

Rethinking Treatment Algorithms in Aggressive B-Cell Lymphoma

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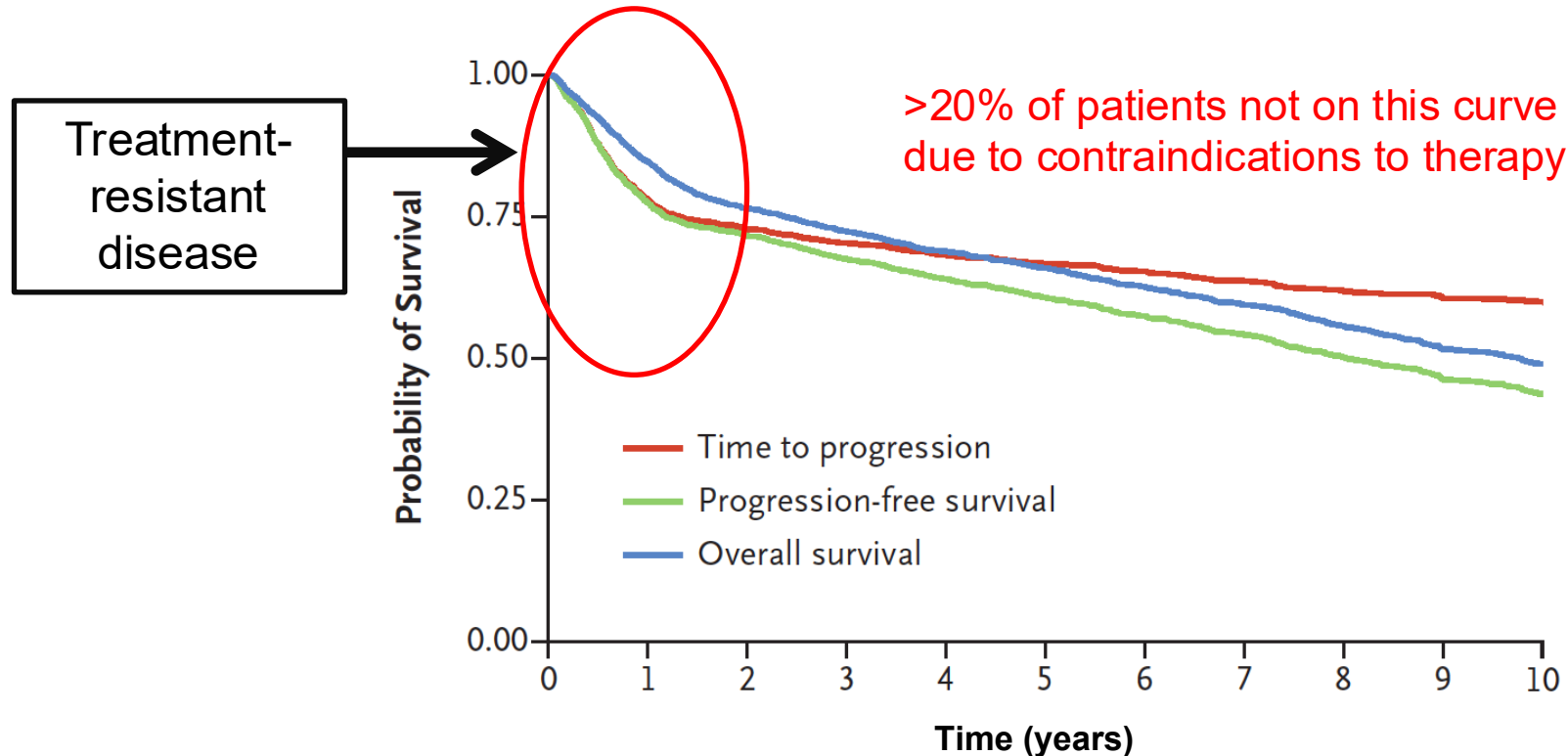
a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

Disclosures

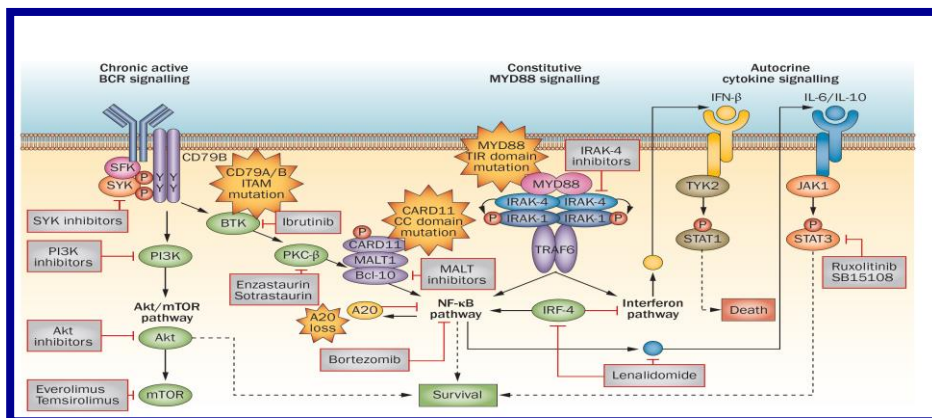
- Consulting/Honoraria: Abbvie, AstraZeneca, BeOne, BMS, Eli Lilly, Chugai, Genmab, Kite/Gilead, Incyte, Janssen, Merck, Roche/Genentech
- Research funding: Roche/Genentech

Population-based Outcomes with R-CHOP in Untreated DLBCL: Room for Improvement

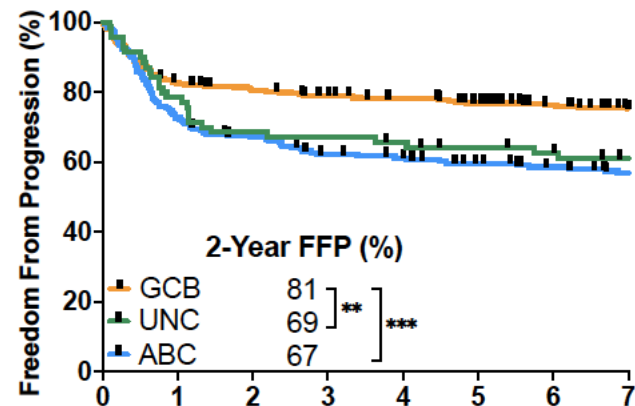
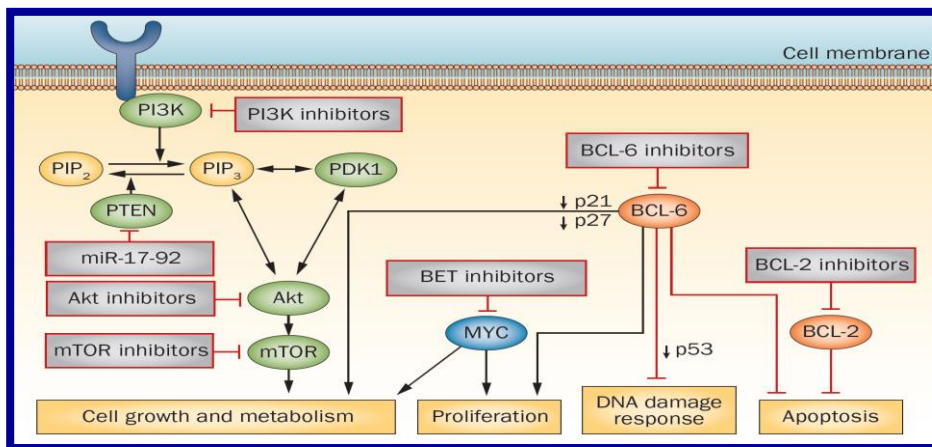


Distinct Signaling Pathways and Outcomes According to Cell-of-Origin

ABC Activated B-Cell



GCB Germinal Center B-Cell



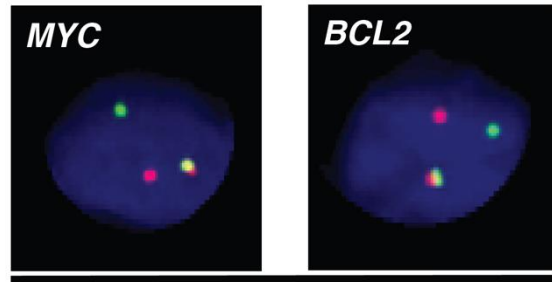
No. at risk:									
		285	273	263	255	246	231	218	
GCB	346	285	273	263	255	246	231	218	
UNC	70	56	49	48	46	43	41	37	
ABC	213	157	140	127	123	114	107	100	

BC Cancer R-CHOP treated Patients

Roschewski, et al. Nat Rev Clin Oncol 2014;
Alduaij et al. J Clin Oncol 2022

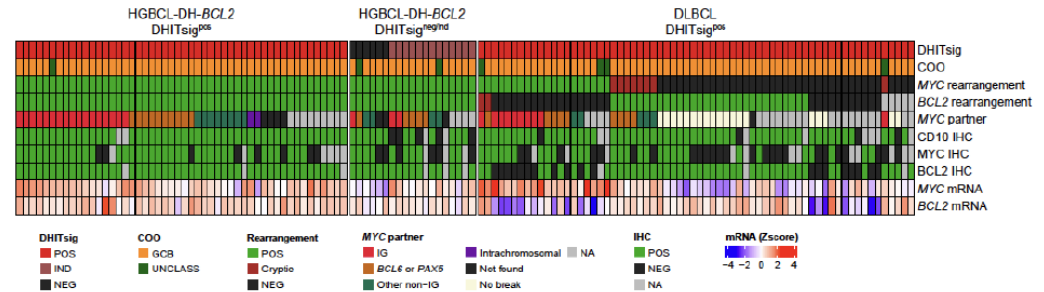
Evolving High Risk DLBCL Entities

HGBCL with *MYC* and *BCL2* rearrangement



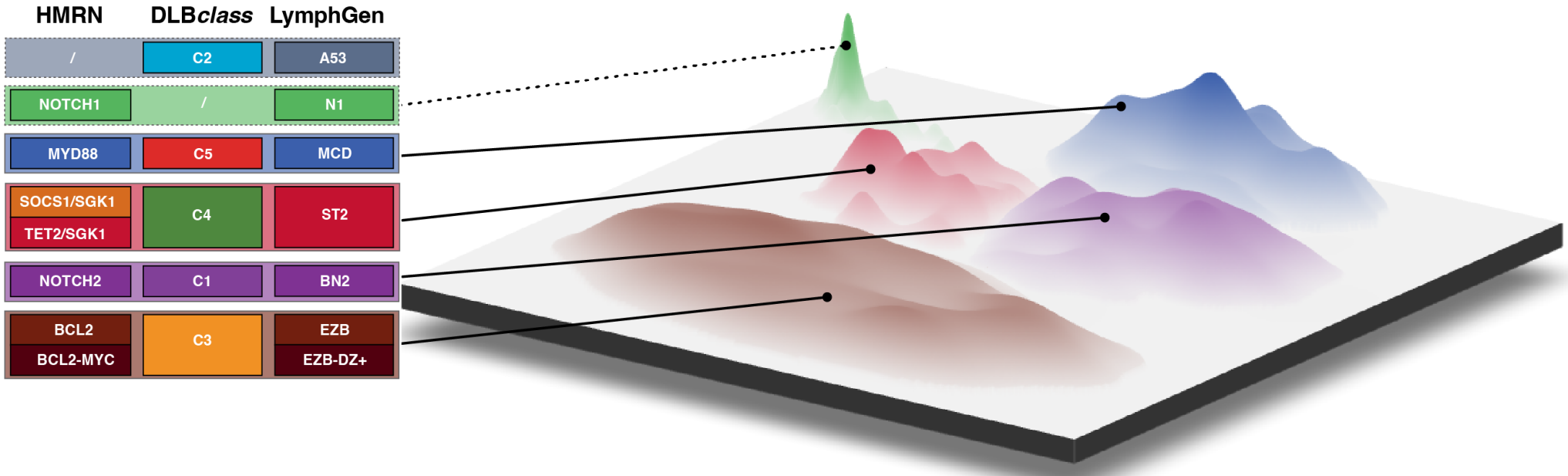
- DLBCL or high grade morphology
- Identified with FISH testing
- Separate entity within WHO/ICC
- Poorer outcome with R-CHOP
- Often treated intensively

Dark Zone Lymphoma



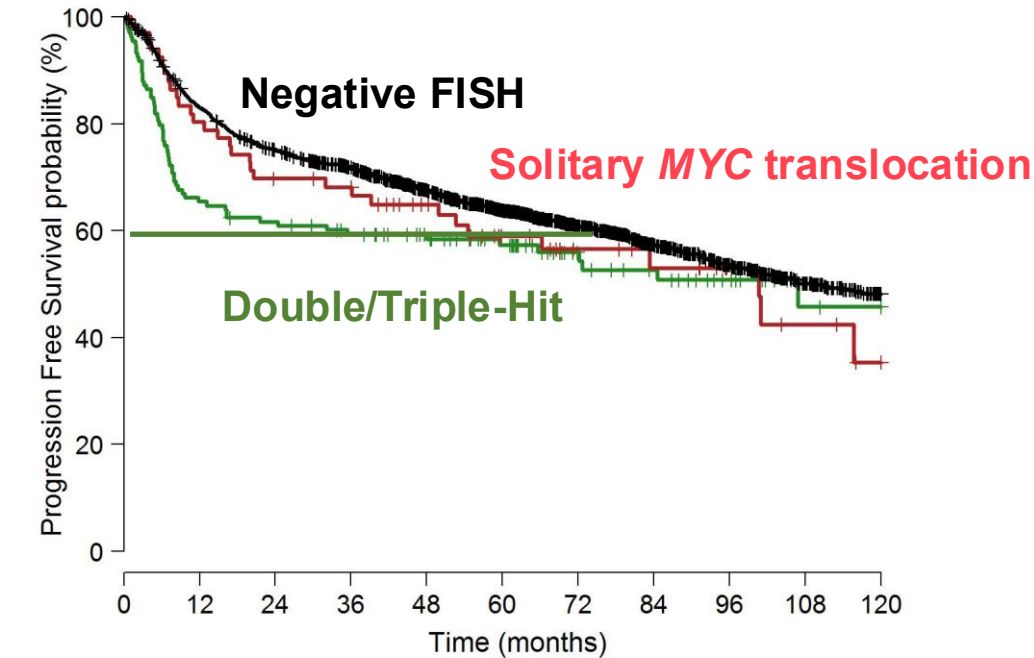
- Initially within GCB subtype
- Identified with GEP testing, with similar profile to germinal center dark zone B cells
- Poorer outcome with R-CHOP

Genomic Classifiers Further Subdivide DLBCL



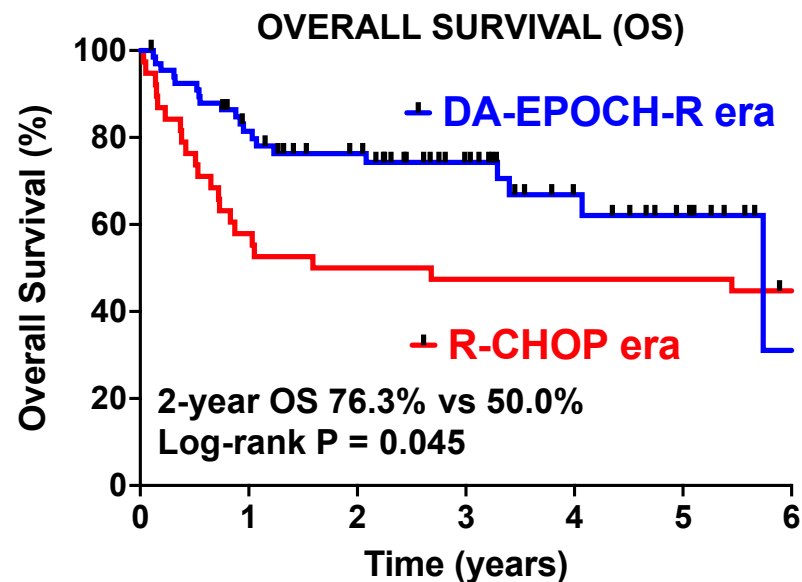
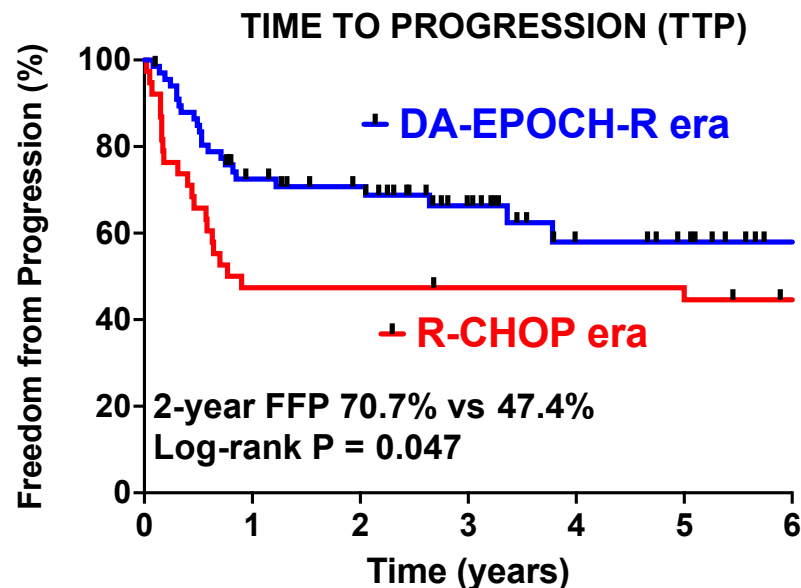
Consensus regarding a unifying classifier not yet reached

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



negative	2049	1687	1508	1371	1173	949	672	463	313	190	109
DH & TH	133	87	81	74	64	52	34	28	20	9	8
SH	67	53	45	43	34	25	18	15	10	7	4

Era-on-era comparison: Outcomes for DHIT Lymphoma in BC



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

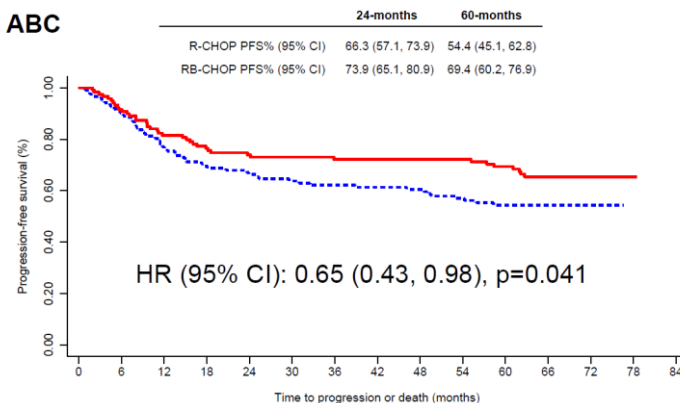
* Age >60 years, Stage III/IV, LDH>normal, PS>1 and extranodal sites>1. HR: adjusted Hazard Ratio, CI: Confidence interval

Randomized Trials of Novel Agents

Author	Trial	Therapy	Better than R-CHOP
Vitolo, JCO 2017	GOYA	Obinutuzumab-CHOP	No
Leonard, JCO 2017	Pyramid	R-CHOP- Bortezomib	No
Davies, Lancet 2019	REMoDL-B	R-CHOP- Bortezomib	No
Younes, JCO 2019	Phoenix	R-CHOP-Ibrutinib	No
Nowakowski, JCO 2021	ROBUST	Lenalidomide-R-CHOP	No
Tilly, NEJM 2023	POLARIX	Pola-R-CHP	YES

Five-Year Update of REMoDL-B: Improved PFS in Molecular Subgroups with Bortezomib-R-CHOP

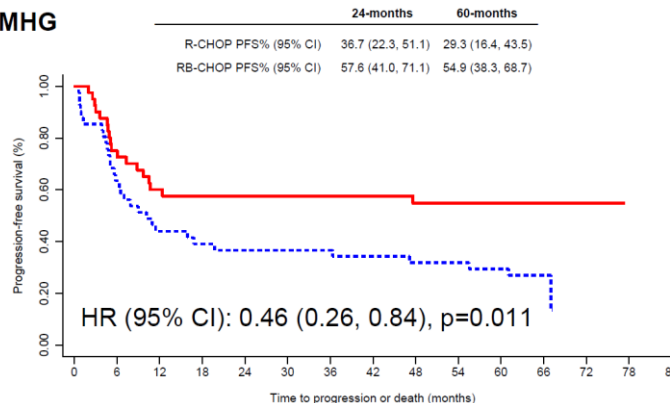
ABC



Number at risk (censored)
 R-CHOP 125 (12) 110 (16) 93 (9) 84 (4) 80 (3) 77 (2) 75 (1) 72 (1) 71 (4) 65 (3) 61 (0) 18 (0) 2 (0) 0 (0) 0
 RB-CHOP 124 (10) 109 (12) 97 (6) 90 (3) 87 (1) 85 (1) 82 (0) 82 (0) 80 (0) 78 (3) 72 (4) 19 (0) 1 (0) 1 (0) 0

--- R-CHOP — RB-CHOP

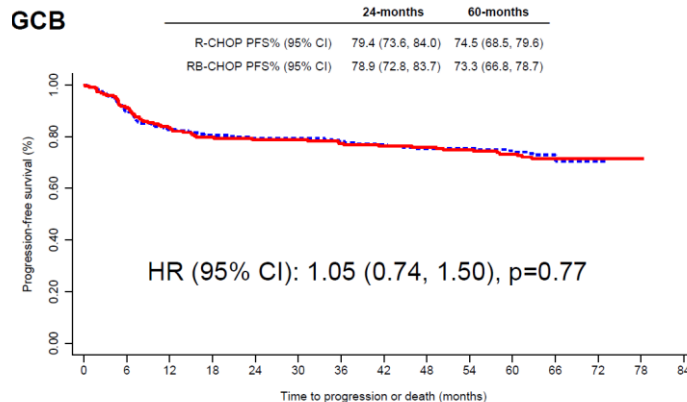
MHG



Number at risk (censored)
 R-CHOP 42 (15) 26 (8) 18 (2) 16 (1) 15 (0) 15 (0) 15 (1) 14 (1) 13 (0) 13 (1) 12 (1) 4 (1) 0 (0) 0 (0) 0
 RB-CHOP 41 (10) 30 (6) 24 (1) 23 (0) 23 (0) 23 (0) 22 (0) 22 (1) 20 (0) 20 (0) 18 (0) 5 (0) 1 (0) 0 (0) 0

--- R-CHOP — RB-CHOP

GCB

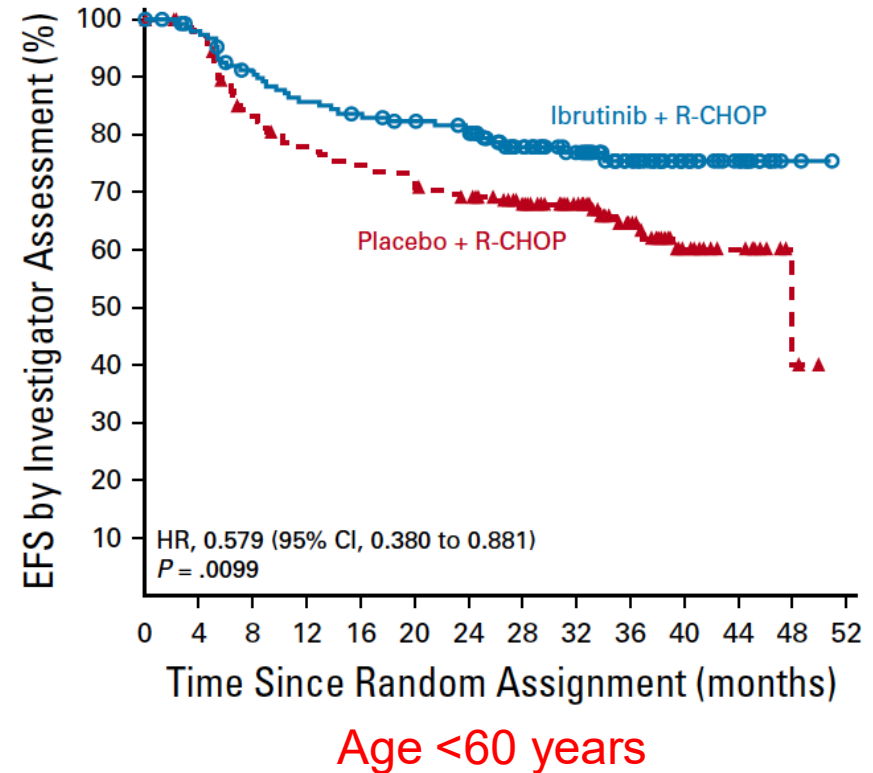
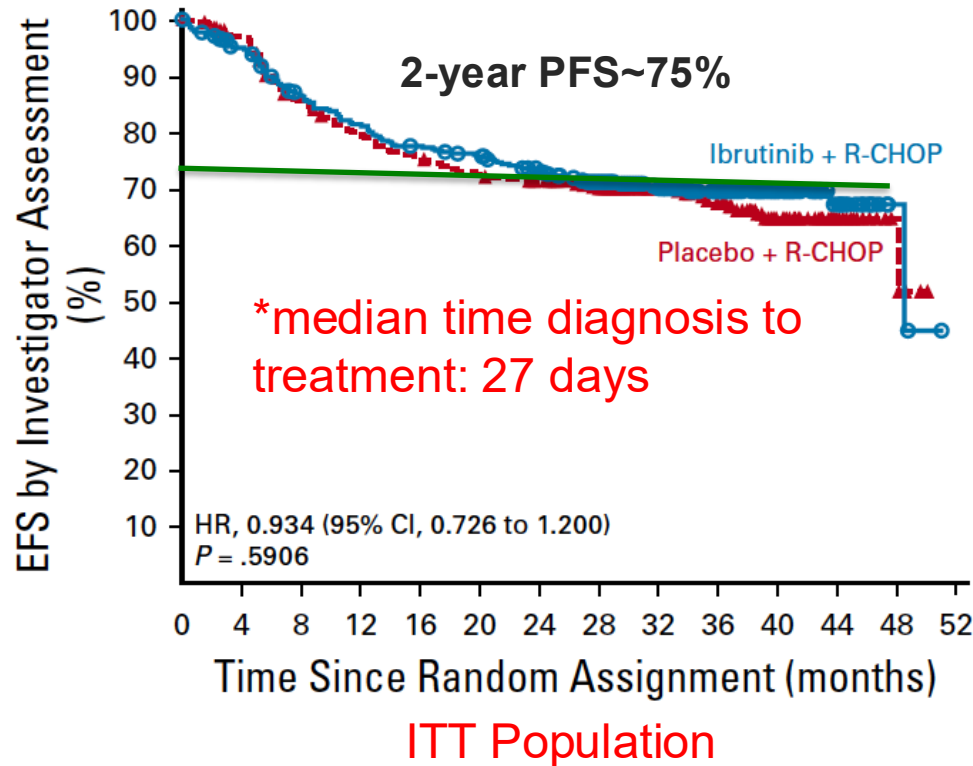


Number at risk (censored)
 R-CHOP 240 (24) 213 (17) 196 (5) 191 (3) 188 (0) 187 (3) 184 (3) 176 (3) 171 (0) 168 (2) 152 (3) 33 (1) 1 (0) 0 (0) 0
 RB-CHOP 229 (19) 199 (17) 180 (8) 170 (2) 168 (0) 165 (3) 159 (2) 153 (1) 149 (2) 142 (3) 129 (3) 42 (0) 4 (0) 1 (0) 0

--- R-CHOP — RB-CHOP

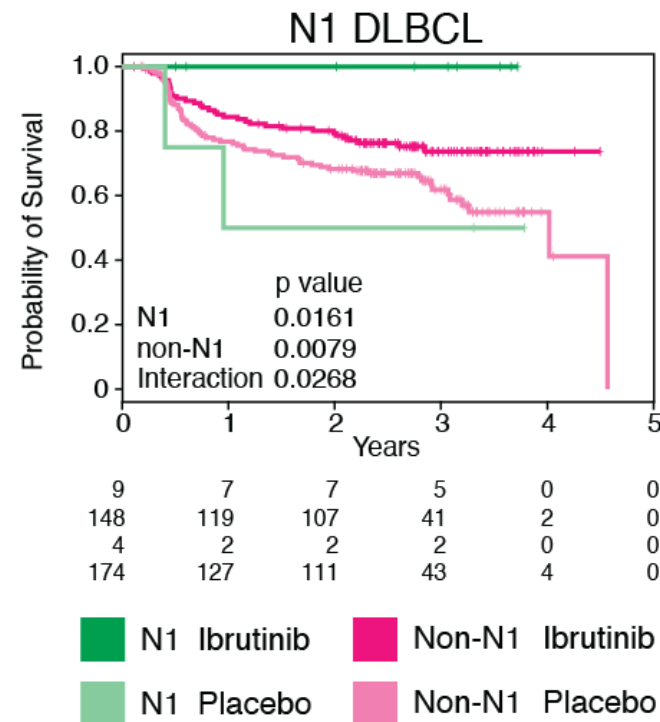
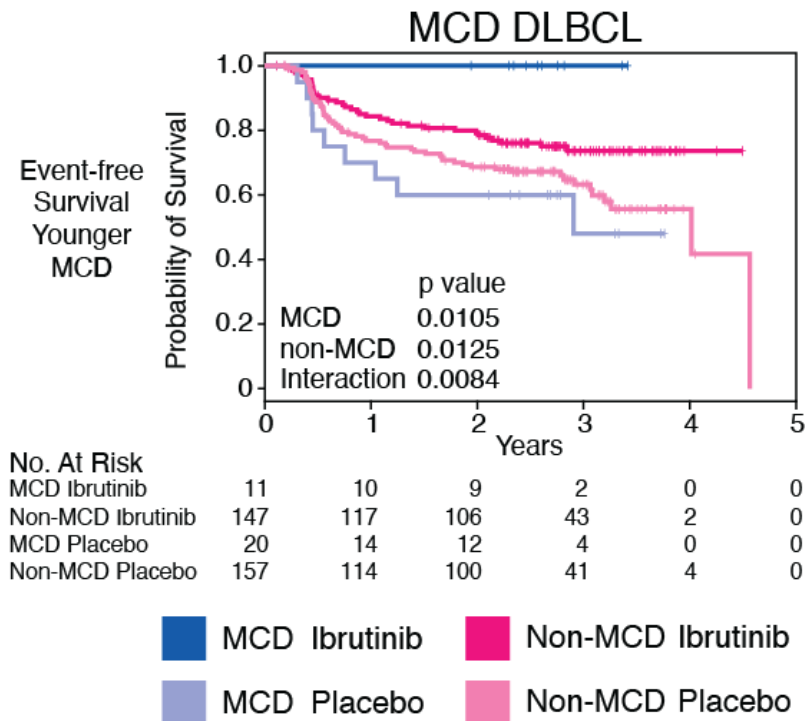
Significant improvement in PFS with Bortezomib-R-CHOP in ABC and Molecular High Grade subgroups, but not in GCB subgroup

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

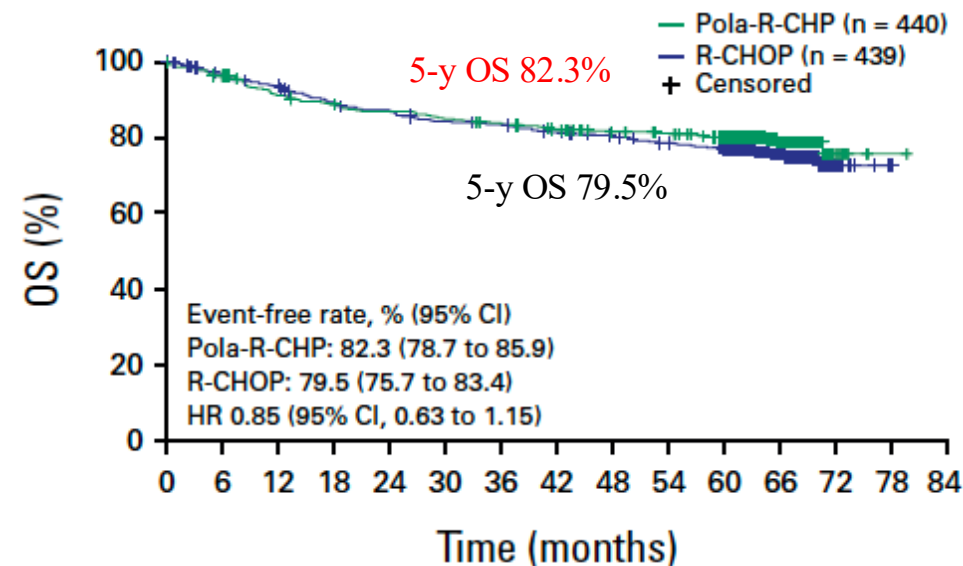
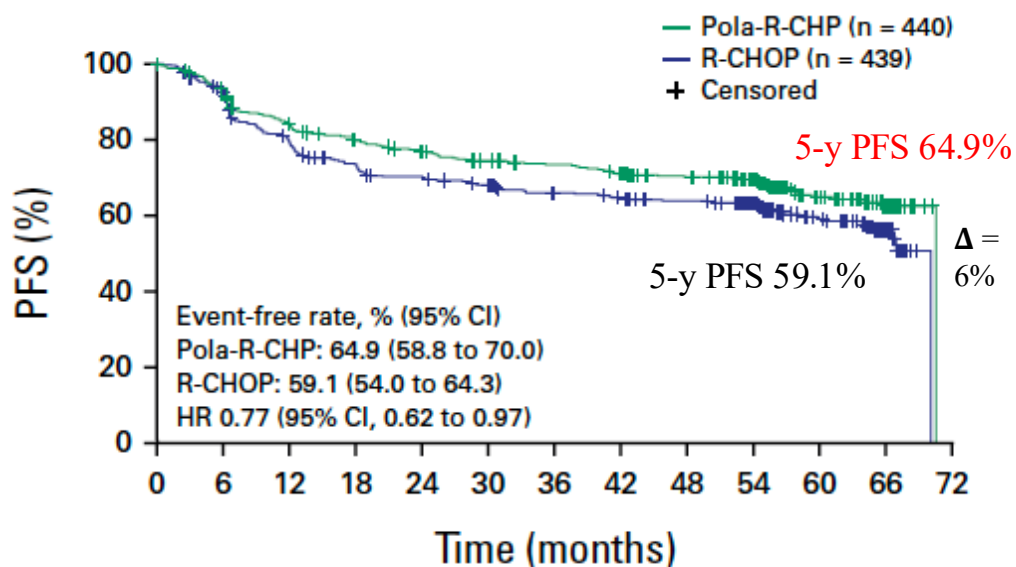


Genetic-Based Subtypes as a Predictive Marker

Retrospective Analysis of Phoenix Trial



5-Year Data POLARIX: Pola-R-CHP vs R-CHOP in DLBCL with IPI Score of 2-5



IPI 3-5:

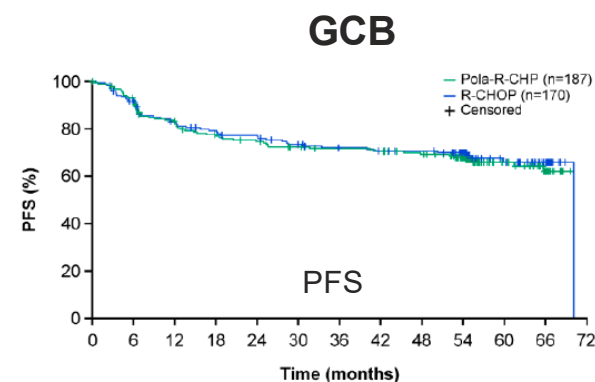
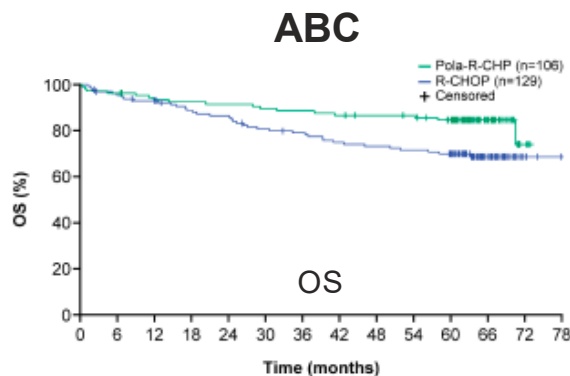
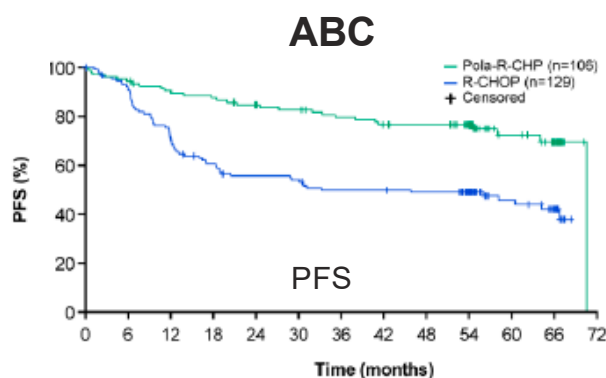
5-y PFS 63.2% v 53.5%; HR 0.72; $\Delta = 9.7\%$

Toxicity comparable between arms

38% more subsequent therapies with R-CHOP

POLARIX Trial: PFS and OS in COO Subgroups

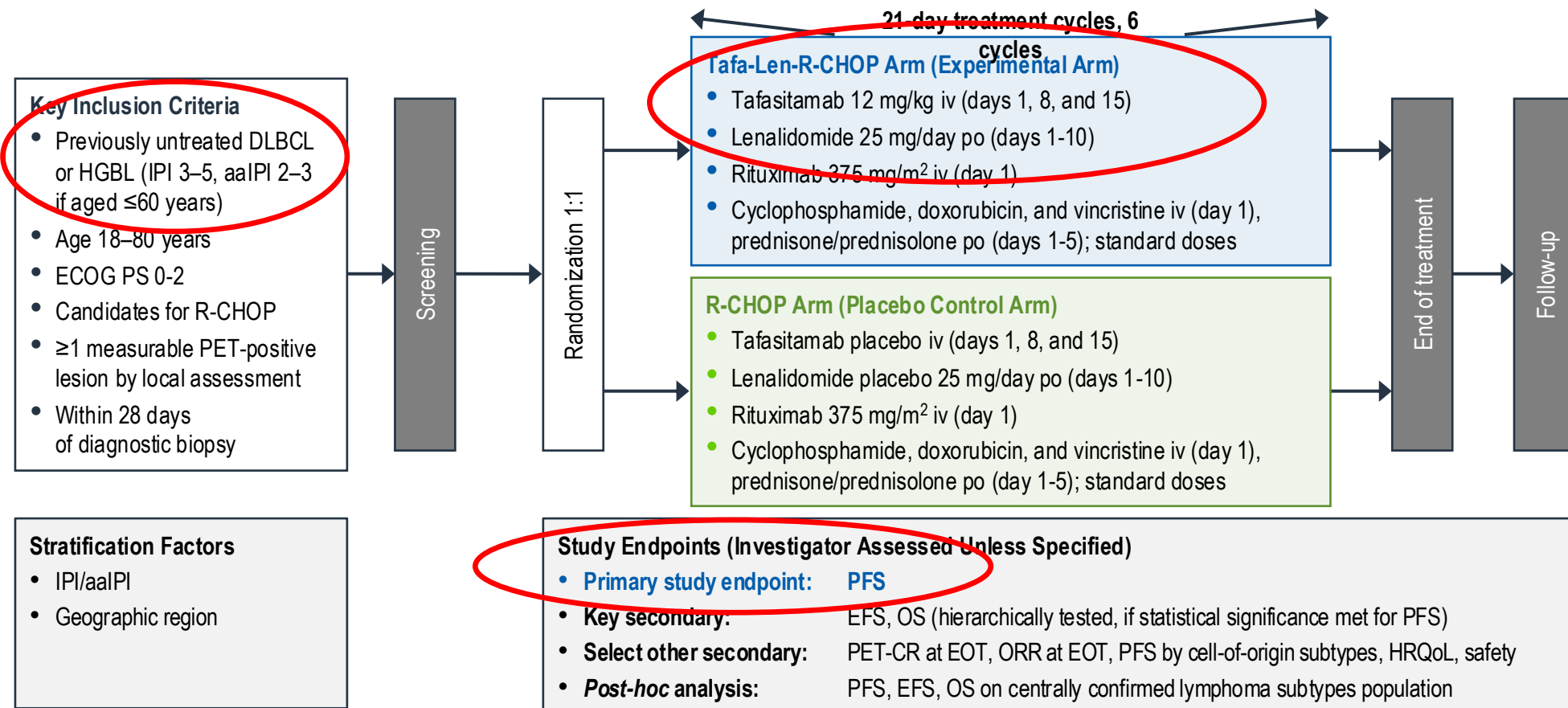
Baseline risk factors		PFS								OS							
		Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better	Pola-R-CHP (n=440)		R-CHOP (n=439)		HR	95% Wald CI	Pola-R-CHP better	R-CHOP better
		n	60 month (%)	n	60 month (%)					n	60 month (%)	n	60 month (%)				
NanoString COO	NanoString GCB	187	65.9	170	65.8	1.07	0.74–1.56			187	82.9	170	82.3	0.99	0.60–1.61		
	NanoString ABC	106	72.5	129	45.8	0.38	0.24–0.59			106	84.6	129	69.9	0.49	0.28–0.88		
	NanoString UNC	44	55.2	53	70.8	1.60	0.79–3.25			44	76.9	53	94.2	4.46	1.23– 16.21		
	Unknown	103	60.2	87	59.7	0.83	0.51–1.33			103	81.3	87	79.0	0.80	0.42–1.51		



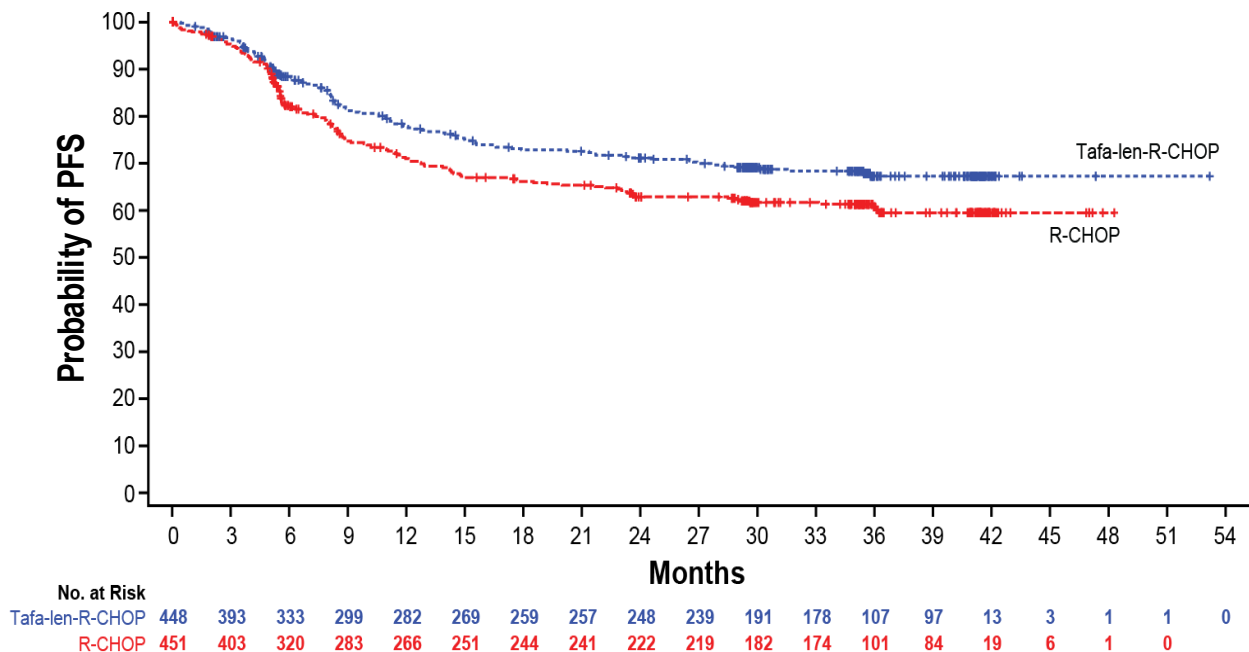
COO by GEP available in ~78% of patients

Morschhauser et al. J Clin Oncol 2025

frontMIND Phase 3, Global, Multicenter, Placebo-Controlled, Double-Blind, Randomized Study



frontMIND Phase 3 Study: Progression-Free Survival



Median follow-up of 35.2 months

Toxicity manageable

Increased risk of neutropenia and infection

HR 0.75* ($P=0.0194$)

95% CI 0.59–0.96

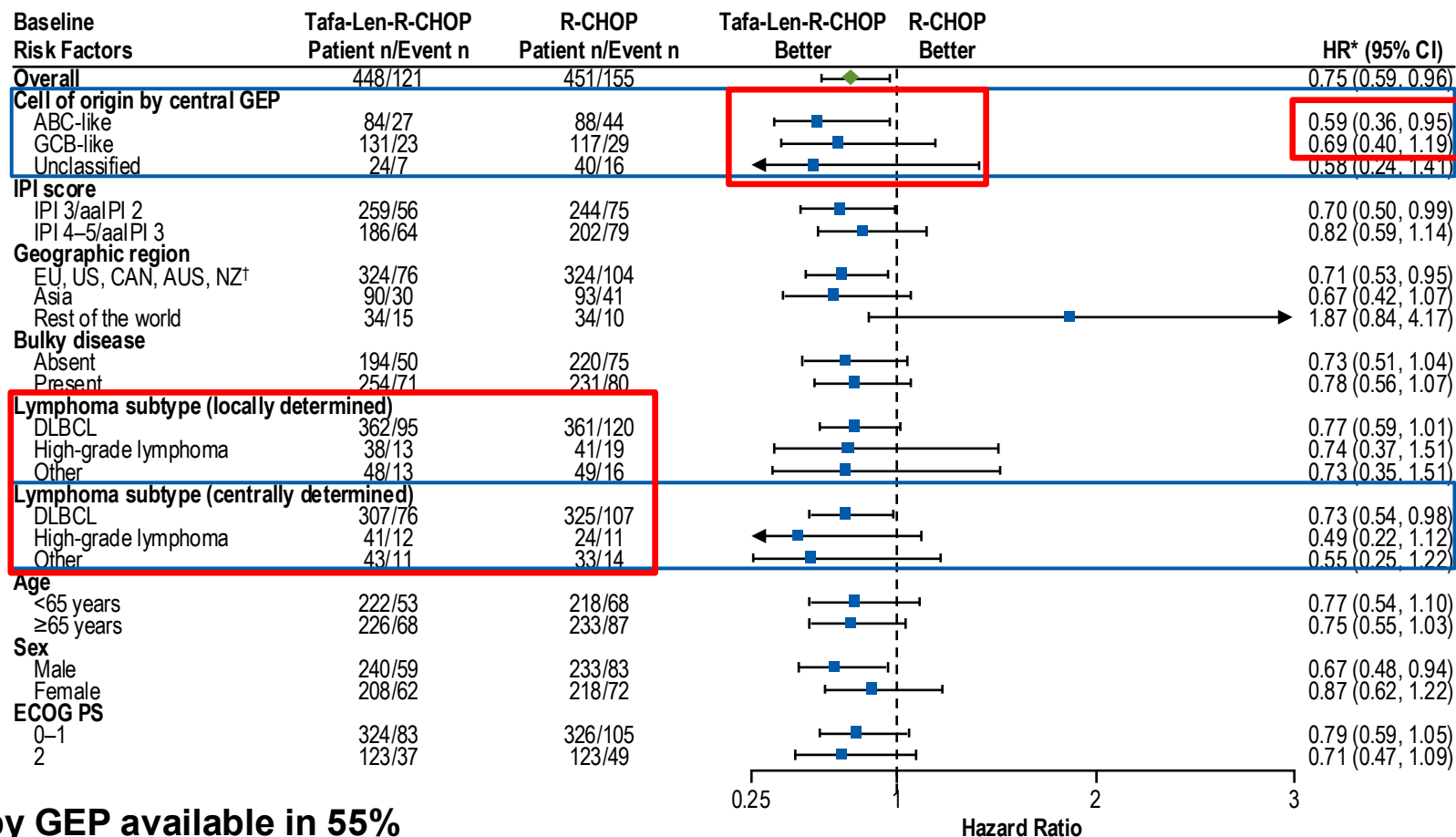
- A 25% reduction in risk of progression or death demonstrated with Tafa-Len-R-CHOP vs R-CHOP
- **2-year PFS:**
71.1% with Tafa-Len-R-CHOP vs 62.9% with R-CHOP ($\Delta=8.2\%$)
- **3-year PFS:**
67.3% with Tafa-Len-R-CHOP vs 60.7% with R-CHOP ($\Delta=6.6\%$)

3-year OS:

81.5% with Tafa-Len-R-CHOP vs 77.8% with R-CHOP

PFS by Investigator Assessment

Prespecified subgroups

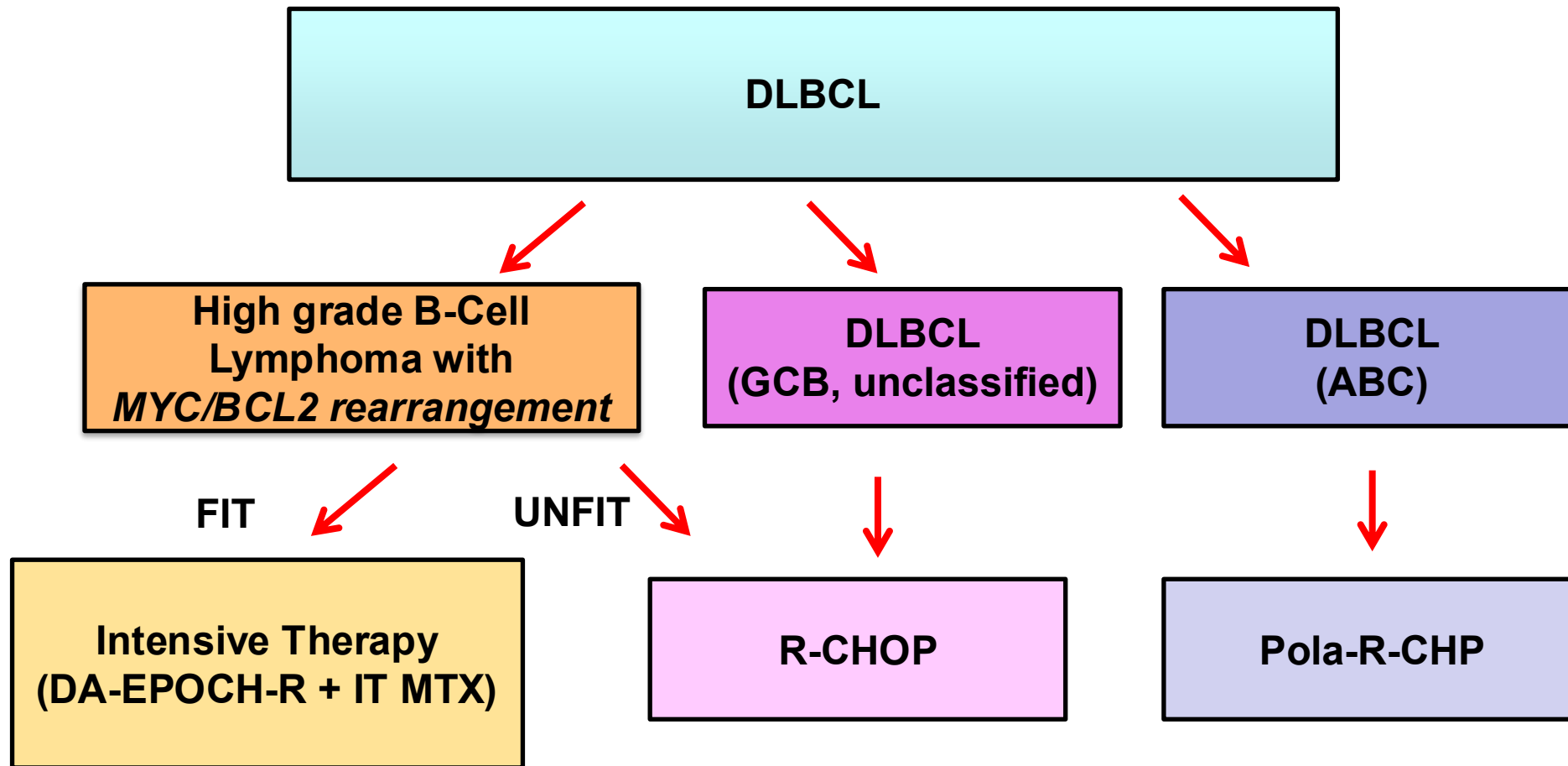


COO by GEP available in 55%

ITT population. *Calculated using a stratified Cox proportional hazards model. †Europe, USA, Canada, Australia, and New Zealand.

aalPI, age-adjusted IPI; ABC, activated B-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; GEP, gene expression profiling; HR, hazard ratio; IPI, International Prognostic Index; ITT, intention-to-treat; Len, lenalidomide, doxorubicin, vincristine, and prednisone or prednisolone; Tafa, tafasitamab.

Treatment Algorithm for Frontline DLBCL



Frontline Treatment and Ongoing Phase 3 Trials

Advanced Stage DLBCL



Pola-RCHP

Tafa-Len-R-CHOP

R-CHOP

ESCALADE: Acala-R-CHOP v R-CHOP

EPCORE DLBCL-2: Epcor-R-CHOP v R-CHOP

SKYGLO: Glofit-Pola-RCHP v Pola-RCHP

OLYMPIA-3: Odronextamab-CHOP v R-CHOP

ZUMA-23: Axicel v R-CHOP/R-EPOCH

GOLSEEK-1: Golcadomide-R-CHOP v R-CHOP

GUIDANCE-02: R-CHOP-X v R-CHOP

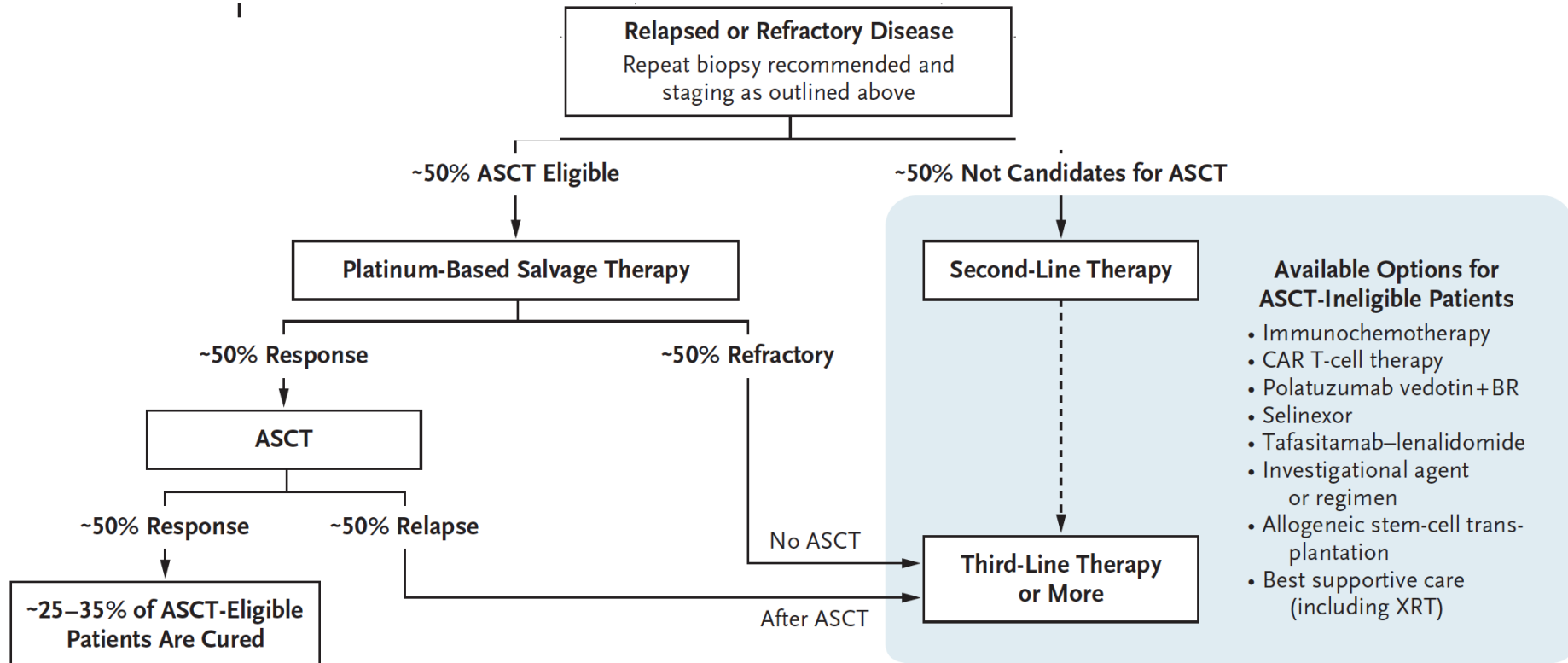
NCT04231448: Tucidinostat-R-CHOP v R-CHOP

BELIEVE-01: Orelabrutinib-R-CHOP v R-CHOP

ENGINE-1: Enzastaurin-R-CHOP v R-CHOP

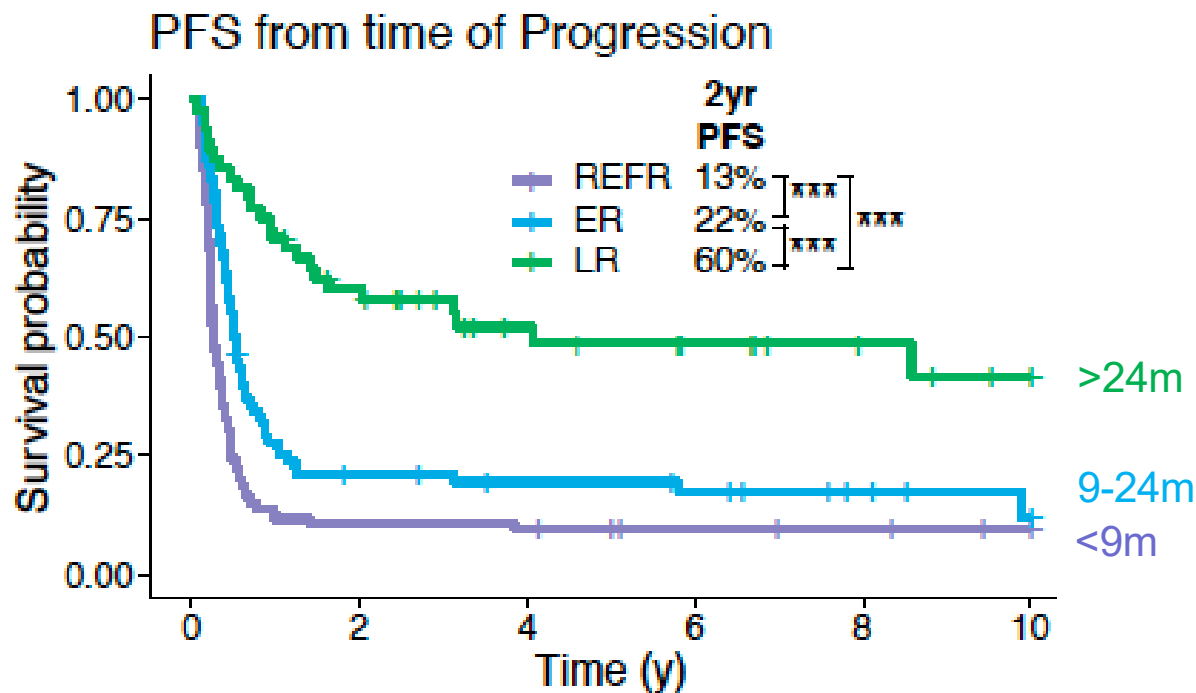
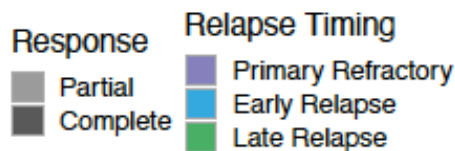
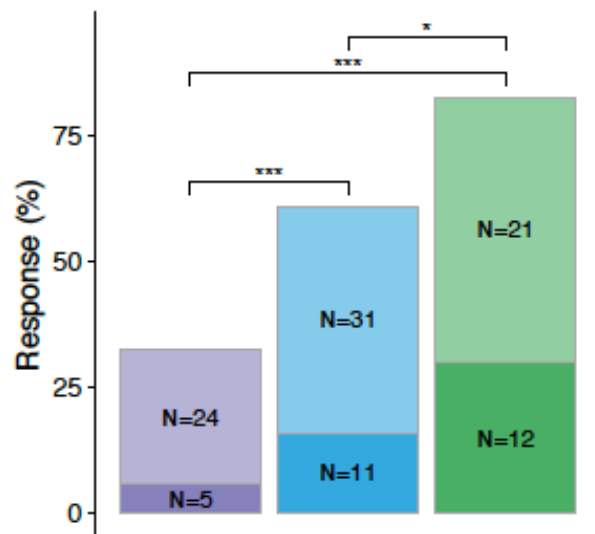
MK-2140-010: Zilovetamab-RCHP v R-CHOP

Historical Management of Rel/Refr DLBCL



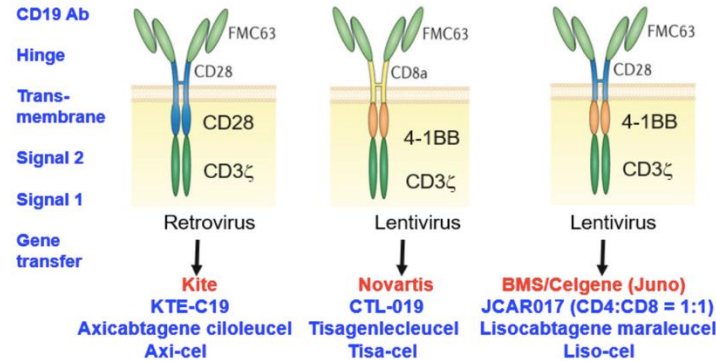
Adapted from Sehn and Salles. NEJM 2021

Outcome in Transplant-Eligible DLBCL Patients According to Timing of Relapse

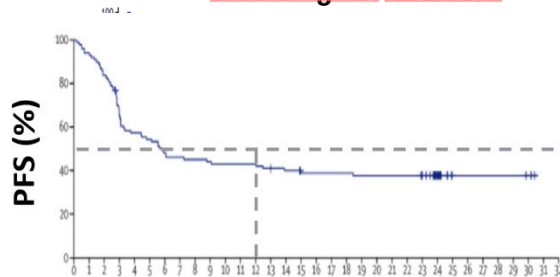


CD-19 Directed CAR T-Cell Therapy

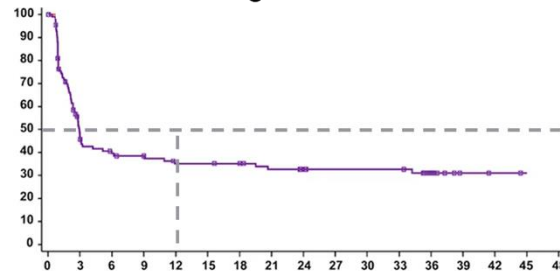
Durable Responses in 3L⁺ Setting



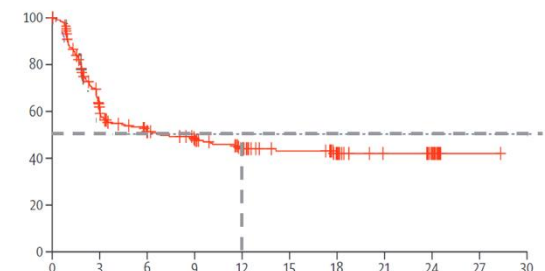
ZUMA-1
Axicabtagene ciloleucel



JULIET
Tisagenlecleucel

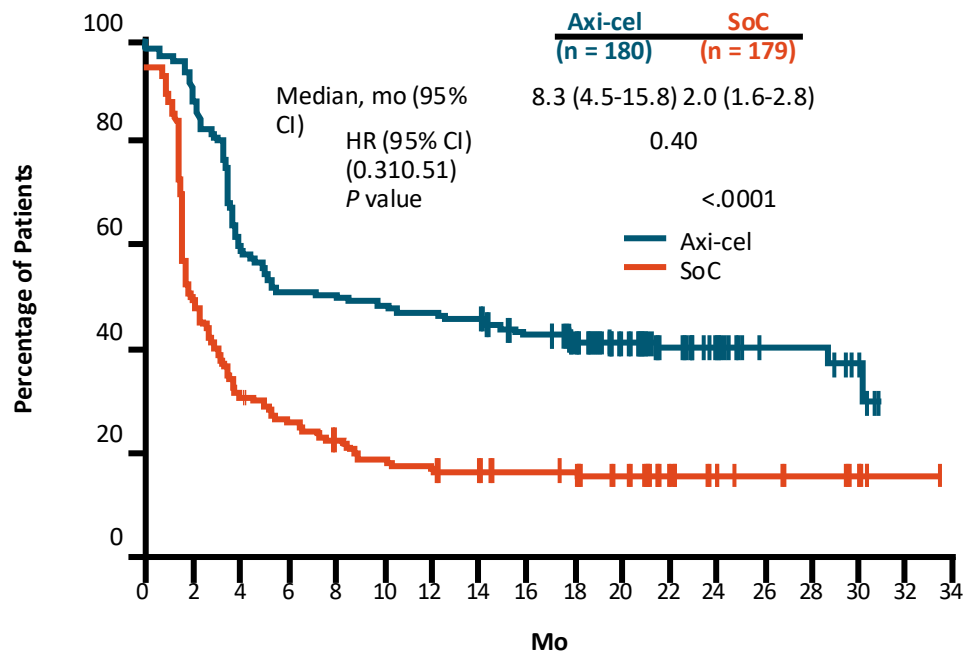


TRANSCEND NHL 001
Lisocabtagene Maraleucel

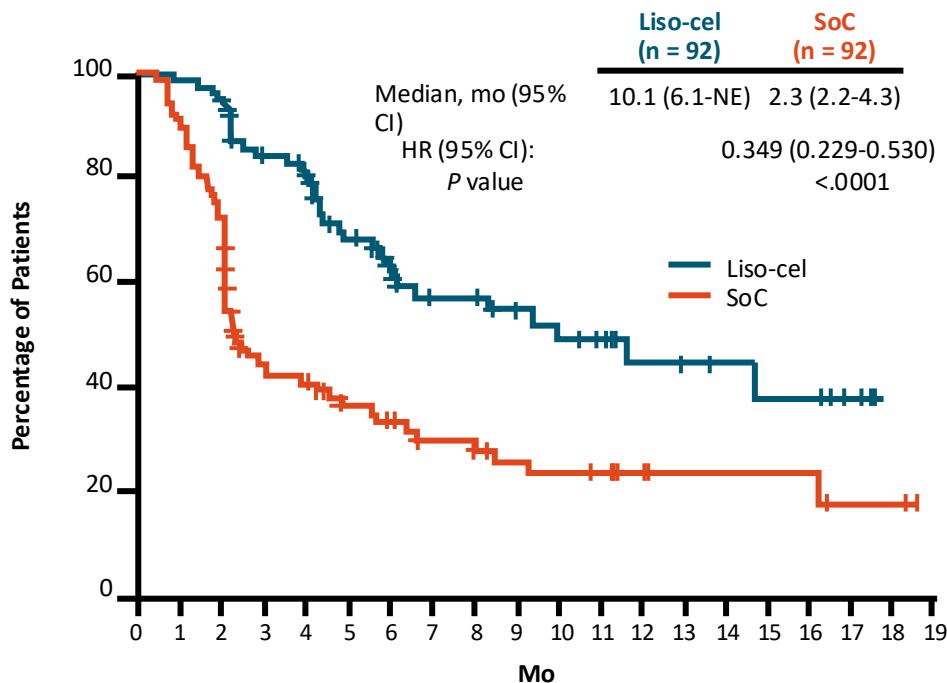


CAR T-cell Therapy in Second-line High-Risk Transplant-Eligible LBCL: EFS

ZUMA-7 (Axi-cel)

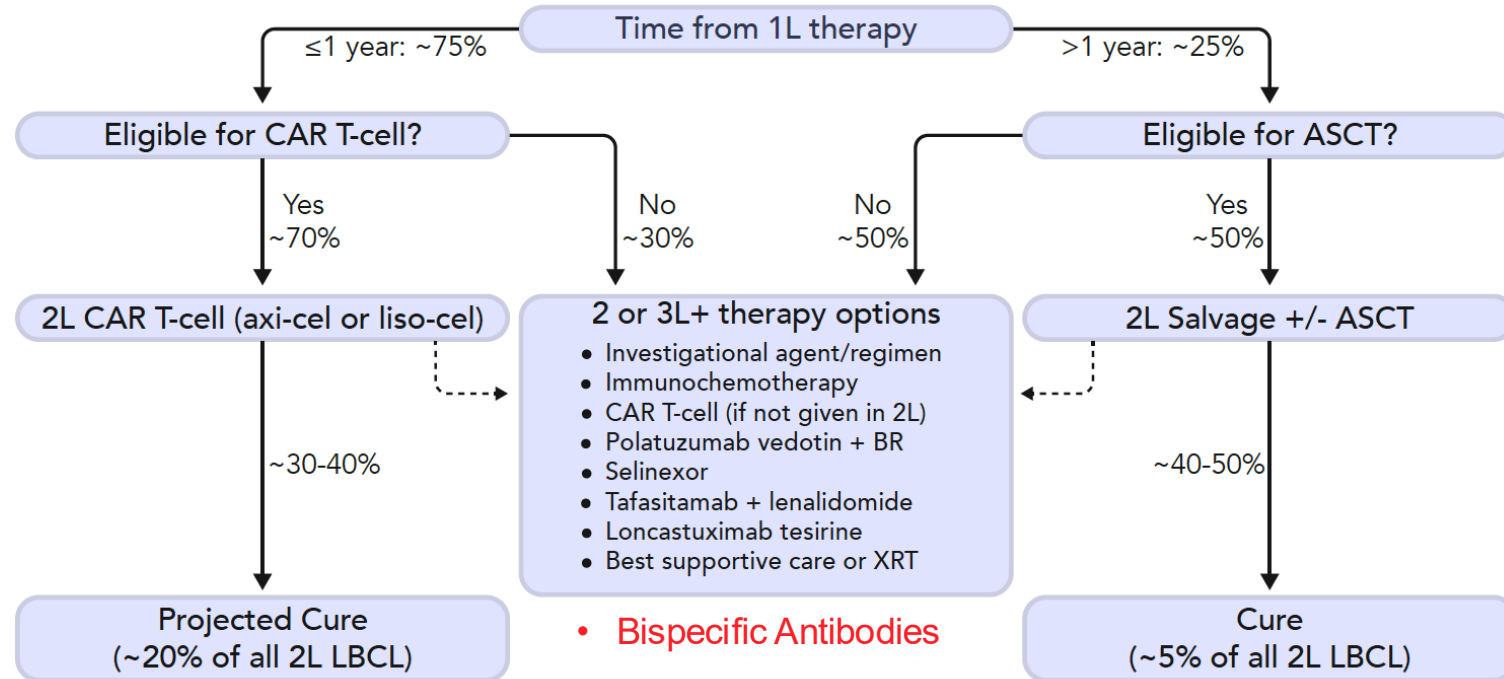


TRANSFORM (Liso-cel)



Locke F et al. NEJM 2021; Kamdar M et al. Lancet 2022; Westin J et al. NEJM 2023

Relapsed/Refractory LBCL



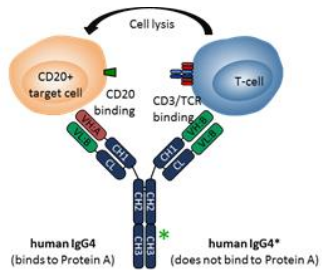
Novel Agents Recently Approved in R/R DLBCL

	Pola-BR	Tafasitamab/ Lenalidomide	Loncastuximab Tesirine	Selinexor
MOA	Anti-CD79b ADC +CIT	Anti-CD19 MAb + Imid	Anti-CD19 ADC	XPO-1 inhibitor
Patients	R/R Transplant-ineligible	R/R Transplant-ineligible Non-Refractory	R/R ≥ 2 lines	R/R ≥ 2 lines
Treatment	6 cycles IV	Indefinite IV	Indefinite IV	Indefinite oral
ORR	45%	58%	48%	28%
CR rate	40%	40%	24%	10%
PFS	9.2m	11.6m	4.9m	2.6m
DOR	12.6m	43.9m	10.3m	9.3m
OS	12.4m	33.5m	9.9m	NR

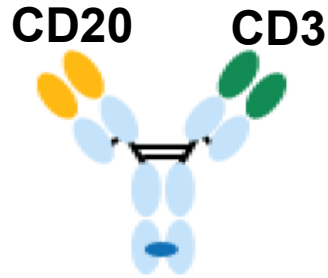
≥ 1 prior line

≥ 2 prior lines

CD20/CD3 Bispecific Antibodies in B-cell lymphomas



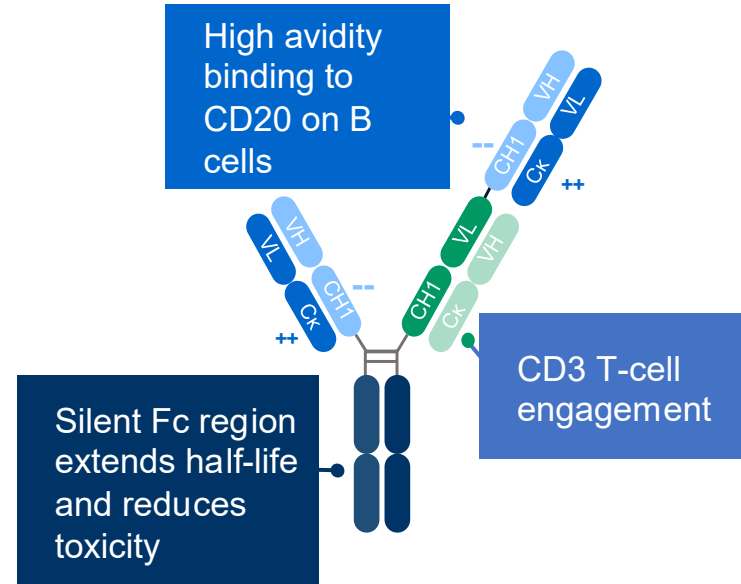
Odronextamab
(IV)
(REGN1979)
IgG4



Mosunetuzumab
(IV/SC)



Epcoritamab
(SC)
Duobody
GEN3013



Glofitamab (IV)
CD20-TCB

Glofitamab in Relapsed/Refractory LBCL

Fixed duration therapy

- Obinutuzumab pretreatment (1 x 1000mg) to mitigate CRS
- Fixed duration treatment maximum 12 cycles (8.3 months)

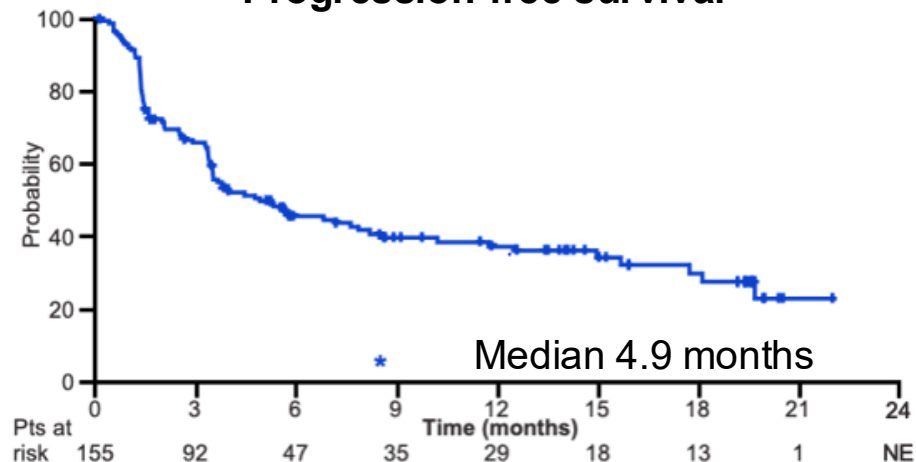
Baseline Characteristics	N=154
Median age (range)	66 (21-90)
Median prior tx (range)	3 (2-7)
Prior ASCT	28 (18%)
Prior CAR	51 (33%)
Refractory to last tx	132 (86%)

Best Response

ORR: 52%

CRR: 40%

Progression-free survival

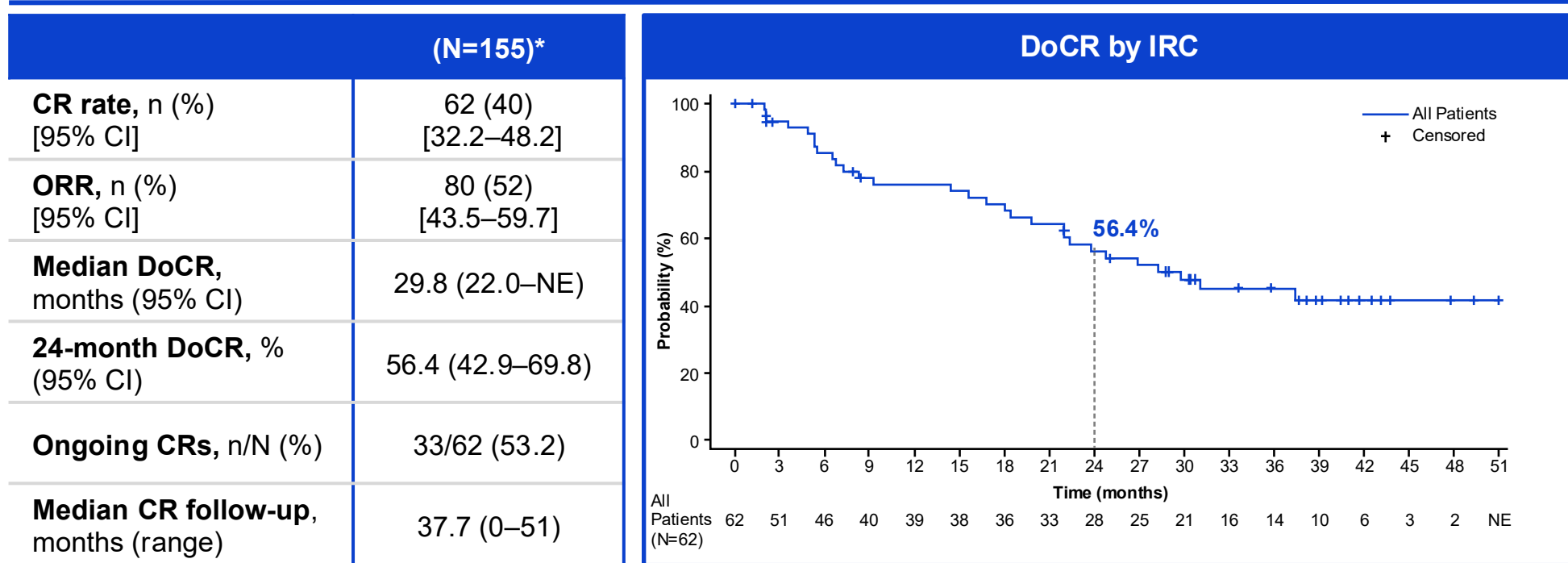


median follow-up of 12.6 months

Notable Adverse Events

- CRS: 63% (grade 3-4: 4%)
- ICANS: 8% (grade 3-4: 3%)
- Neutropenia: 38%

Long-term F/Up: Durable Complete Responses with Fixed-duration Glofitamab



- **Median time on study: 41.0 months** (range: 0–52)

An estimated 56.4% of patients with a CR at any time remained in remission at 24 months

Epcoritamab in Relapsed/Refractory LBCL

Treatment until progression or intolerance

Baseline Characteristics	N=157
Median age (range)	64 (20-83)
Median prior tx (range)	3 (2-11)
Prior ASCT	31 (20%)
Prior CAR T-Cell	61 (39%)
Refractory to last tx	130 (83%)

Best IRC-assessed overall response

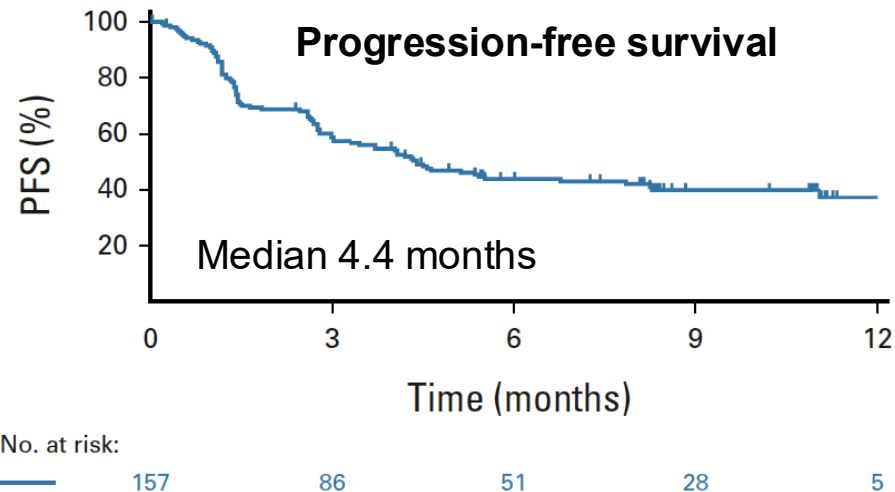
ORR: 63%

CRR: 39%

Median DoR: 12.0 mo

Median DoCR: 21 mo (68% at 15 mo)

median follow-up of 20 months

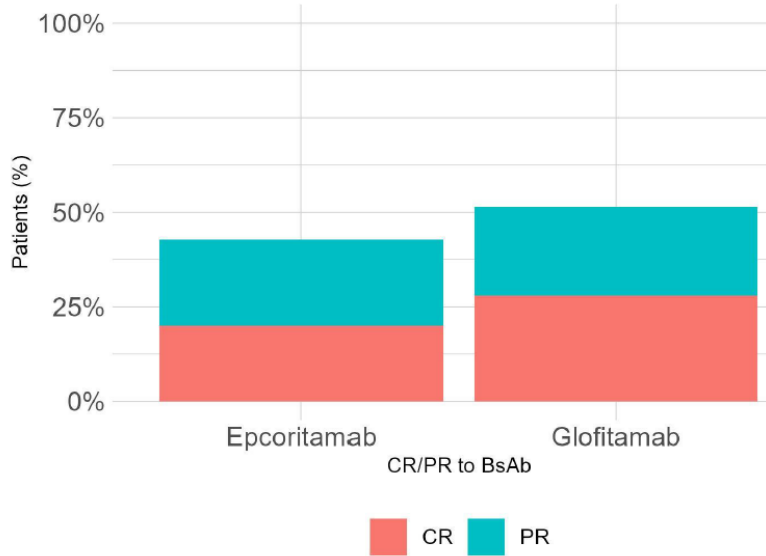


Notable Adverse Events

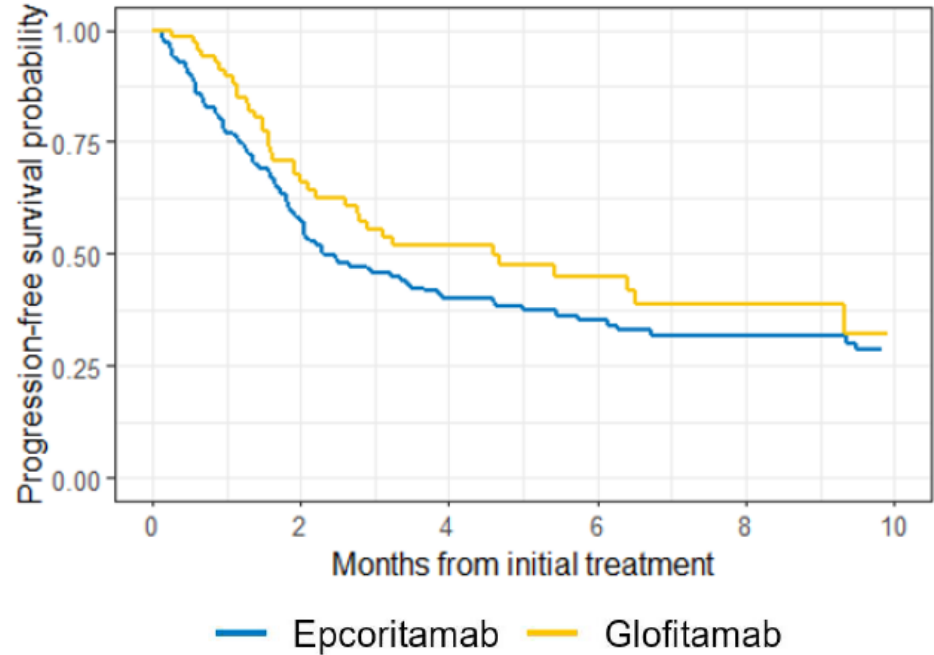
- CRS: 50% (grade 3-4: 2.5%)
- ICANS: 6% (grade 3-4: 0.6%)
- Neutropenia: 22% (grade 3-4: 15%)
- Injection site reactions 20%

Thieblemont, et al. JCO 2022. Thieblemont, et al. ICML 2023

Real World Outcomes of Bispecifics in R/R LBCL



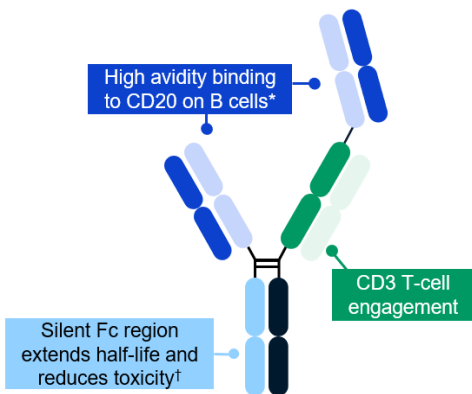
- **Entire cohort:** N=245
- ORR – 53%
- CR – 26%
- PR – 27%
- PD – 41%



60% with prior CAR T-cell therapy had comparable outcomes, unless within 90 days

* 90% of patients (17/19) with paired biopsies lost CD20 expression post treatment (by flow and IHC)

Bispecific Antibodies for 2nd line DLBCL: STARGLO Trial



Patients R/R DLBCL (N=274)

- R/R DLBCL NOS after ≥ 1 prior systemic therapy
- Patients with one prior line must be transplant ineligible
- ECOG PS 0–2

Stratification factors

- Relapsed vs refractory disease†
- 1 vs ≥ 2 prior lines of therapy

Glofit-GemOx (n=183)

Glofitamab plus gemcitabine and oxaliplatin*
Step-up dosing in Cycle 1,
30mg administered on Day 1 from Cycle 2 onwards

Glofitamab
30mg administered on
Day 1 of each cycle

Cycles 9–12

Cycles 1–8
(21-day cycles)

R 2:1

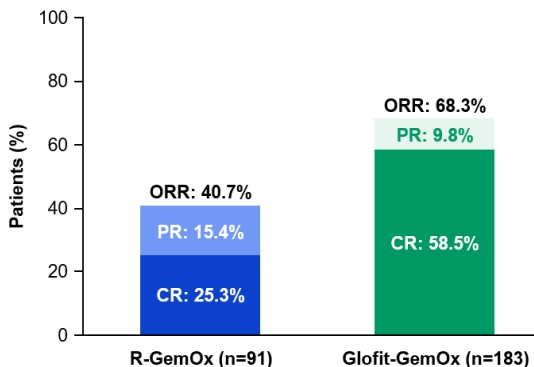
R-GemOx (n=91)

Rituximab† plus gemcitabine and oxaliplatin
Administered on Day 1 of each cycle

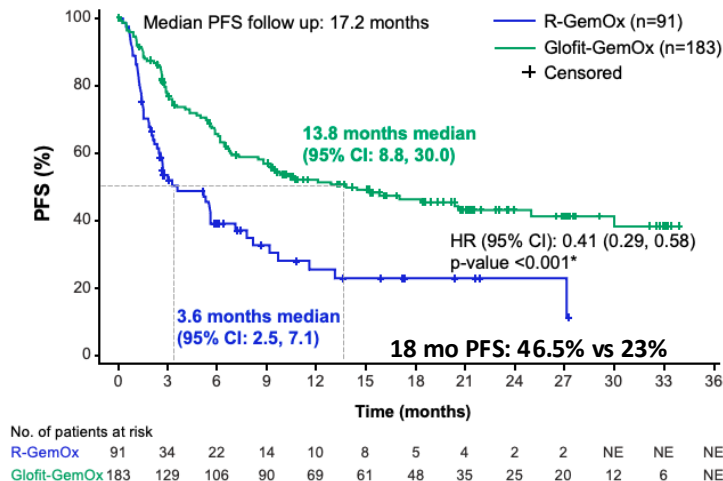
Baseline Characteristics	R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, y, median (range)	68.0 (20–84)	68.0 (22–88)
Prior lines of therapy, median (range)	1 (1-4)	1 (1-4)
1	57 (63)	115 (63)
≥ 2	34 (37)	68 (37)
Primary refractory, n(%)	47 (52)	106 (58)
Refractory to last prior therapy, n(%)	54 (59)	112 (61)
Prior CAR T-cell therapy, n(%)	8 (9)	13 (7)

Glofit-GemOx Improves Response, PFS and OS

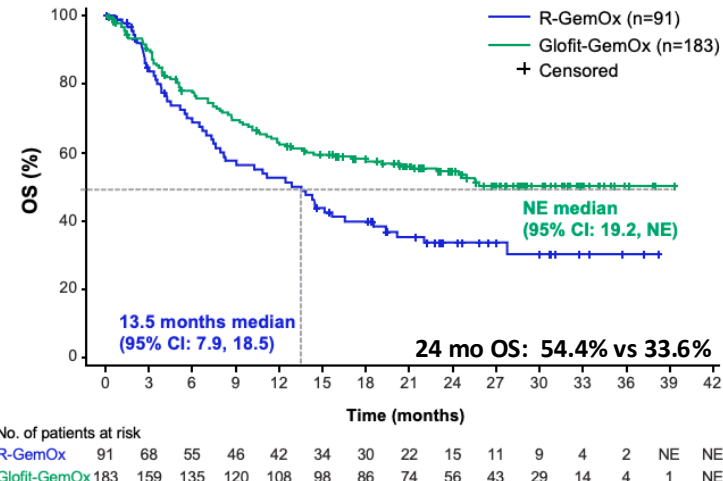
Response



PFS



OS (primary endpoint)



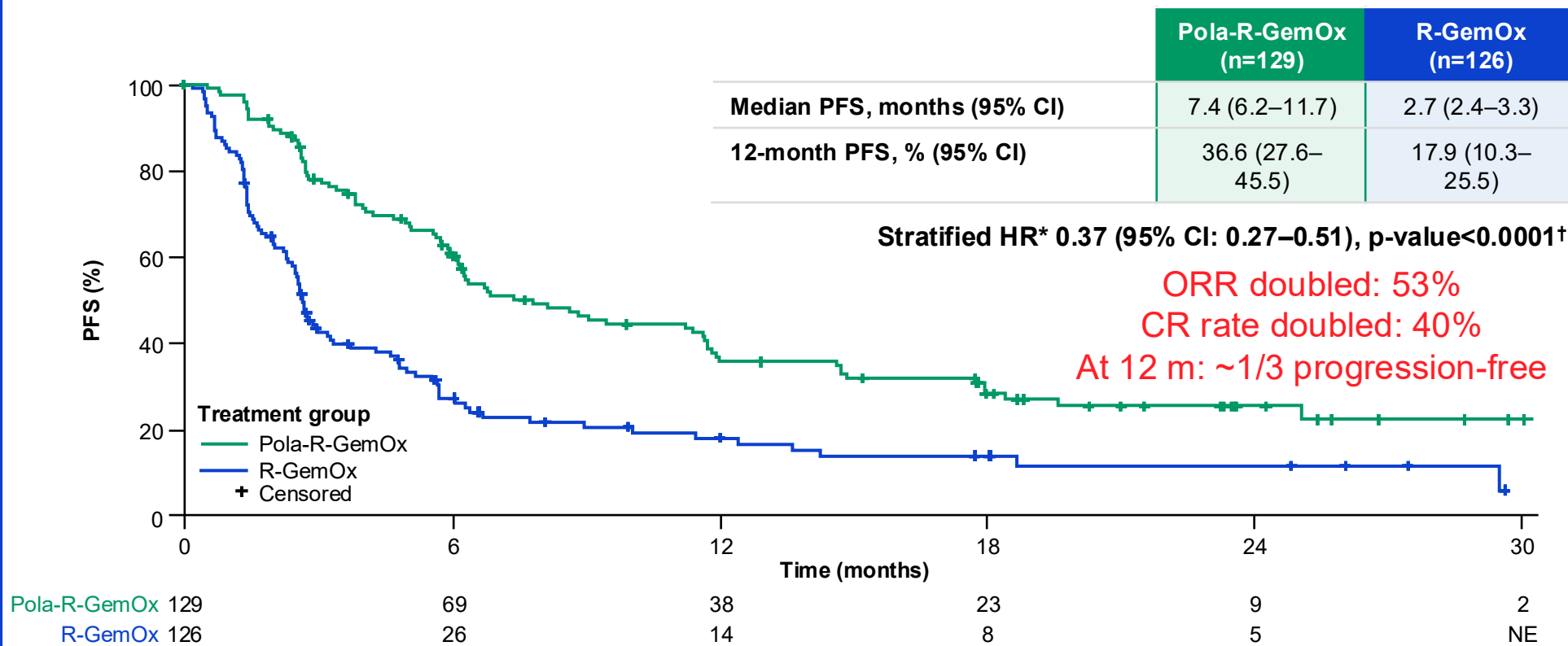
CRS, n (%)	Glofit-GemOx n=172
Any grade	76 (44)
Grade 1	54 (31)
Grade 2	18 (10.5)
Grade 3	4 (2)

CRS occurred predominantly during cycle 1 step up dosing

n (%)	R-GemOx (n=88)	Glofit-GemOx (n=180)
ICANS	NA	4 (2.3) [†]
Grade ≥3	NA	1 (0.6)
Infections, Grade ≥3	11 (12.5)	42 (23.3)
Neutropenia, Grade ≥3	16 (18.2)	61 (33.9)
Febrile neutropenia	1 (1.1)	6 (3.3)

POLARGO Phase 3 Trial: Pola-R-GemOx achieved significant improvement in PFS vs R-GemOx

Median PFS follow-up: 18.7 months (95% CI: 17.8–23.3)

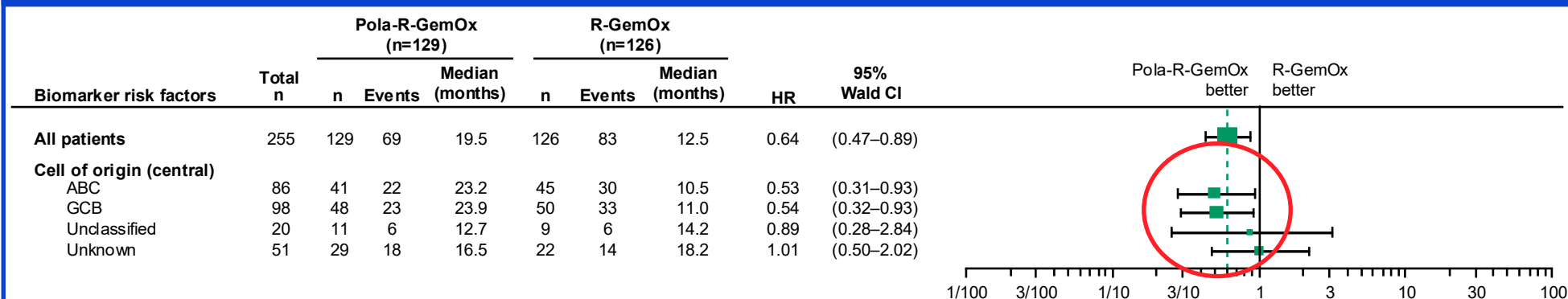


PFS is censored at earliest subsequent therapy or two or more missing tumor assessments.

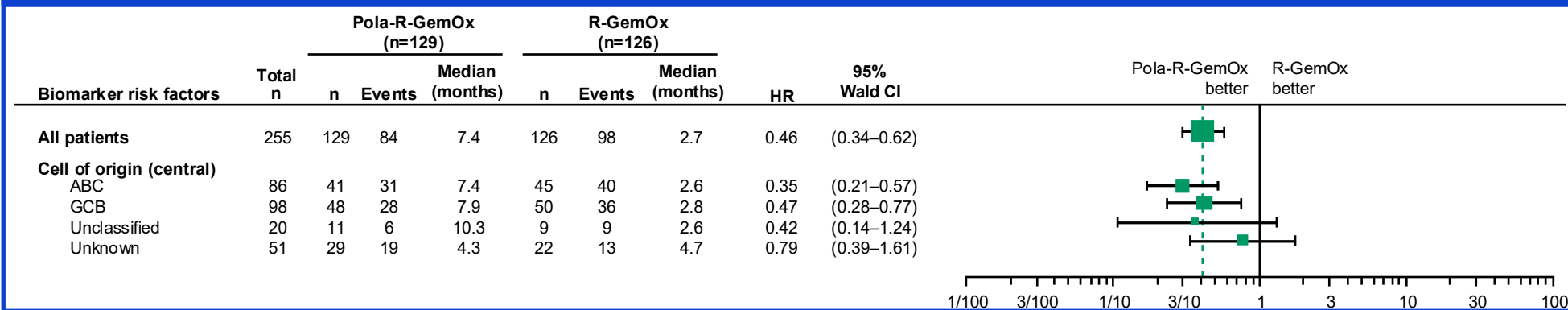
*Stratified for age (≤ 70 vs > 70 years), prior lines of systemic therapy (1 vs ≥ 2), outcome of last systemic therapy (relapsed vs refractory). †Log rank.

Survival benefit seen in both ABC and GCB cell-of-origin subgroups

Overall survival

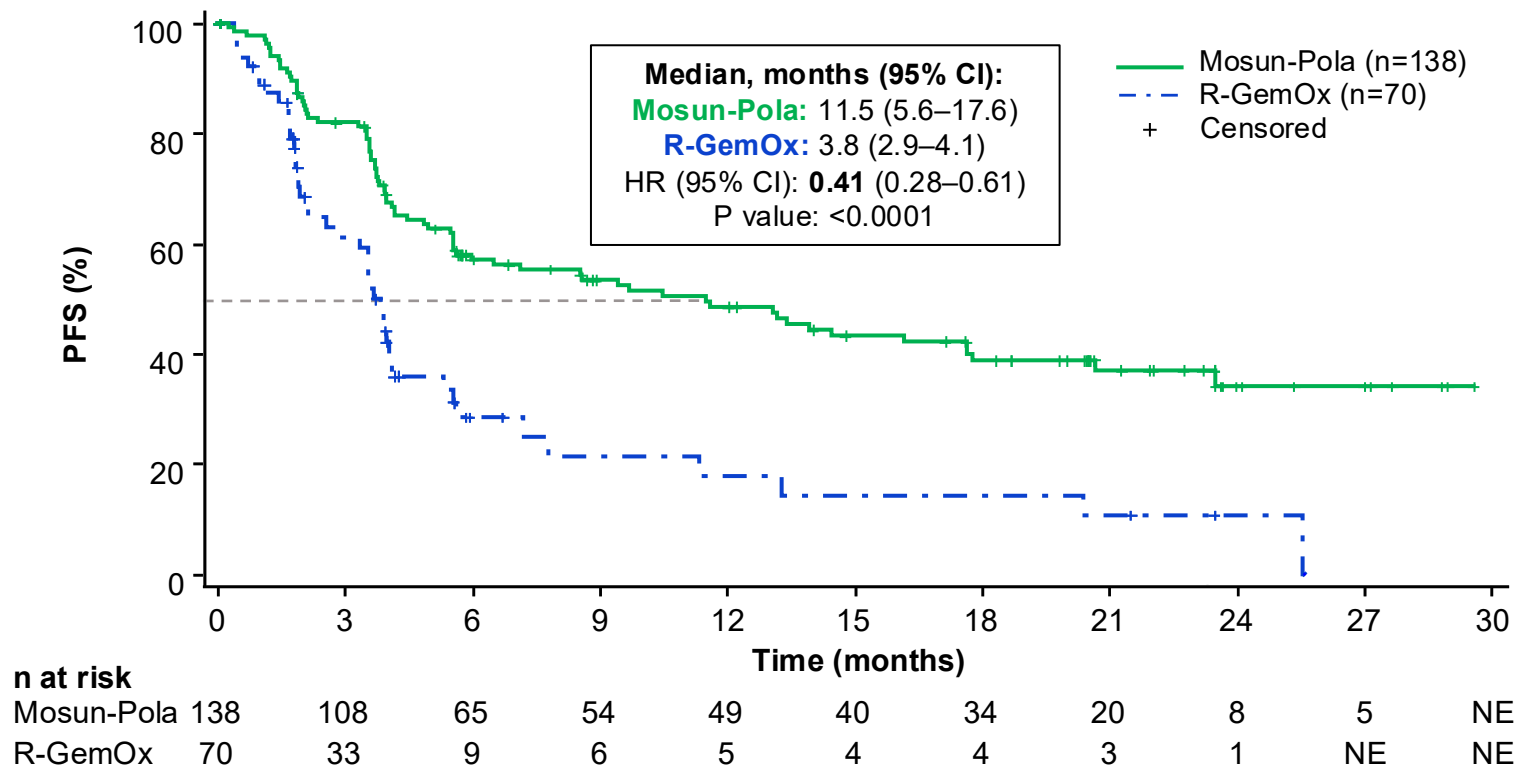


Progression-free survival



SUNMO Phase 3 Trial: Mosun-Pola significantly prolonged PFS versus R-GemOx

Primary endpoint: Progression-free survival by IRC



Significant improvement
in Response

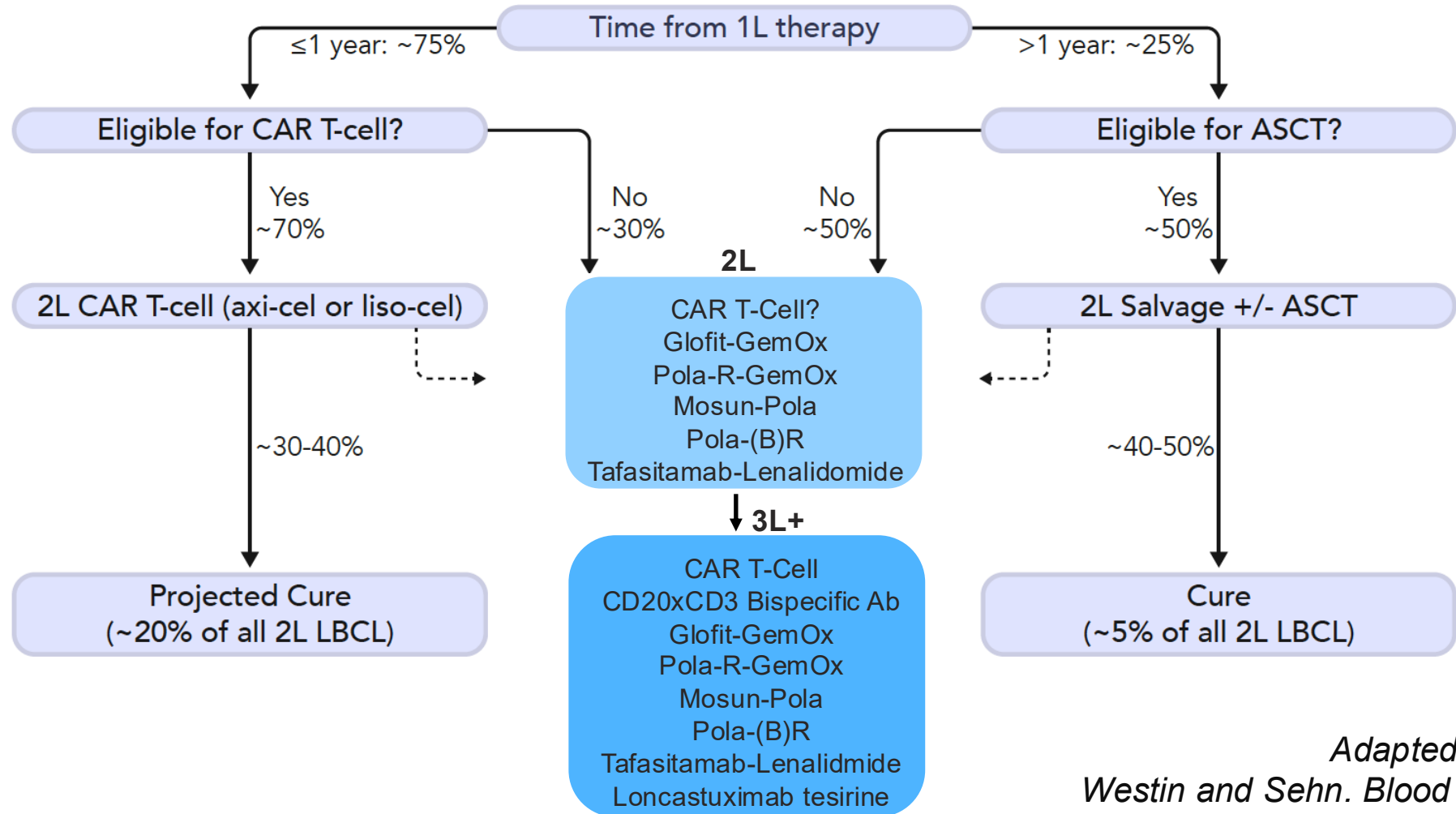
ORR: 70.3% vs 40%
CR rate: 51.4% vs 24.3%

12-month PFS, % (95% CI):
Mosun-Pola: 48.5 (39.6–57.4)
R-GemOx: 17.8 (5.4–30.3)

Median follow-up: 23.2 m

Budde LE et al, J Clin Oncol 2025

Algorithm for Relapsed/Refractory LBCL



*Adapted from
Westin and Sehn. Blood 2022*

Summary

- The standard of care is evolving in frontline DLBCL
- CAR T-cell therapy should be considered second-line for high risk transplant-eligible patients
- Novel agents can overcome chemotherapy resistance, with numerous combinations emerging or under investigation
- Sequencing of agents should account for goal of therapy, comparative efficacy/toxicity and patient preferences
- Predictive biomarkers or response-based therapy (using ctDNA) will be necessary for tailored approaches