



SINTOMA²⁶

14 A 16 DE MAIO | HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA **soho**
society of hematologic oncology

APOIO INSTITUCIONAL Faculdade **bp**

GERENCIAMENTO
E PRODUÇÃO

RV+
EVENTOS

First-line DLBCL: Molecular Subtypes and the Future of First-Line Therapy

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- Consultancy: Roche, Genentech, Genmab, Schrodinger, ADC Therapeutics, BeOne, Bristol-Myers Squibb, Incyte.
- Research funding: Genmab, Schrodinger, Genentech, Inc., Precision Biosciences, Artiva, Pfizer, Kymera Therapeutics, Incyte, Bristol-Myers Squibb, Immugene.



Idyllic era:
RCHOP
for all

R-CHOP
CHEMOTHERAPY INFUSION

- RITUXIMAB
- CYCLOPHOSPHAMIDE
- DOXORUBICIN
- VINCRISTINE
- PREDNISONE

♥ FOR YOU. FOR EVERYONE.

Healing
Hope
Harmony

DLBCL: curable since 1990's

No benefit of intensifying CHOP

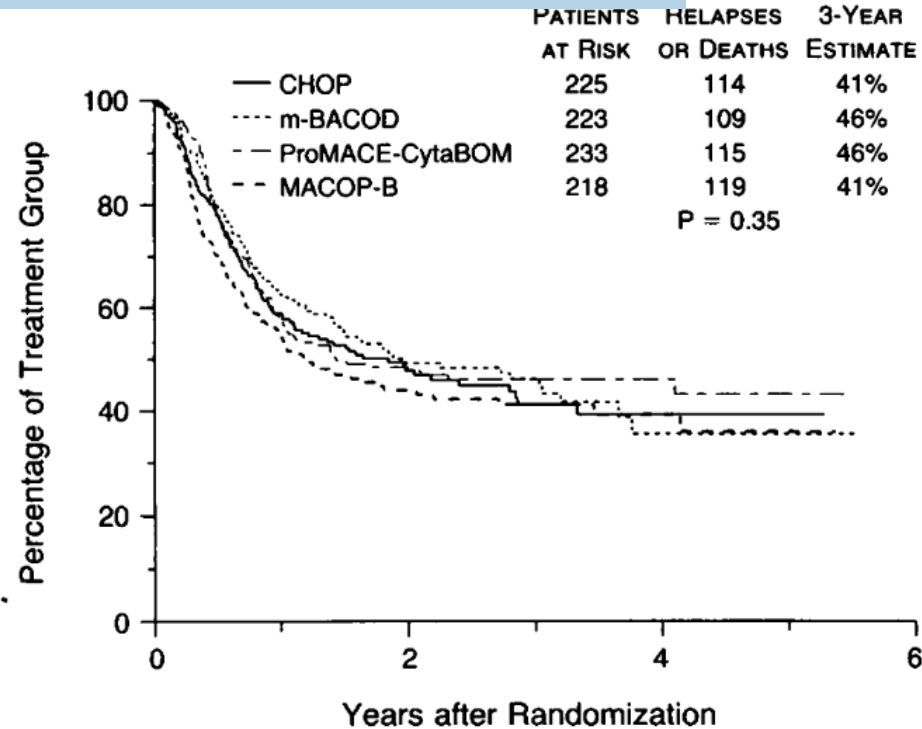
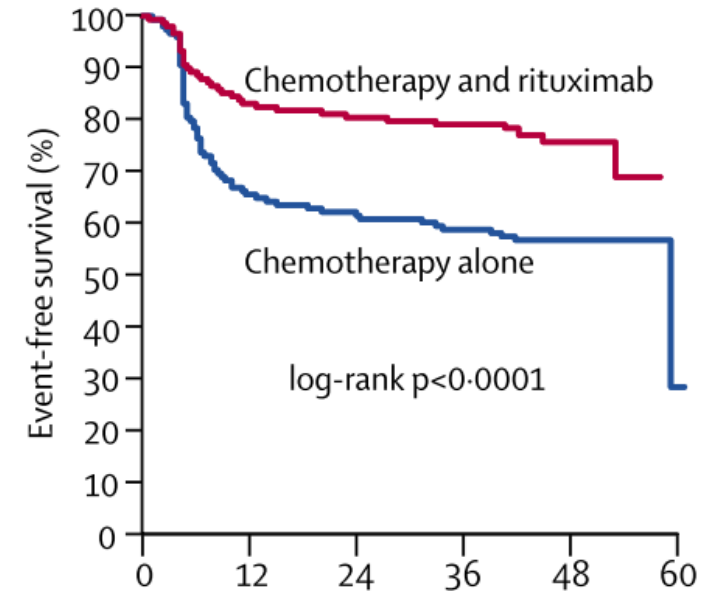


Figure 1. Time to Treatment Failure in the Treatment Groups.
The three-year estimate is of survival without disease.

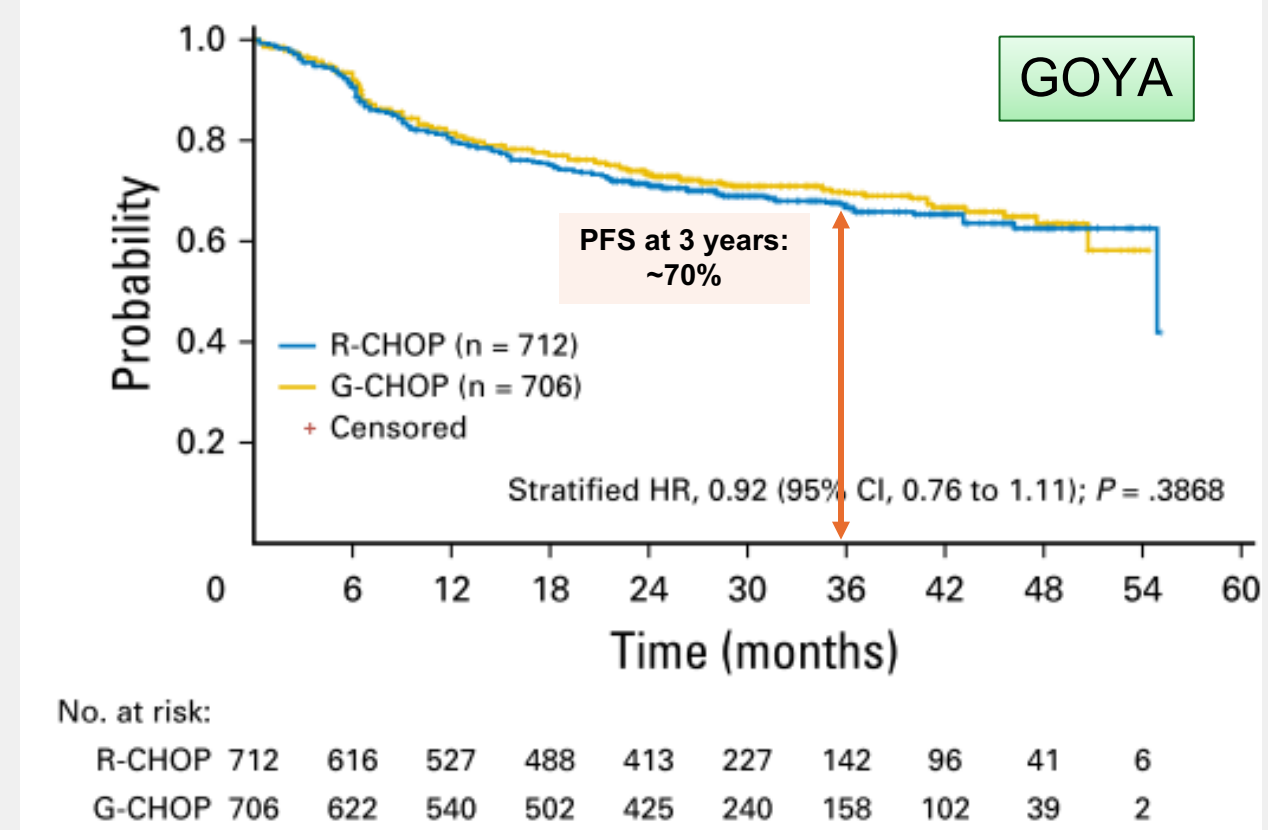
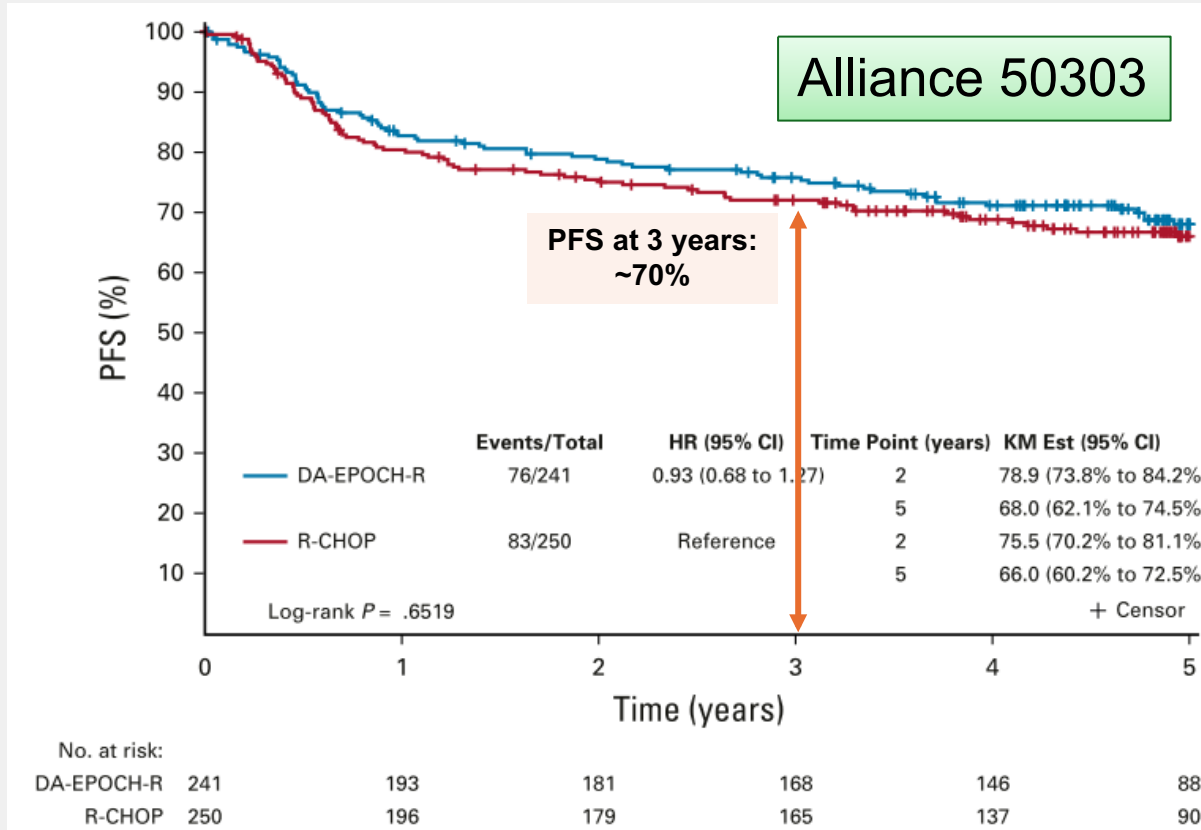
Rituximab increases cure rate



Numbers at risk

Chemotherapy and rituximab	413	296	256	145	37	0
Chemotherapy alone	410	229	194	101	28	1

But 30-40% of patients relapse



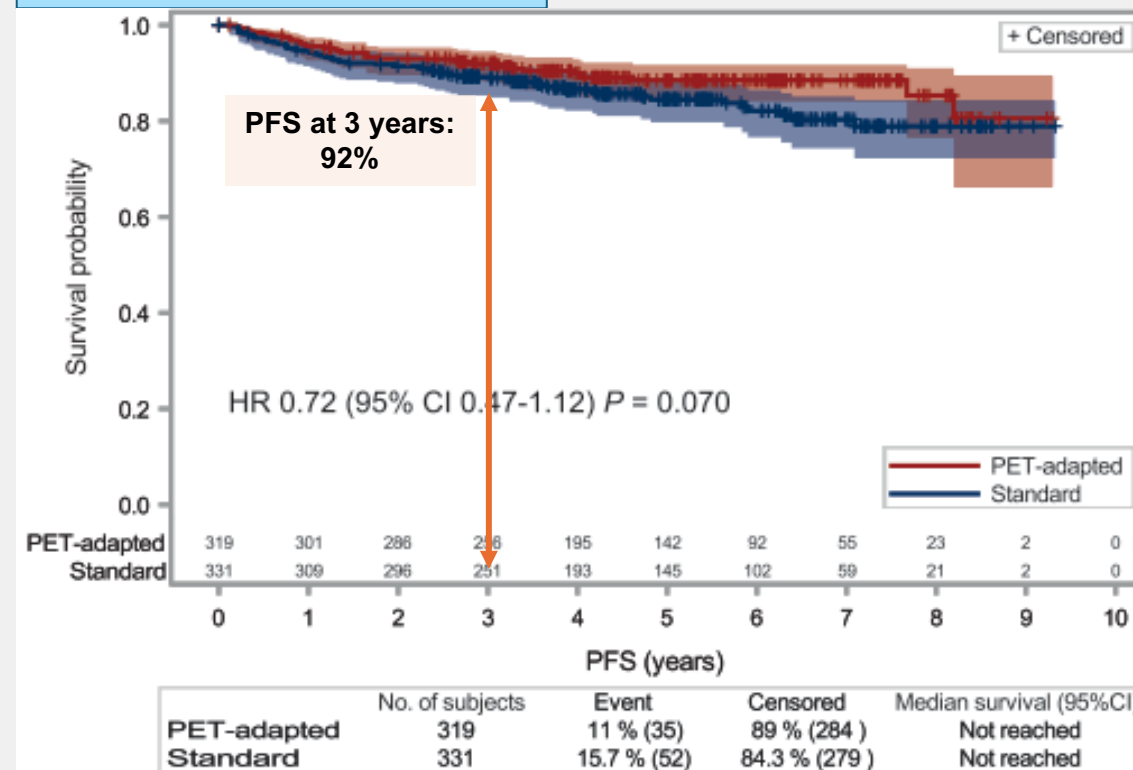
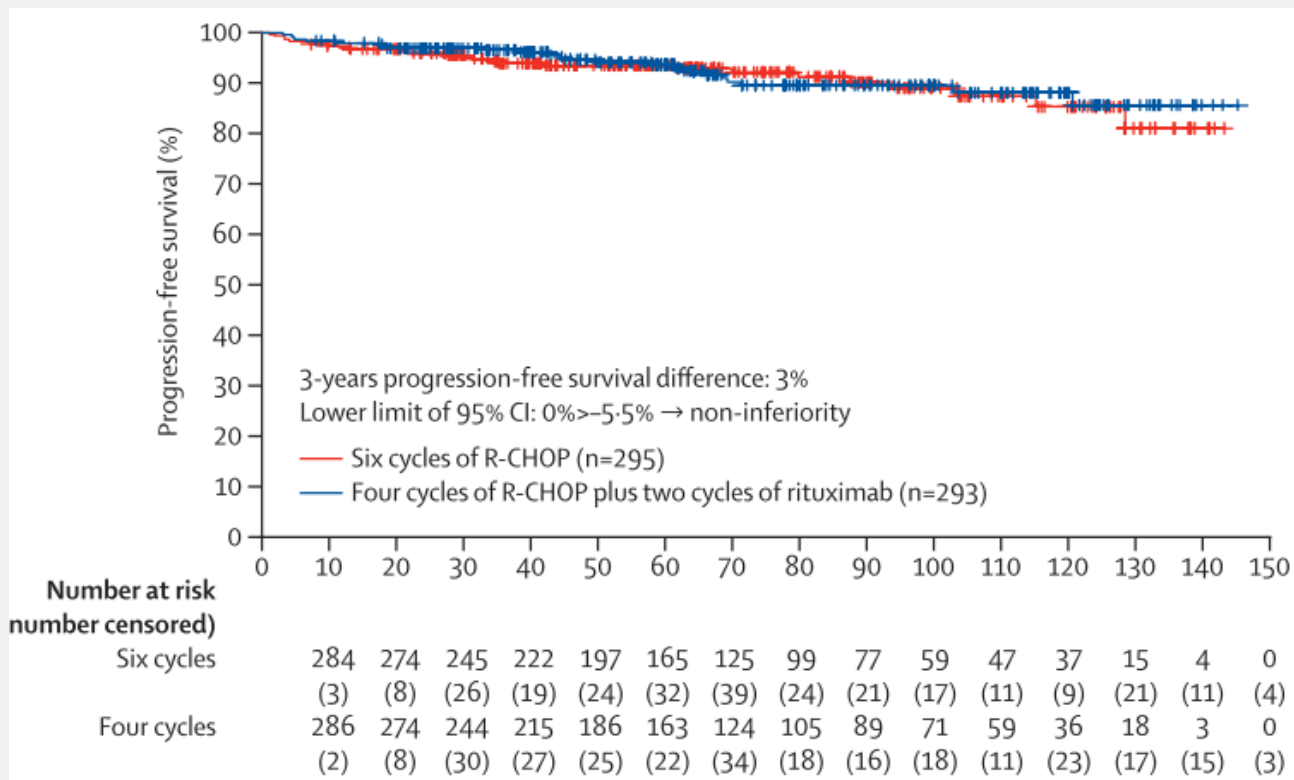
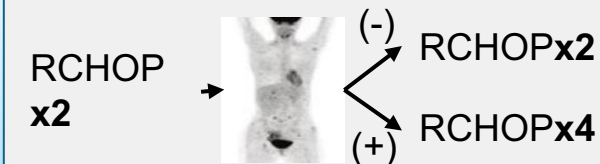
Low risk DLBCL: abbreviated RCHOP

FLYER

- Age ≤60
- IPI = 0,
- <7.5 cm (non-bulky)

LYSA LNH 09-1B

- Stage 1 or 2
- aalPI = 0
- Bulky >10cm: 4.2%





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NCCN Guidelines Version 3.2026 Diffuse Large B-Cell Lymphoma

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SUGGESTED TREATMENT REGIMENS^{a,b}

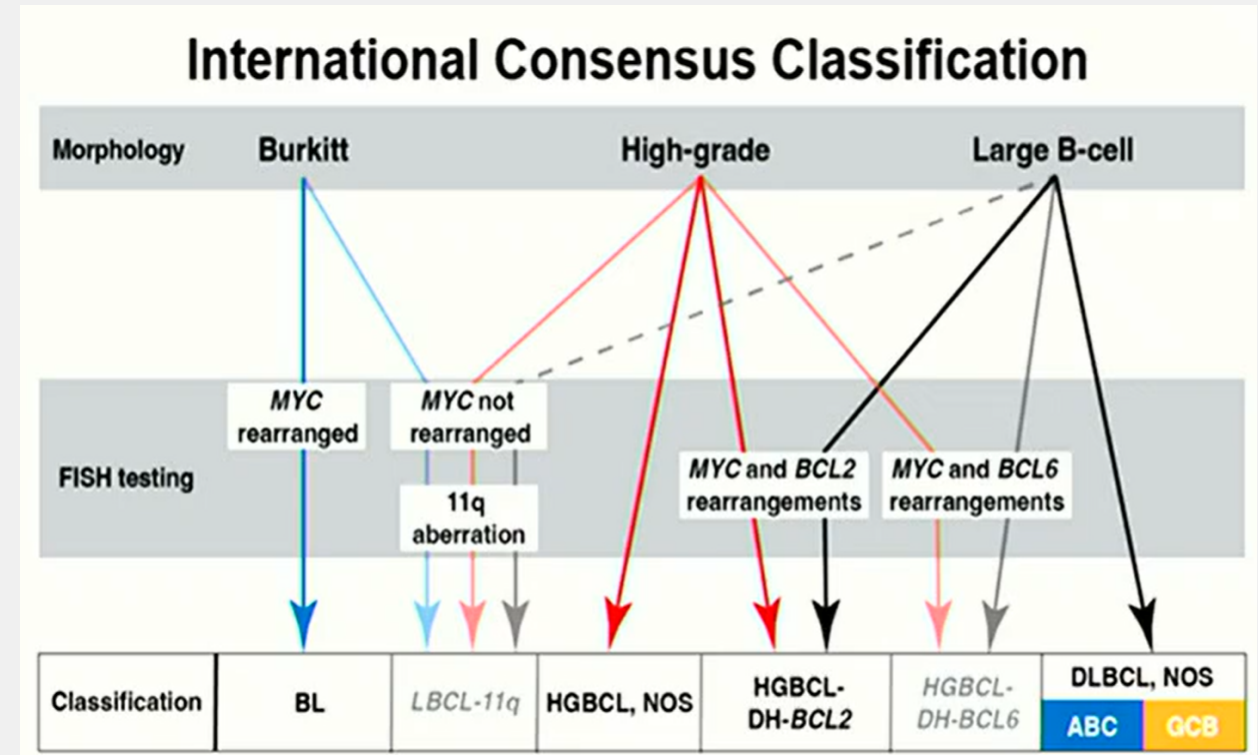
FIRST-LINE THERAPY			
Stage I (excluding stage II with extensive mesenteric disease)	Stage II (with extensive mesenteric disease) or Stage III-IV	Patients with Poor Left Ventricular Function (all stages)	Patients Who are Very Frail and Patients ≥ 80 Years of Age with Comorbidities ^{f,9} (all stages)
<ul style="list-style-type: none"> • CHOP + Rituximab^c • Polo P-CHP (CHP [Cyclophosphamide/Doxorubicin/Prednisone] + Polatuzumab vedotin-piig + Rituximab) (smIPI >1)^d (category 1) 	<p>Preferred</p> <ul style="list-style-type: none"> • CHOP + Rituximab^c (category 1) • Polo P-CHP (IPI ≥2)^d (category 1) <p>Other recommended</p> <ul style="list-style-type: none"> • Dose-adjusted EPOCH (Etoposide/Prednisone/Vincristine/Cyclophosphamide/Doxorubicin) + Rituximab 	<p>Other recommended (in alphabetical order by category)</p> <ul style="list-style-type: none"> • DA-EPOCH^h + Rituximab • CDOP (Cyclophosphamide/Liposomal Doxorubicin/Vincristine/Prednisone) + Rituximab • CEOP (Cyclophosphamide/Etoposide/Vincristine/Prednisone) + Rituximab • GCVP (Gemcitabine/Cyclophosphamide/Vincristine/Prednisone) + Rituximab 	<p>Other recommended (in alphabetical order by category)</p> <ul style="list-style-type: none"> • CDOP + Rituximab • Mini-CHOP + Rituximab • GCVP + Rituximab

DLBCL.

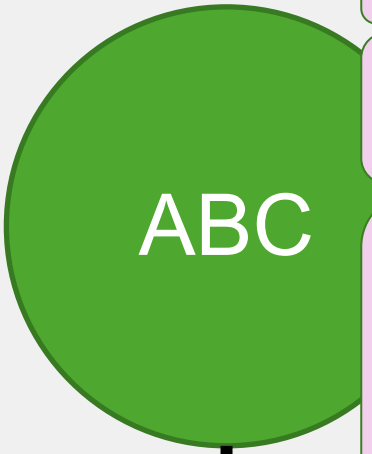
— ARE YOU SURE YOU KNOW WHAT IT IS? —



- **DLBCL, NOS**
 - Germinal B-cell-like,
 - Non-GCB-like
- **Other forms of LBCL**
 - T-cell/histiocyte-rich LBCL (THRLBCL)
 - ALK+ LBCL,
 - LBL with *IRF4* rearrangement
 - EBV-positive DLBCL, NOS
 - Primary LBCL of immune-privileged sites
 - Primary cutaneous DLBCL, leg type
 - Intravascular LBCL
 - DLBCL associated with chronic inflammation
 - Lymphomatoid granulomatosis
 - Primary mediastinal B-cell lymphoma
- **High-grade B-cell lymphoma**
 - with *MYC* and *BCL2* rearrangements
 - with 11q aberration
 - NOS

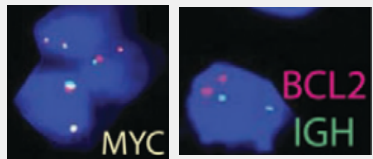


DLBCL: cell-of-origin-based classification



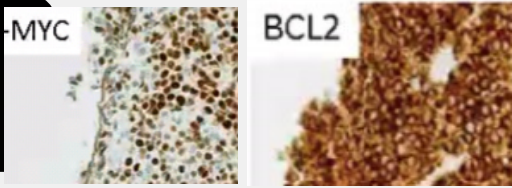
- Better prognosis
- BCL2-IGH* t(14;18)
- Epigenetic lesions
EZH2, KMT2D
- No specific treatment

- Worse prognosis
- Dependent on BTK, NFκB
- Response to:
 - Lenalidomide
 - Bortezomib
 - Ibrutinib

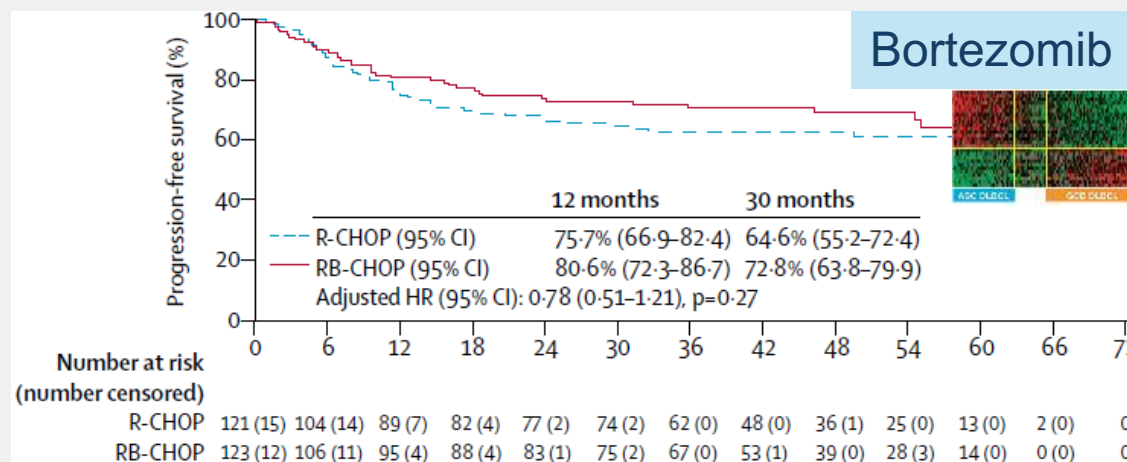
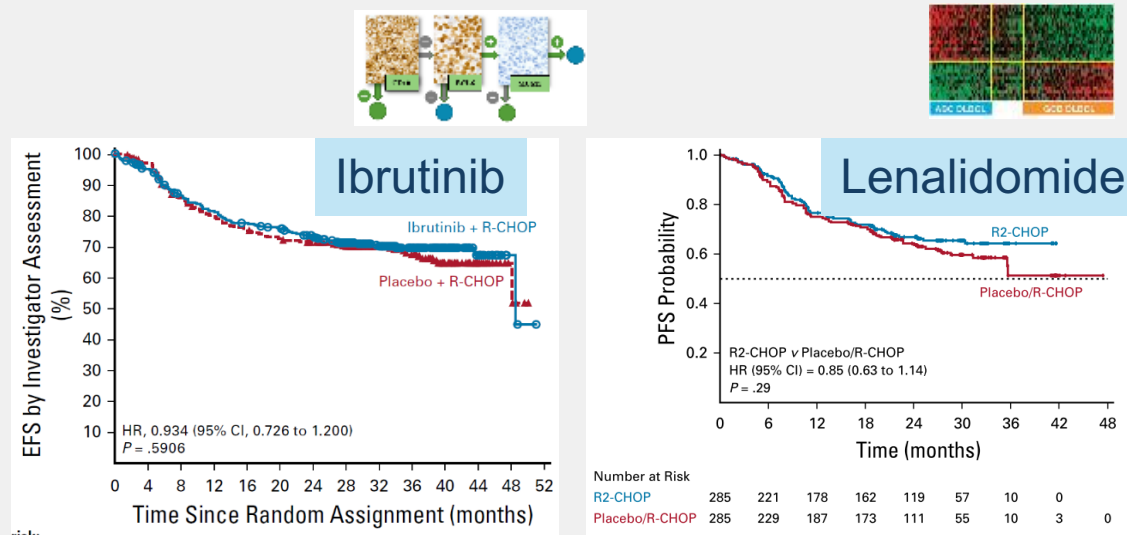
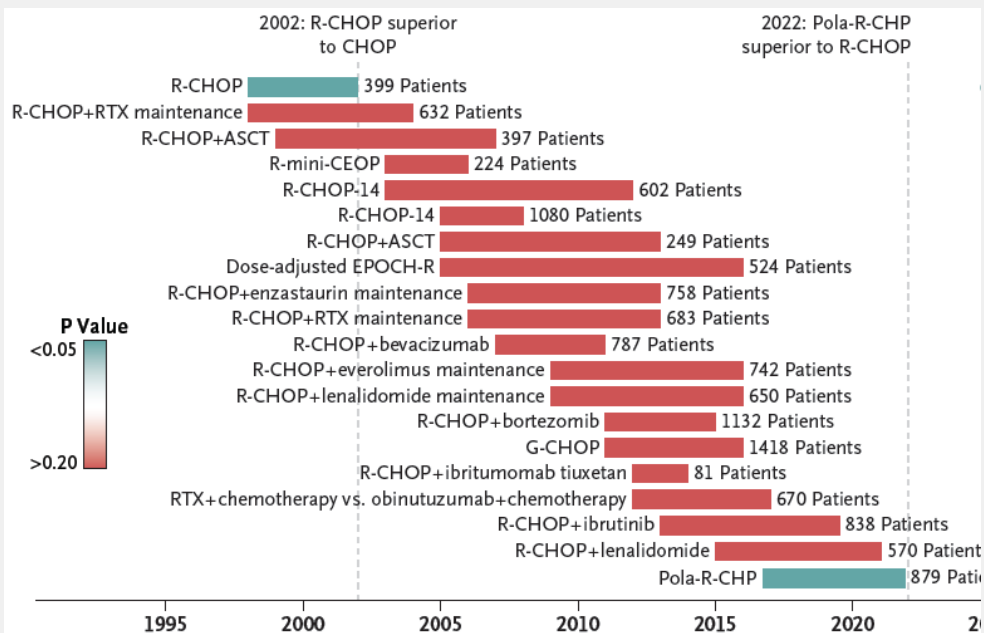


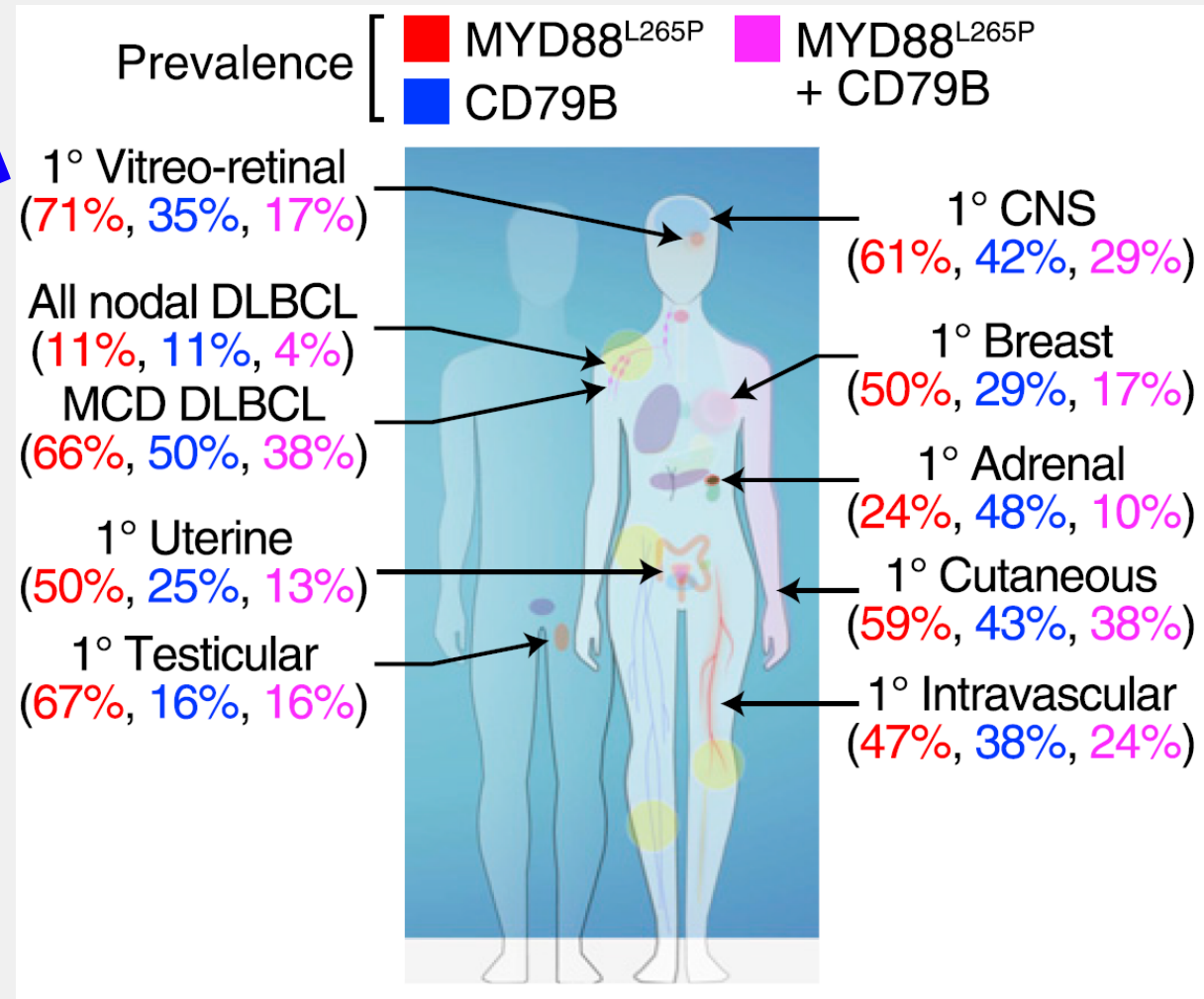
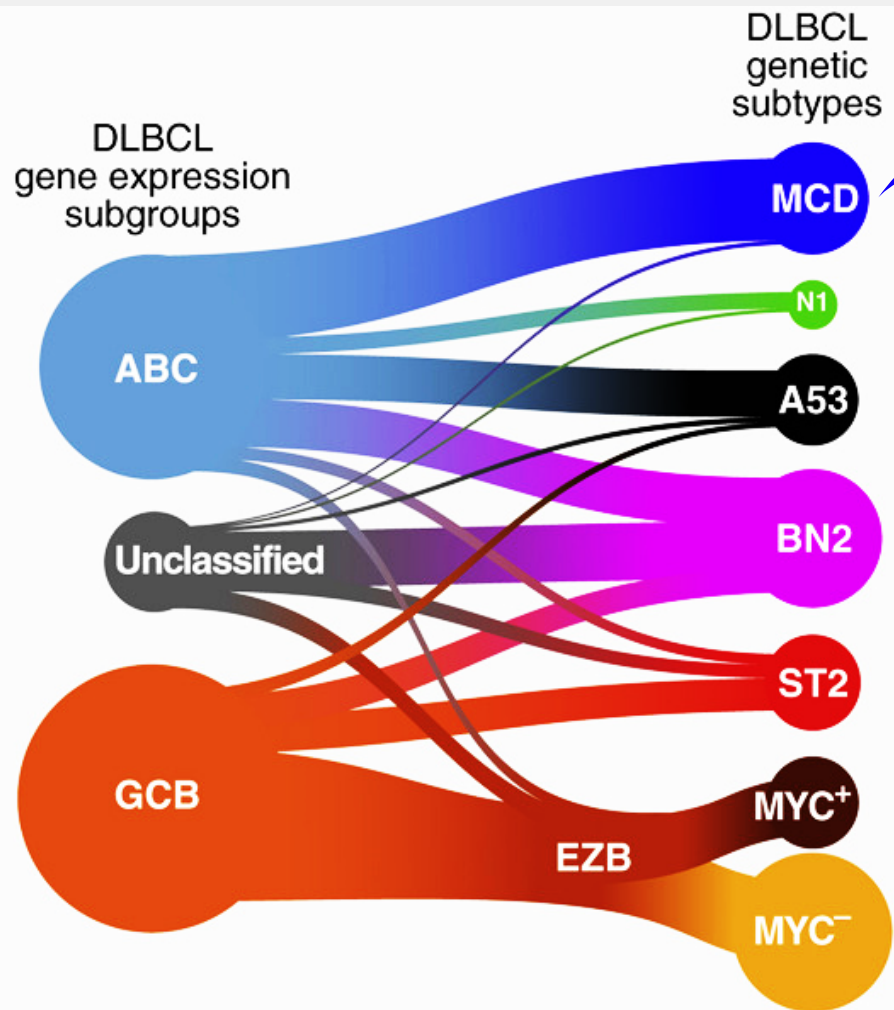
MYC rearrangement
Double-hit lymphoma

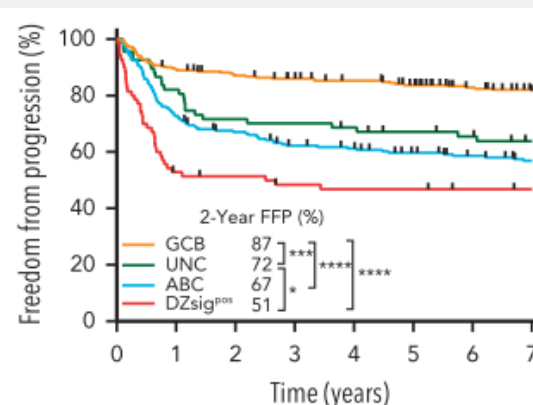
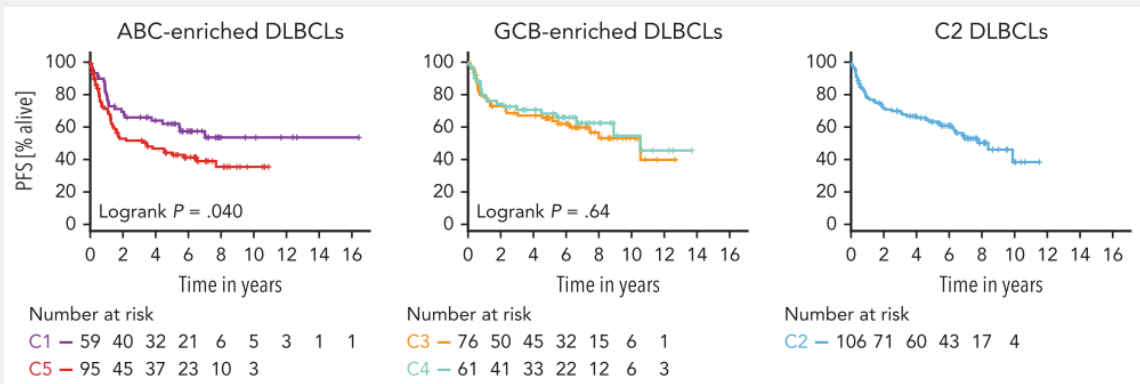
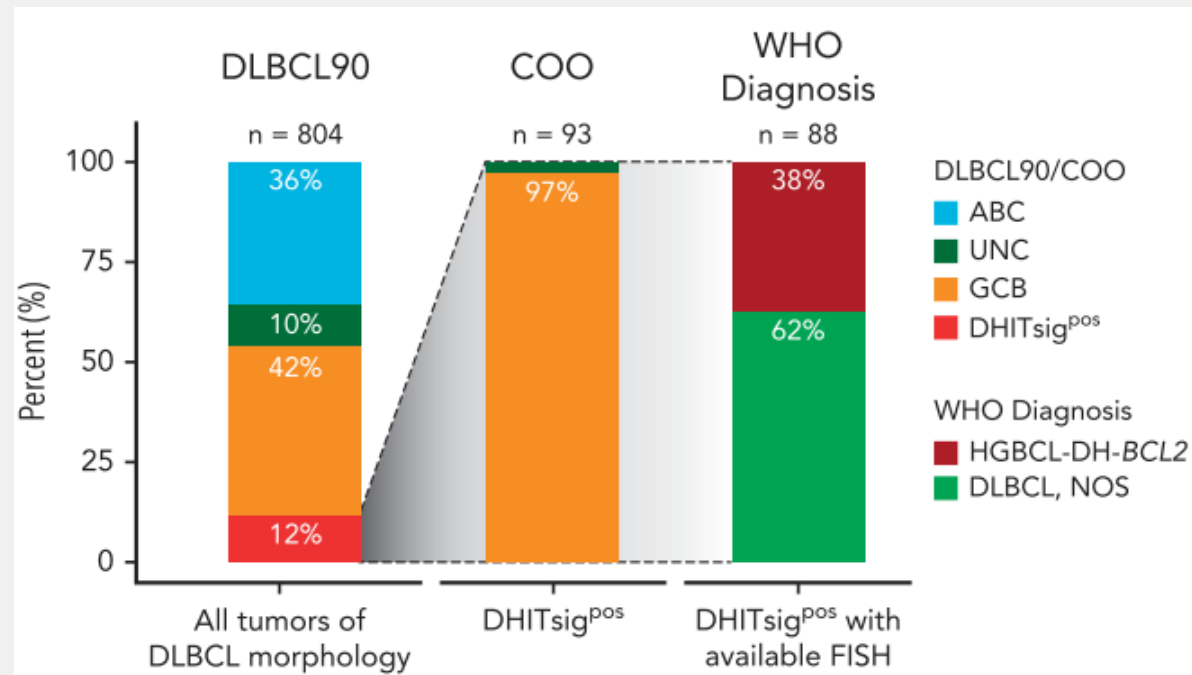
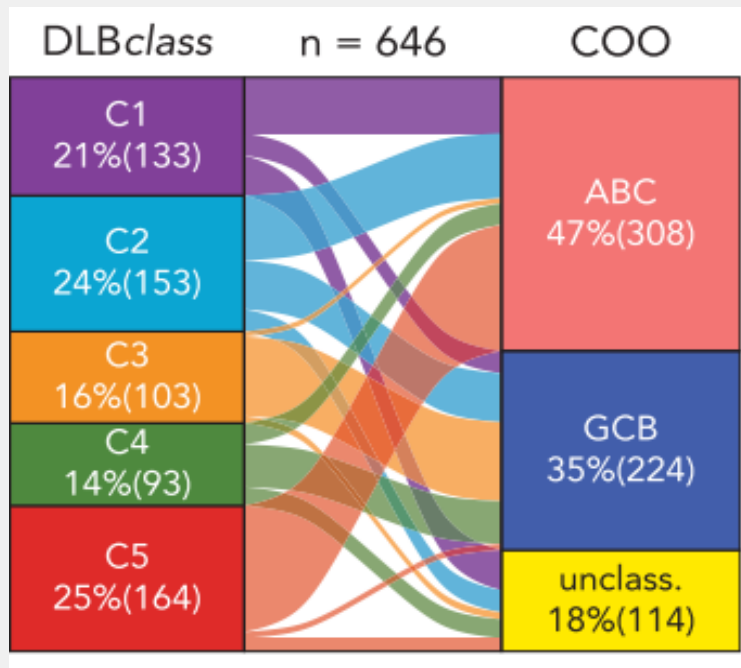
MYC + *BCL2* IHC
"Dual expresser"



No clinical trial has shown improved outcomes with COO-directed therapy

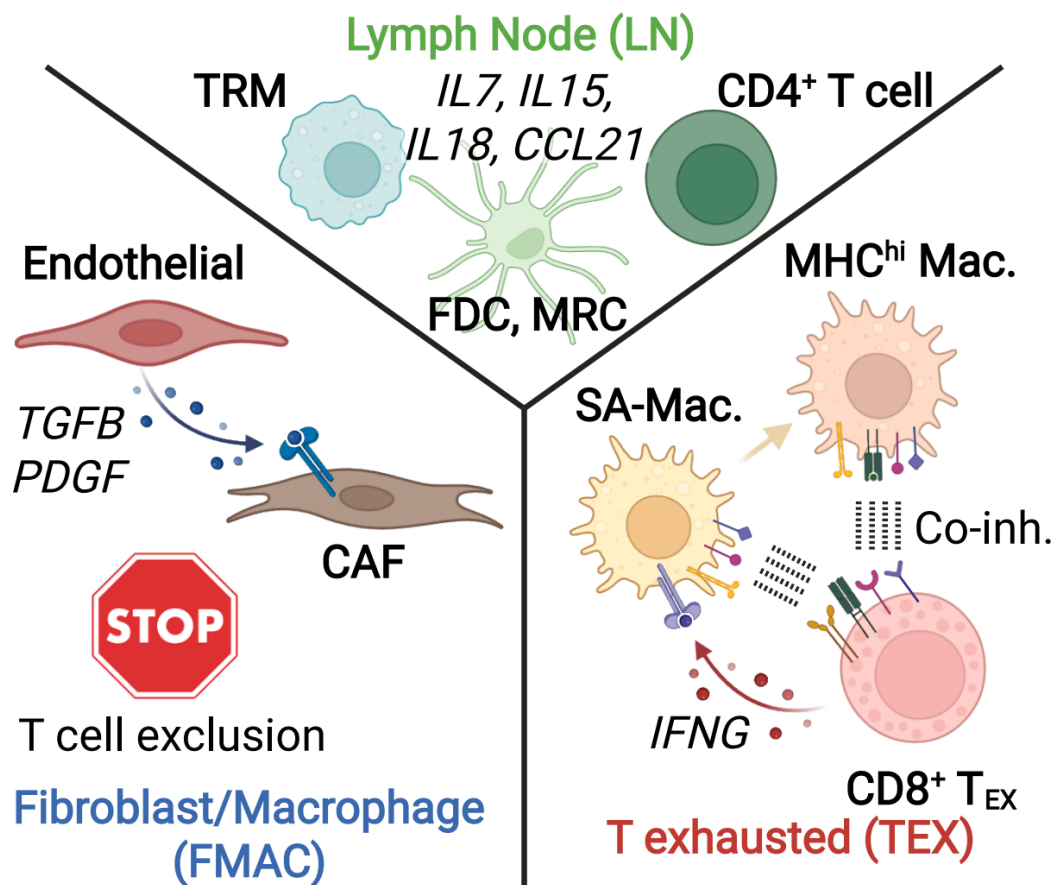






Wait! There is more!! Microenvironment matters!!!

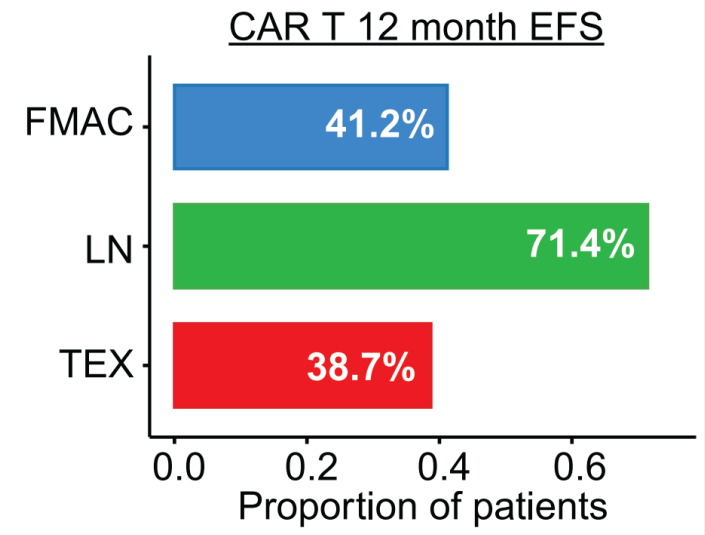
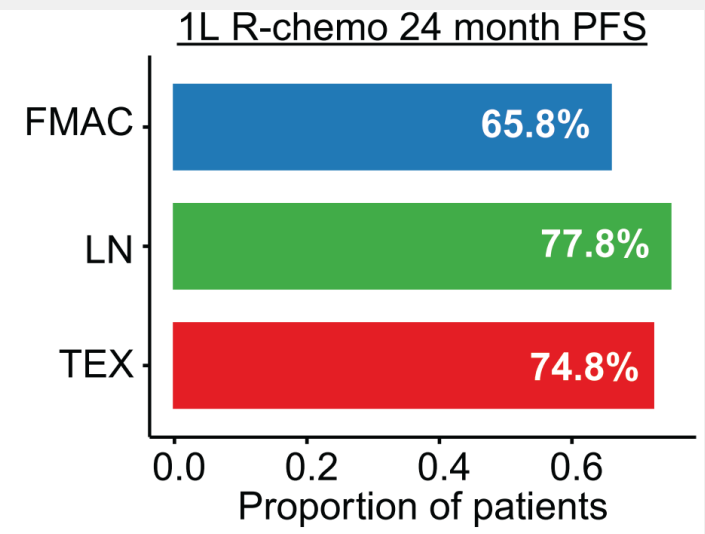
Lymphoma Microenvironment Archetype Profiles (LymphoMAPs)



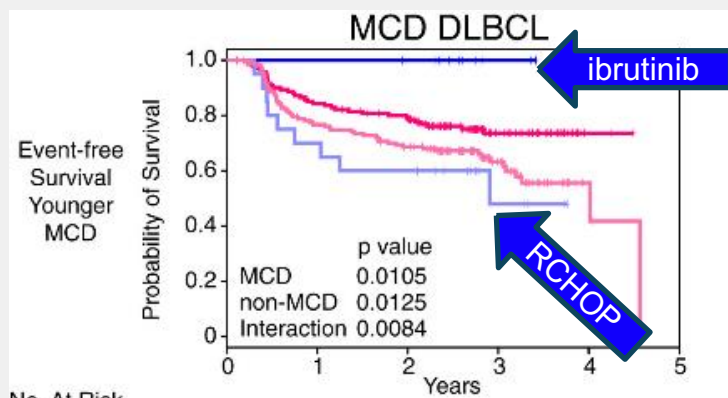
FMAC
Enriched for DZsig+ mol. subtype
Enriched for high-risk features
More frequent in later LOT
Inferior outcomes to 1L R-chemo

LN
Enriched for GCB mol. subtype
Low SUVmax
More frequent in earlier LOT
Best outcomes post CAR T

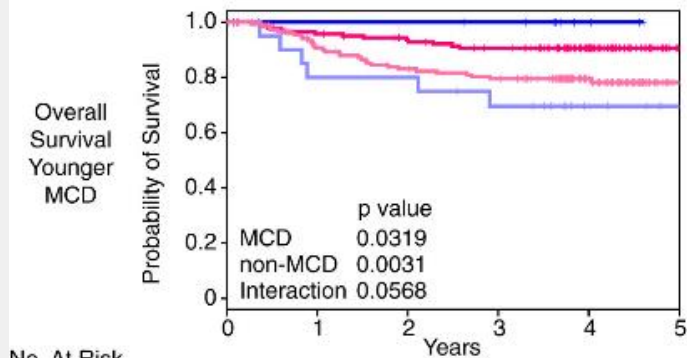
TEX
Enriched for ABC mol. subtype
No assoc. with high-risk features
Consistent across LOT
No sig. benefit from CAR T



Does this matter for treatment? PHOENIX trial

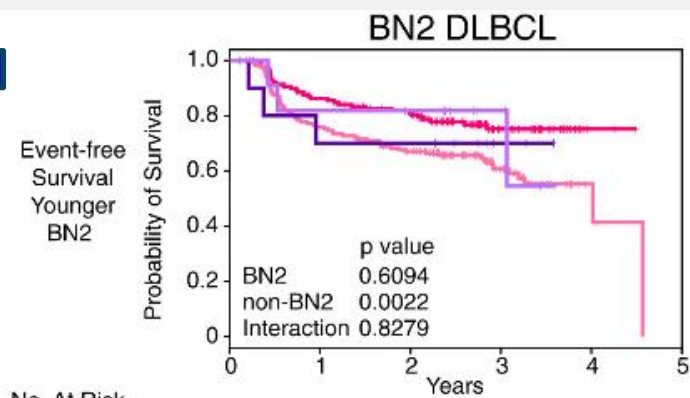


No. At Risk	0	1	2	3	4	5
MCD Ibrutinib	11	10	9	2	0	0
Non-MCD Ibrutinib	147	117	106	43	2	0
MCD Placebo	20	14	12	4	0	0
Non-MCD Placebo	157	114	100	41	4	0

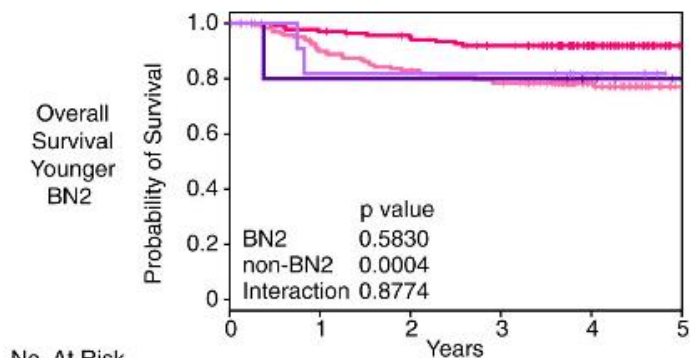


No. At Risk	0	1	2	3	4	5
MCD Ibrutinib	11	10	10	9	3	0
Non-MCD Ibrutinib	147	134	127	120	77	12
MCD Placebo	20	16	16	13	6	1
Non-MCD Placebo	157	134	119	113	62	9

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

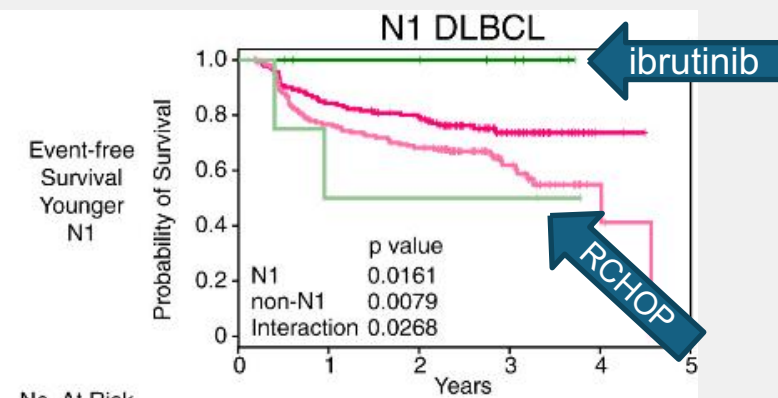


No. At Risk	0	1	2	3	4	5
BN2 Ibrutinib	10	7	7	2	0	0
Non-BN2 Ibrutinib	146	118	106	43	2	0
BN2 Placebo	11	9	9	4	0	0
Non-BN2 Placebo	168	121	105	43	4	0

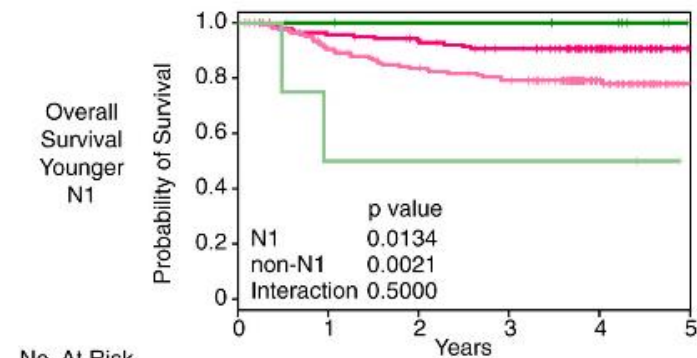


No. At Risk	0	1	2	3	4	5
BN2 Ibrutinib	10	8	8	8	4	1
Non-BN2 Ibrutinib	146	134	127	119	75	11
BN2 Placebo	11	9	9	9	5	0
Non-BN2 Placebo	168	143	128	119	65	10

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



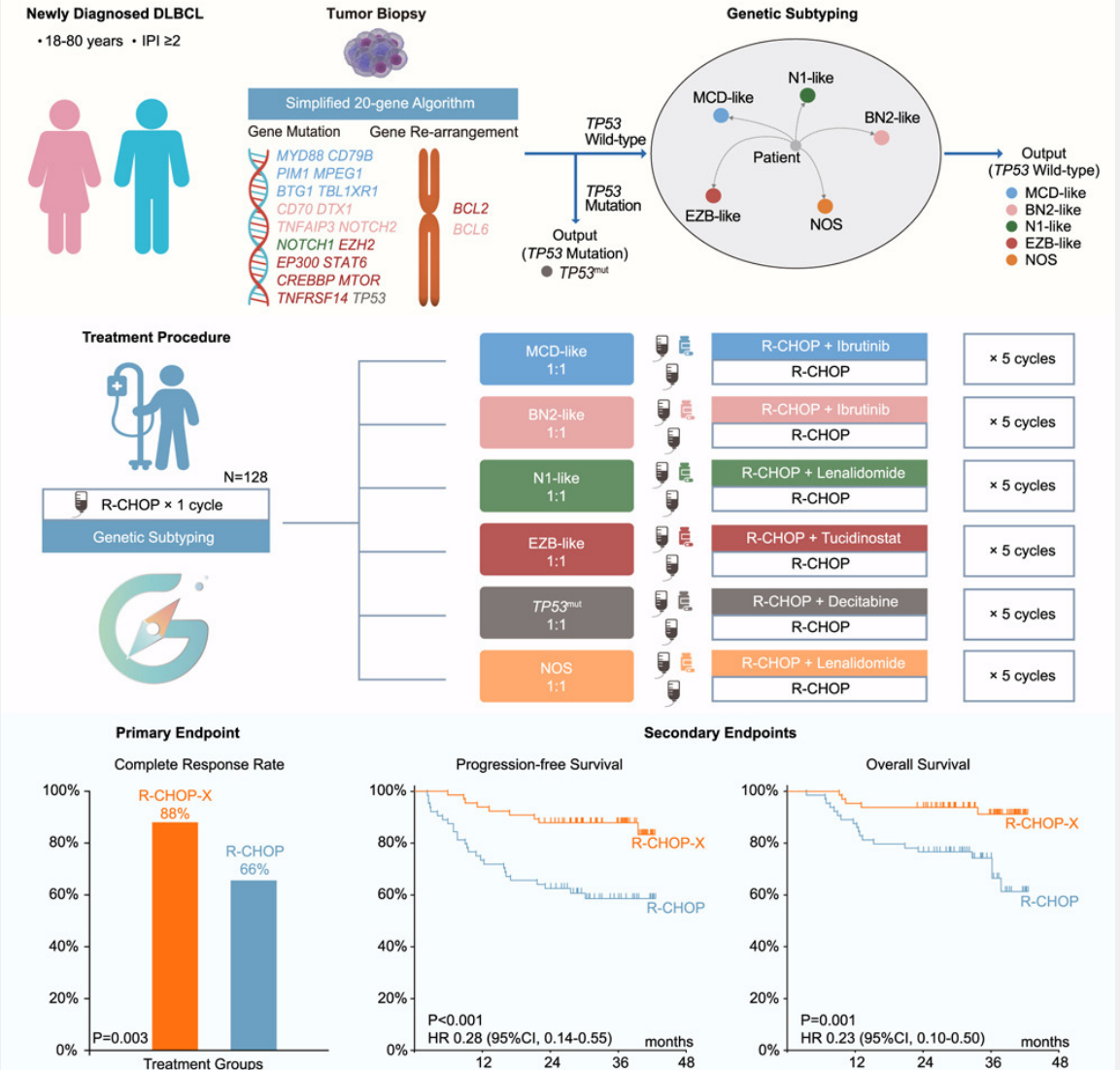
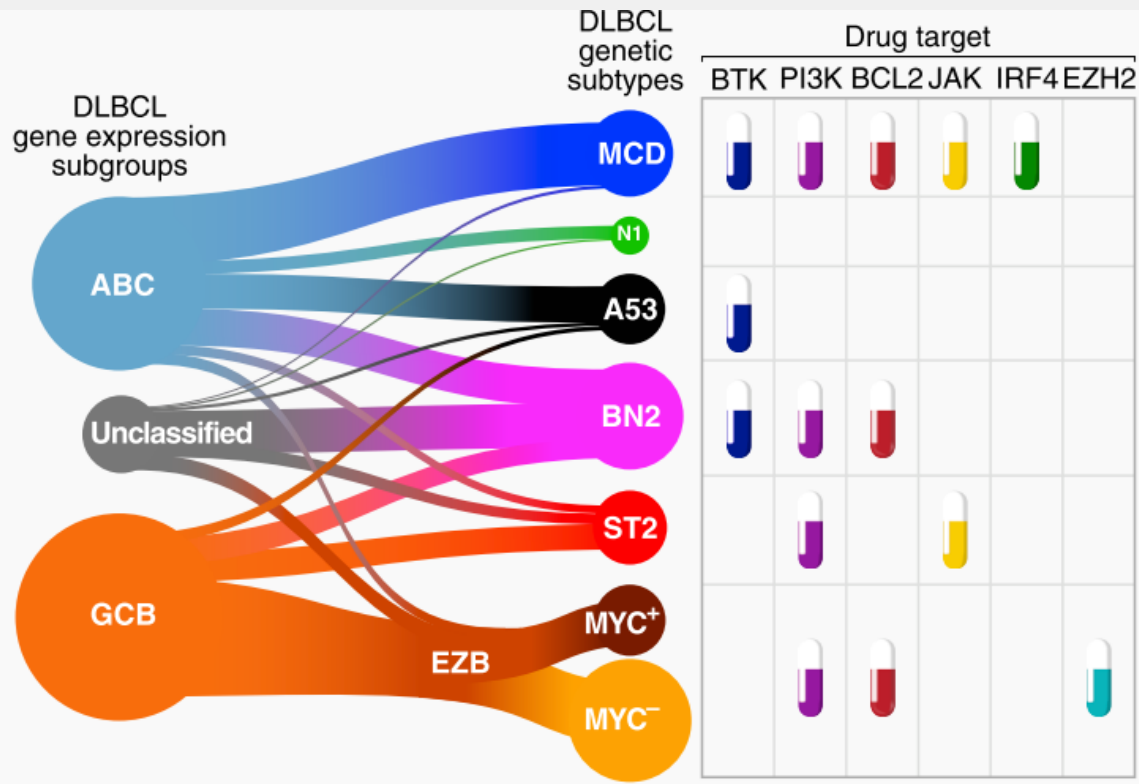
No. At Risk	0	1	2	3	4	5
N1 Ibrutinib	9	7	7	5	0	0
Non-N1 Ibrutinib	148	119	107	41	2	0
N1 Placebo	4	2	2	2	0	0
Non-N1 Placebo	174	127	111	43	4	0



No. At Risk	0	1	2	3	4	5
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

Matching genomic subtype to targeted drug

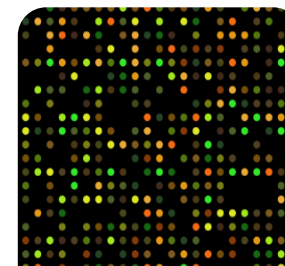
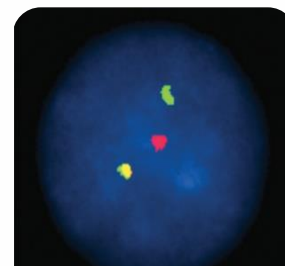
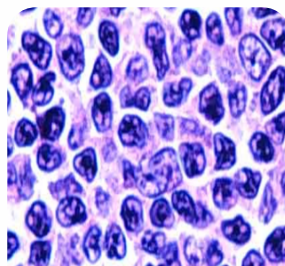


What to order?

How to interpret?

How does it change treatment in 2026?

Do not order!
 (unless you feel confident about interpreting)



Standard

Experimental

COO by IHC

- CD10
- BCL6
- MUM1
- **Not accurate!**
- **Does NOT change treatment** 👍👎

FISH

- Essential to detect HGBL
- **MYC**
- *Optional:* BCL2::IGH, BCL6

GEP

- **Nanostring**
- Confirm PMBCL
- Confirm molecular DZsig

NGS

- Currently limited use
- **DOES NOT CHANGE 1L TREATMENT** in 2026
- Confirm **C5:** IVLBCL, PCLBCL (leg-type), Extranodal

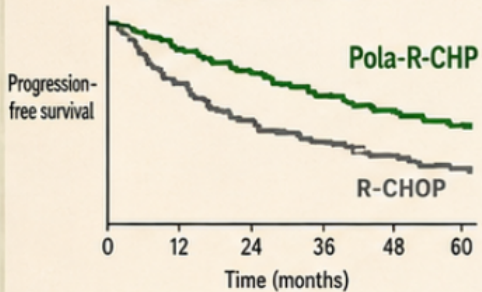
POLARIX ON TRIAL

A meaningful advance — or not yet the standard?

THE CASE FOR



PFS benefit



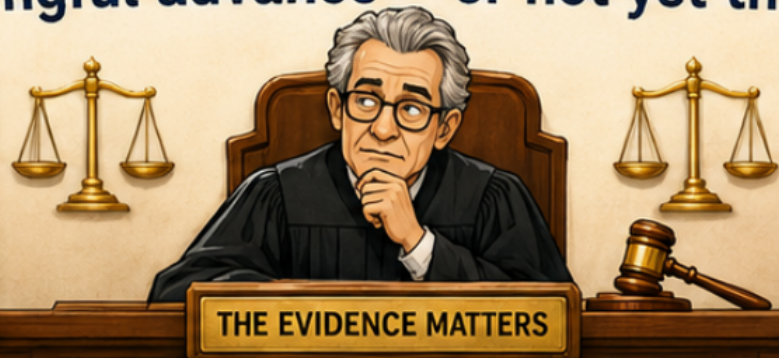
First positive frontline phase 3 signal in 20 years



Improved PFS



Could change practice



THE KEY QUESTION

COO CONTROVERSY

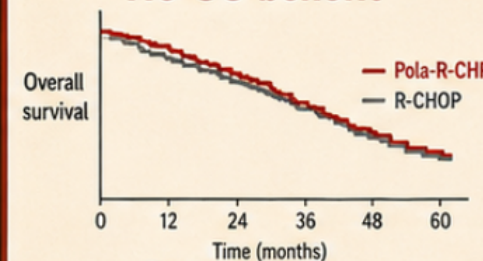


Does benefit depend on cell of origin?

THE CASE AGAINST



No OS benefit



No overall survival difference



Higher acquisition cost



Unclear value for all patients



HIGHER COST

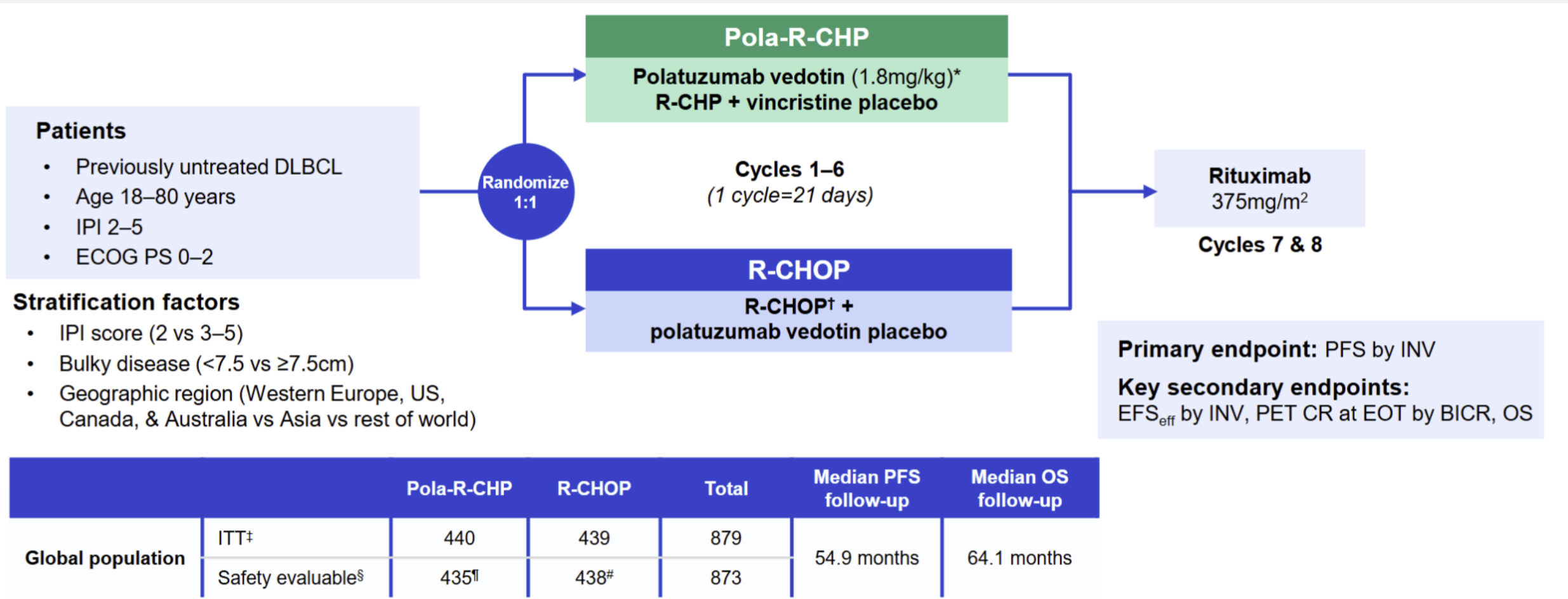


VERDICT: Important advance, but still controversial.

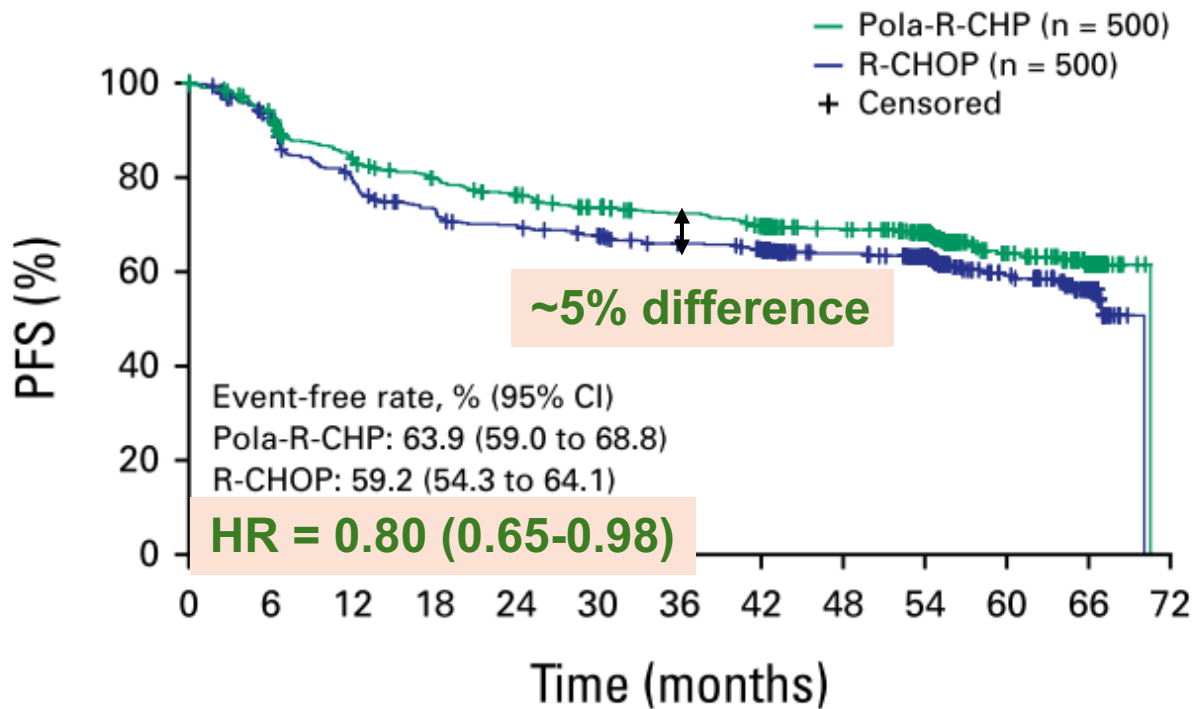
PFS WIN • NO OS GAIN • COO UNCERTAINTY



POLARIX: 5 year follow up



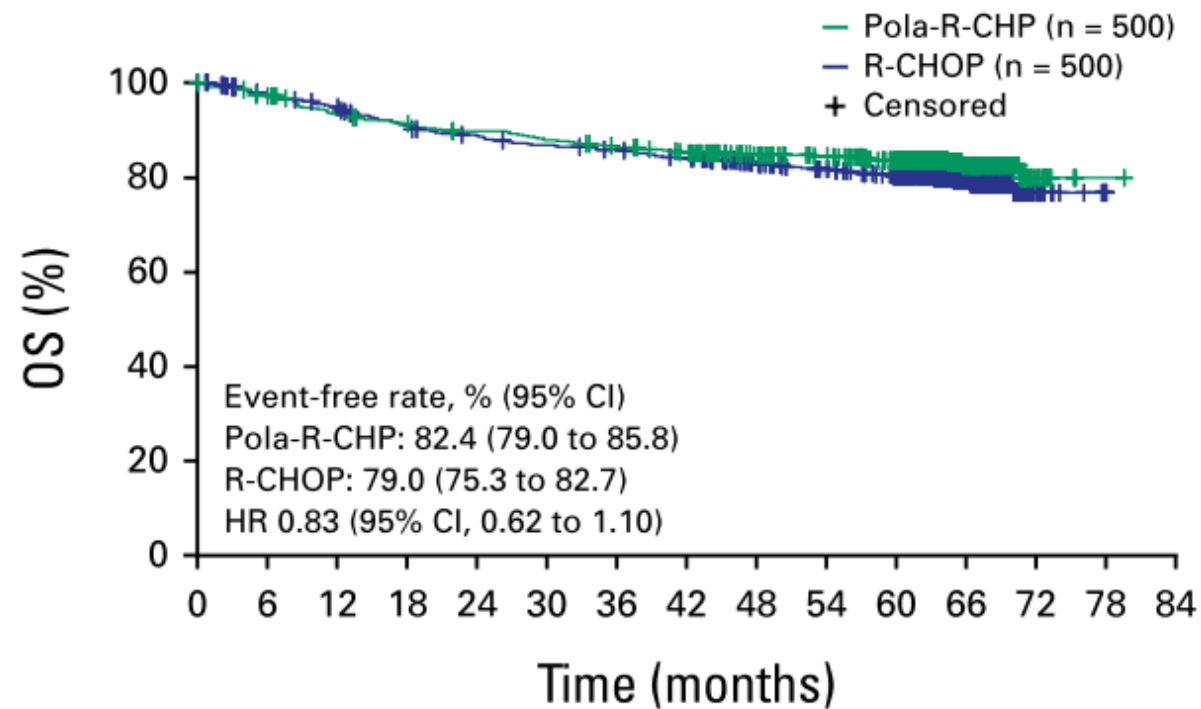
NNT = 20



Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72
Pola-R-CHP	500	463	404	378	357	337	322	305	270	224	100	56	NE
R-CHOP	500	445	379	344	326	312	294	284	249	201	95	54	NE

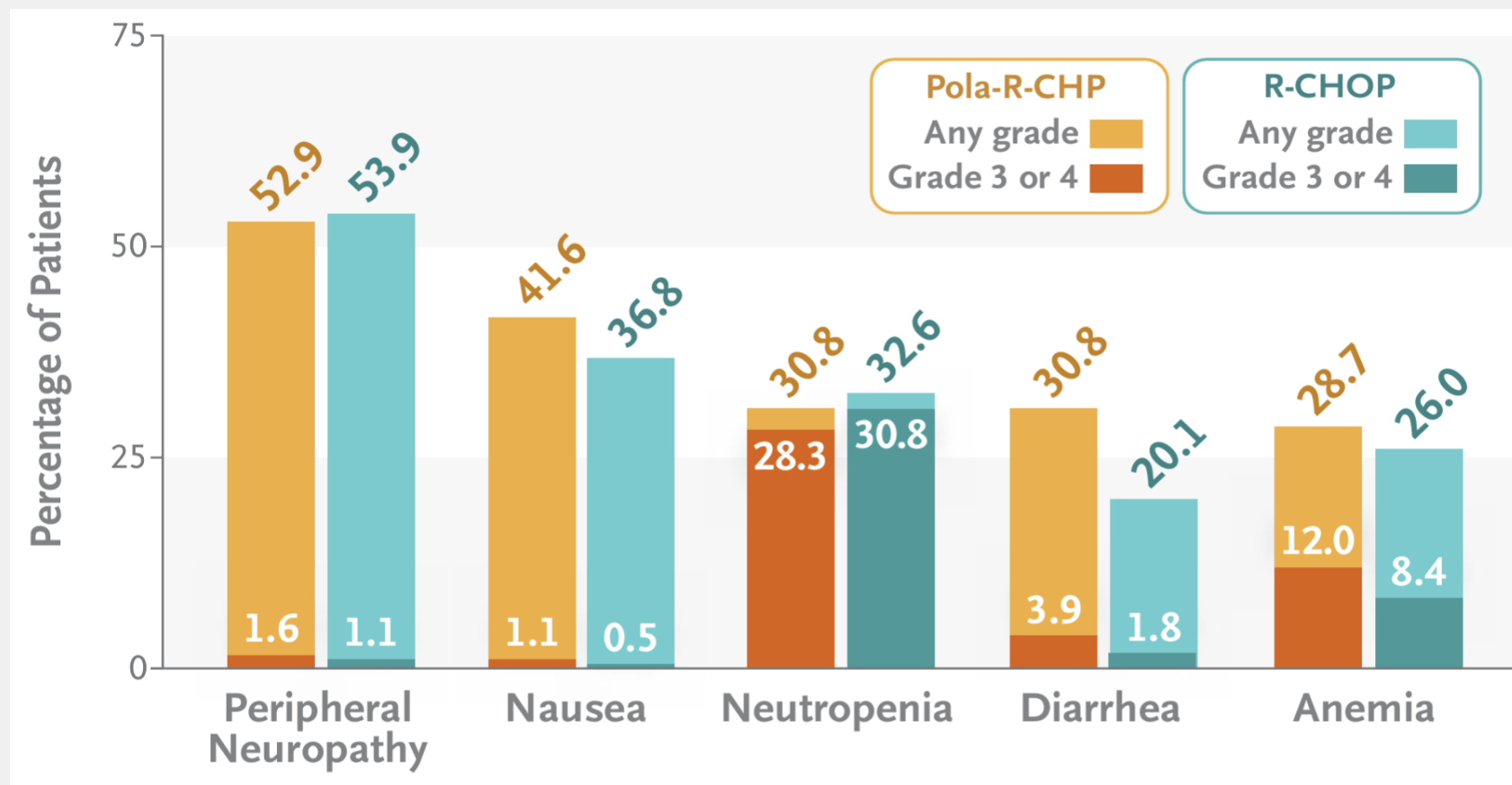
No difference in OS



Number at risk

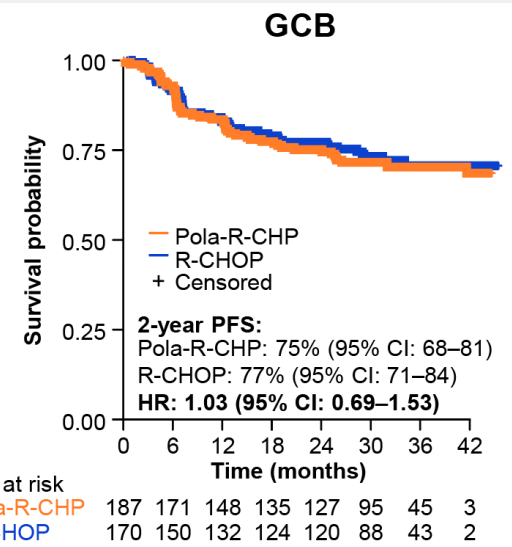
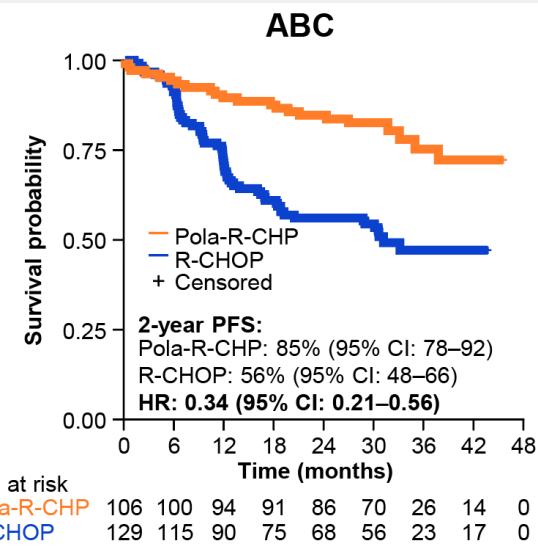
	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Pola-R-CHP	500	482	456	444	433	423	413	400	370	354	319	124	12	1	NE
R-CHOP	500	473	458	433	419	408	401	390	364	343	311	128	13	1	NE

- Similar toxicity profiles
- SAE: **34%** (Pola-RCHP) vs. **31%** (RCHOP)

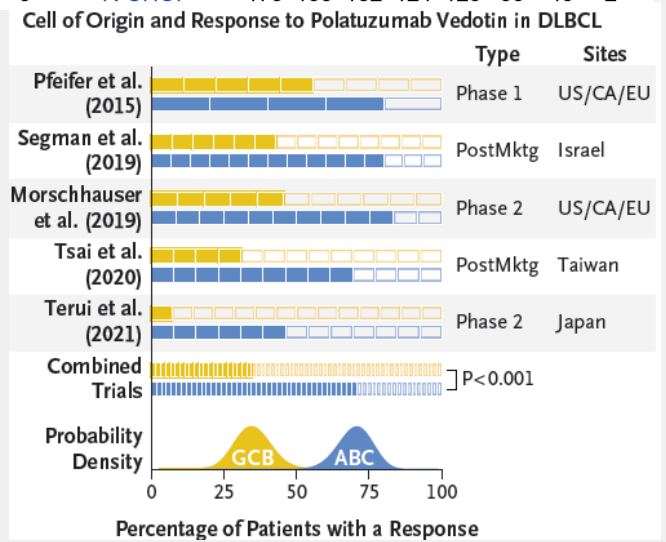


Baseline Risk Factors	Total N	Pola-R-CHP (N=440)		R-CHOP (N=439)		Hazard Ratio	95% Wald CI	Pola-R-CHP Better	R-CHOP Better
		n	2-year Rate	n	2-year Rate				
Age group									
≤60	271	140	74.1	131	71.9	0.9	(0.6 to 1.5)		
>60	608	300	77.9	308	69.5	0.7	(0.5 to 0.9)		
Sex									
Male	473	239	75.9	234	65.9	0.7	(0.5 to 0.9)		
Female	406	201	77.7	205	75.2	0.9	(0.6 to 1.4)		
ECOG PS									
0-1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)		
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)		
IPI score									
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)		
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)		
Bulky disease									
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)		
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)		
Geographic region									
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0.6 to 1.1)		
Asia	160	81	74.3	79	65.6	0.6	(0.4 to 1.5)		
Rest of world	116	57	70.8	59	67.3	0.9	(0.6 to 1.5)		
Ann Arbor stage									
I-II	99	47	89.1	52	85.5	0.6	(0.2 to 1.8)		
III	232	124	80.7	108	73.6	0.8	(0.5 to 1.3)		
IV	548	269	72.6	279	66.1	0.8	(0.6 to 1.1)		
Baseline LDH									
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)		
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)		
No. of extranodal									
0-1									
≥2									
Cell-of-origin									
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)		
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)		
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)		
Unknown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)		
Double expressor by IHC									
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)		
Non DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)		
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)		
Double- or triple-hit lymphoma									
Yes	45	26	69.0	19	88.9	3.8	(0.8 to 17.6)		
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)		
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)		

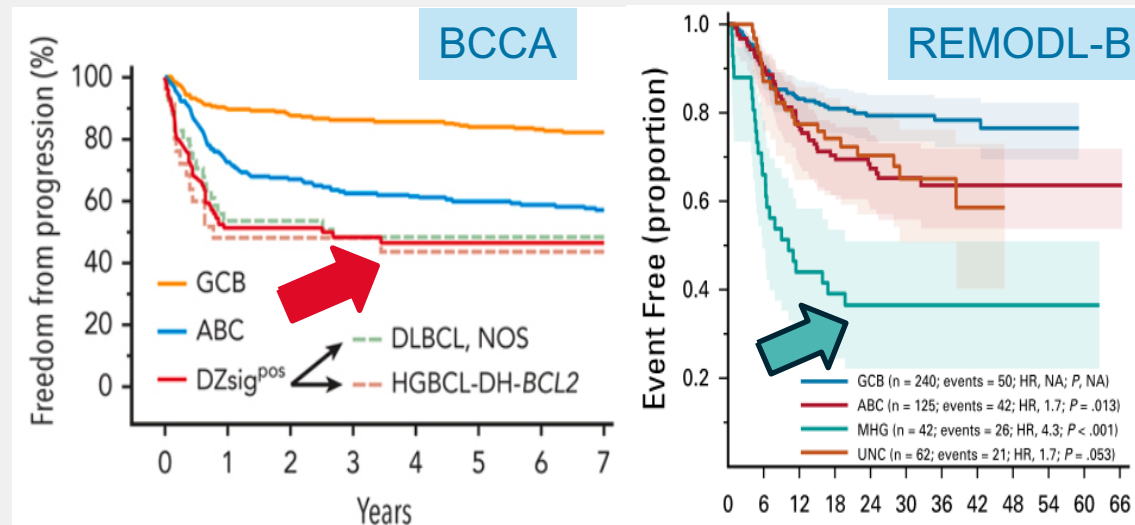
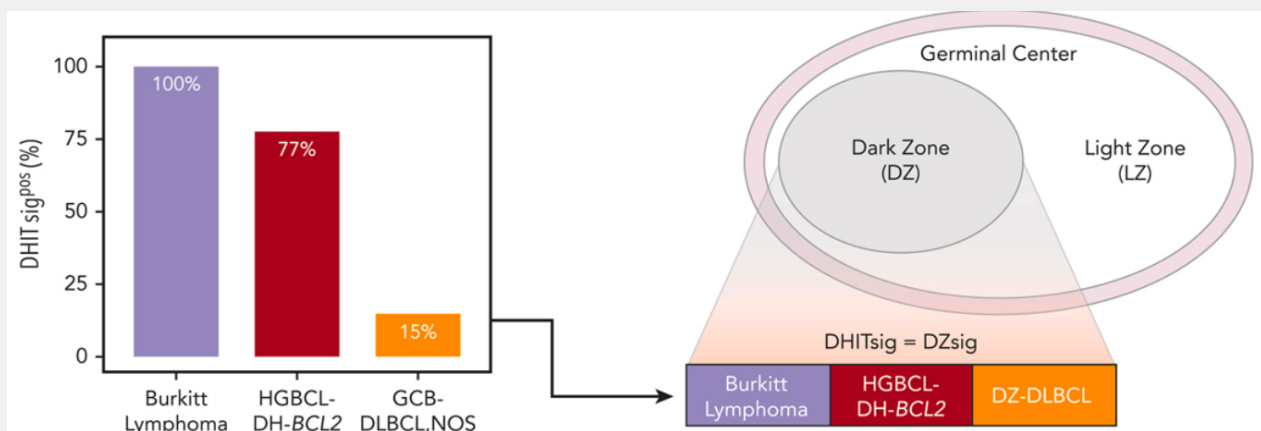
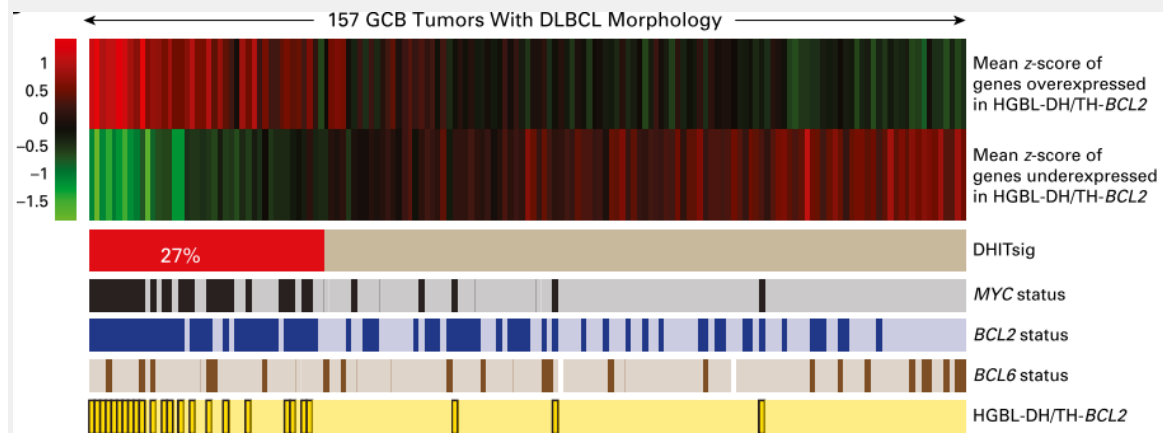
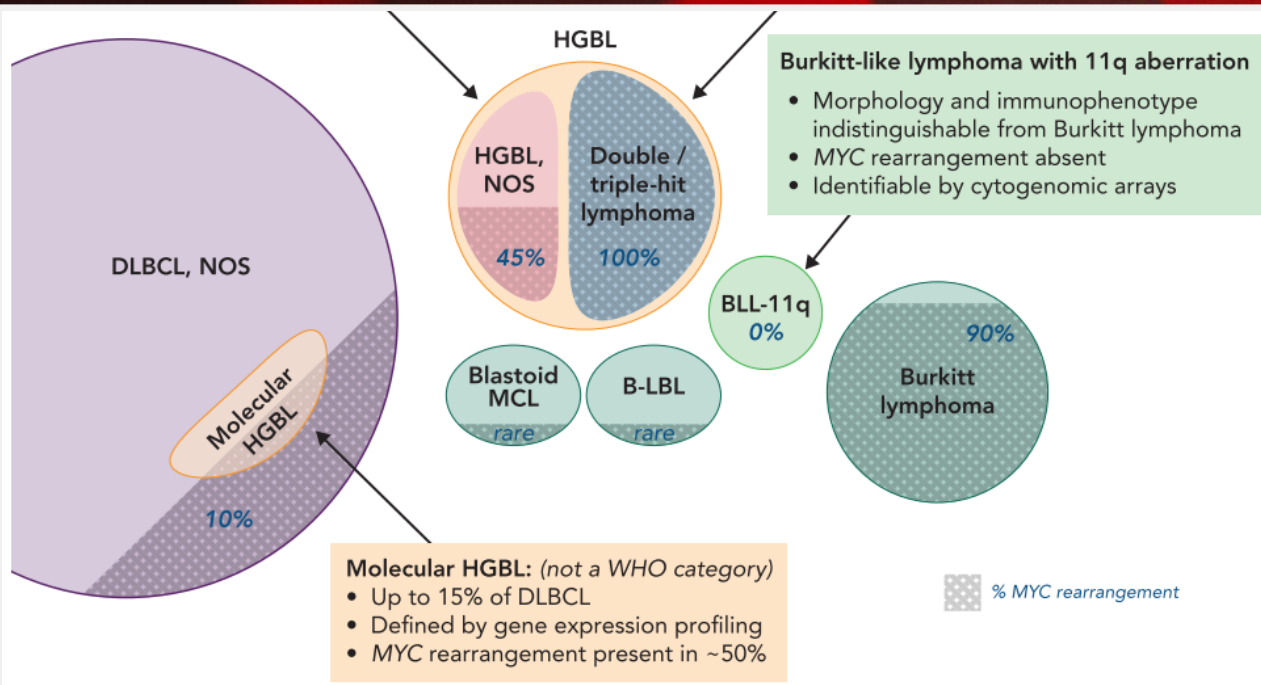
Differential effect by COO?



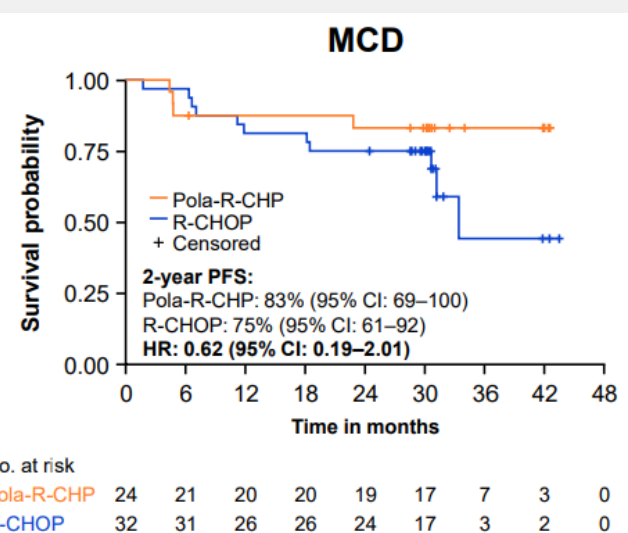
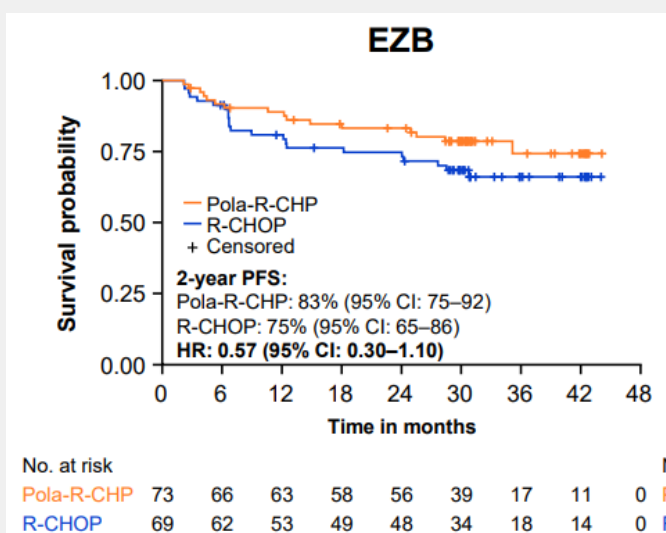
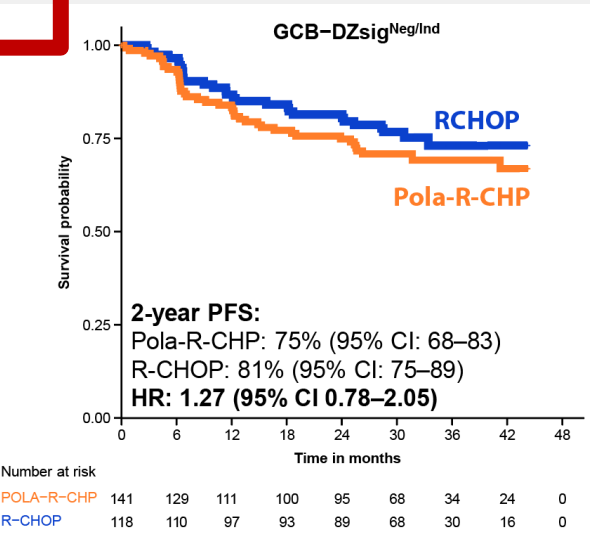
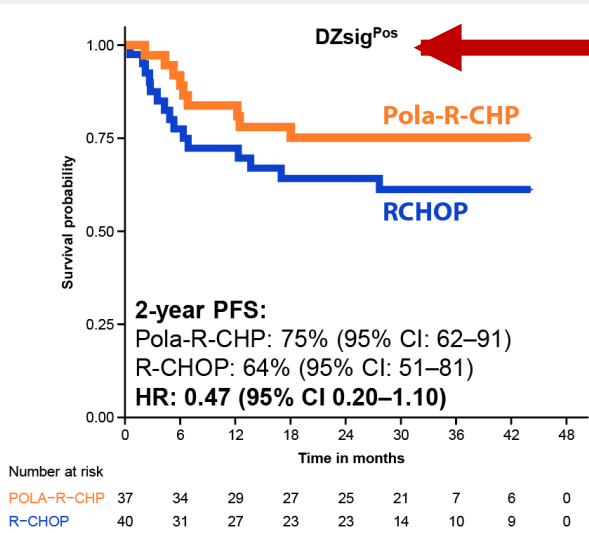
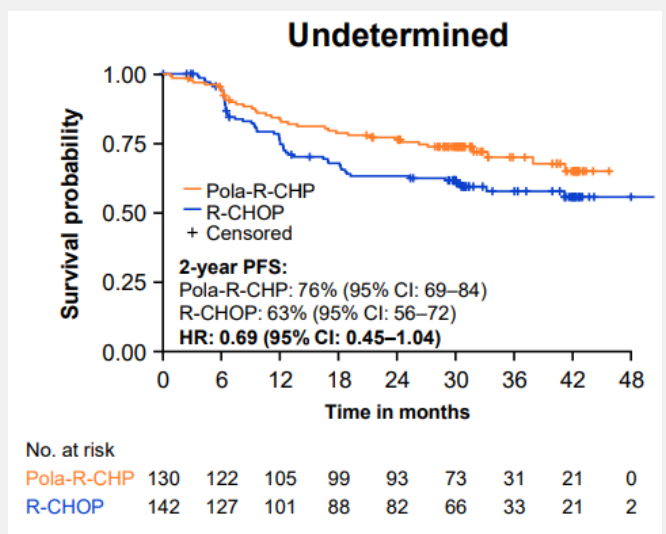
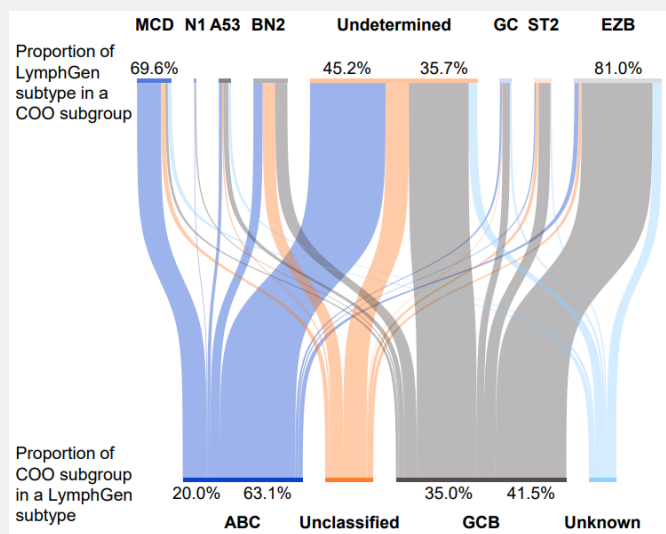
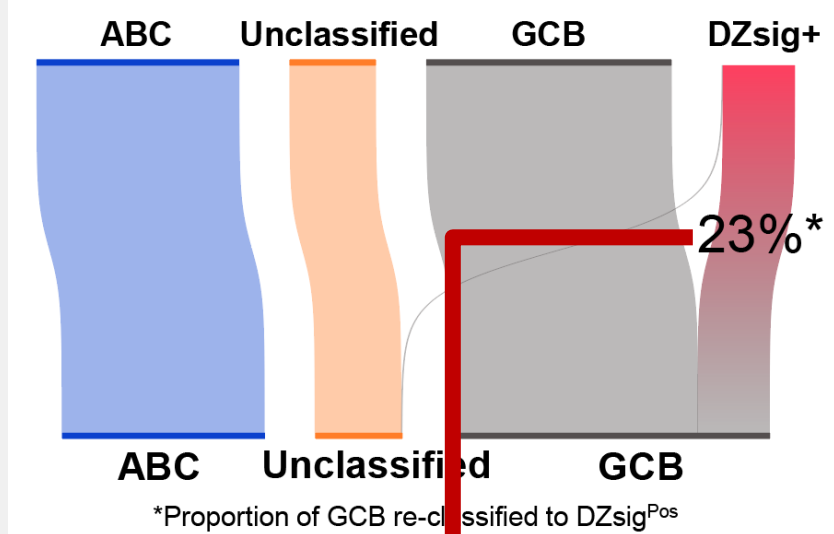
Responses to polatuzumab vedotin are more common in ABC-DLBCL



15% of GCB-DLBCL share GEP with HGBL

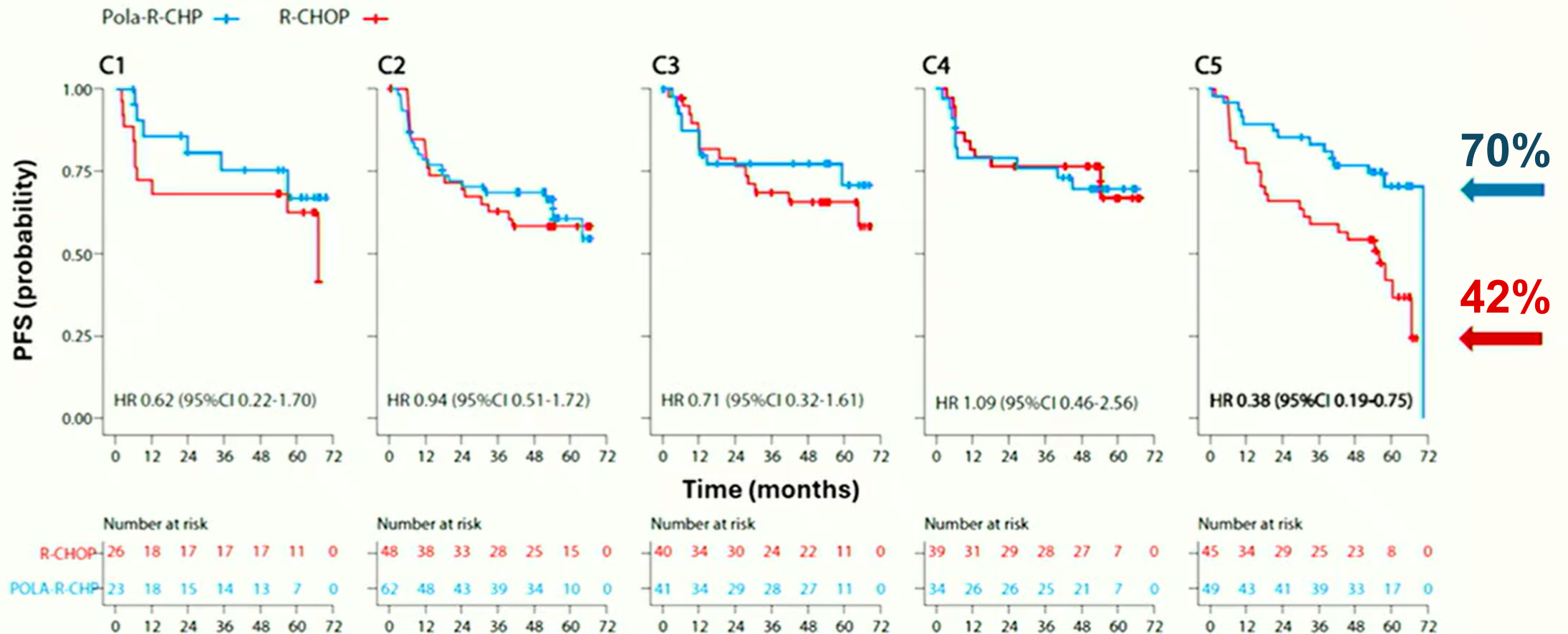


Dark-zone sig+ DLBCL in POLARIX



Genomic subtypes in POLARIX

Benefit of Pola-R-CHP in Patients with Cluster 5 DLBCLs



Pola-RCHP:

- **High benefit in ABC-DLBCL** – particularly in **MCD-DLBCL**,
- **Equivalent** in GCB-DLBCL
- Potential **benefit for DZSig+** GCB DLBCL
- Ultimately:
 - COO would need to be determined by **GEP not IHC**
 - No evident harm of giving it to “everybody”, and no survival detriment to giving RCHOP to everybody
 - No overall survival benefit
 - Possibly higher risk of febrile neutropenia and PJP events in older patients – but deliverable as R-mini-PolaRCHP
 - High cost vs. cost of 2nd-line CAR T-cell

~ **\$70,000** per QALY gained
Drug costs:

- Pola-R-CHP: **\$122,525**
- RCHOP: **\$27,692**
- *“appears cost-effective”*

~ **\$546,956** ICER for Pola-RCHP
~ **\$309,813** ICER for CAR-T

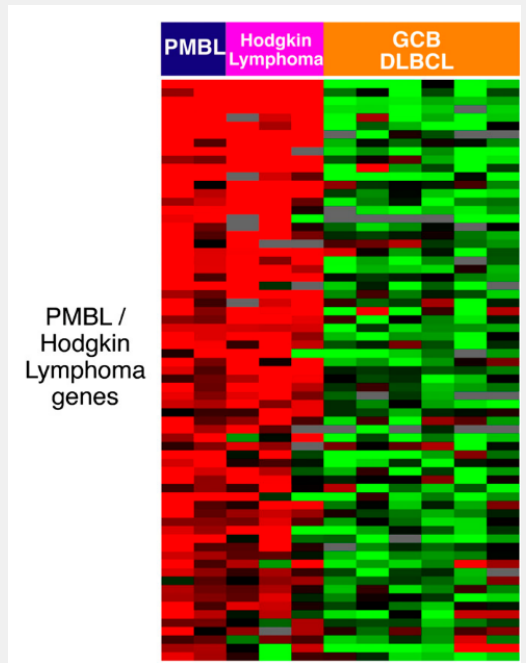
- *“not cost effective”*

~ **\$84,308** per QALY gained

- *“cost effective, but highly dependent on cost of CAR T-cell therapy”*

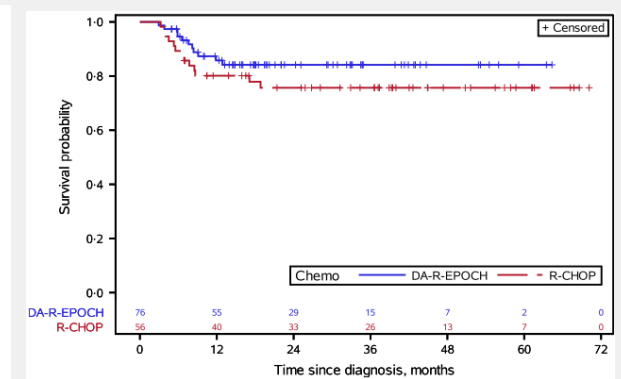
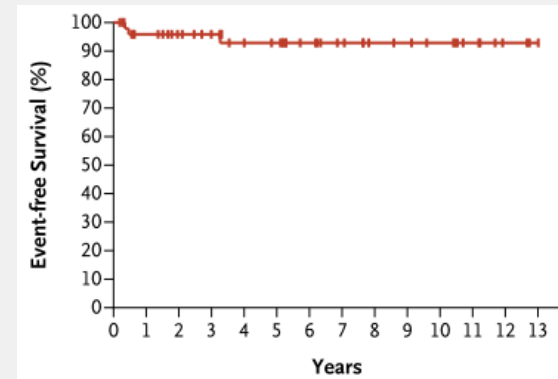
Special case: PMBCL

- Often young women
- Large, life-threatening tumors
- Non-GCB, CD30+, PD-L1/2+
- GEP resembles Hodgkin lymphoma

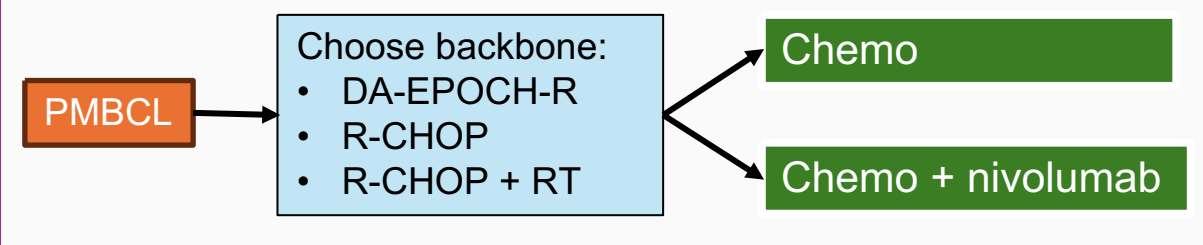


DA-EPOCH-R:

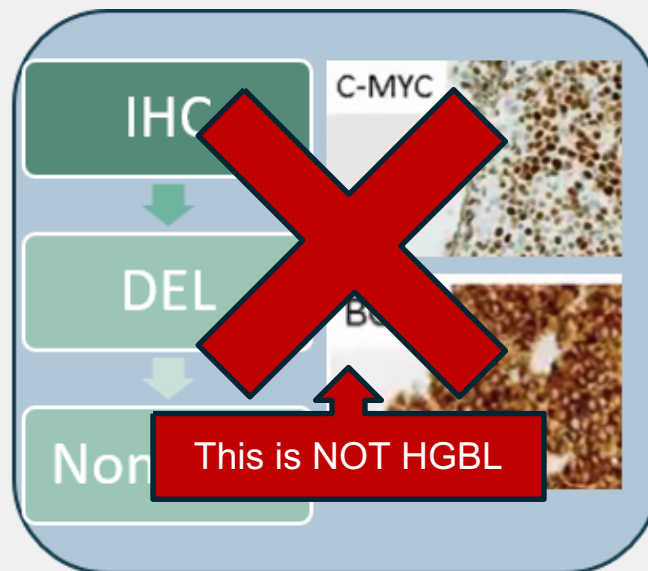
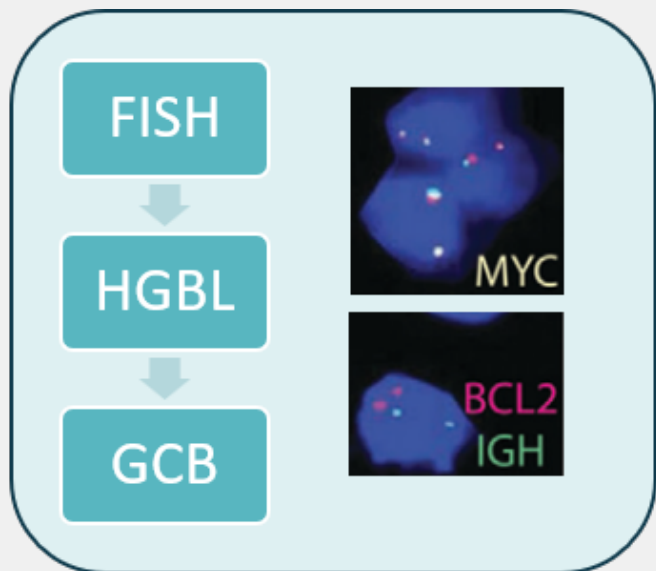
- No randomized data
- Real-world – not as good
- Omits radiation therapy



ANHL1931

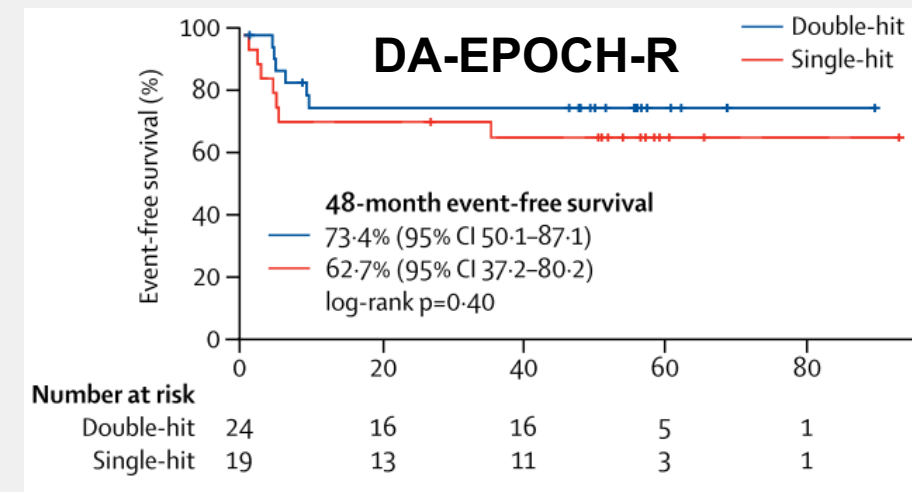


- Double-hit lymphoma: **MYC-R** and **BCL2-R**
- HGBL, NOS: only 50% MYC-R
- Essentially always GCB
- Shares GEP with Burkitt lymphoma (DZSig+)
- This is **NOT** “double expressor”

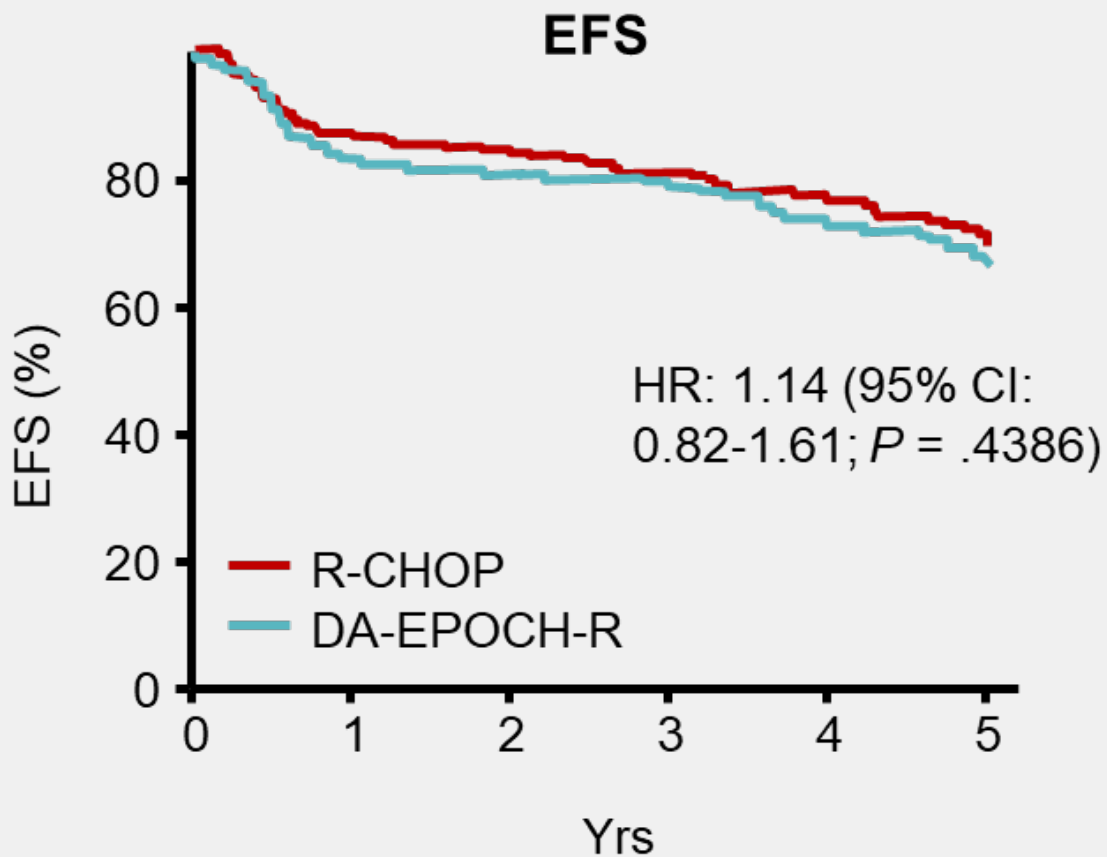


DA-EPOCH-R:

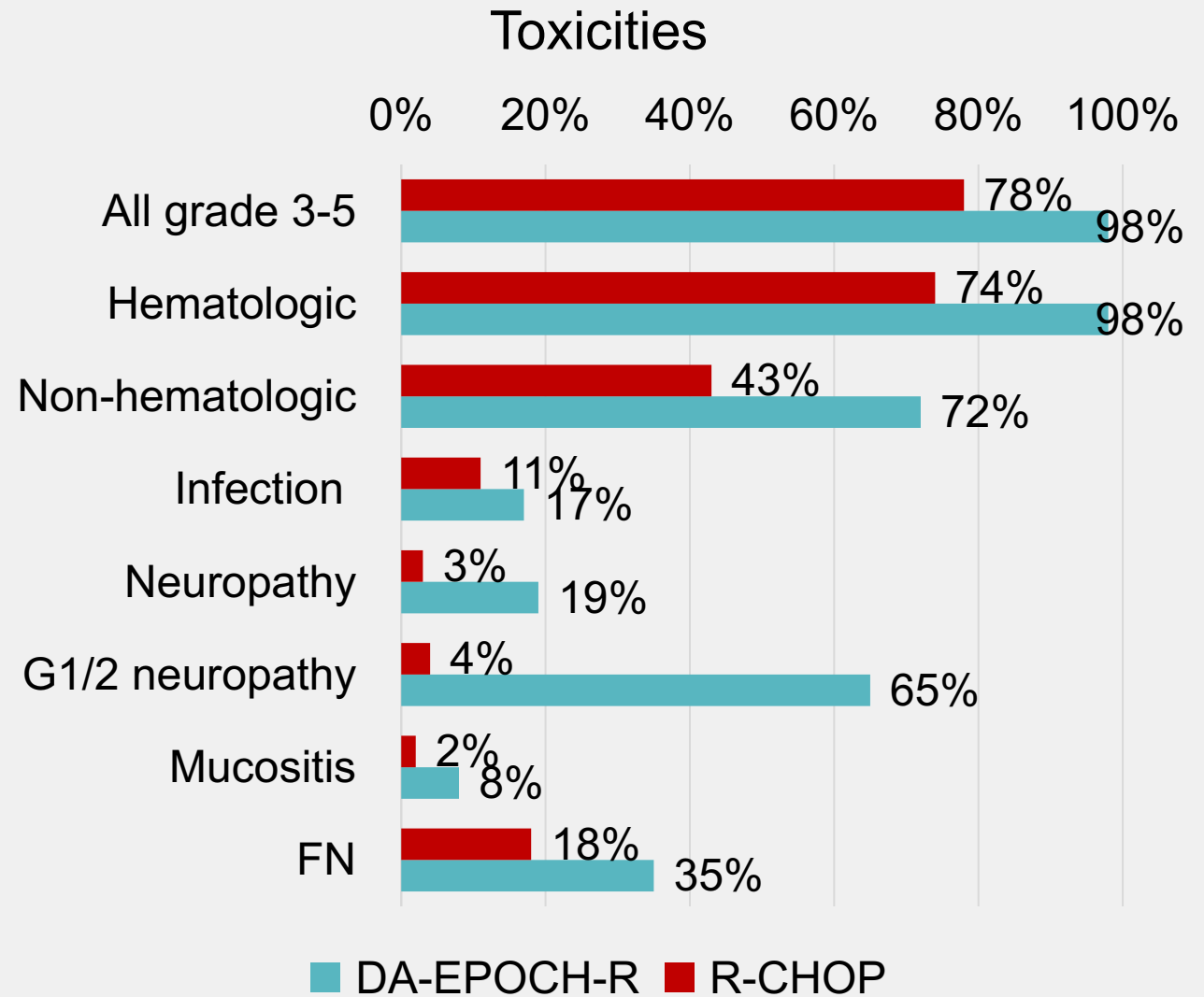
- Effective in Burkitt lymphoma
- **No randomized data**
- Uncertain if better than **Pola-R-CHP**



DA-EPOCH-R should NOT be used for DLBCL



Arm	N	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	0.79 (0.73-0.84)	0.66 (0.59-0.72)



POLARIX criteria
IPI ≥ 2

- **Pola-RCHP**
- Early-stage: **R-CHOP x4**
- tFL / G3B FL: **R-CHOP**
- tCLL/MZL: **Pola-RCHP**

HGBL with
MYC/BCL2 rear.
PMBCL

- **DA-EPOCH-R**

CNS involvement

- **MCD**: MATRiX with ASCT or R-CHOP+HDMTX
- **HGBL**: R-CODOX-M/IVAC

Unfit / frail

- **Pola-R-miniCHP**
- **Pola-R**



CHAOTIC ERA

— IS COMING —

Personalized therapy

Umbrella trials:
genomic subtypes

Subtype-specific
trials (MCD, HGBL)

Depersonalized immunotherapy

RCHOP/PolaRCHP
+ BsAbs

MRD escalation
(CAR T cells)

Chemo-sparing strategies

Bispecific
combinations

Multi-targeted
regimens
(SMART-Start/Stop)

POLARIX:

- PFS benefit
- No OS / QOL benefit

frontMIND:

- RCHOP ± Tafasitamab + Len
- HR = 0.75 for PFS (P=0.019)

frontMIND: Phase 3 study of tafasitamab (Tafa) plus lenalidomide (Len) and R-CHOP for patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL).



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[Abstract](#)

The full, final text of this abstract will be available on May 30 at 08:00 AM EST.

SKYGLO: 2027

- Pola-R-CHP + glofitamab

ESCALADE: 2027

- R-CHOP + acalabrutinib (non-GCB)

waveline-010: 2029

- R-CHP + zilovetamab vedotin

GOLSEEK-1:

- R-CHOP + golcadomide

OLYMPIA-3:

- CHOP + odronextamab

EPCORE

DLBCL-2:

- RCHOP + Epcor

ZUMA-23:

- R-CHOP → Axi-cel

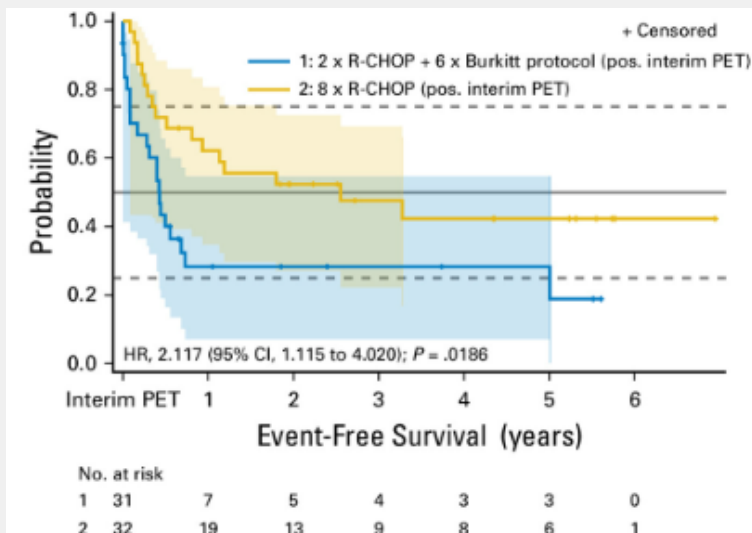
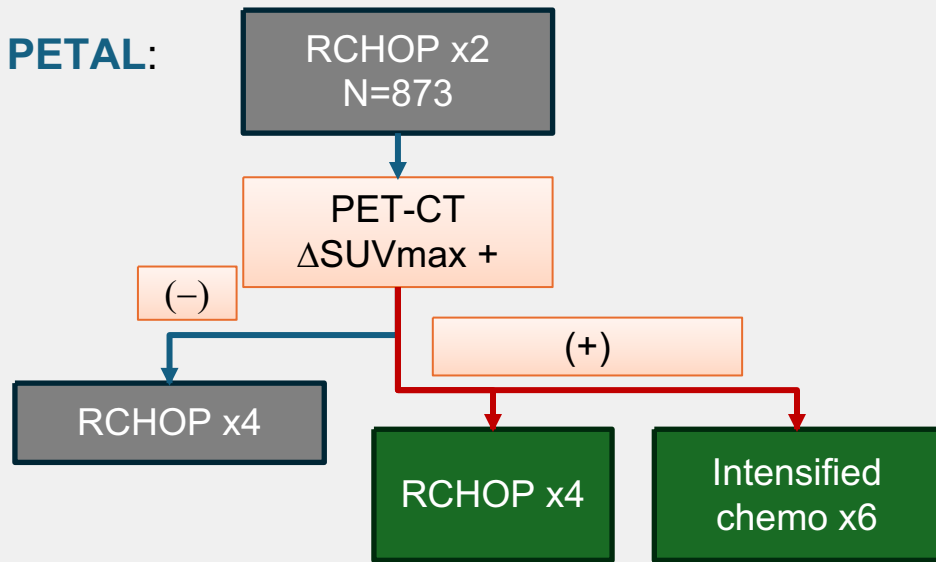
ALPHA3:

- R-CHOP → Cema-cel

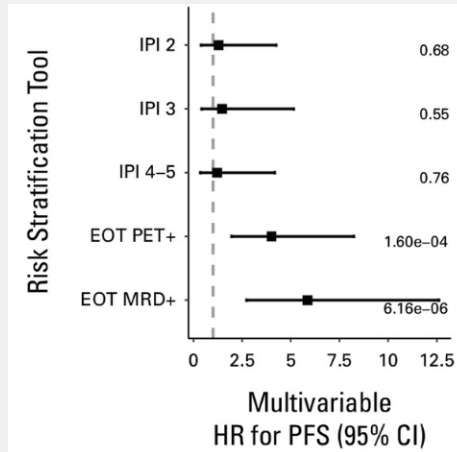
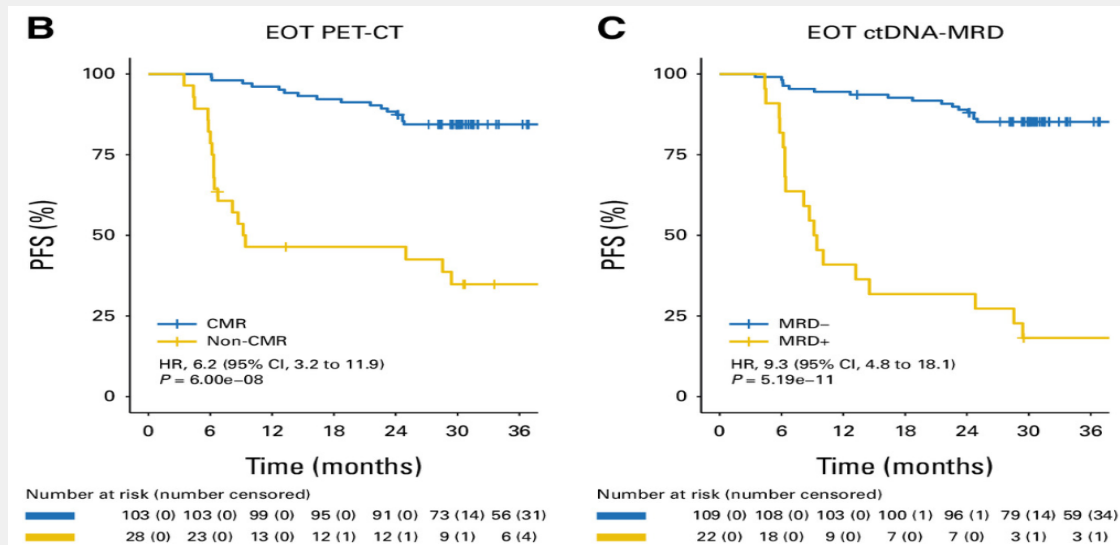
GUIDANCE-02

- R-CHOP + X
- NGS-driven

● **PETAL:**



● **HOVON-902:** 250 1L patients on RCHOP/EPOCH



clonoSEQ
By Adaptive

ID: FFPE tumor
(clonotype)

MRD: plasma

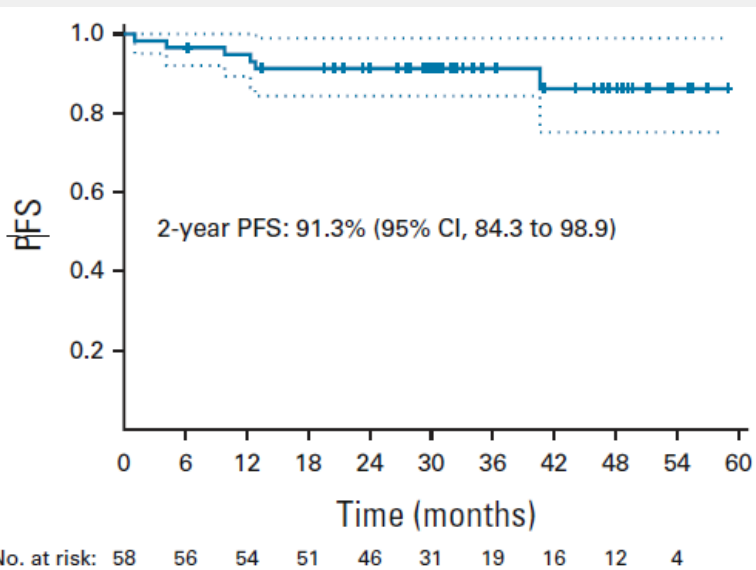
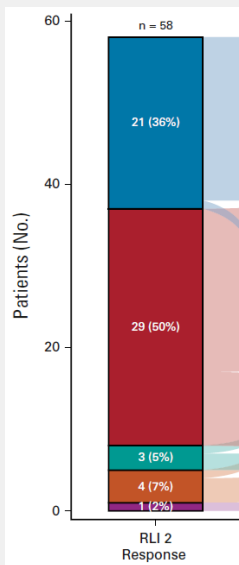
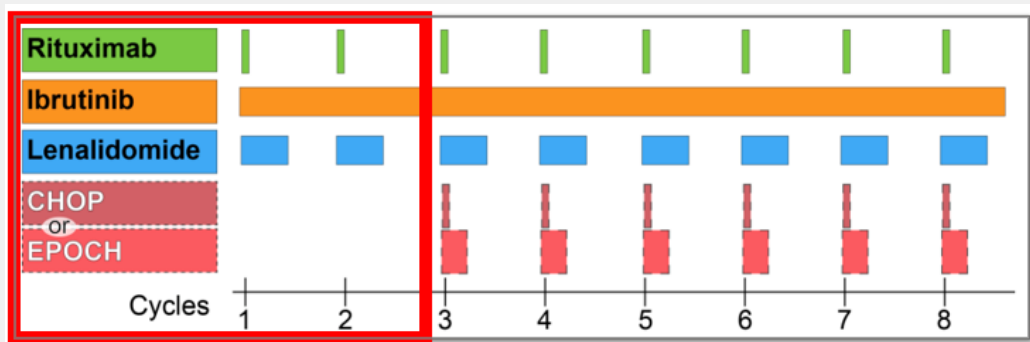
ID: tumor (WES)
+ germline
sample

(select SNV)

MRD: plasma

Do we need RCHOP?

Smart START

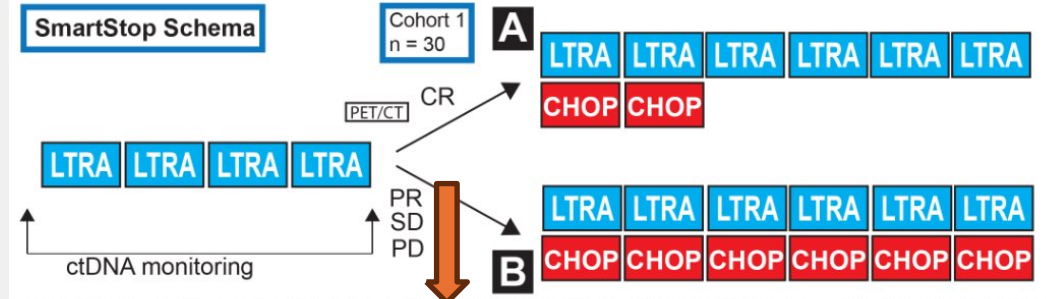


Smart STOP

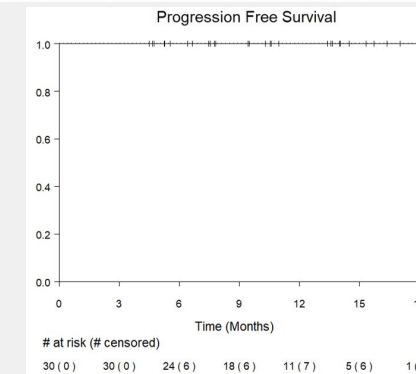
Doses of "Smart Start" portion of the clinical trial, cycle = 21 days

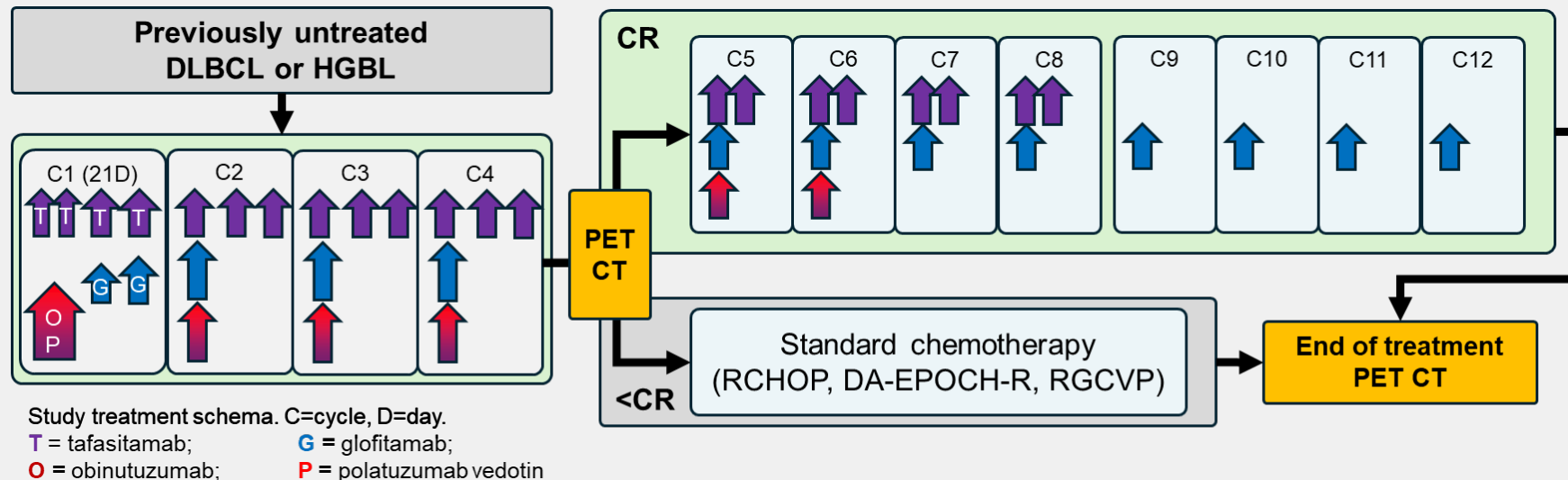
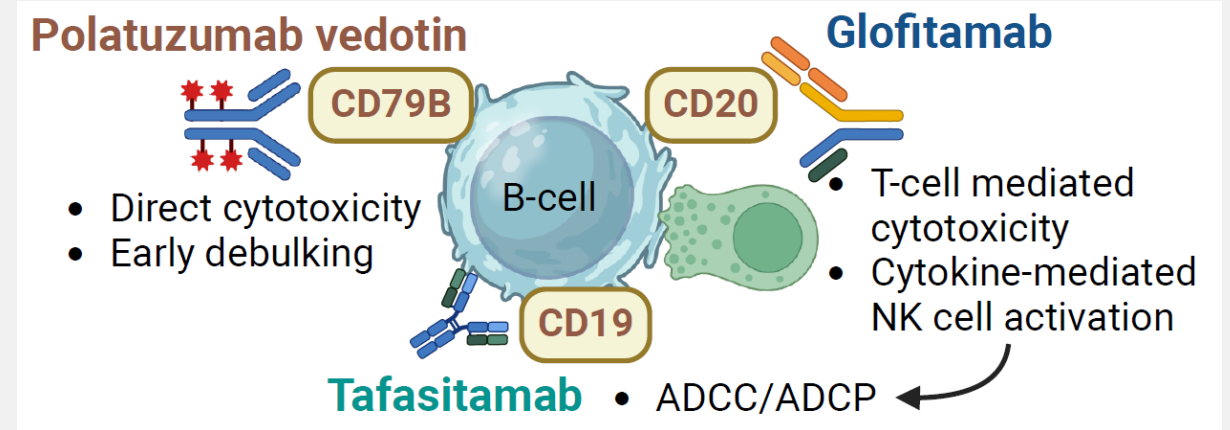
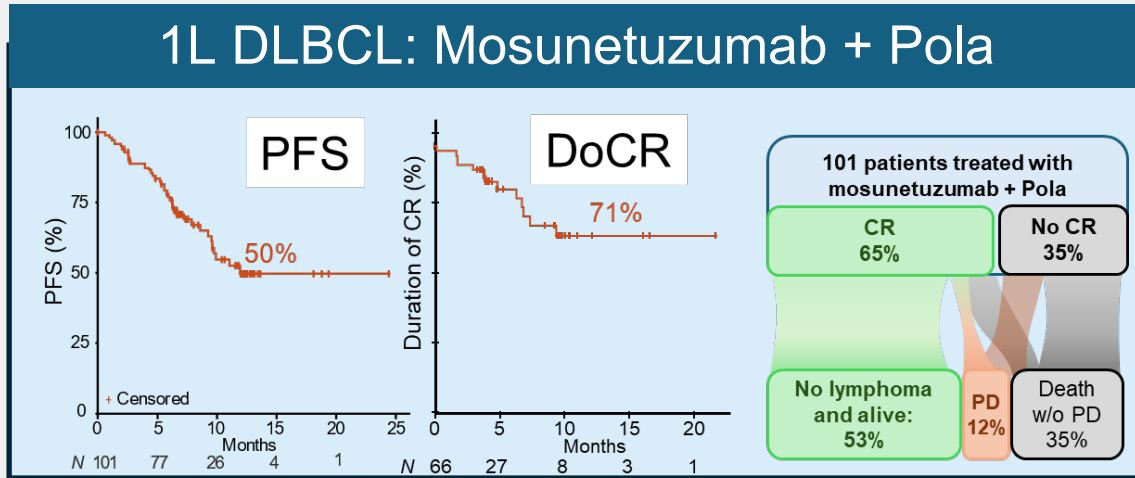
Drug Name	Dose	Route	Dosing per cycle	Day of therapy
Lenalidomide (L)	25mg	PO	Daily	1-10
Tafasitamab (T)	12mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375mg/m ²	IV	Once	1
Acalabrutinib (A)	100mg	PO	BID	1-21

SmartStop Schema



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





- DLBCL – multiple diseases but current 1L therapy still “depersonalized”
- Multiple new options beyond R-CHOP, no good selection criteria:
 - Pola-RCHP
 - Tafa-Len-RCHOP
 - Imminently: BsAbs + (R)CHOP/Pola-(R)CHP
- Which classification is **predictive** of treatment success?
 - Genomic → ongoing umbrella trials
 - TME → ASCO 2026: LymphoMAP in POLARIX
- Alternatives to RCHOP+X:
 - Escalation/de-escalation by MRD
 - Multi-targeted therapies
 - BsAb-based combinations

Thank you!

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