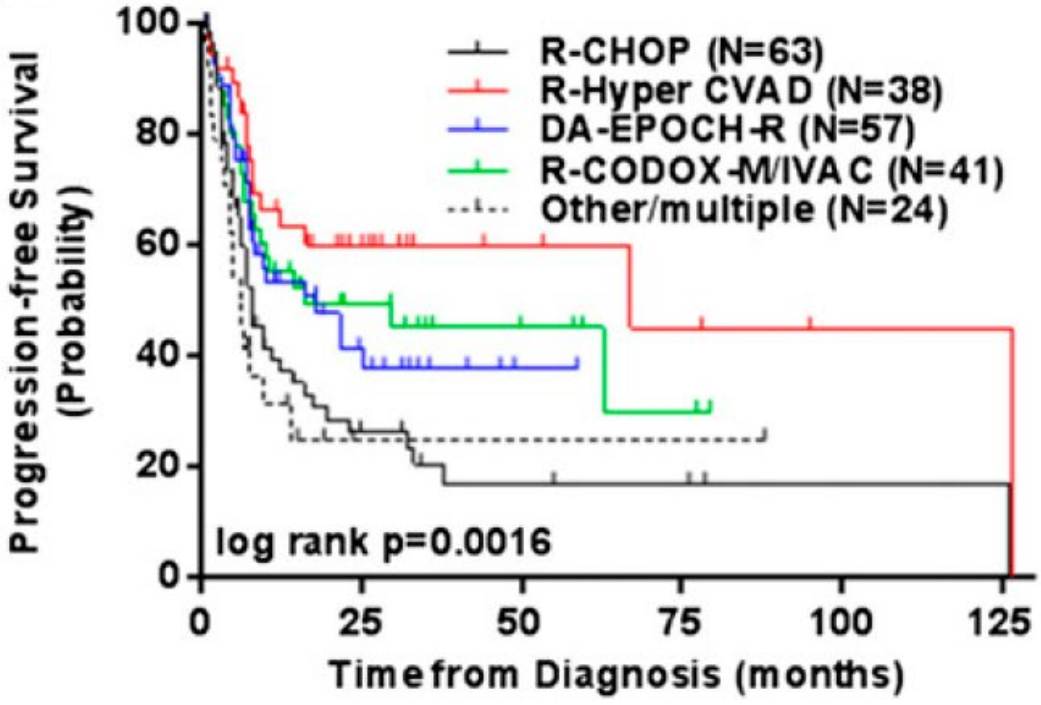
PFS in Patients with DLBCL Morphology Treated with R-CHOP According to FISH



Rosenwald, et al JCO 2019

Outcome According to Induction Regimen in Double-Hit Lymphoma

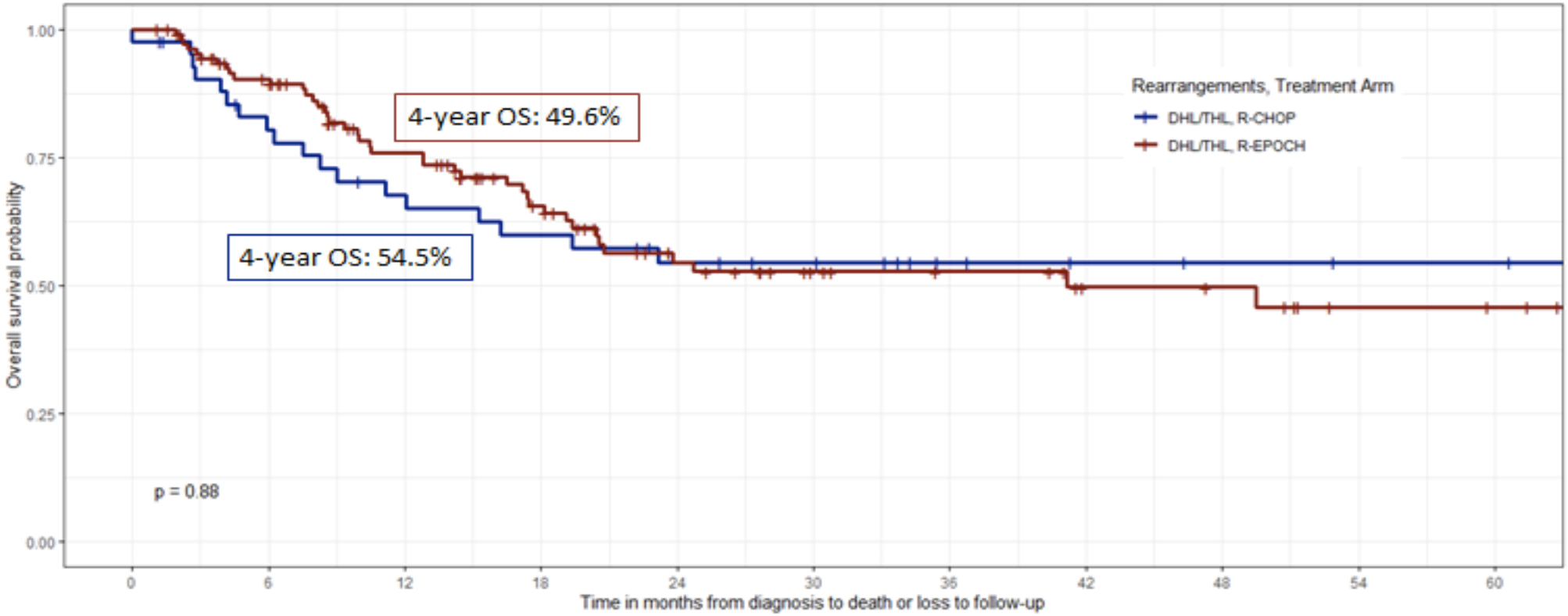




2y PFS 40%; 2y OS 49%

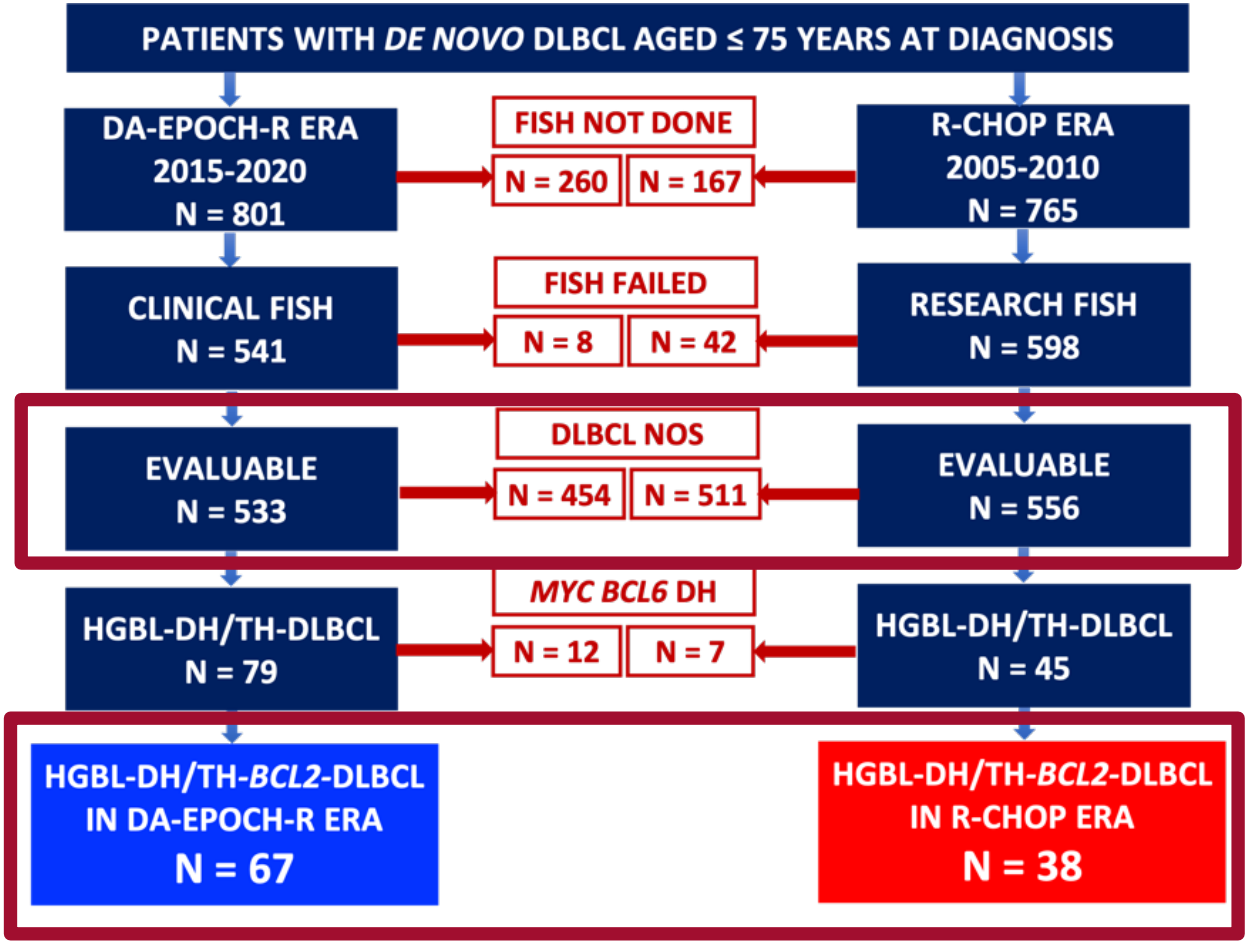
Petrich A et al, Blood 2014

Retrospective Review Of R-EPOCH vs R-CHOP in Double/Triple-Hit DLBCL



Magnusson T et al, EHA 2021

Population Analysis: DA-EPOCH-R Era (Routine FISH) vs Historic Control



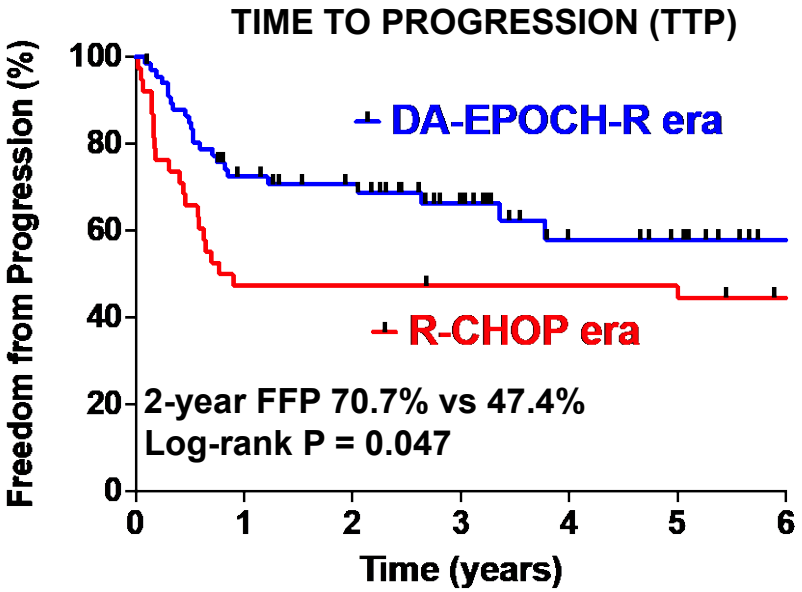
Alduaij W et al, ASH 2021

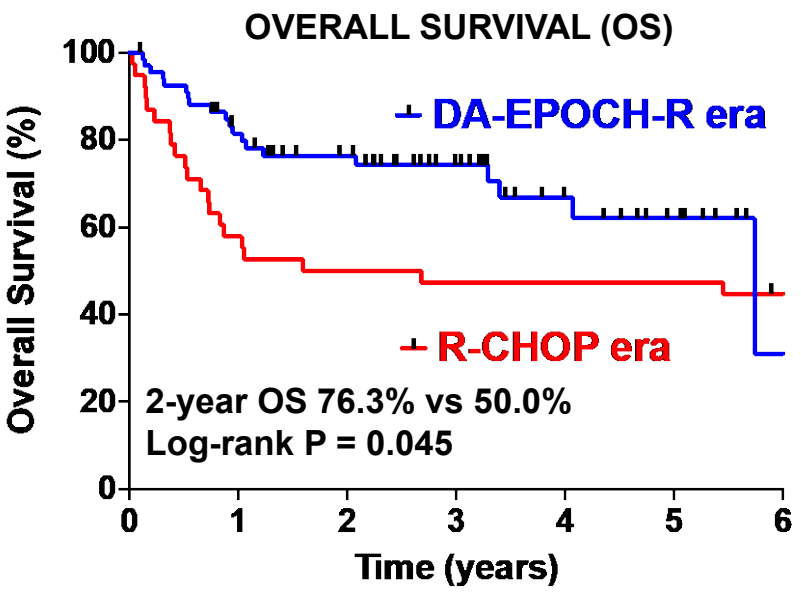
Baseline characteristics

Characteristic	DA-EPOCH-R era 2015-2020 (n = 67)	R-CHOP era 2005-2010 (n = 38)	*p*
Age, Median (range, years)	64 (30-75)	63 (28-75)	0.89
Female (n, %)	24 (36)	14 (37)	1
Gene Rearrangements (n, %) *MYC* and *BCL2* (double-hit) *MYC*, *BCL2* and *BCL6* (triple-hit)	 52 (78) 15 (22)	 29 (76) 9 (24)	 1
Stage III/IV (n, %)	57 (85)	27 (71)	0.13
PS > 1 (n, %)	27 (40)	15 (39)	1
LDH > normal (n, %)	42 (63)	23 (61)	1
Extranodal sites >1 (n, %)	33 (49)	12 (32)	0.10
B symptoms (n, %)	31 (46)	16 (42)	0.84
Bulky disease ≥ 10 cm (n, %)	35 (52)	14 (37)	0.30
IPI risk group (n, %) Low (0-2) High (3-5) Missing	 22 (33) 42 (63) 3 (4)	 18 (47) 20 (53) 0	 0.15
Treatment regimen (n, %) DA-EPOCH-R R-CHOP Highly Intensive* Palliative	 47 (69) 16 (26) 3 (4) 1 (1.4)	 0 32 (84) 4 (10) 2 (5)	

* CODOXMR/IVACR with consolidative autologous hematopoeitic cell transplant.
PS: ECOG perfomance status, IPI: International Prognostic Index.

Era-on-era comparison: clinical outcomes

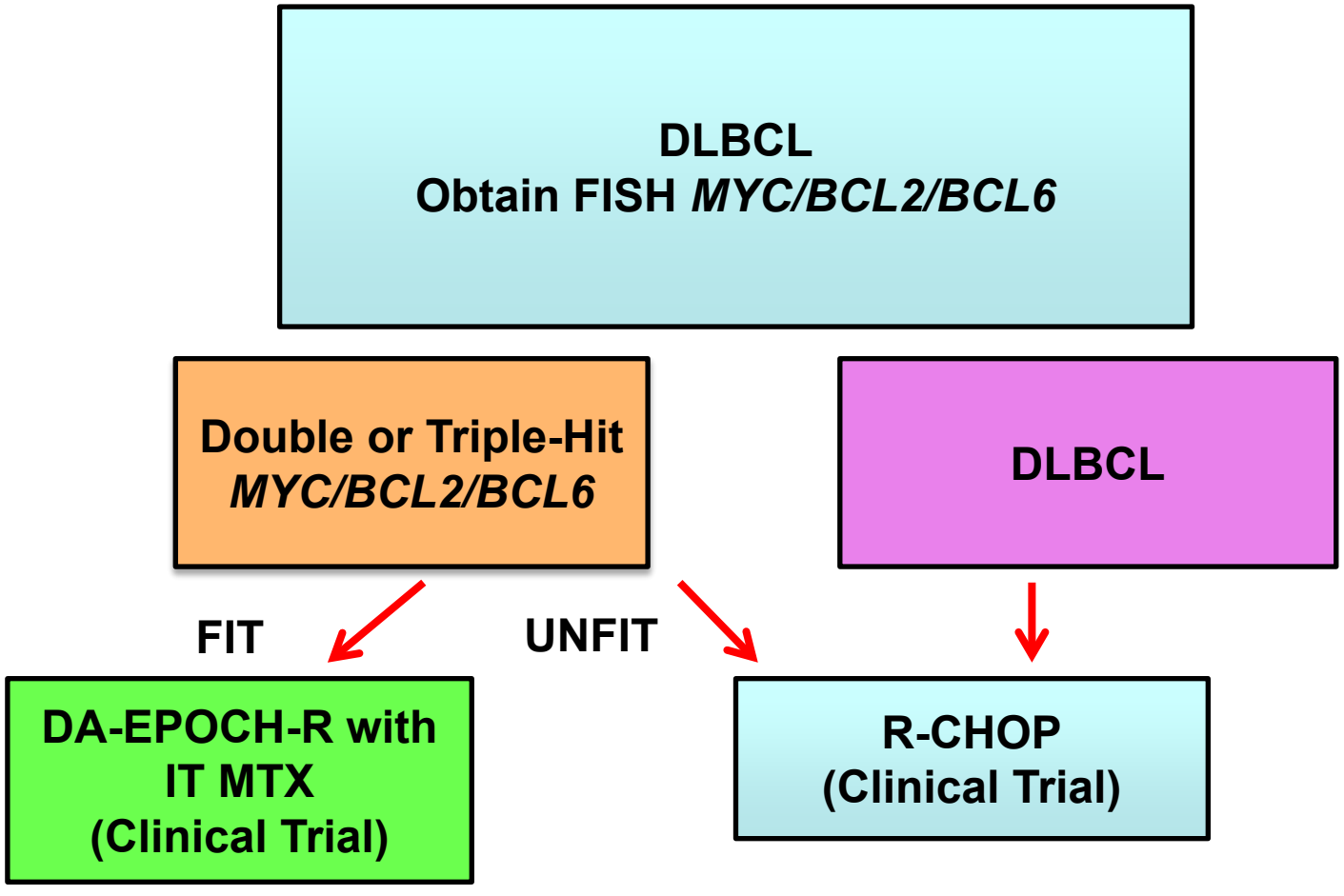




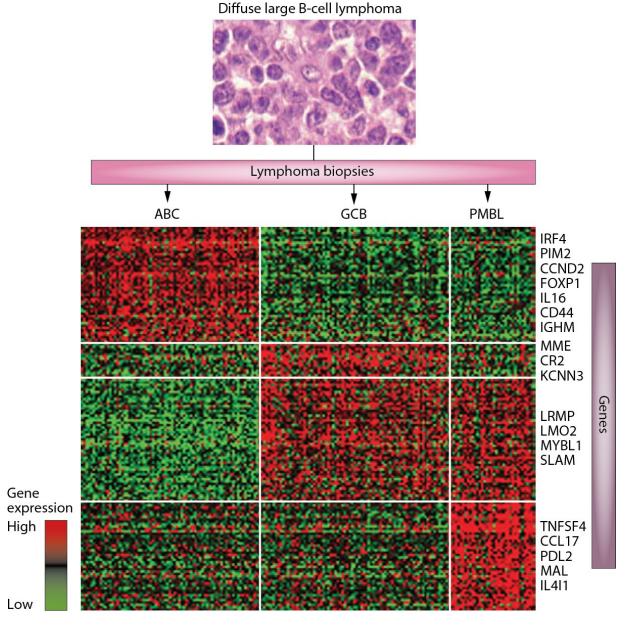
Cox model	DA-EPOCH-R era relative to R-CHOP era			
	TTP		OS	
	HR (95% CI)	p	HR (95% CI)	p
IPI low (0-2) vs high (3-5)	0.48 (0.26-0.89)	0.02	0.44 (0.23-0.83)	0.01
Individual IPI factors*	0.41 (0.21-0.82)	0.01	0.42 (0.21-0.85)	0.02

* Age >60 years, Stage III/IV, LDH>normal, PS>1 and extranodal sites>1. HR: adjusted Hazard Ratio, CI: Confidence iInterval

Treatment Algorithm for DLBCL

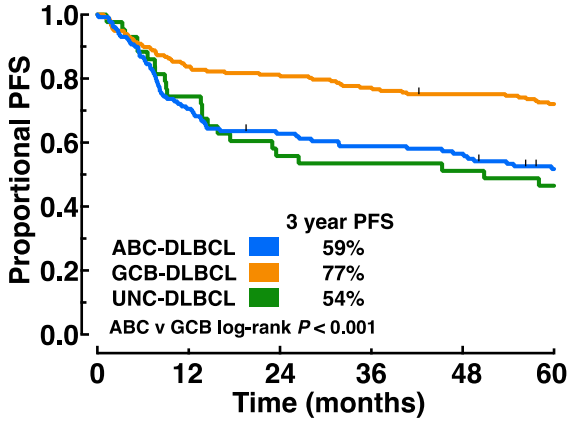


Prognosis According to Cell-of-Origin (ABC vs GCB) by GEP



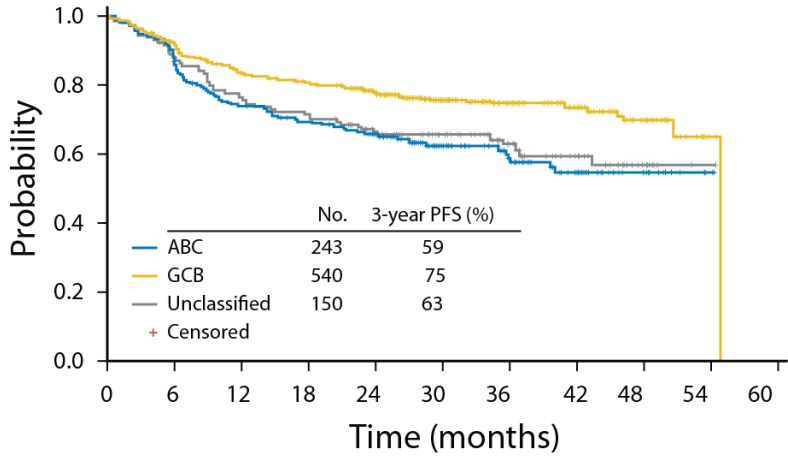
Alizadeh et al Nature 2000
Rosenwald et al, NEJM 2002
Lenz et al, NEJM 2008

15-20% difference in 3 year PFS



BC Cancer
2005 – 2010
R-CHOP treated

Unpublished Data

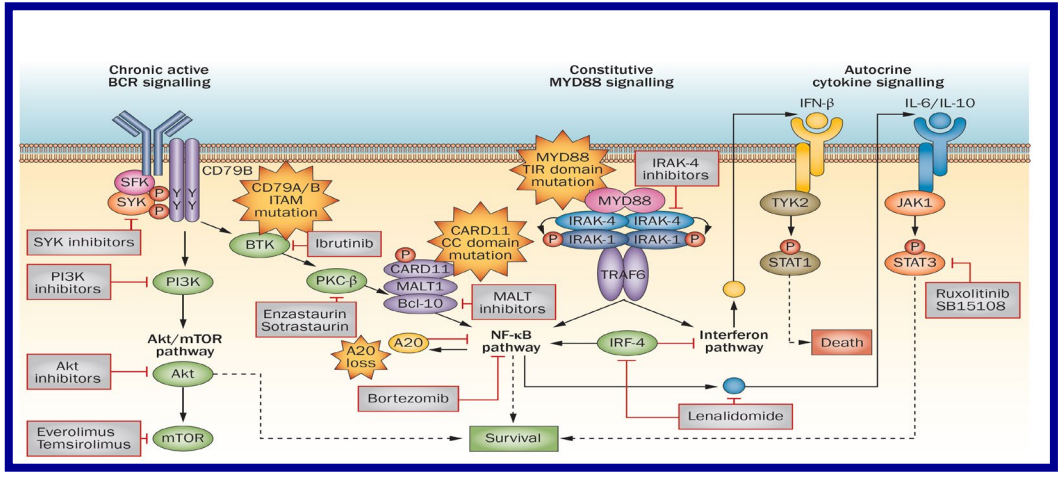


GOYA Trial
R-CHOP v G-CHOP
PFS including both arms

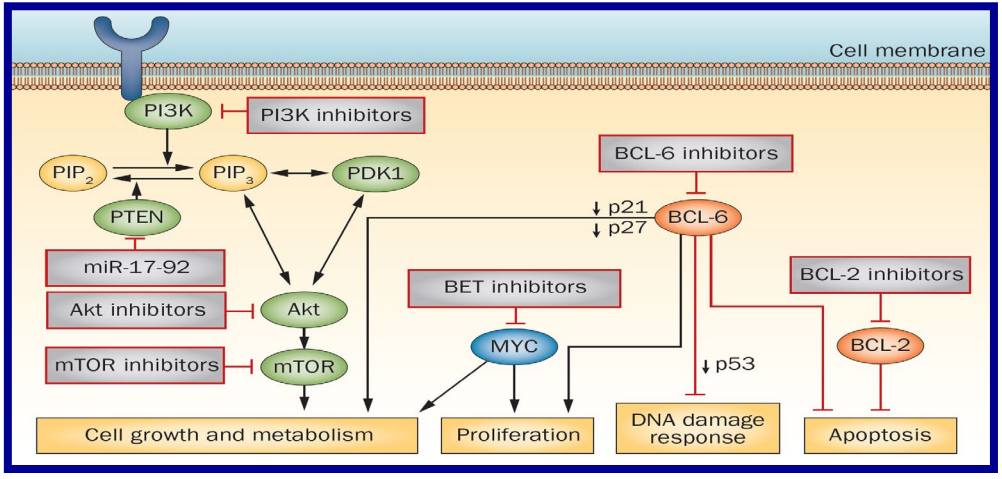
Vitolo et al J Clin Oncol 2017

Distinct Signaling Pathways According to Cell-of-Origin & Potential Agents

ABC

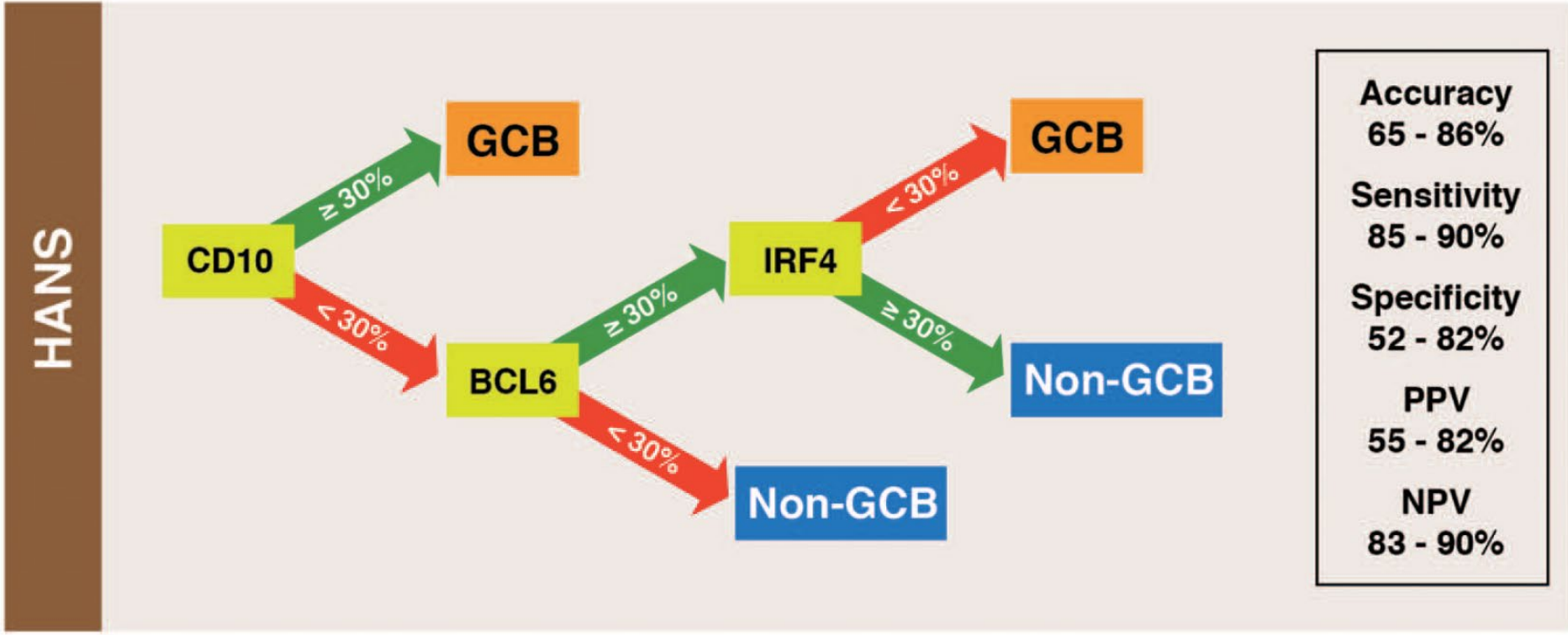


GCB



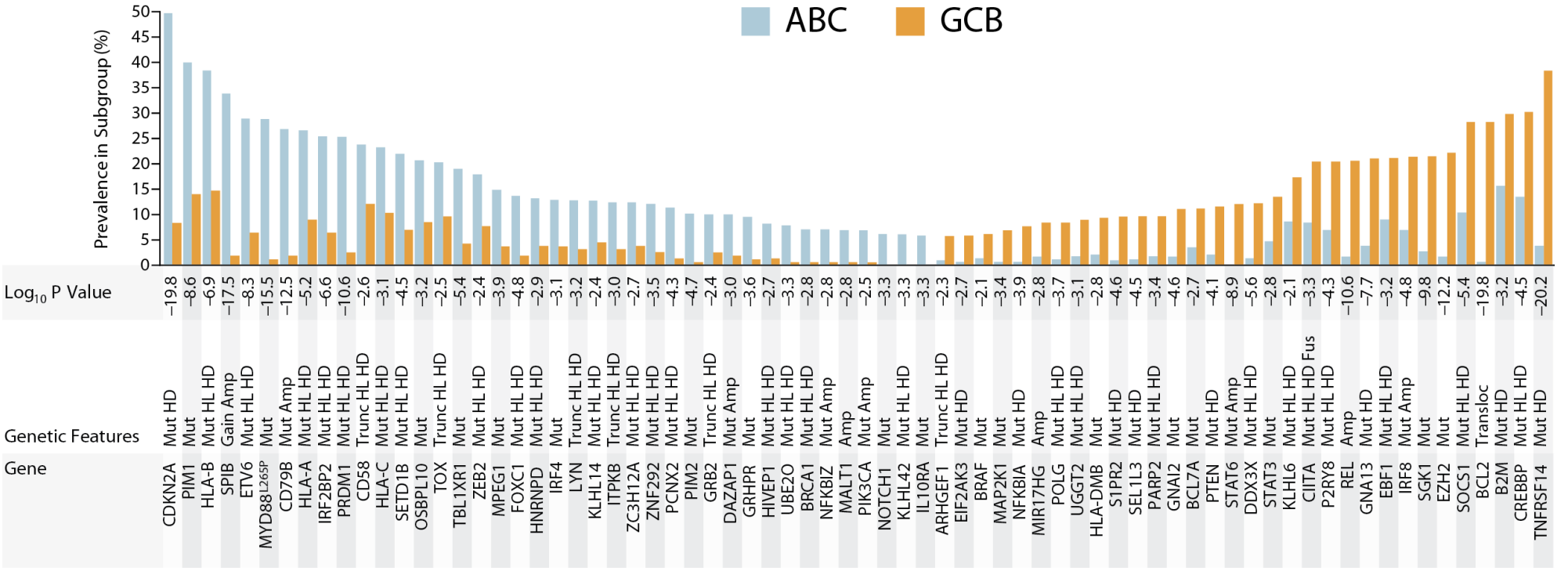
Roschewski, et al Nat Rev Clin Oncol 2014

Using Immunohistochemistry to Assign COO



Scott DW. ASCO Education Book 2015

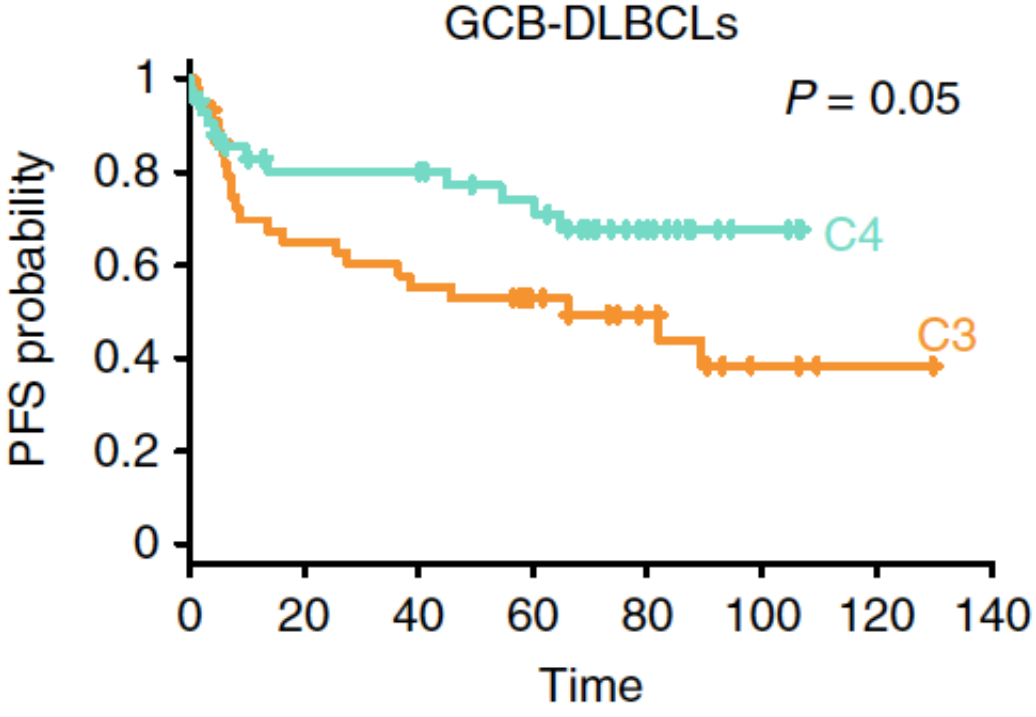
Cell-of-Origin – Distinct Mutational Landscapes

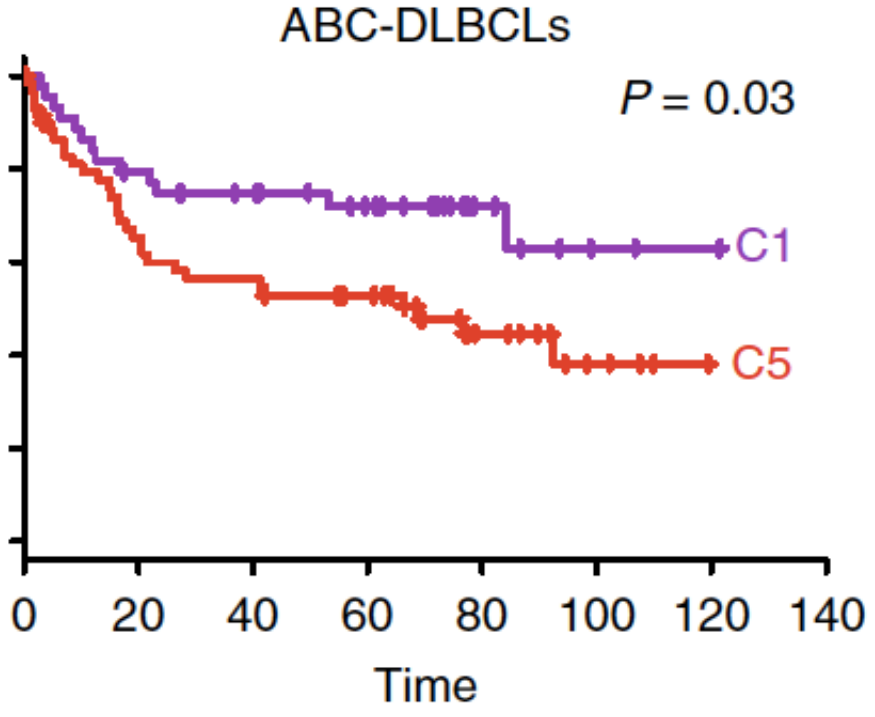


Heterogeneity within the COO subtypes is the likely explanation for variability in prognosis across populations

Schmitz et al N Eng J Med 2018

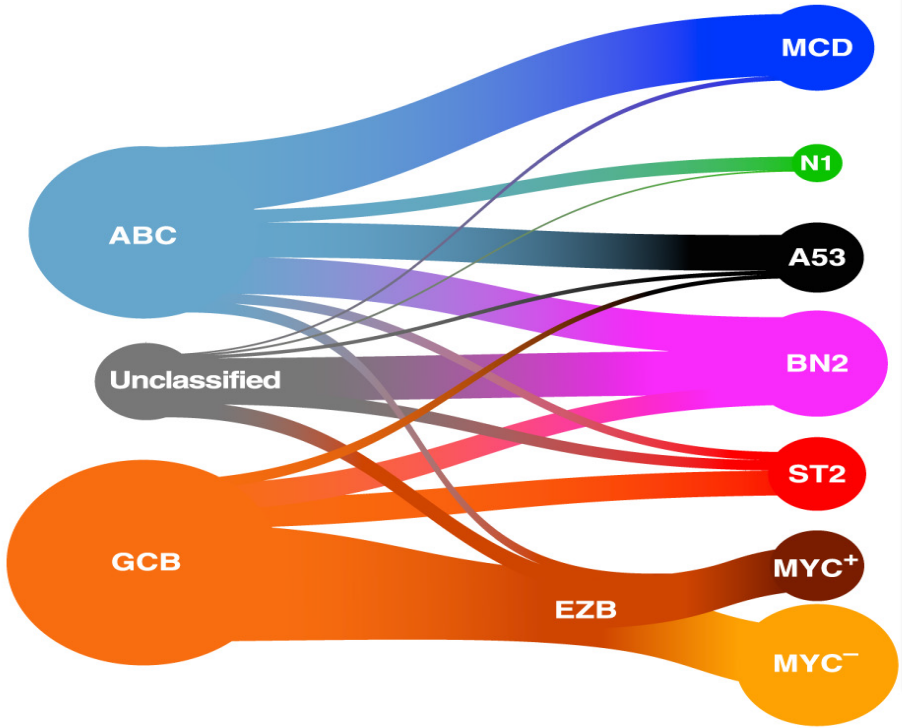
Novel Molecular Taxonomies of DLBCL Reveal Heterogeneity within COO Subtypes





Chapuy B et al., Nature Medicine, 2018

Novel subtypes within ABC and GCB DLBCL have been Identified

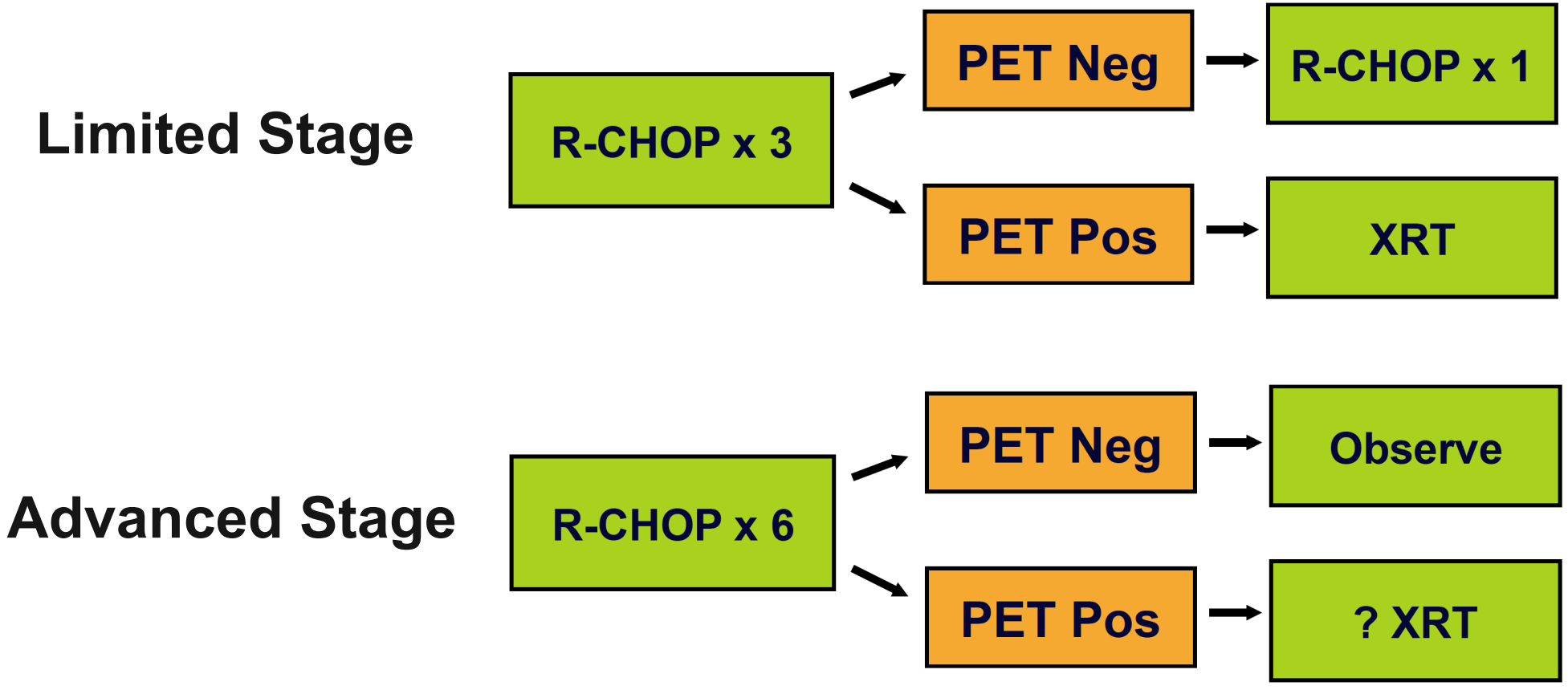


	Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
MCD	8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2-$BCLX_L$-MCL1 JAK1 IRAK4 IRF4
N1	1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
A53	5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	–	p53 Immune low	BCR-dep. NF-κB
BN2	13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - *CD70* loss Proliferation - Cyclin D3 BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
ST2	6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation *P2RY8 – GNA13* inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
MYC+ MYC−	5.9% (MYC^+) 17.6% (MYC^-)	48% (MYC^+) 82% (MYC^-)	Chromatin modification Anti-apoptosis PI3 kinase signaling *S1PR2 – GNA13* inactivation Altered T_{FH} interactions MYC (EZB-MYC^+) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC^+)	GC LZ (MYC^-) GC IZ (MYC^+) BCL6 (MYC^+) TCF3 (both) T_{FH} cells (MYC^-) Stromal (MYC^-) Immune low (MYC^+)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

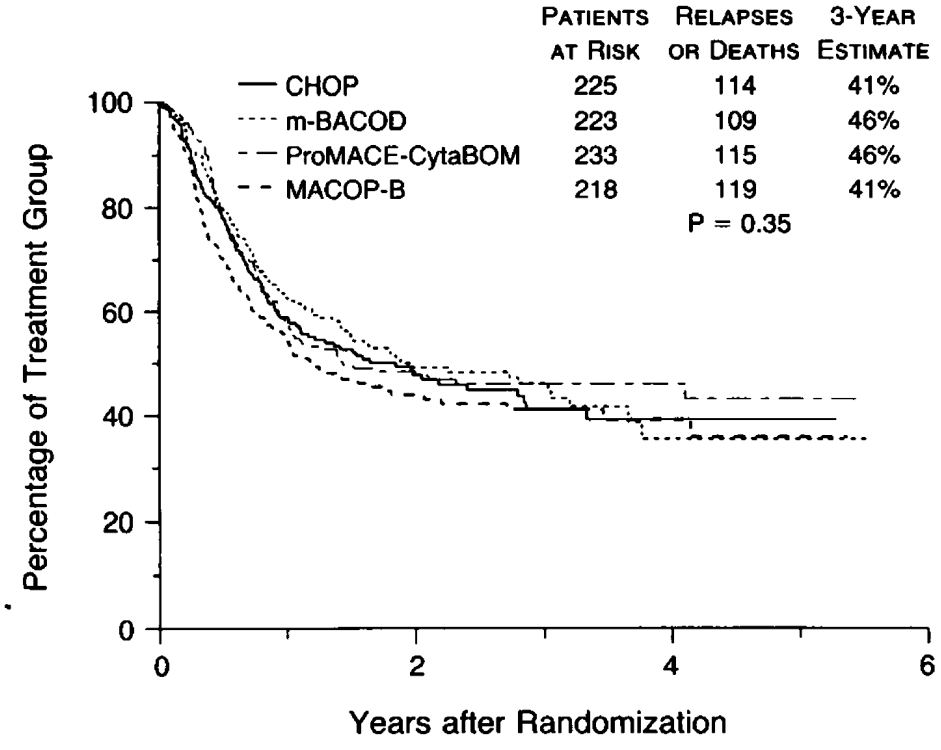
Wright et al., Cancer Cell, 2020

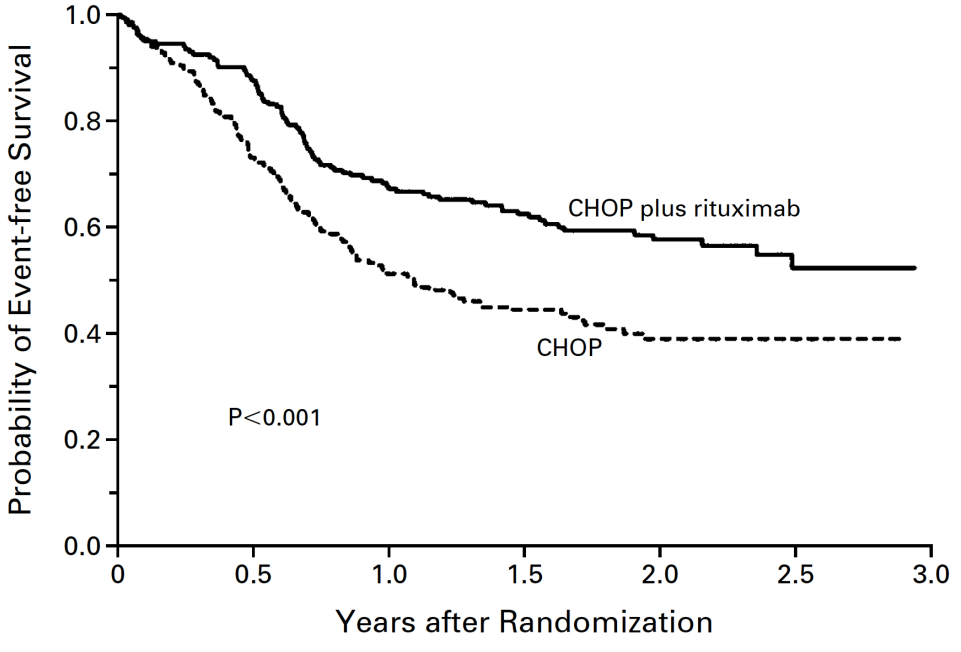
Despite our growing understanding of biology…we continue to treat patients with DLBCL the same

BC Cancer DLBCL Treatment Algorithm



R-CHOP Established as Standard of Care





Fisher et al, NEJM 1993

Coiffier, NEJM 2002

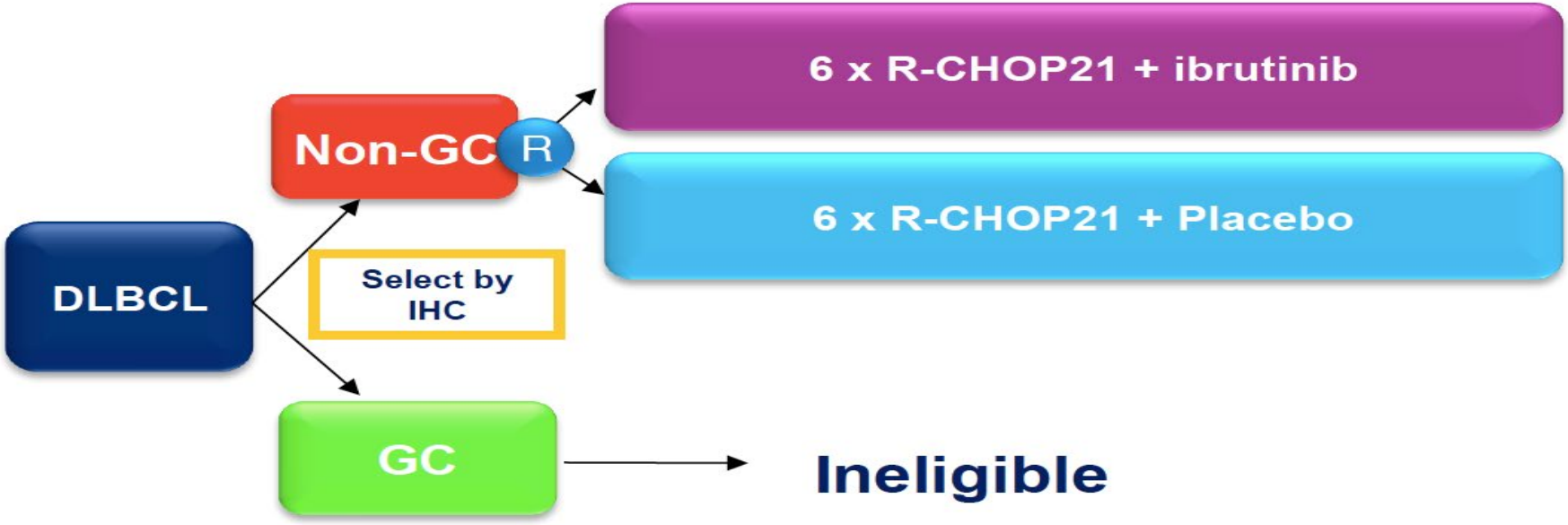
The Limit of Chemotherapy

Author	Therapy	Better than R-CHOP?
Cunningham, Lancet 2013	**R-CHOP-14**	**No**
Delarue, Lancet Oncol 2013	**R-CHOP-14**	**No**
Pfreundshuh, Lancet Oncol 2011	**R-CHOEP**	**No**
Recher, Lancet 2011	**R-ACVBP**	**Yes (Age <60 y, IPI 1)**
Wilson ASH 2016, **Bartlett** JCO 2019	**DA-EPOCH-R**	**No**
Le Gouill, ASCO 2011	**ASCT *v* R-CHOP-14**	**No**
Schmitz, Lancet Oncol 2012	**R-Mega-CHOEP *v* R-CHOEP-14**	**No**
Vitolo, ASH 2012 (#688)	**ASCT v R-dose dense chemo**	**PFS Only**
Stiff, NEJM 2013	**ASCT *v* (R)-CHOP-21**	**PFS Only**

Randomized Trials of Novel Agents

Author	Therapy	Better than R-CHOP
Leonard, JCO 2017	**R-CHOP- Bortezomib**	**No**
Davies, Lancet 2019	**R-CHOP- Bortezomib**	**No**
Vitolo, JCO 2017	**Obinutuzumab-CHOP**	**No**
Younes, JCO 2019	**R-CHOP-Ibrutinib**	**? No**
Nowakowski, JCO 2021	**Lenalidomide-R-CHOP**	**? Yes (Phase II)**
Nowakowski, JCO 2021	**Lenalidomide-R-CHOP**	**No**

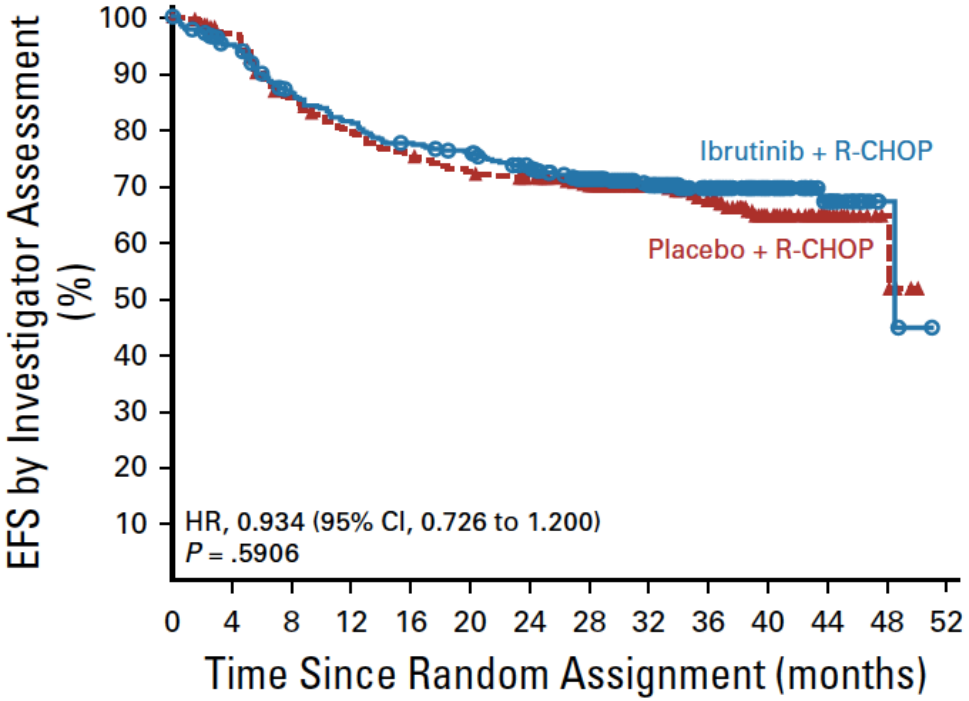
Phoenix Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



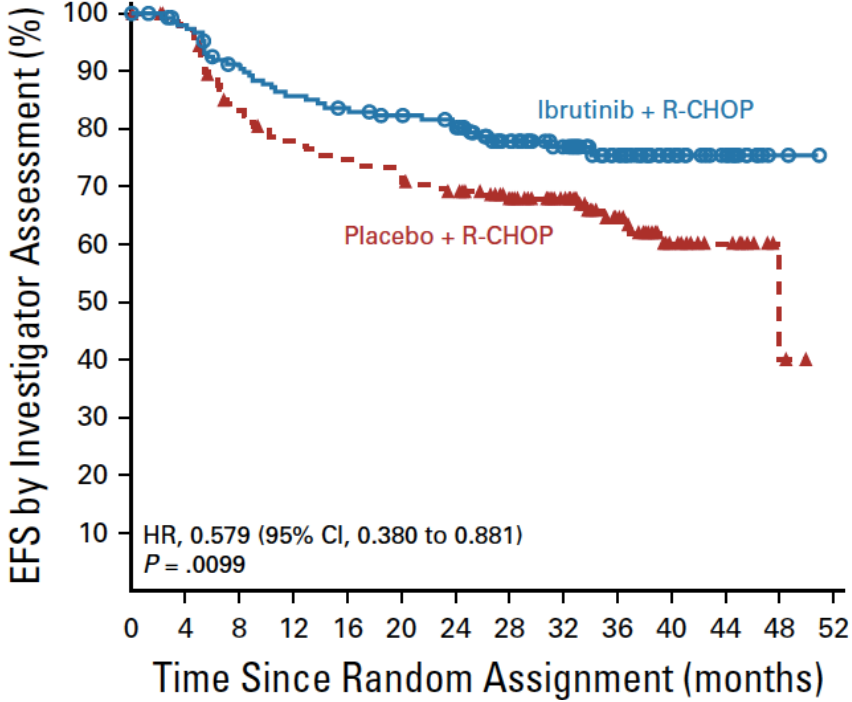
- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = EFS
- N = 800

*** Ibrutinib 560 mg daily x 6 cycles or placebo**

Phoenix Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



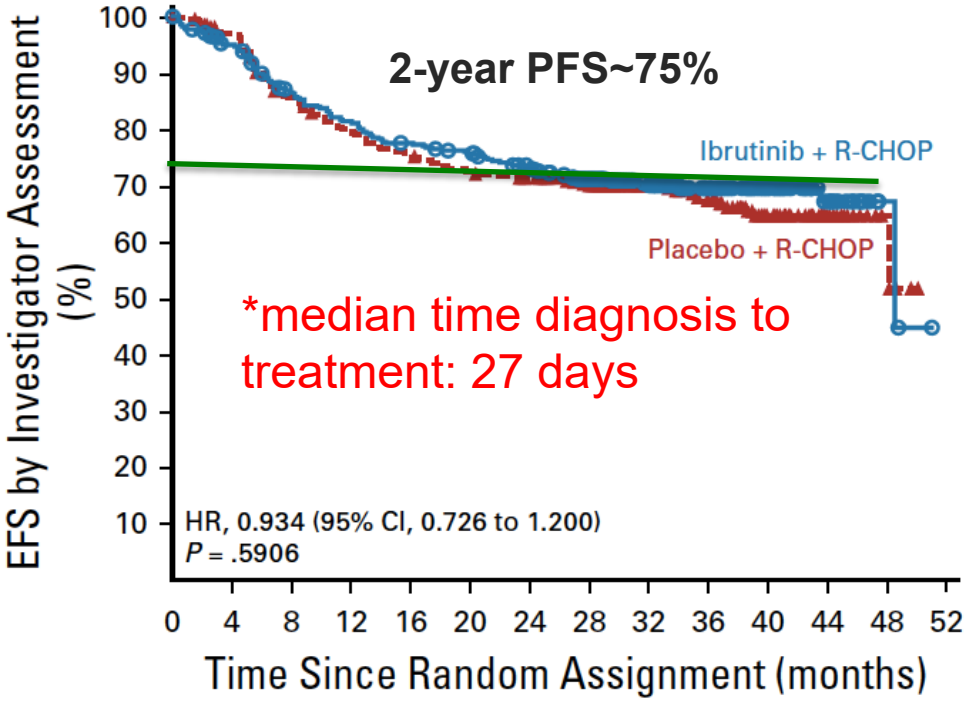
ITT Population



Age <60 years

Younes, A et al, JCO 2019

Phoenix Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



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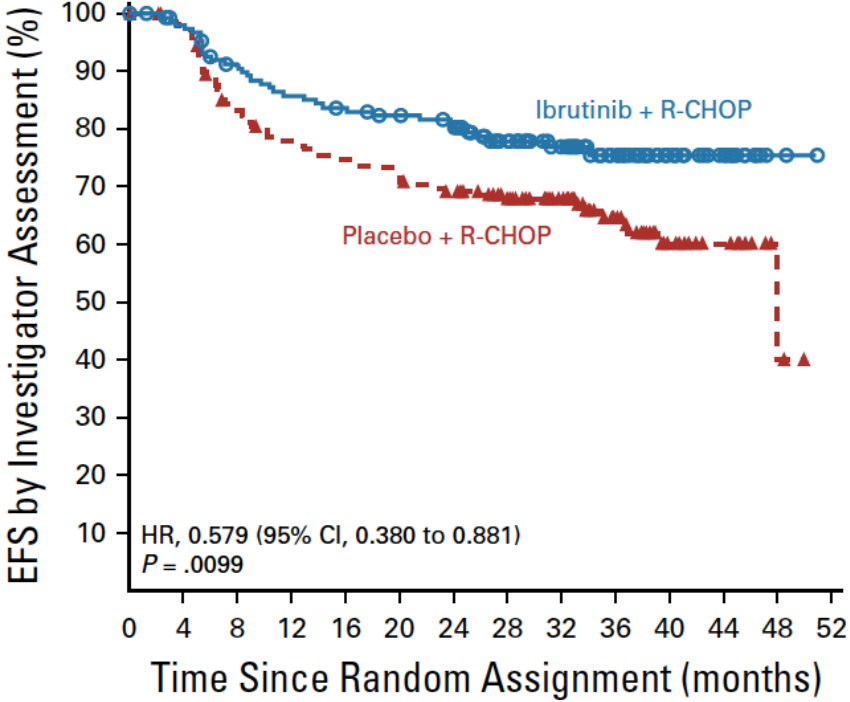


Age <60 years

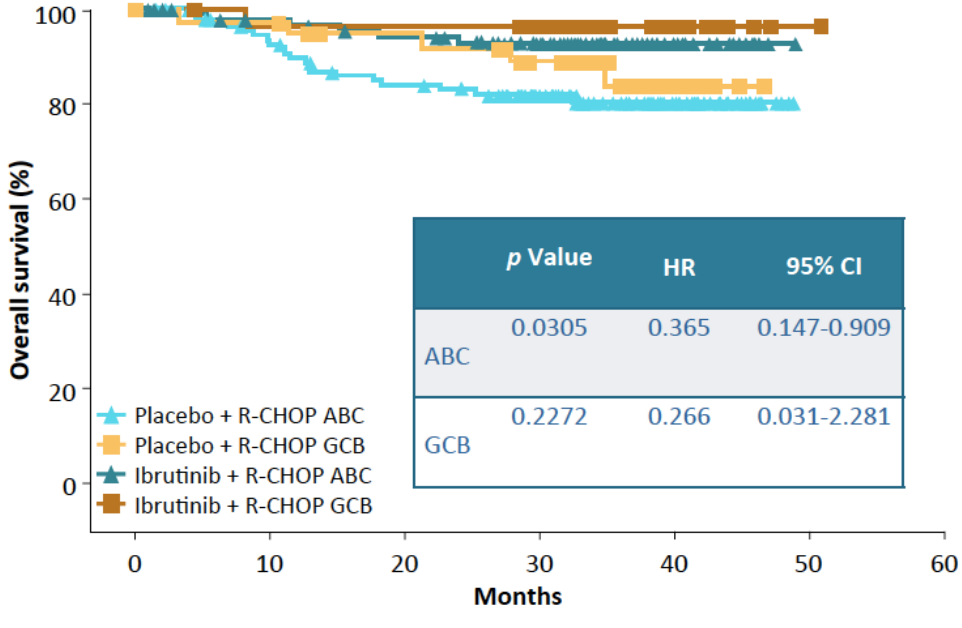
Younes, A et al, JCO 2019

Concordance Between IHC and GEP

- 747 samples were evaluable from 838 enrolled patients
- 75.9% of enrolled (non-GCB by IHC) patients were ABC by GEP
- Non-GCB concordance = 82.7%

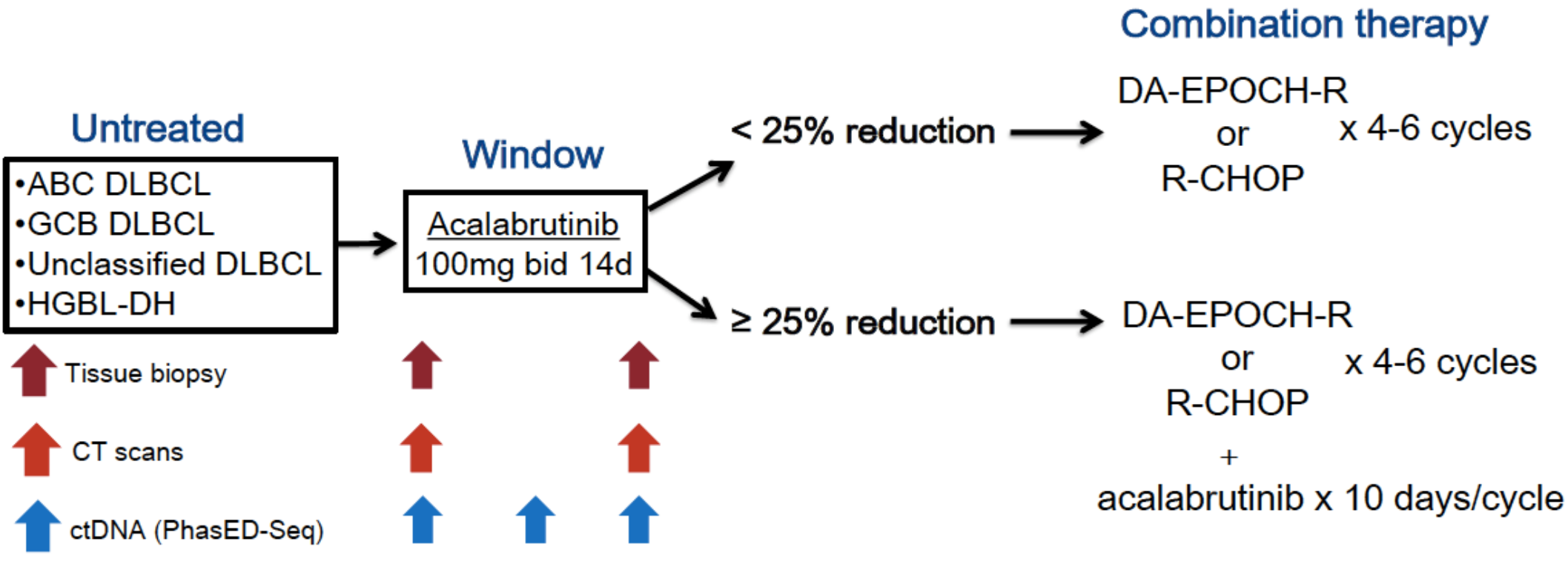
		EdqeSeq COO GEP			
			Non-GCB		
		GCB	ABC	UNC	Total
Hans-based IHC	Non-GCB, n (%)	129 (17.2)	567 (75.9)	51 (6.8)	747 (100)

OS in Patients <60 years



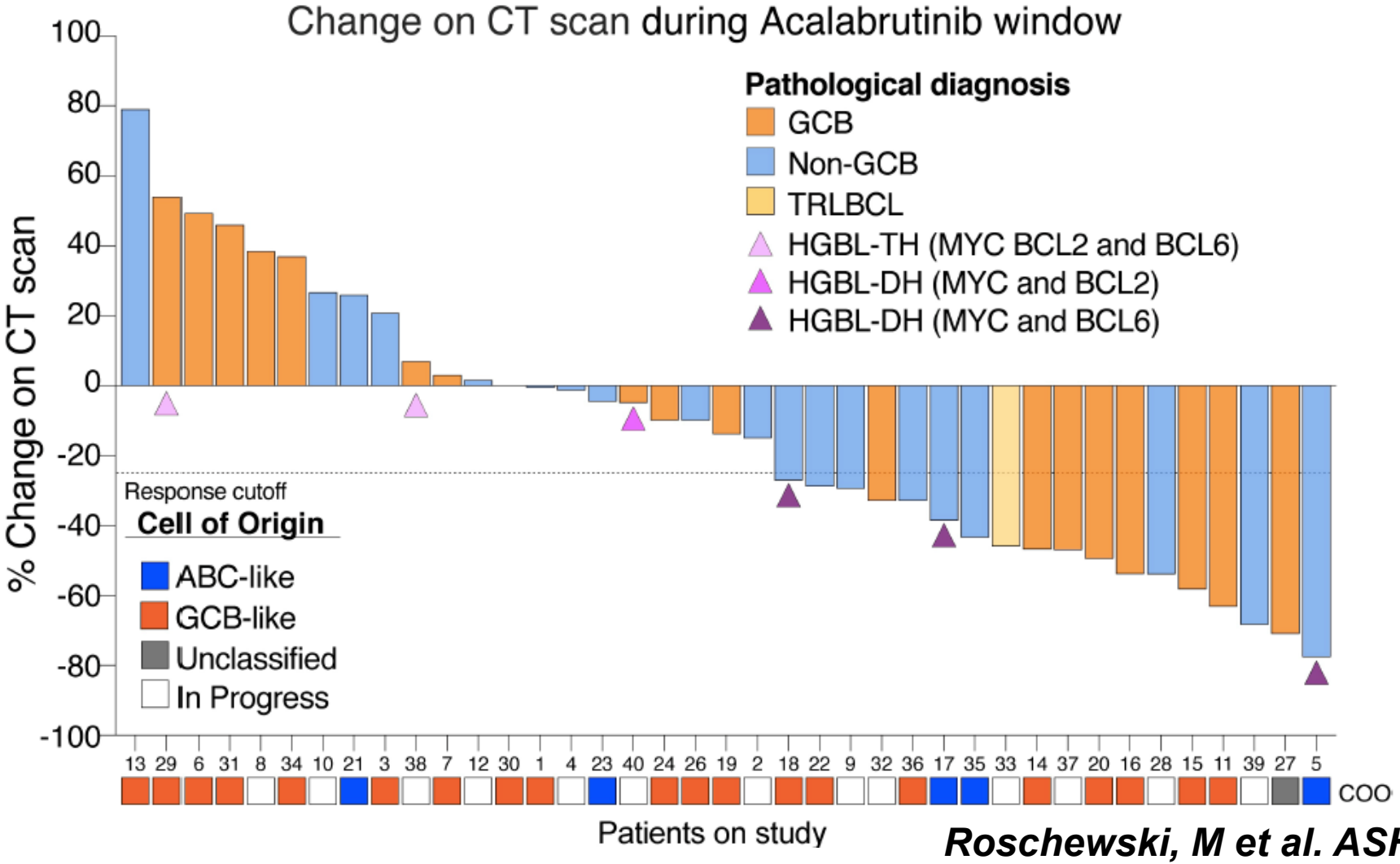
Balasubramanian, S et al, ICML 2019

Response-Adapted Acalabrutinib Window Study Design



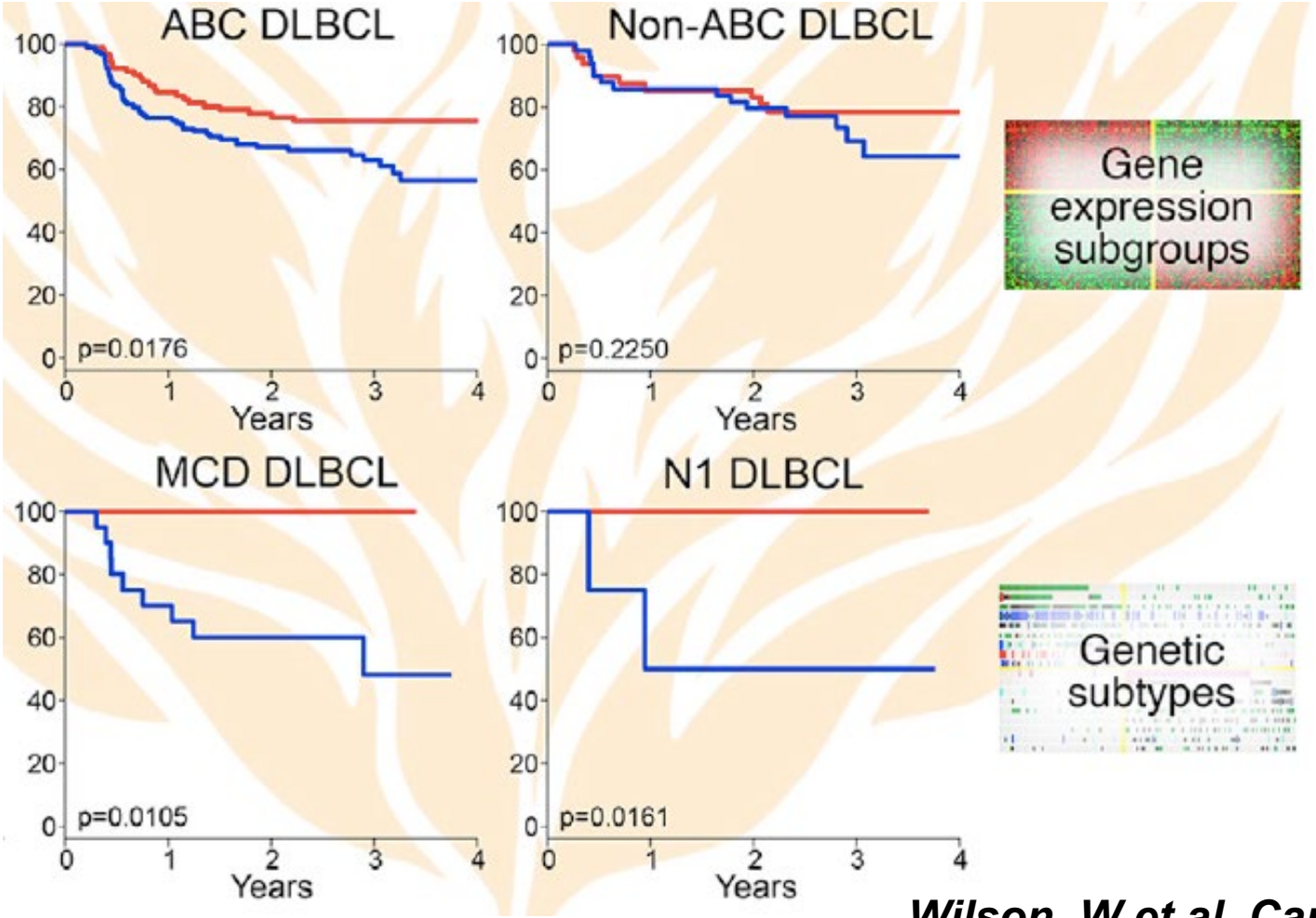
Roschewski, M et al. ASH 2021

Acalabrutinib has Activity Across DLBCL Subtypes



Roschewski, M et al. ASH 2021

EFS According to GEP and Genetic Subtype



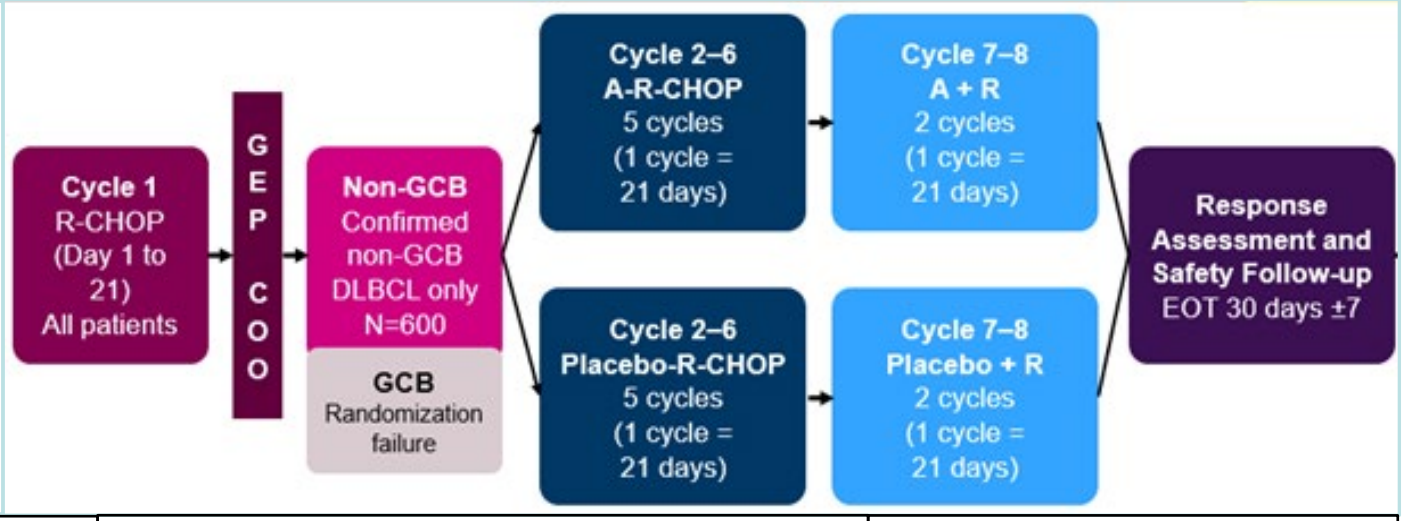
Wilson, W et al. Cancer Cell 2021

Learnings from PHOENIX informed the ESCALADE design

- Age ≤ 65 yo - instead of age-all comers
- COO by GEP – instead of IHC
- G-CSF – mandatory
- 1st R-CHOP cycle prior to randomization

Key Inclusion Criteria

- 18 - 65 years
- Histologically documented DLBCL
  - FFPE tumor tissue sample sent to the central laboratory prior to C1D1
  - Central laboratory confirmation by GEP of non-GCB subtype of DLBCL
- No prior treatment for DLBCL
- ECOG 0-2
- IPI 2-5
- Stage II-IV
- Measurable lesion by CT with contrast (or MRI)



Primary objective:

A+R-CHOP vs P+R-CHOP efficacy: INV assessed PFS

Key secondary objectives:

A+R-CHOP vs P+R-CHOP efficacy:

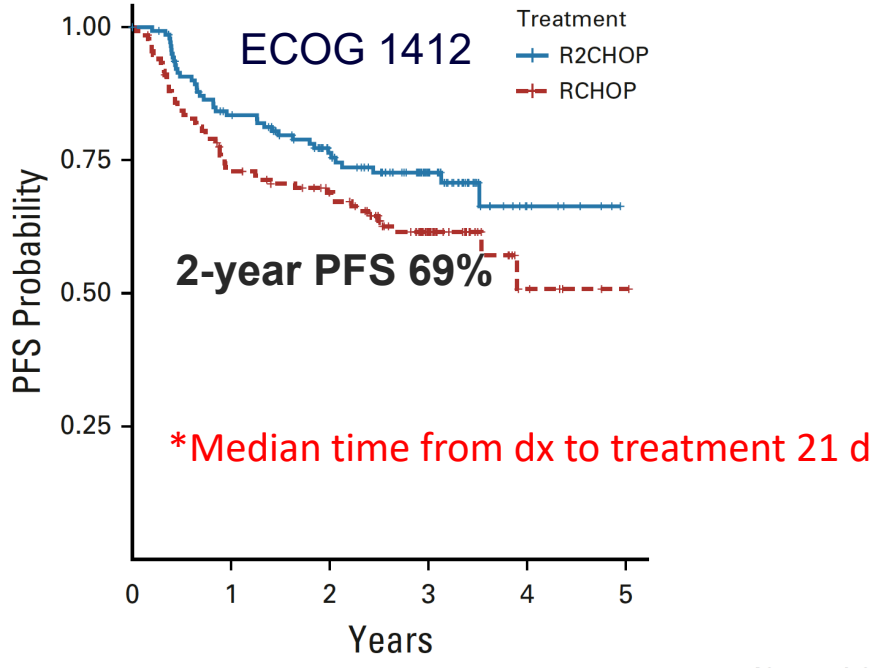
- INV assessed EFS
- BICR assessed CR rate at end of study treatment
- OS

Treatment and Duration:

- R-CHOP given every 21 days for 6 cycles starting on C1D1
- From Cycle 2 (randomized on Cycle 2 (C2D1)) to Cycle 6, pts with non-GCB DLBCL will receive either Acalabrutinib 100 mg twice daily plus R-CHOP or placebo plus R-CHOP
- Followed by 2 additional cycles of Rituximab + Acalabrutinib or placebo in Cycle 7 and Cycle 8, as 8 cycles of rituximab is recognized as a common standard per ESMO guidelines with 6 cycles of CHOP

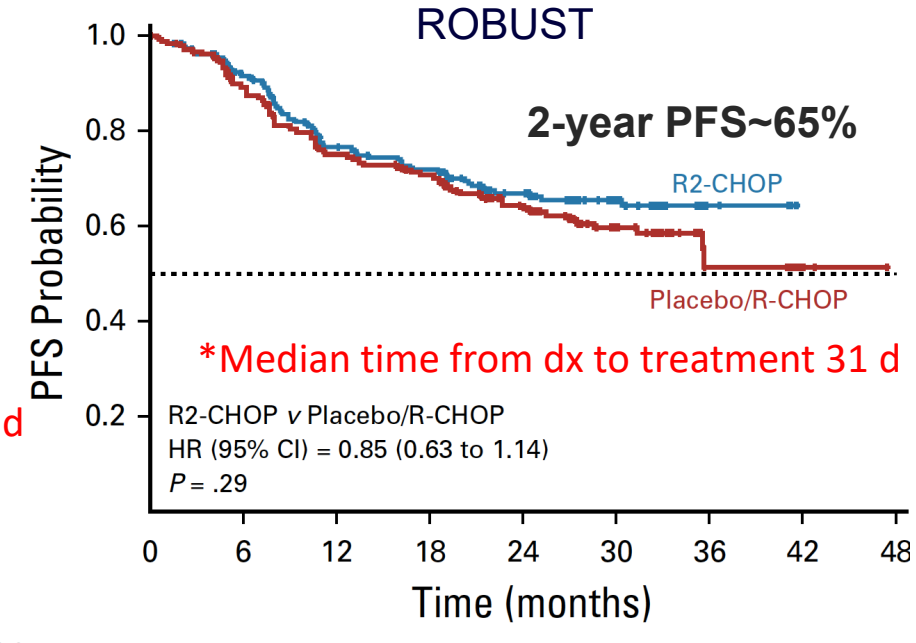
Interim and Final Analysis: One interim analysis for futility only and the final analysis will occur when **102** (45% of final) and **227,** respectively, INV-assessed PFS events combined in Arms A and B have been observed. IA is projected to occur 40 months after first subject randomized (FSR).

Lenalidomide-R-CHOP: ECOG 1412 Phase II and ROBUST Phase III



No. at risk:

R2CHOP	145	113	85	46	7	0
RCHOP	135	95	80	42	7	1



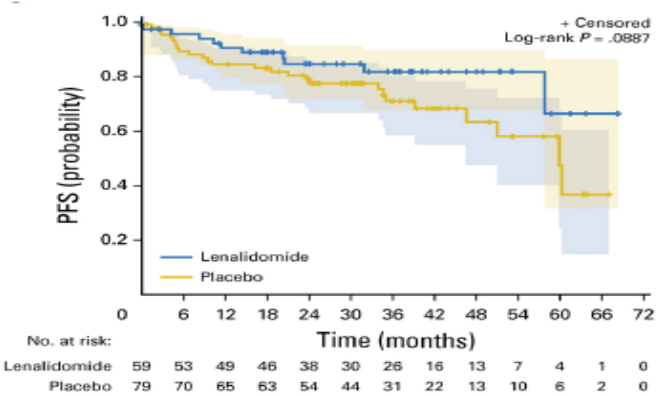
No. at risk:

R2-CHOP	285	221	178	162	119	57	10	0	
Placebo/R-CHOP	285	229	187	173	111	55	10	3	0

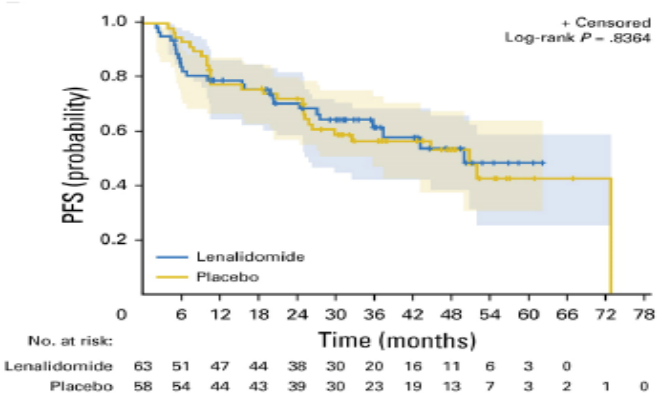
Nowakowski, G et al, JCO 2021 x 2

REMARC Trial: R-CHOP followed by Lenalidomide Maintenance in DLBCL

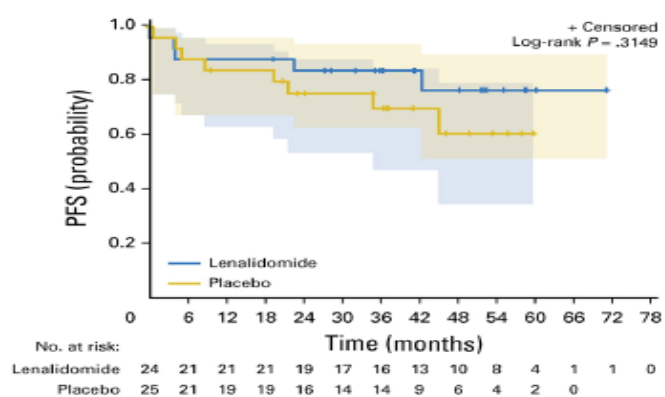
GCB



ABC

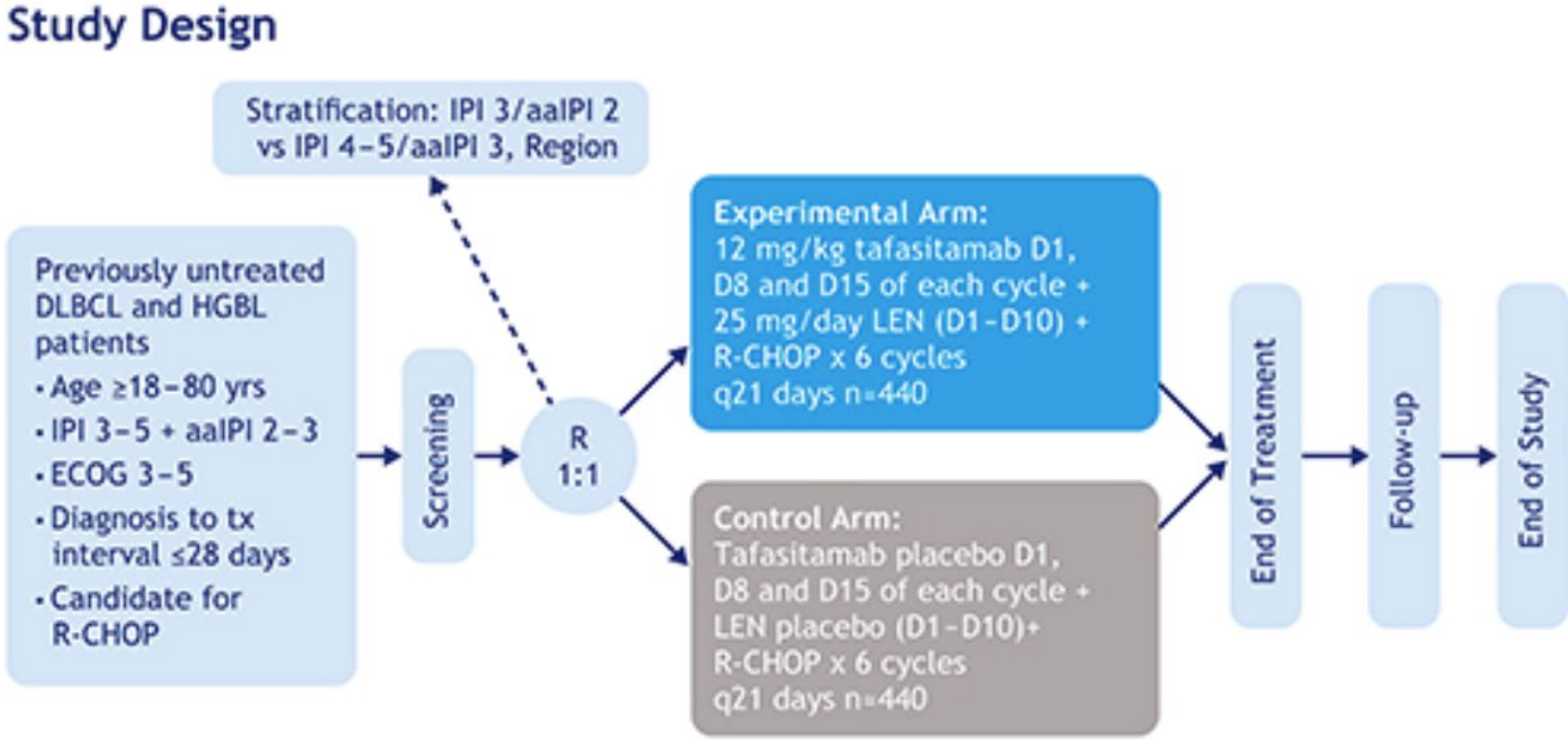


Unclassified



Thieblemont C et al, JCO 2017

Front-MIND Trial:
Tafa-Len-R-CHOP vs R-CHOP in DLBCL



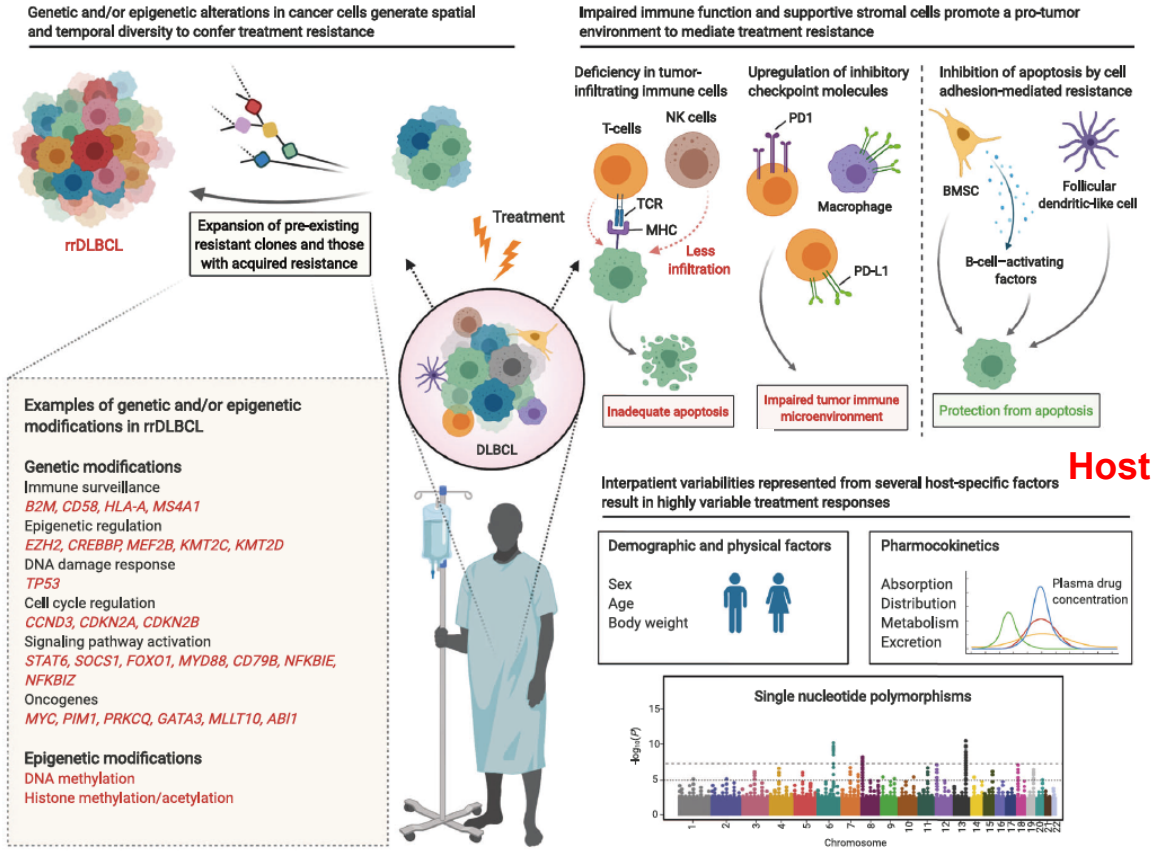
Challenges with Recent Phase 3 Trials

- High bar to beat with R-CHOP
- Large patient numbers required
- Biomarker requirement caused delay in treatment leading to patient selection
- Highest risk patients excluded
- Biological heterogeneity despite patient enrichment

Treatment Resistance in DLBCL

Tumor Heterogeneity

Tumor Microenvironment



Host Variabilities

He and Kridel, Leukemia 2021

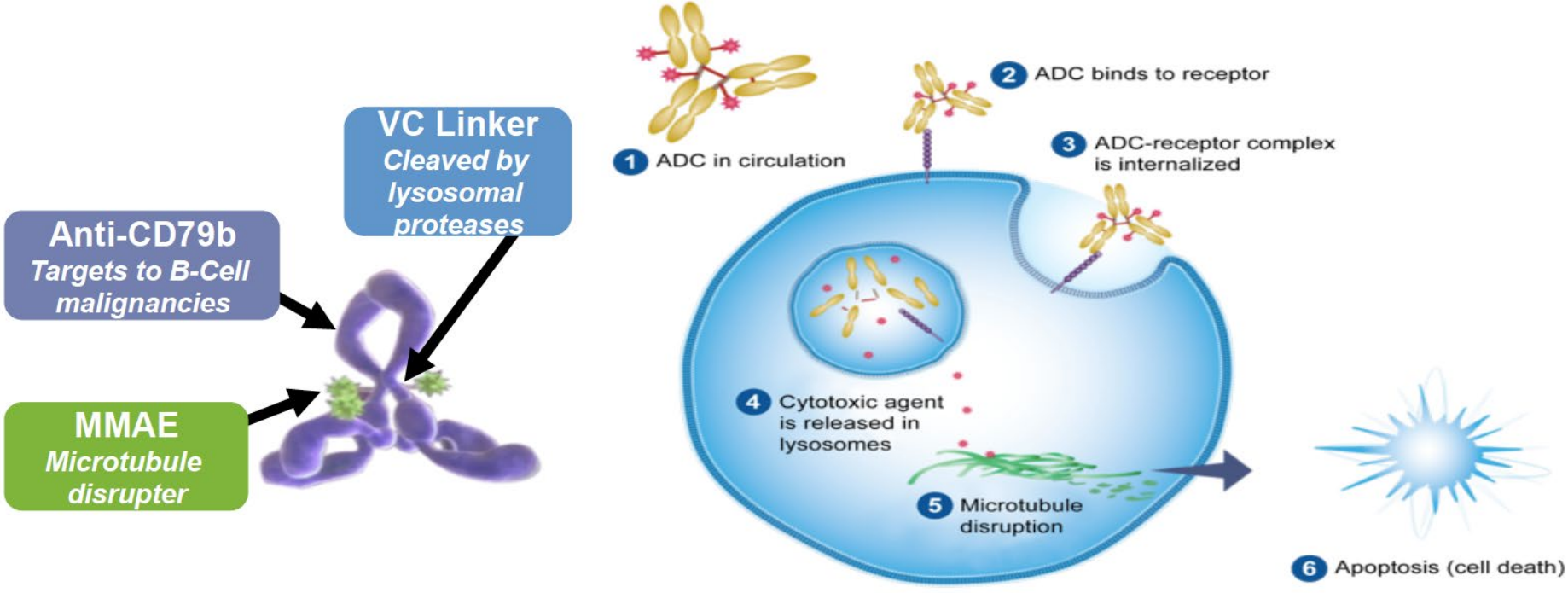
Novel Agents have Emerged Allowing Durable Disease Control

Novel Agents Recently Approved in R/R DLBCL

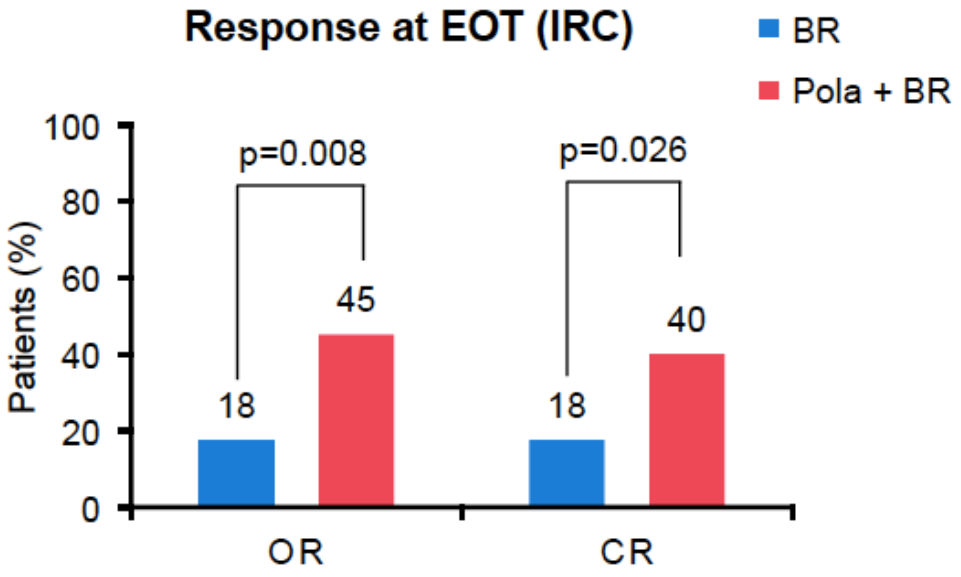
	Pola-BR	Selinexor	Tafasitamab/Lenalidomide	Loncastuximab Tesirine
MOA	Anti-CD79b ADC	XPO-1 inhibitor	Anti-CD19 MAb/Immunomodulator	Anti-CD19 ADC
ORR	45%	28%	58%	48%
CR rate	40%	10%	40%	24%
PFS	9.2m	2.6m	11.6m	4.9m
DOR	12.6m	9.3m	43.9m	10.3m
OS	12.4m	NR	33.5m	9.9m

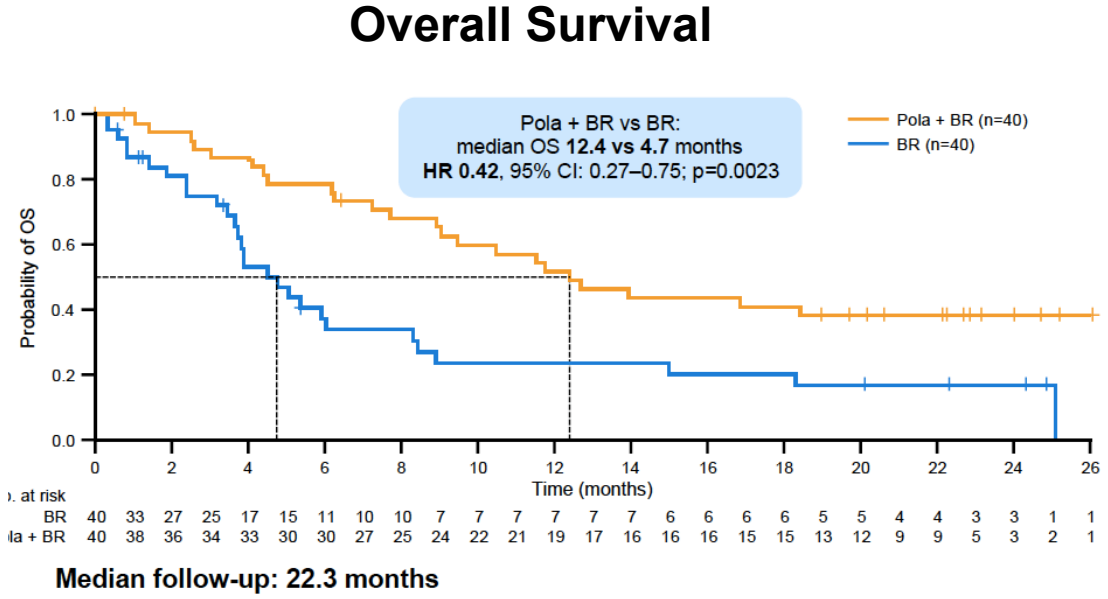
Polatuzumab Vedotin: Anti-CD79b Drug Conjugate

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



Randomized Phase II: Pola-BR vs BR



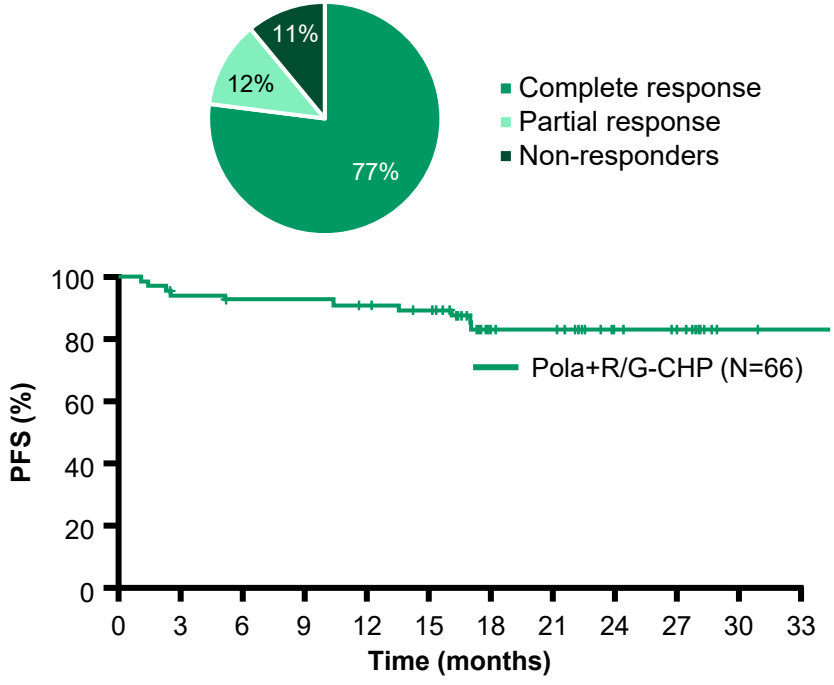


Sehn et al, JCO 2020

Pola + R/G-CHP in First-line DLBCL

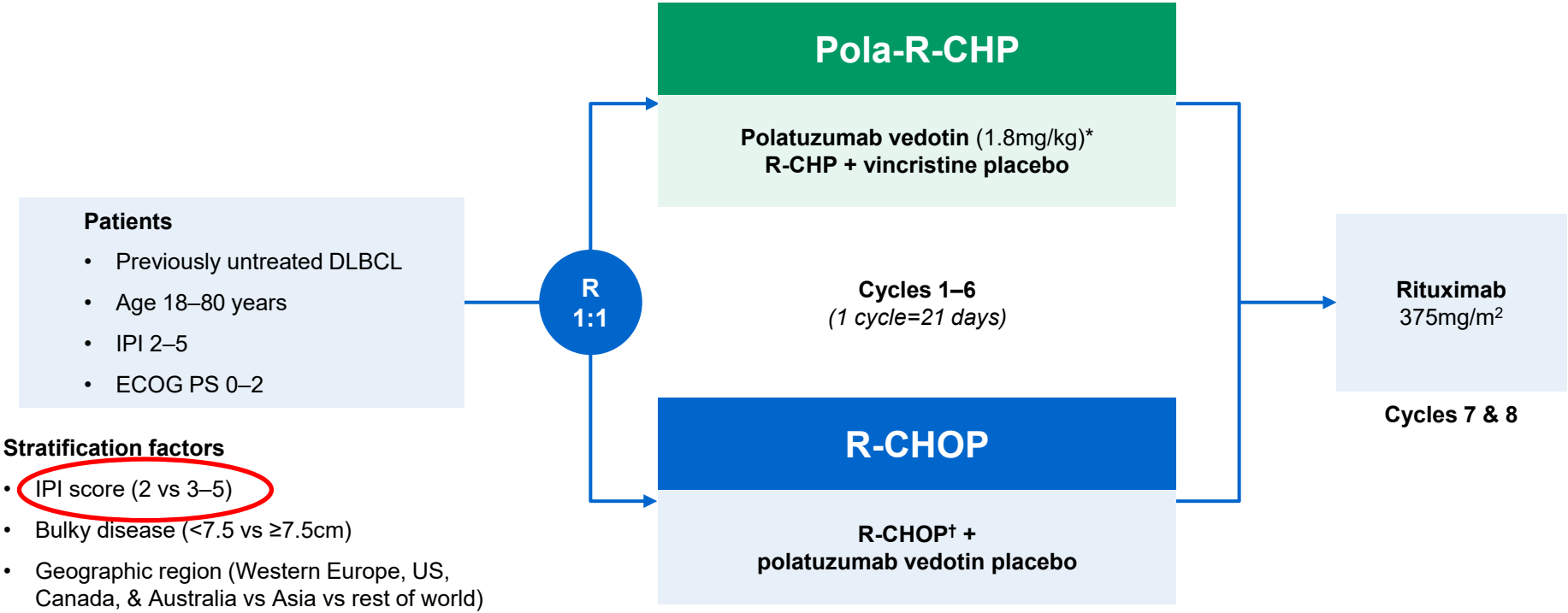
- Open-label phase1b/2 study
- Phase 2 population: DLBCL, IPI ≥ 2
- ORR: 89%; CR 77%
- Median f/up: 21.5 months
- 2-yr PFS: 83%

Pola+R/G-CHP demonstrated activity in first-line DLBCL



Tilly H, et al. Lancet Oncol 2019;20:998–1010.

POLARIX: A randomized double-blinded study



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Tilly H et al, NEJM 2021

POLARIX: Key endpoints and analysis timing

Key endpoints	
Primary endpoint	**Progression-free survival (Investigator-assessed)**
Secondary endpoints	Event-free survival Complete response rate at end of treatment (PET/CT, IRC-assessed) Disease-free survival Overall survival
Safety endpoints	Incidence, nature, and severity of adverse events

Statistical design and timing of primary analysis:

- 875 patients, all on study for ≥24 months with approximately 228 PFS events, were required for the primary analysis. This occurred on June 28, 2021 (clinical cut-off date)
- Median follow up at the primary analysis was **28.2 months**

IRC, Independent Review Committee.

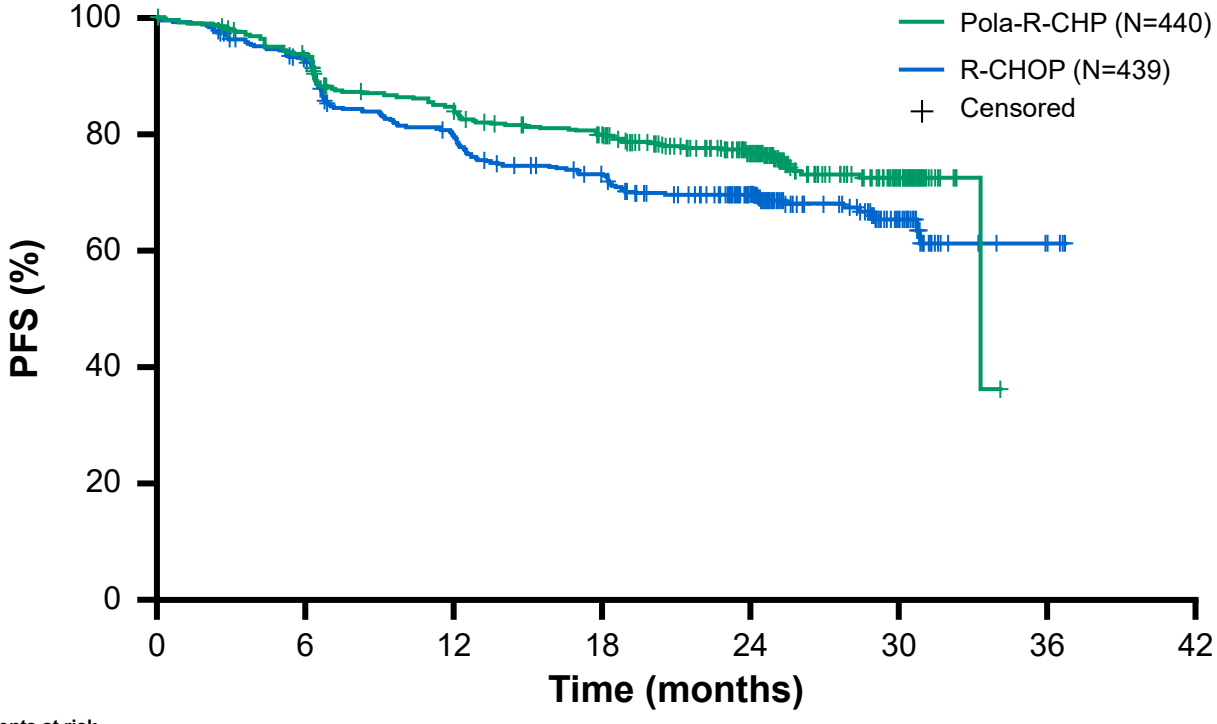
Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1	374 (85)	363 (83)
	2	66 (15)	75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	2	167 (38)	167 (38)
	3–5	273 (62)	272 (62)
Cell-of-origin, (%)*	ABC	102 (31)	119 (35)
	GCB	184 (56)	168 (50)
	Unclassified	44 (13)	51 (15)
MYC/BCL2 expression, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.
ABC, activated B-cell; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; LDH, lactate dehydrogenase.

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



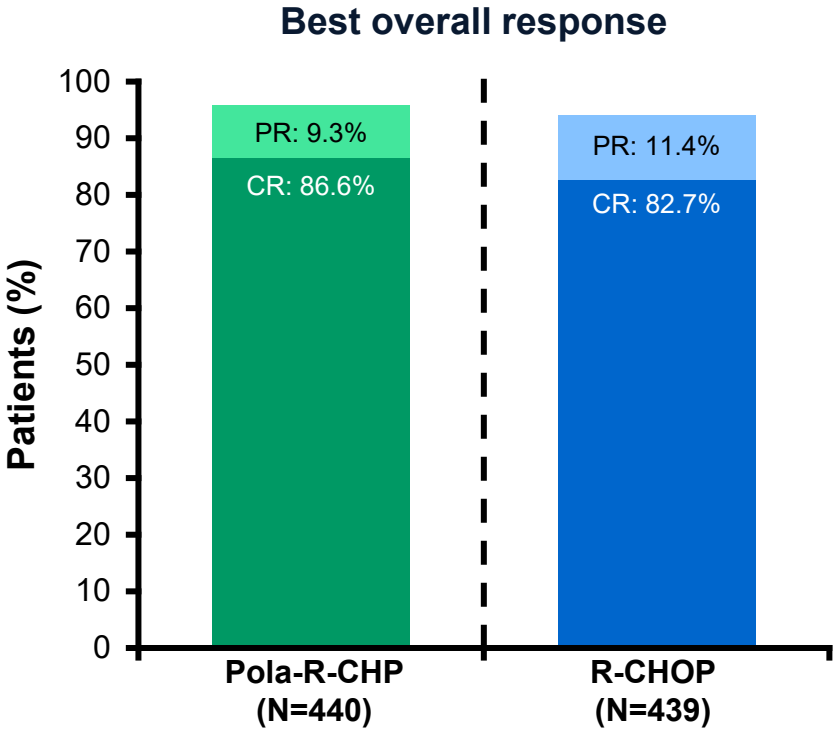
No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

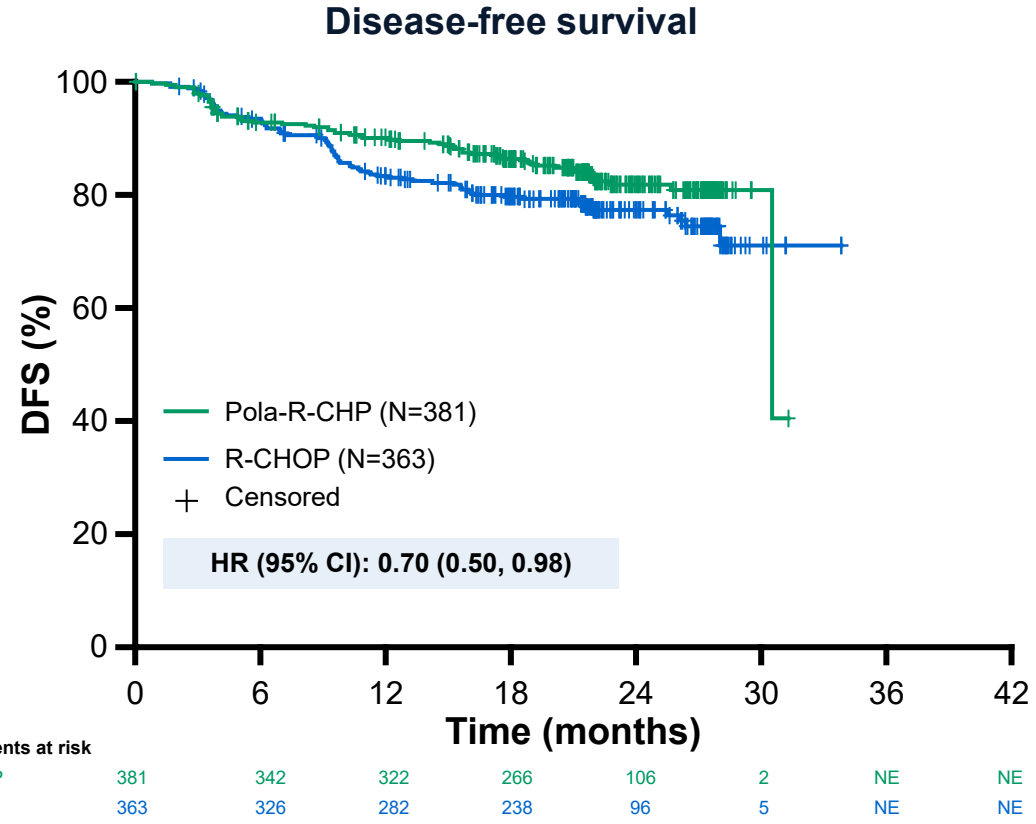
HR 0.73 **(P<0.02)**
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Response rates and disease-free survival

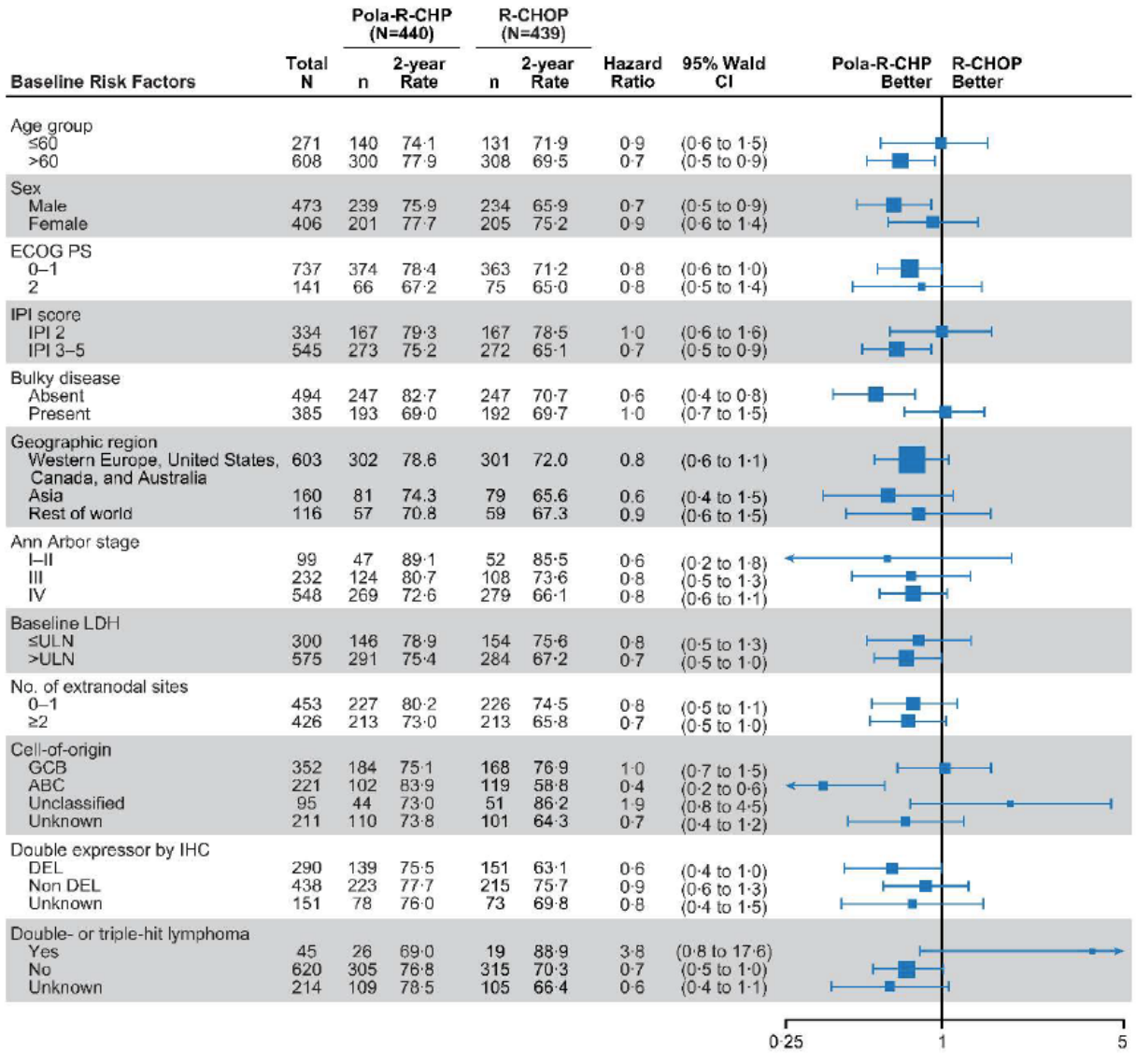




No. of patients at risk

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

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up. Disease-free survival (DFS) defined as the time from the date of the first occurrence of a documented complete response to the date of progression, relapse, or death from any cause for the subgroup of patients with a best overall response of CR.



? Benefit

Younger ≤ 60y

Females

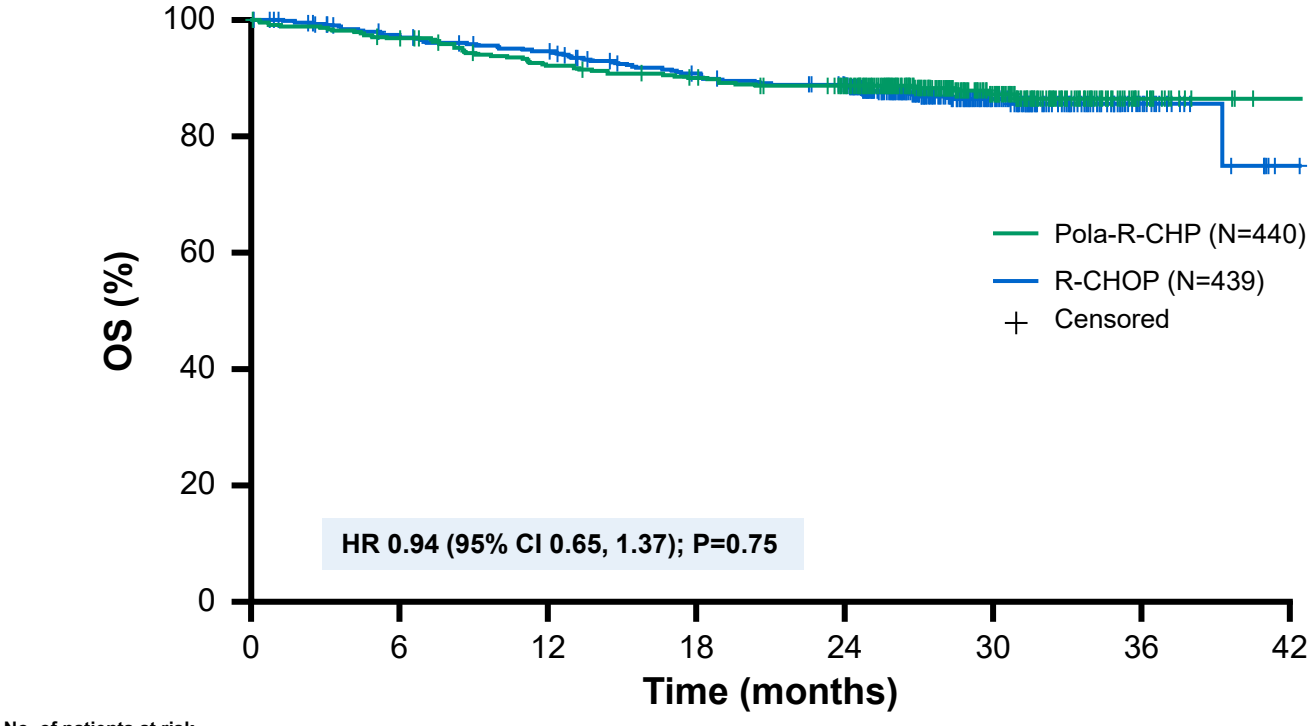
IPI = 2

Bulk ≥ 7.5 cm

GCB Subtype

DH/TH lymphoma

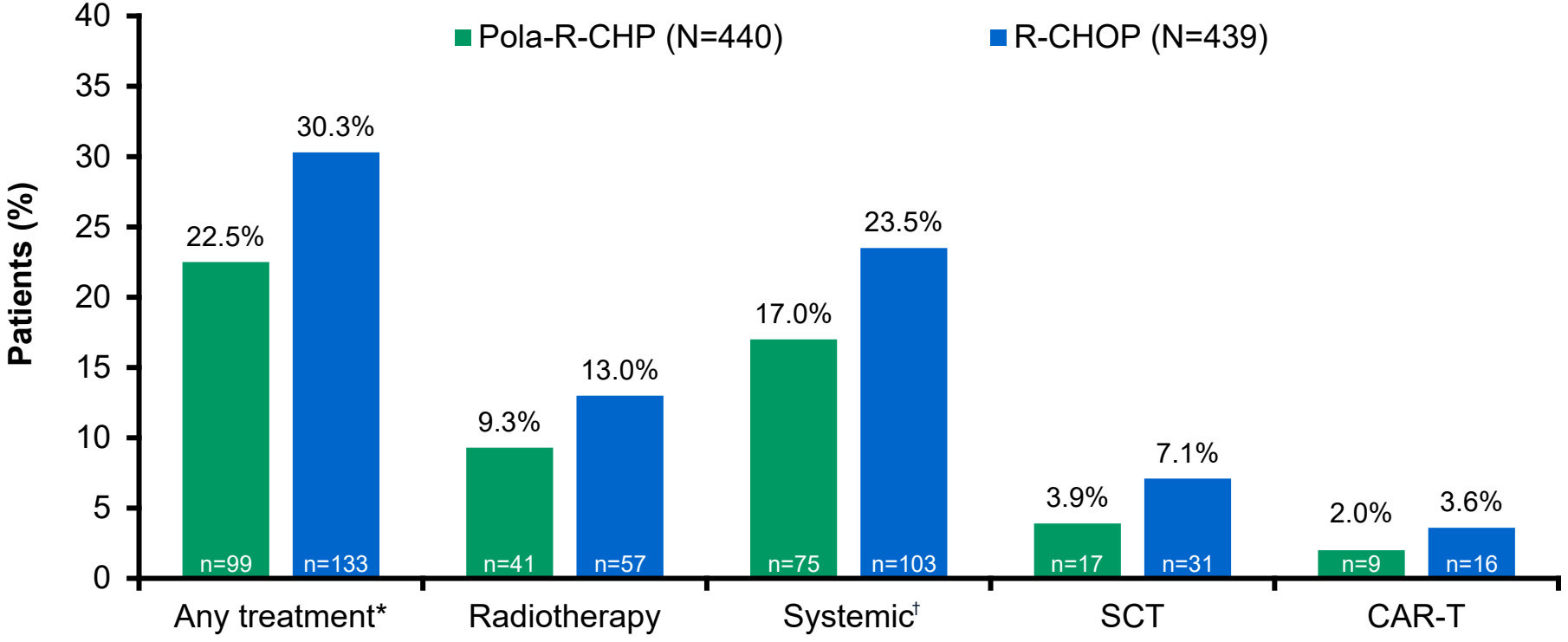
Overall survival



No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.

Patients receiving subsequent treatments



Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.
CAR-T, chimeric antigen receptor T-cell therapy; SCT, stem cell transplant.

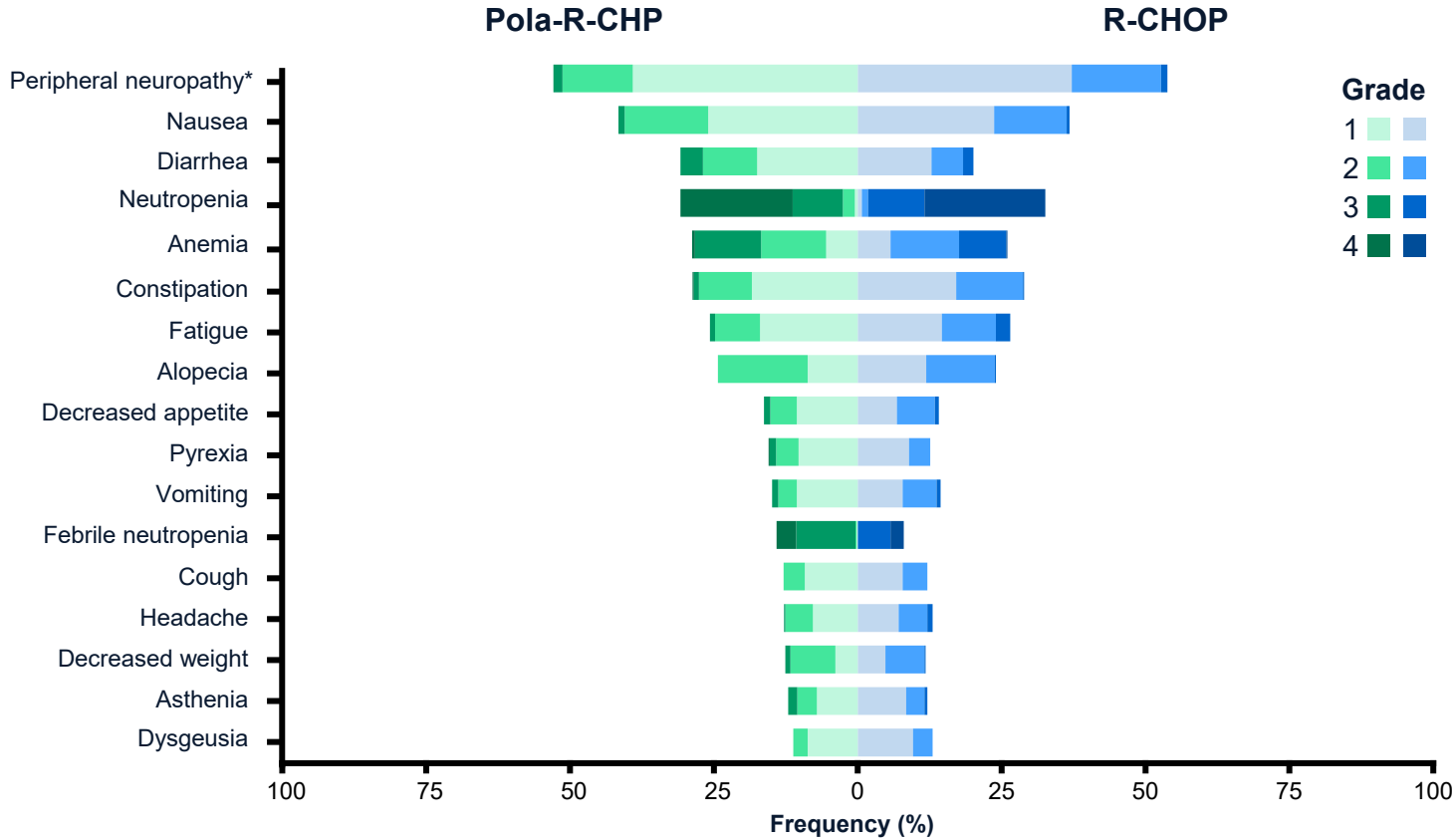
Safety summary

Safety profiles were similar with Pola-R-CHP and R-CHOP

n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

Data cut-off: June 28, 2021.

Common adverse events



Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

What will be Required to Replace R-CHOP

- Phase III trial confirming better efficacy or lower toxicity
- Must be tolerable in the majority of patients
  - Increase in toxicity must be offset by greater increase in benefit
- Must be broadly deliverable and affordable
- If targeted to a molecular subgroup, require a validated biomarker to identify appropriate patients

Questions

- Is pola-R-CHP the new standard of care?
- Should it be used in all patients?
  - Regardless of IPI, COO?
  - What about limited stage protocols?
- Should pola-R-CHP be the comparator in all clinical trials?

Future Trial Design

- Require adaptive designs to capture higher risk population
  - Limit exclusion criteria (lab restrictions, ECOG PS)
  - Decentralize biomarker testing
  - Allow initial cycle of therapy prior to randomization
  - Allow initial cycle prior to enrollment (retrospective screening)
  - Statistical power for realistic expectation of outcomes

Alternative Approaches

R-CHOP + X

R-CHOP → X

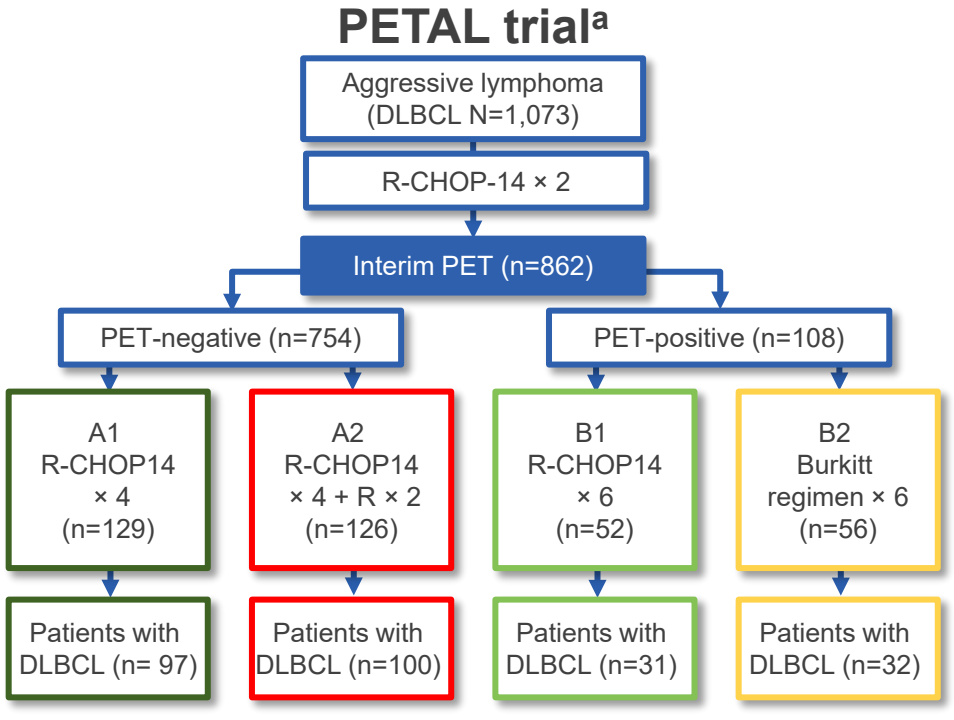
Response Adapted R-CHOP

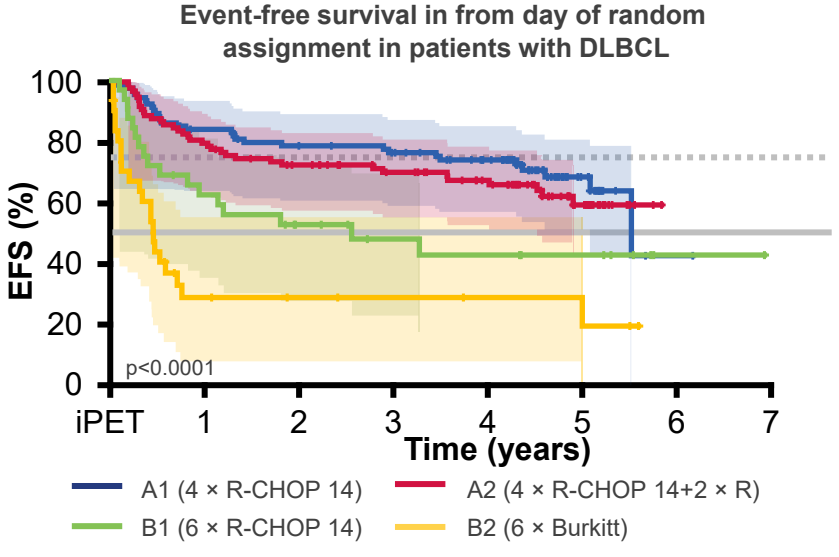
Negative trials:
rituximab, enzastaurin, lenalidomide, everolimus

Negative trials:
PET-adapted intensification
? PET-adapted CAR T-cell
? ctDNA response adapted

Interim PET

PETAL trial: Intensification of therapy based on interim PET status does not improve outcomes





A1 (4xR-CHOP 14)	97	79	71	66	56	18	1
A2 (4xR-CHOP 14+2xR)	100	78	68	57	46	19	0
B1 (6xR-CHOP 14)	32	19	13	9	8	6	1
B2 (6xBurkitt)	31	7	5	4	3	3	0

Dührsen U, *et al. J Clin Oncol* 2018; 36:2024–2034.

ZUMA-12: Phase II study using axi-cel as 1L therapy in patients positive PET after 2 cycles

Study Design

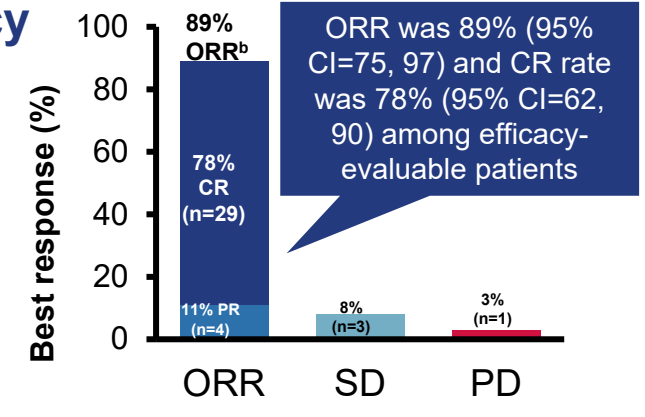
Eligibility:
High-risk LBCL
Positive interim PET after 2 cycles of an anti-CD20 mAb + anthracycline-containing regimen
Age: ≥18 years
ECOG 0–1

Enrolment/Leukapheresis

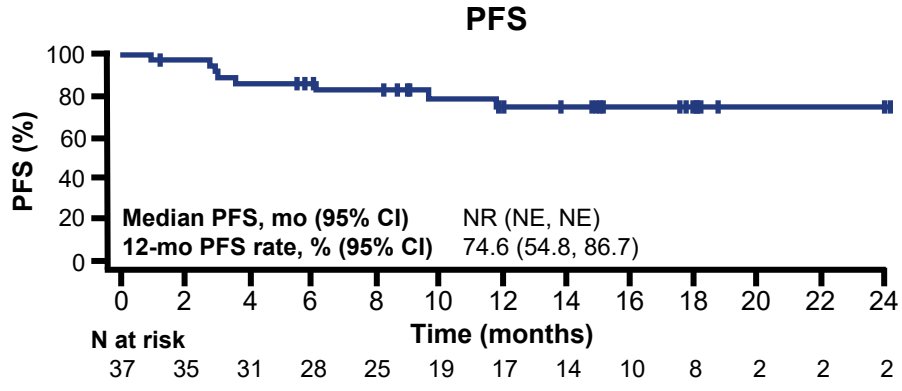
Optional nonchemotherapy bridging therapy[a]

Conditioning chemotherapy +Axi-cel infusion

Efficacy



ORR was 89% (95% CI=75, 97) and CR rate was 78% (95% CI=62, 90) among efficacy-evaluable patients



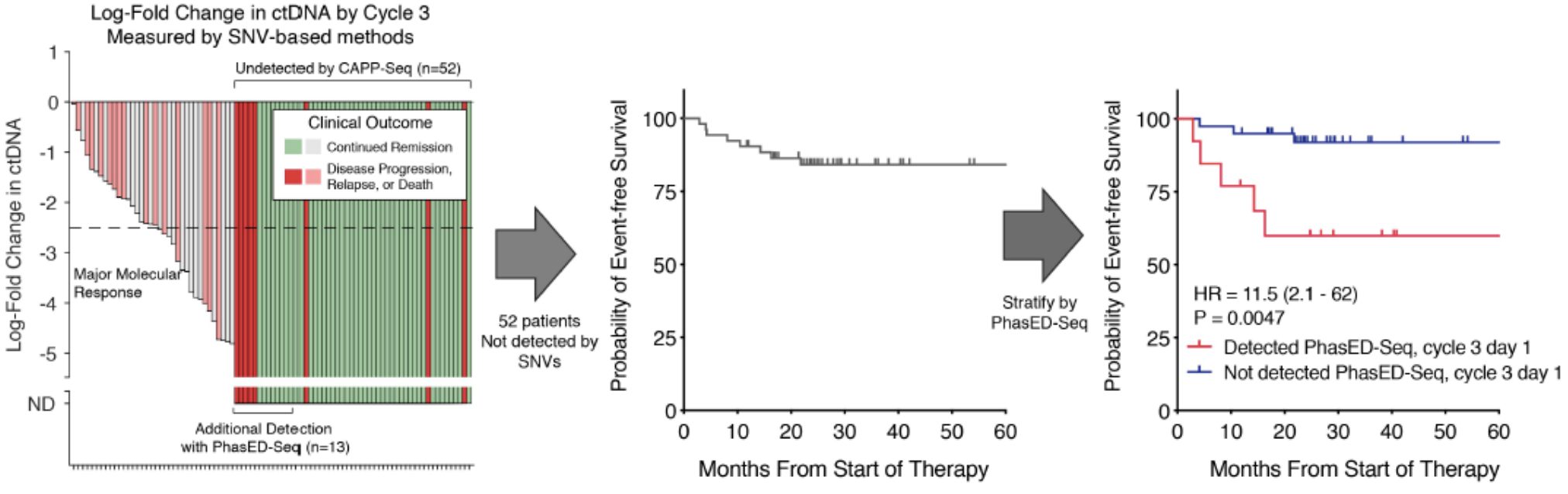
Safety

Toxicities	N=40
Any grade CRS, n (%)[c]	40 (100)
Grade 3	3 (8)
Any grade NE, n (%)[d]	29 (73)
Grade ≥3	9 (23)

Neelapu SS, *et al.* ASH 2021 (Abstract 739; oral).

ctDNA detection by PhasED-Seq improves outcome prediction at interim time-points

- 88 patients with DLBCL undergoing first-line treatment with cycle 3, day 1 samples available
  - ctDNA by CAPP-Seq stratifies patients based on Major Molecular Response (Kurtz et al, JCO 2018)
  - 52 patients undetectable at cycle 3, day 1 by SNV-based CAPP-Seq
- PhasED-Seq further stratifies patients who have undetectable ctDNA by CAPP-Seq



Kurtz, DM et al. *Nat Biotechnol* 2021.

Alternative Approaches

R-CHOP + X

R-CHOP → X

→ **Negative trials:**
rituximab, enzastaurin,
lenalidomide, everolimus

Response Adapted R-CHOP

→ **Negative trials:**
PET-adapted intensification
? PET-adapted CAR T-cell
? ctDNA response adapted

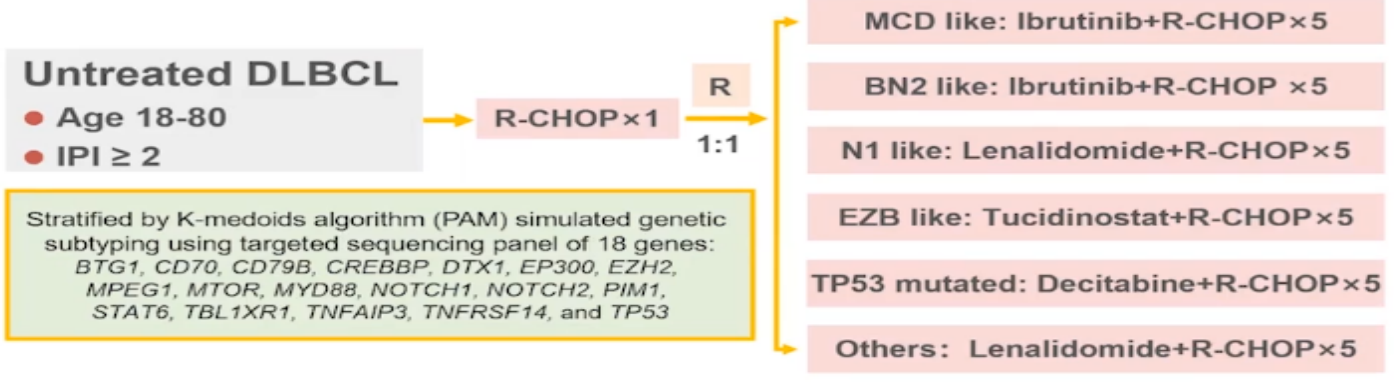
Replace R-CHOP

→ ? Novel agents (Bispecific Abs)
?CAR T-cell therapy

Guidance-01: Randomized Phase 2 Trial of Genetic Subtype Guided Immunochemotherapy

Study Design (NCT04025593)

- The study started from **July, 2019**.
- All patients were treated with ONE cycle of standard R-CHOP immediately at diagnosis.
- Patients were randomly assigned 1:1 and stratified by genetic subtype.
- Using targeted sequencing and FISH for BCL2, MYC translocation and BCL6 fusion to classify patients into six genetic subtypes MCD like, BN2 like, N1 like, EZB like, according to **NEJM classification (2018)**, *TP53* mutation, and others.



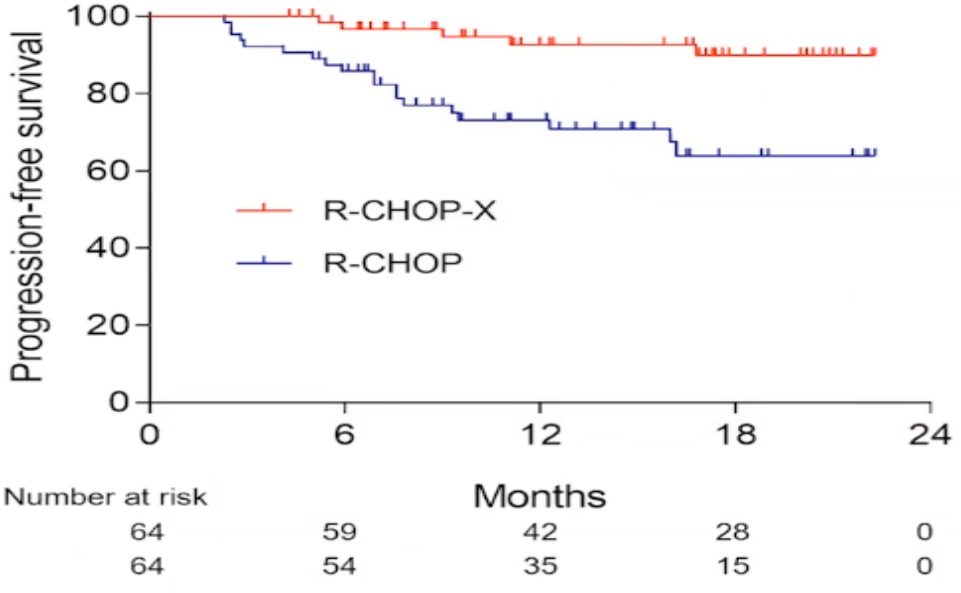
Ibrutinib[1]	420mg po qd
Lenalidomide[2]	25mg d1-10 po
Tucidinostat[3]	20mg d1, 4, 8, 11 po
Decitabine[4]	10 mg/m² d1-5
R-CHOP	Standard dose

G-CSF prophylaxis was given from the second cycle of chemotherapy if grade ≥ 3 neutropenia was present in the first cycle.

1. *Younes et al., J Clin Oncol* 2019. 2. *Nowakowski et al., J Clin Oncol* 2021. 3. *Zhang et al., Clin Epigenet* 2020. 4. *Zhang et al.*, ICML 2019 abstract (NCT02951728)

Zhang et al., ICML 2021, #026

Secondary Endpoint: PFS



Median follow-up 16.1 months

	R-CHOP-X	R-CHOP
1-year PFS (95%CI)	93% (81%-97%)	73% (60%-83%)

Zhang et al., ICML 2021, #026

Ongoing/Planned Trials in Upfront DLBCL

- **BTK-inhibitor R-CHOP trials**
  - Escalade (acala); UK trial; zanabrutinib
- **First-Mind Trial**
  - Tafasitamab/Lenalidomide + R-CHOP
- **Bispecific antibodies + R-CHOP**
- **Biology-driven trials**
- **Response-adapted trials (ctDNA, quantitative PET/CT)**

Summary

- Moving beyond R-CHOP has been a challenge
- Pola-R-CHP results in improved PFS with similar toxicity
- Improving the cure rate in frontline setting is important as secondary therapies associated with higher toxicity, cost and poor outcomes
- Further improvement needed and trials of novel therapies remain important
- Identification of predictive biomarkers (using validated tools) will be essential to optimize outcome in individual patients