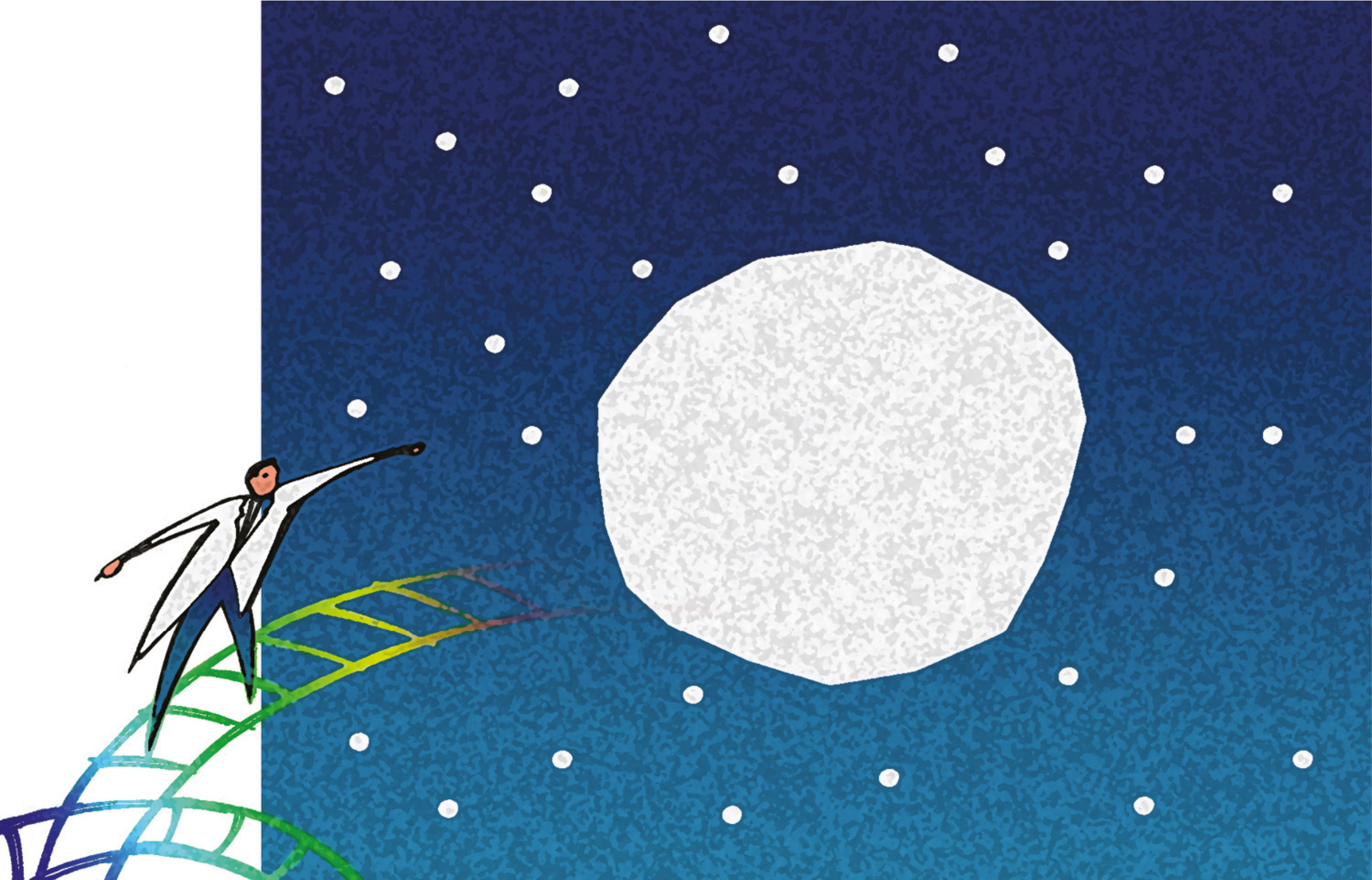




The young side of **LYMPHOMA**

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

Terapia di prima linea nel paziente giovane con DLBCL: presente e futuro

Mattia Novo

SC Ematologia

AOU Città della Salute e della Scienza di Torino



Disclosures of Mattia Novo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						x	x
BMS						x	x
Istituto Gentili						x	

Alvaro, ♂ 40 aa

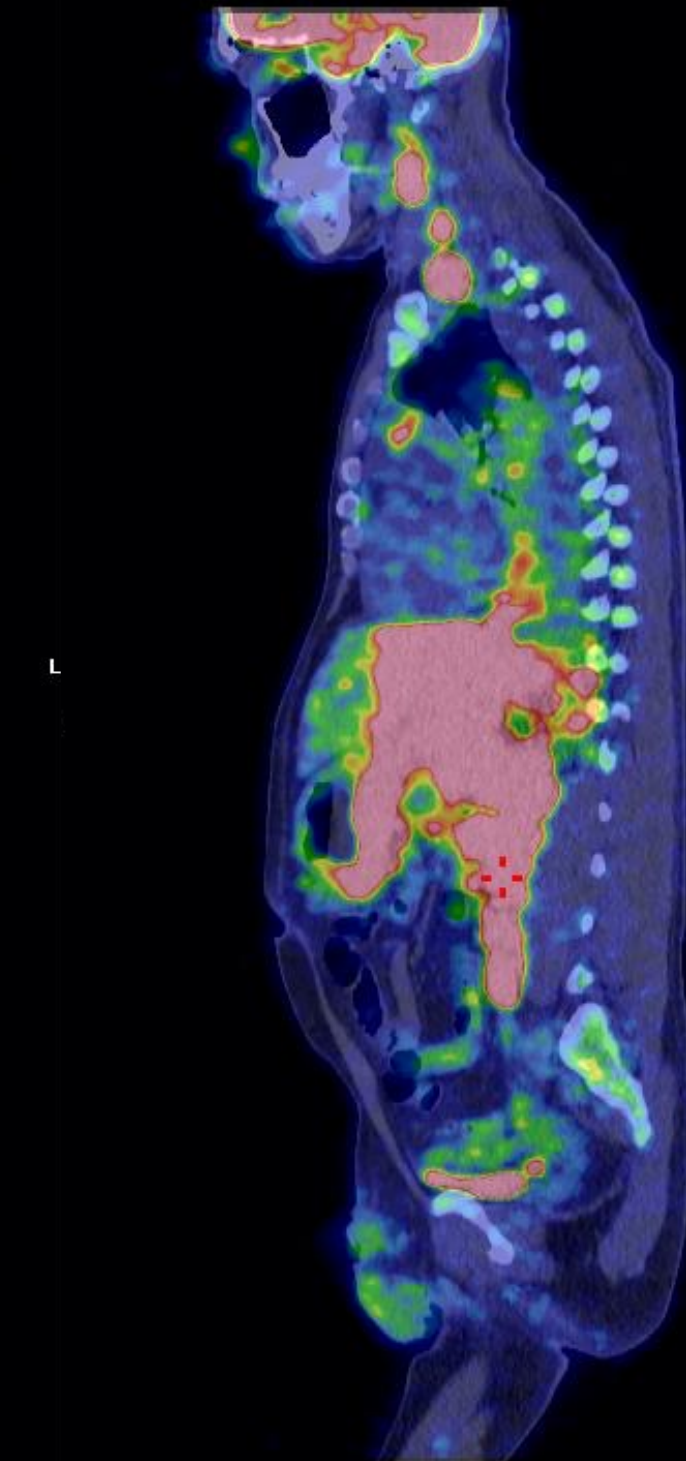
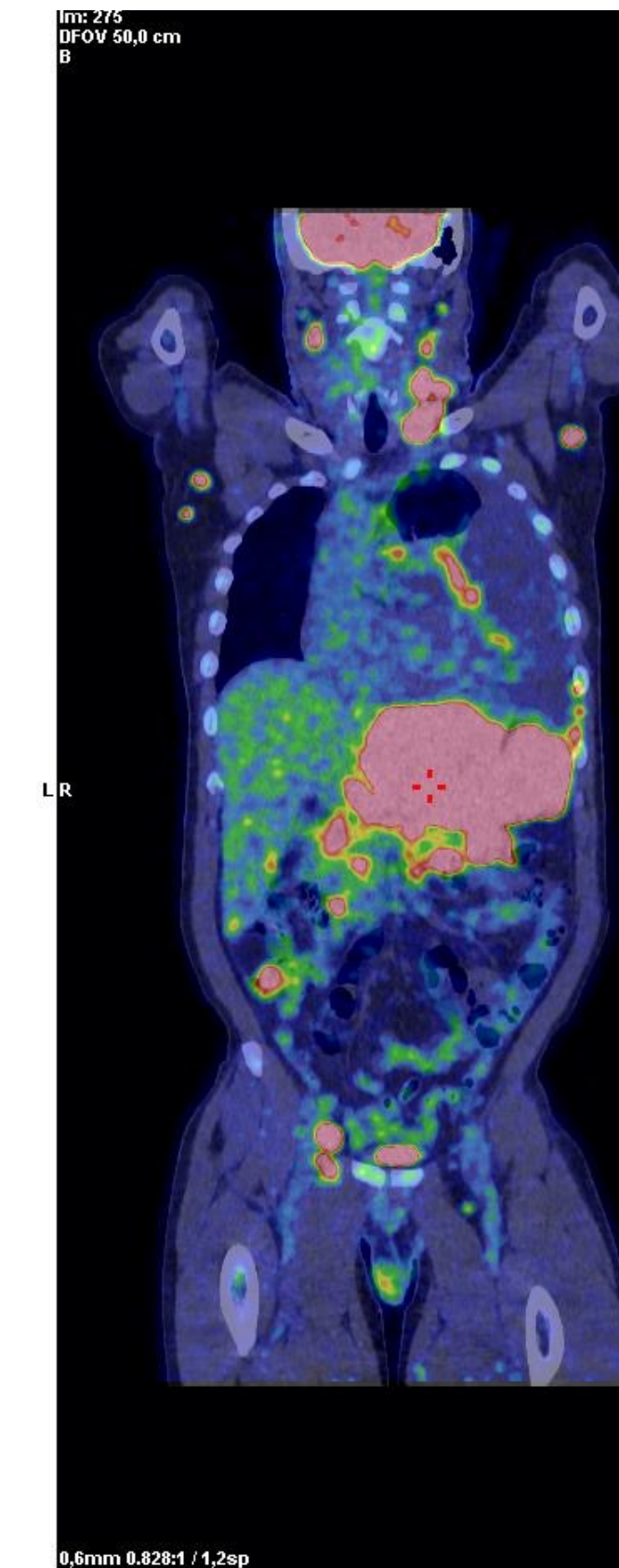
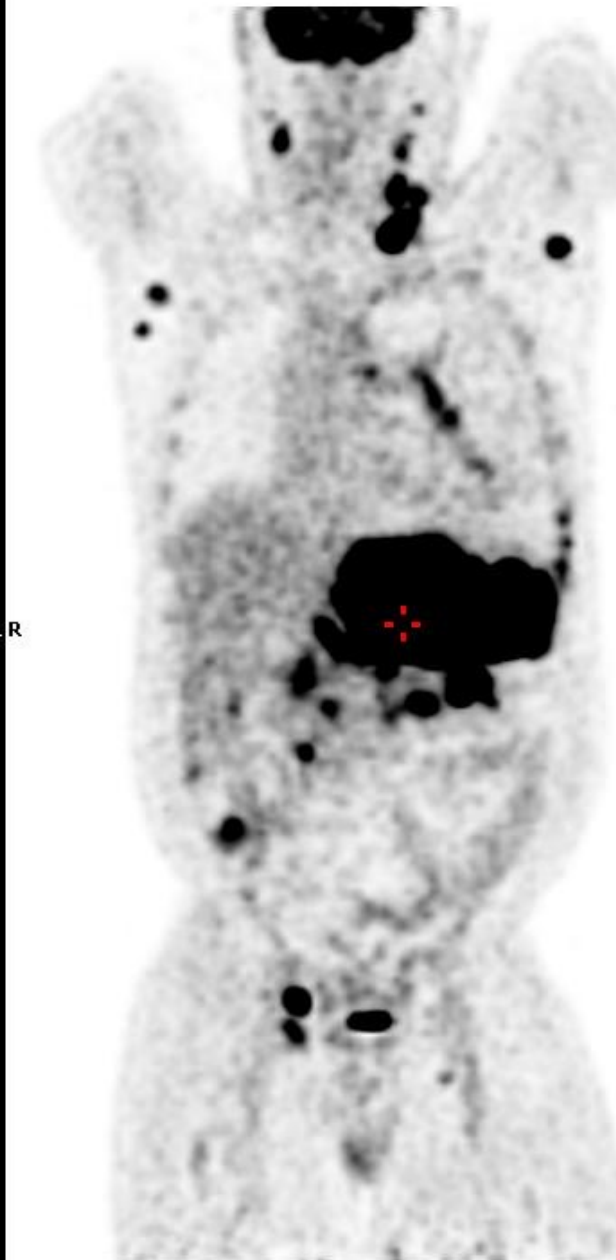
Anamnesi:

- Origini Filippine
- Fumatore (3-4 sigarette/die)
- no comorbidità

Giugno 2025

- Accesso in PS per dolore al fianco sn e febbre.
- EE: GB 9400/mmc, N 2150/mmc, Hb 12.2 g/dl, PLTs 612000/mmc, LDH 421 (ULN 245), creat 0.78 mg/dl

TC/PET: **adenopatie** laterocervicali (SUVmax 14.9), paratracheali, ascellari e mediastiniche (SUVmax 12.7), addominali, iliache e inguinali (SUVmax 13.1), **massivo versamento pleurico sn** con dislocazione **dell'aia cardiaca con captazione sul versante mediale** (SUVmax 6.2) di dubbia pertinenza (pleurica? Polmonare?), **captazione splenica** e coinvolgimento **peritoneale**, di **parete gastrica** e coinvolgimento di altri organi ipocondriaci tra cui **pancreas** e **surrene sn**



agobiopsia eco-guidata su linfonodo inguinale sn: linfoma Diffuso a grandi Cellule B a fenotipo non-GCB sec.
Hans, CD20+, CD10- BCL6+, MUM1+, BCL2 +, MYC 60%, MIB1 90%
FISH MYC neg, BCL2 pos

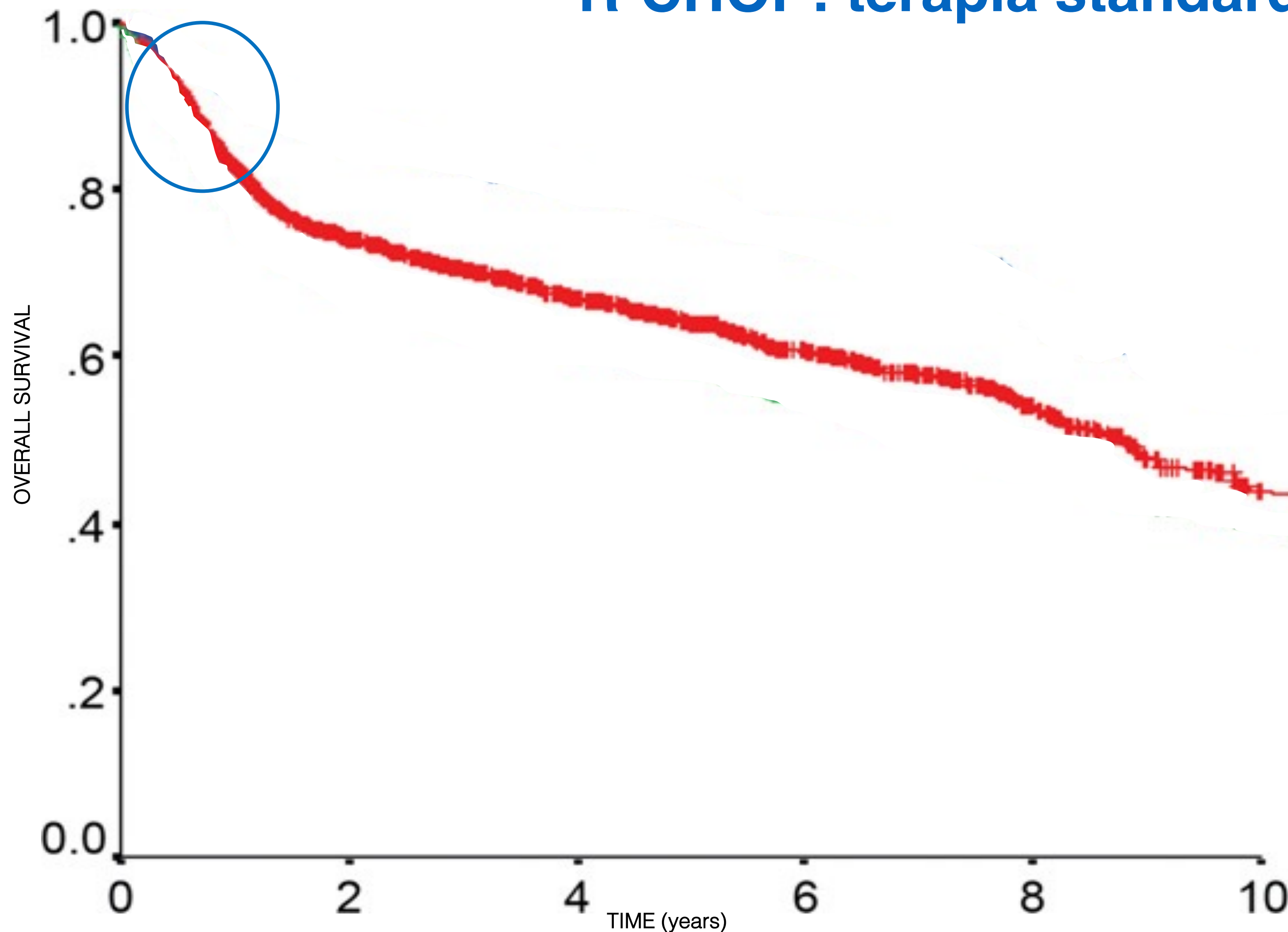
DOMANDA n. 1

Paziente di 40 aa con diagnosi di DLBCL (non GCB), in stadio IVB (localizzazioni pleuropolmonari, gastrica, peritoneale, surrene), IPI 3, CNS IPI4 (stadio, LDH, sedi extranodali, surrene)

Quale terapia?

- a. R-CHOP
- b. R-DA-EPOCH
- c. Pola-R-CHP
- d. Trial Clinico

R-CHOP: terapia standard 1L DLBCL

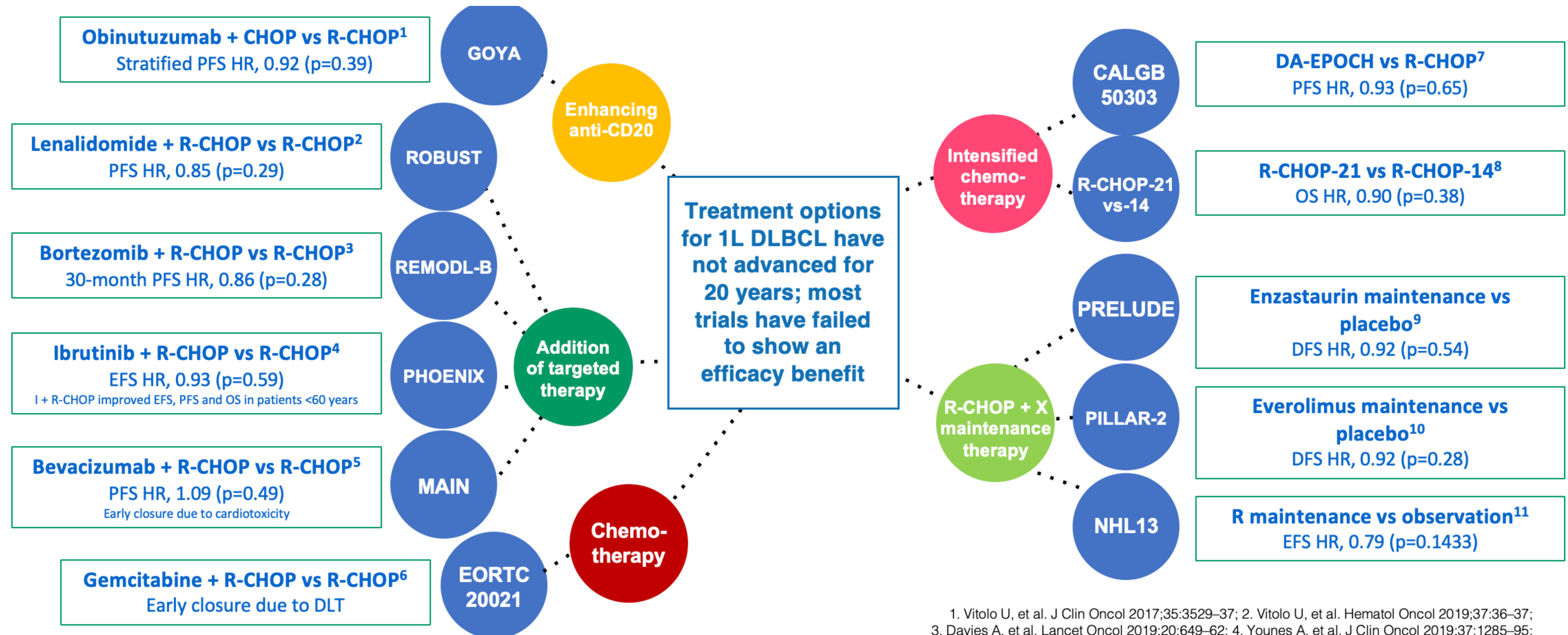


R-CHOP is insufficient in 35% of DLBCL:

- High-Risk “Clinical” (IPI 3-5)
- High-Risk “Biological”

Sehn LH and Salles G, NEJM 2021

How to improve R-CHOP



DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DFS, disease-free survival; DLT, dose-limiting toxicity; EFS, event-free survival; HR, hazard ratio; I, ibrutinib; MTD, maximum tolerated dose; OS, overall survival.

1. Vitolo U, et al. J Clin Oncol 2017;35:3529–37; 2. Vitolo U, et al. Hematol Oncol 2019;37:36–37;
3. Davies A, et al. Lancet Oncol 2019;20:649–62; 4. Younes A, et al. J Clin Oncol 2019;37:1285–95;
5. Seymour JF, et al. Haematologica 2014;99:1343–49; 6. Aurer I, et al. Eur J Haematol 2011;86:111–16;
7. Bartlett NL, et al. J Clin Oncol 2019;37:1790–99; 8. Cunningham D, et al. Lancet 2013;381:1817–26;
9. Crump M, et al. J Clin Oncol 2016;34:2484–92; 10. Witzig TE, et al. Ann Oncol 2018;29:707–14;
11. Jaeger U, et al. Haematologica 2015;100:955–63.

POLARIX trial

- Double-blind, randomized controlled
- Collaboration with LYSA
- NCT03274492

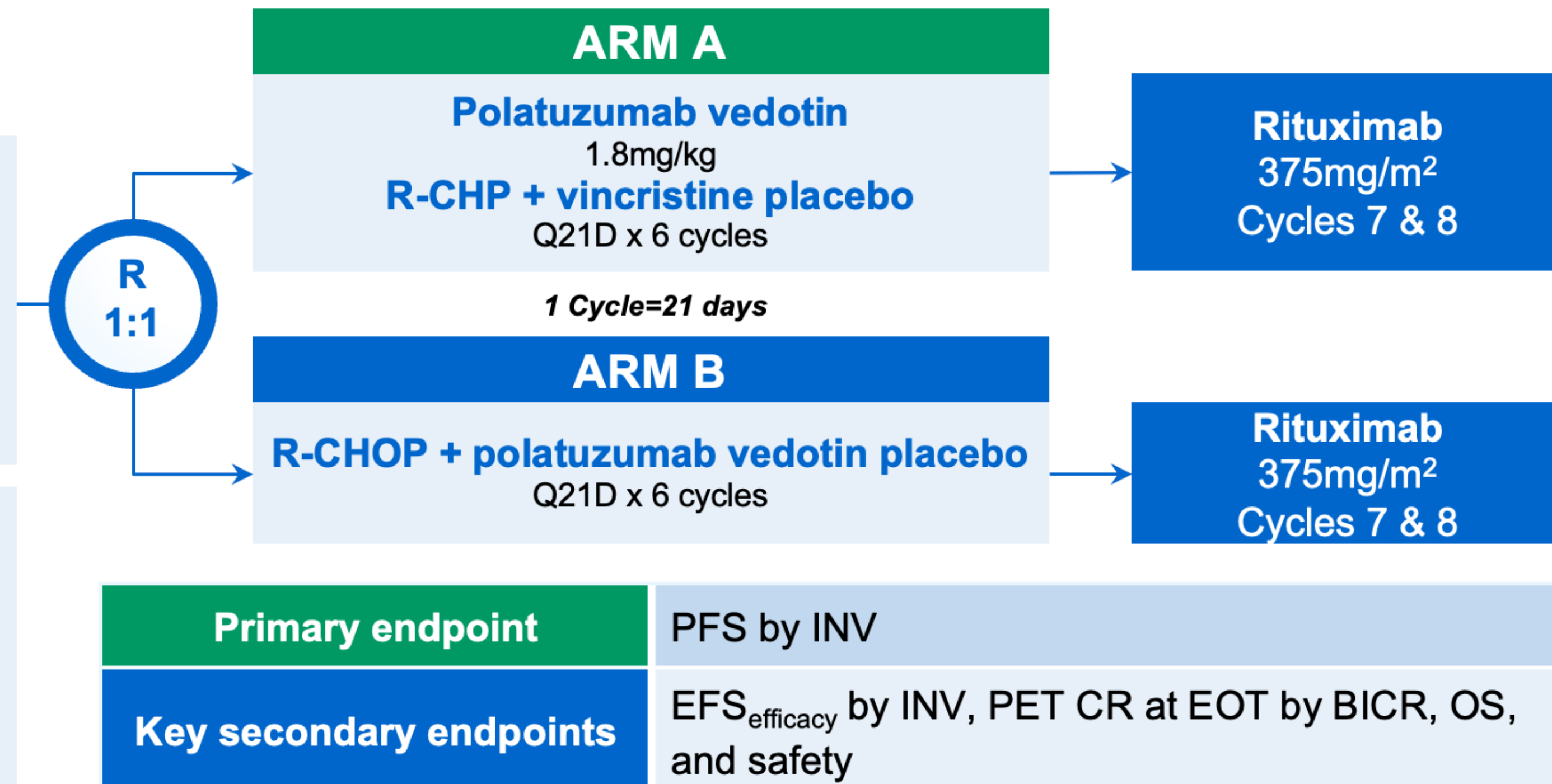
Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

N=879

Stratification factors

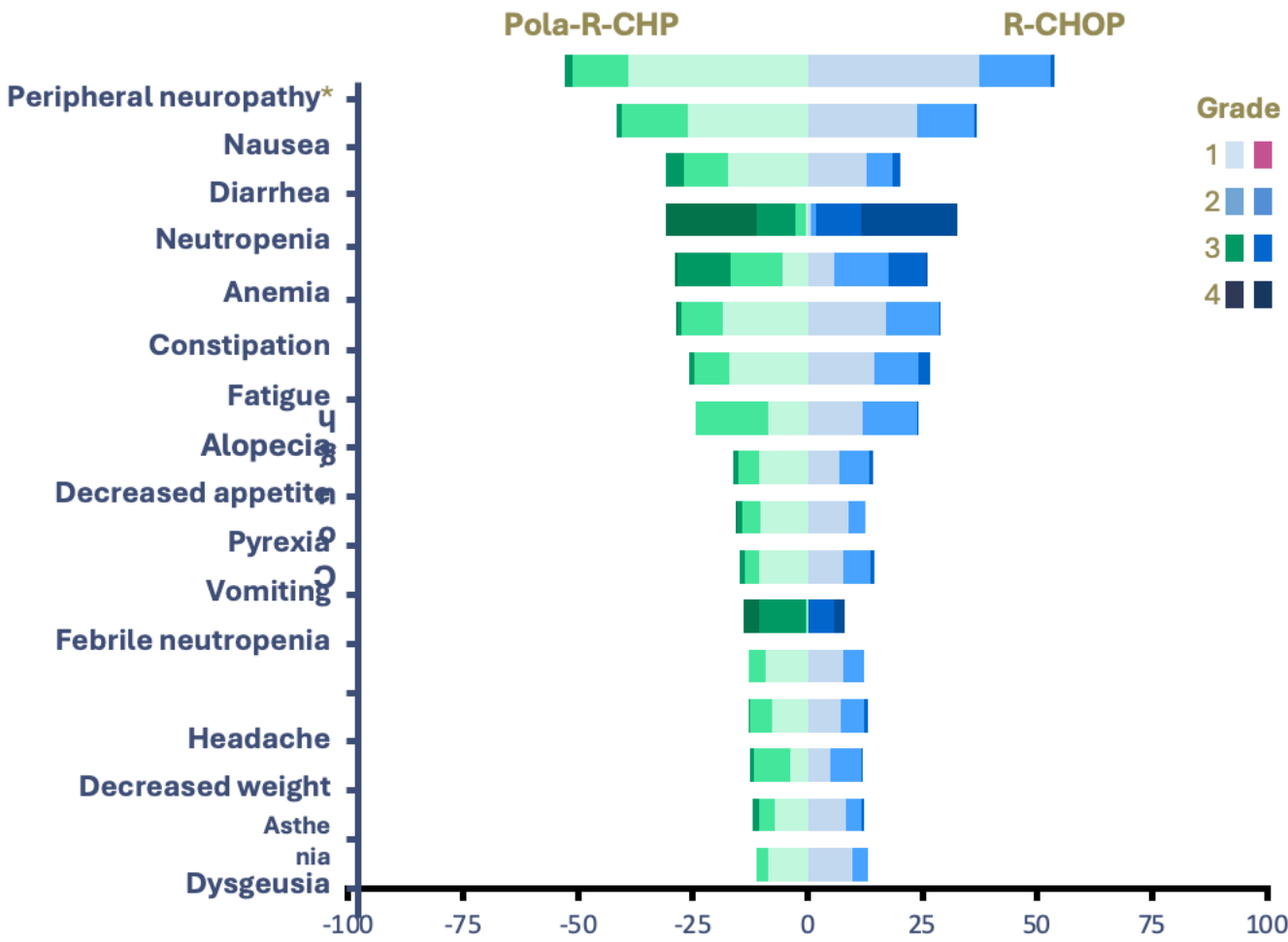
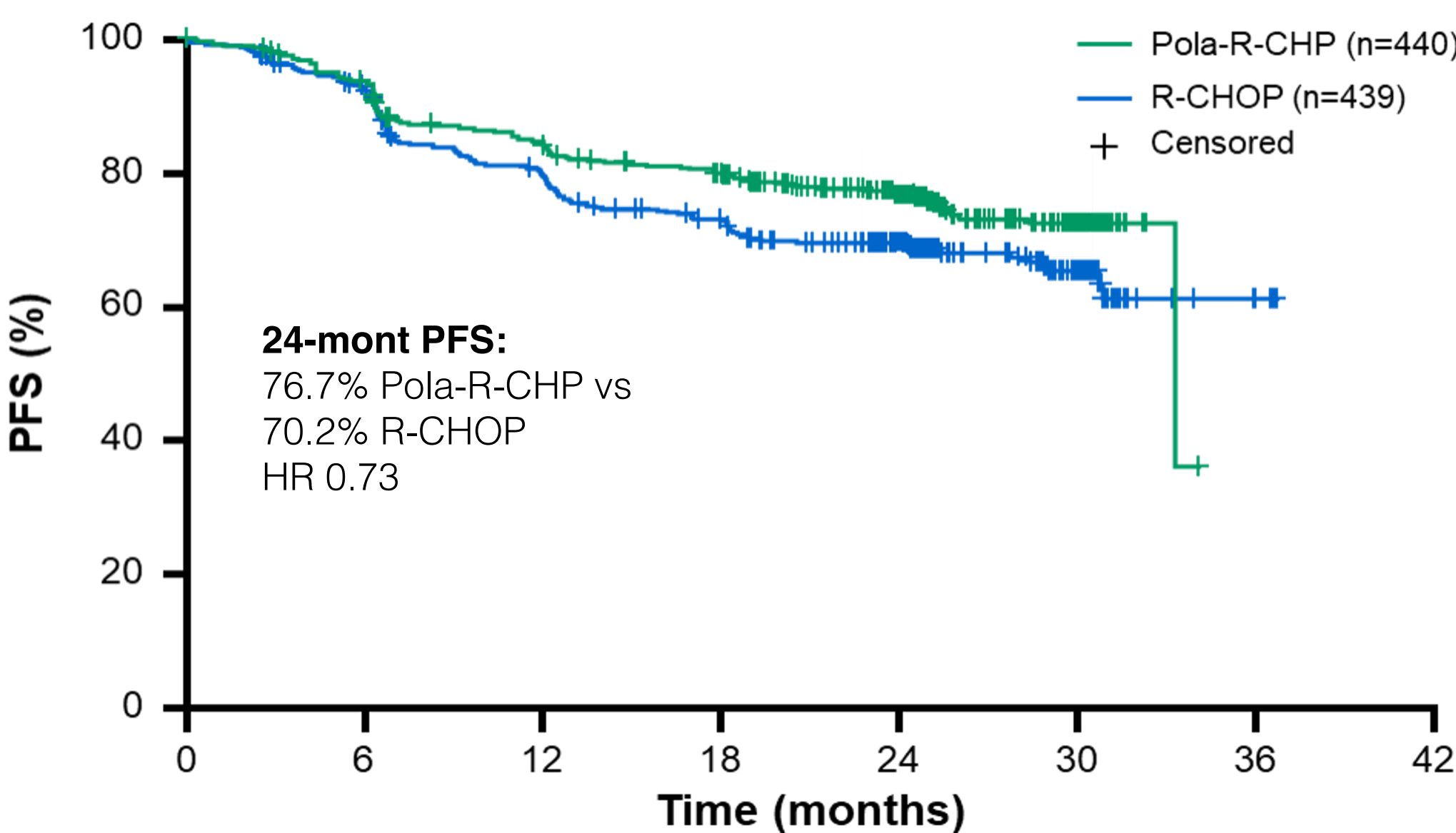
- IPI score (2 vs 3–5)
- Bulky disease (≥ 7.5 cm vs absence)
- Geographic region*



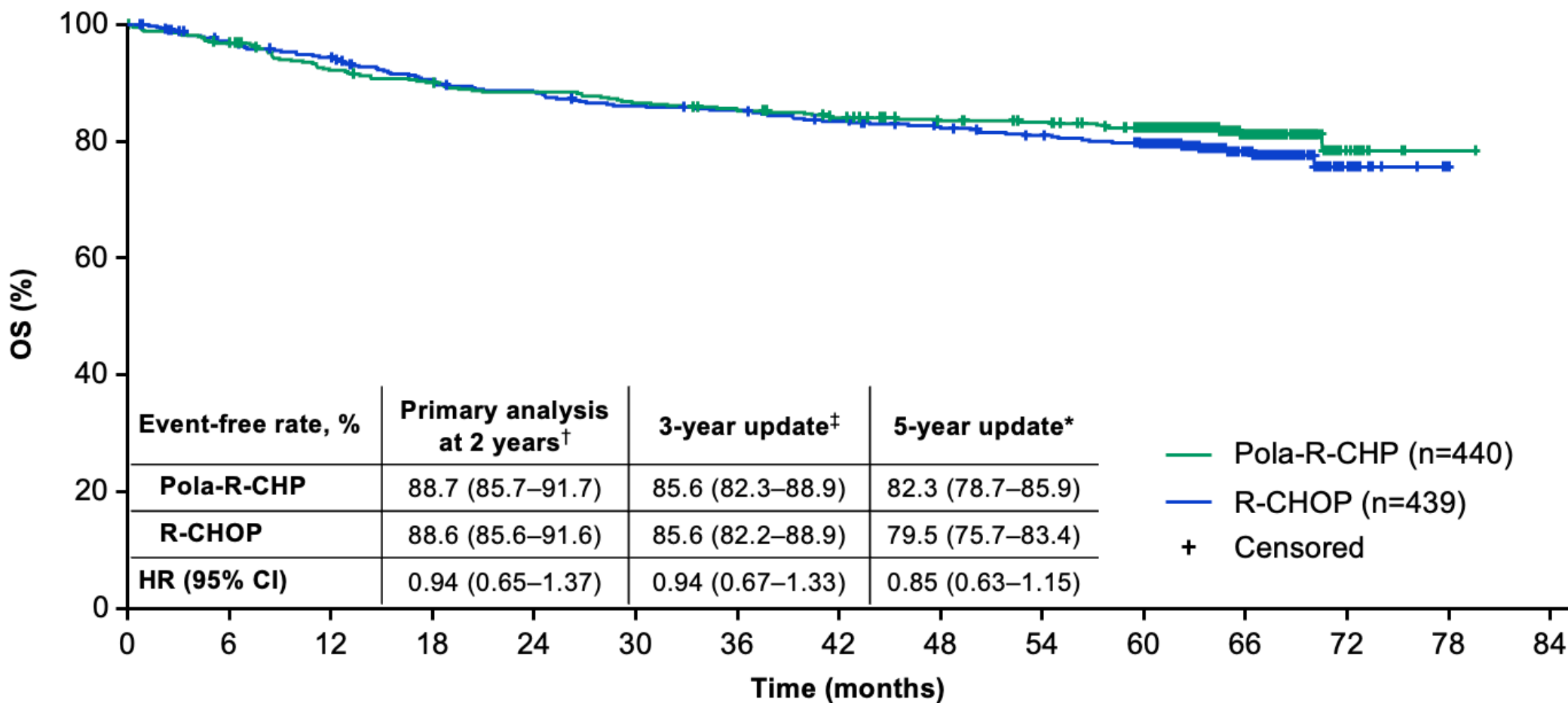
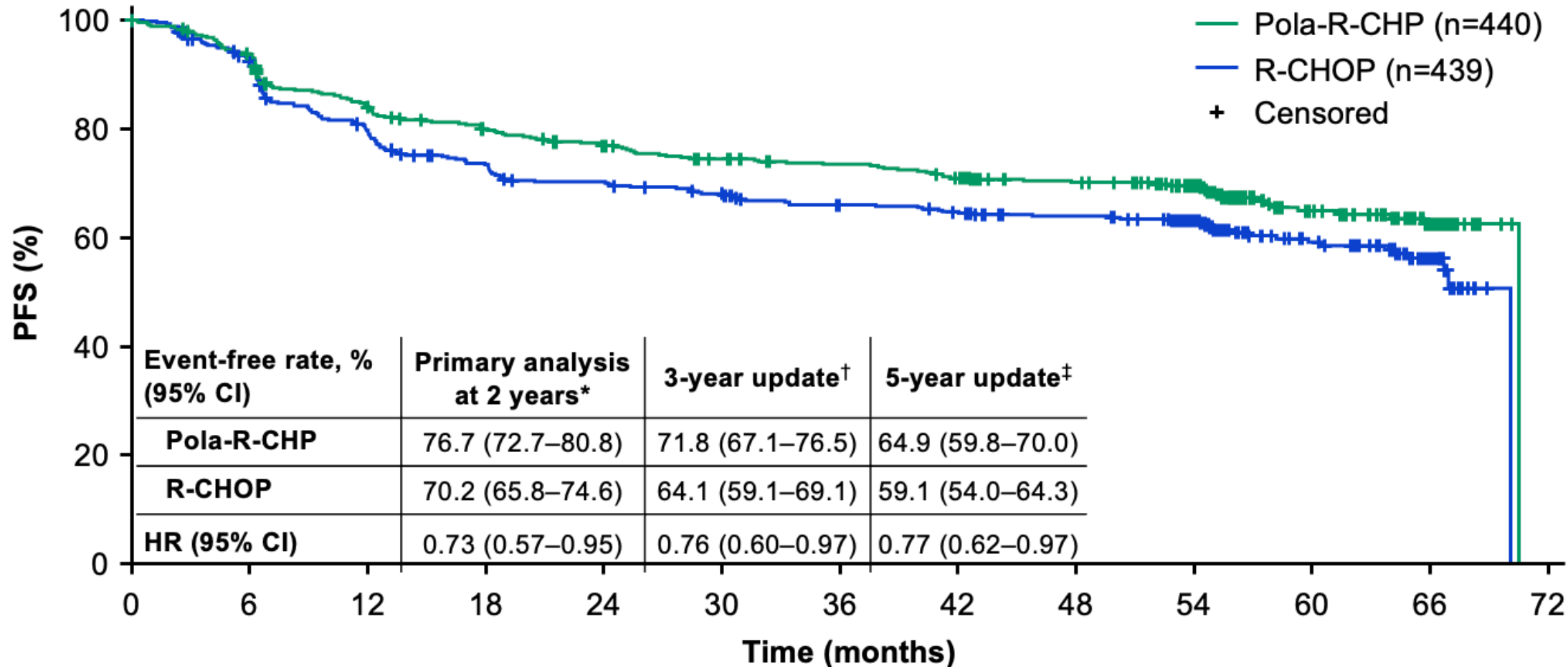
*Western Europe, United States, Canada and Australia vs Asia vs Rest of World. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS_{efficacy}, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion); EOT, end of treatment; INV, investigator; IPI, International Prognostic Index; LYSA, Lymphoma Study Association; PET, positron emission tomography; Q21D, every 21 days; R, randomization; R-CHP, rituximab plus cyclophosphamide, doxorubicin, prednisone.

Tilly H et al, New Engl J Med 2022

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



5-year follow-up analysis



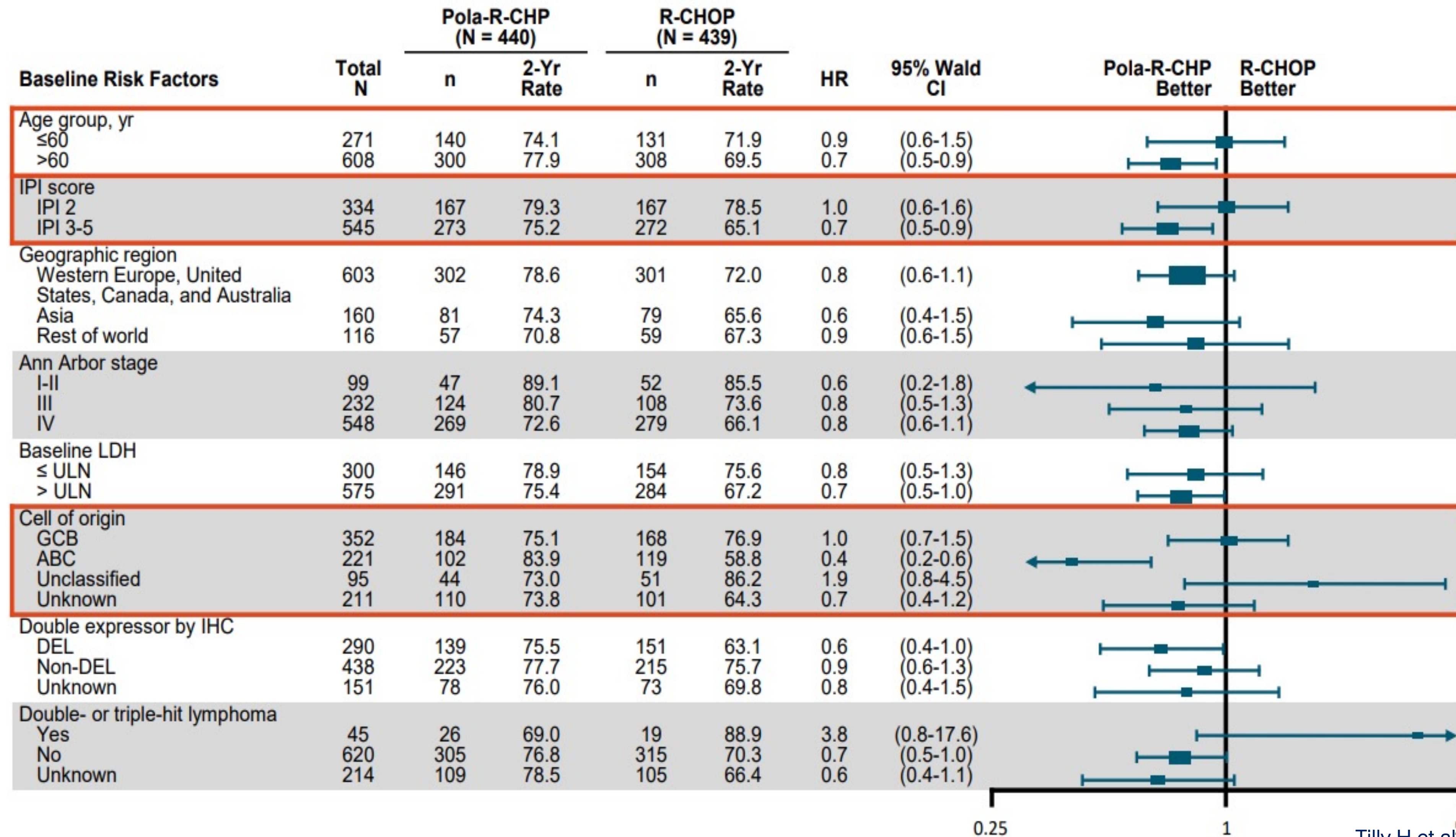
Patients remaining at risk															
Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

Tilly H et al, New Engl J Med 2022; Salles.G et al; Oral Presentation ASH 2024

The young side of LYMPHOMA

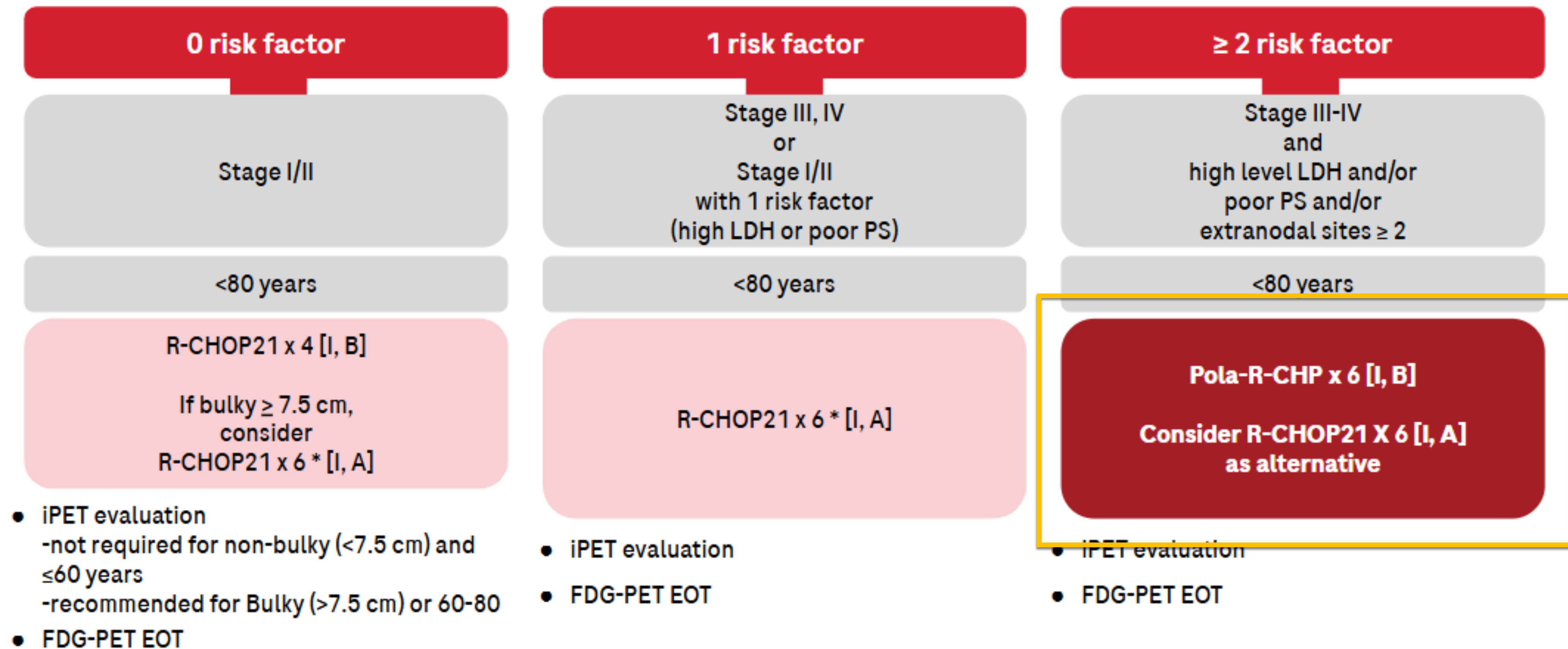
gli under 40 a confronto

Investigator-assessed PFS by subgroup (unstratified)



Tilly H et al, New Engl J Med 2022

Newly released EHA guidelines: 1L DLBCL



Dicembre 2023 rimborsabilità AIFA (IPI 3-5)

Ricovero dal 3/7 al 9/7/25

- PL: chimico fisico nn, IF negativo
- Toracentesi: evacuazione 1100 cc di liquido sieroso-ematico
- **5/7/25 avvio I ciclo Pola-R-CHP**

Aggiornamento settembre 2025:

- regressione dei sintomi dopo ciclo 1
- TC 17/9 (post 4° ciclo): PR

treatment ongoing...

What next ?

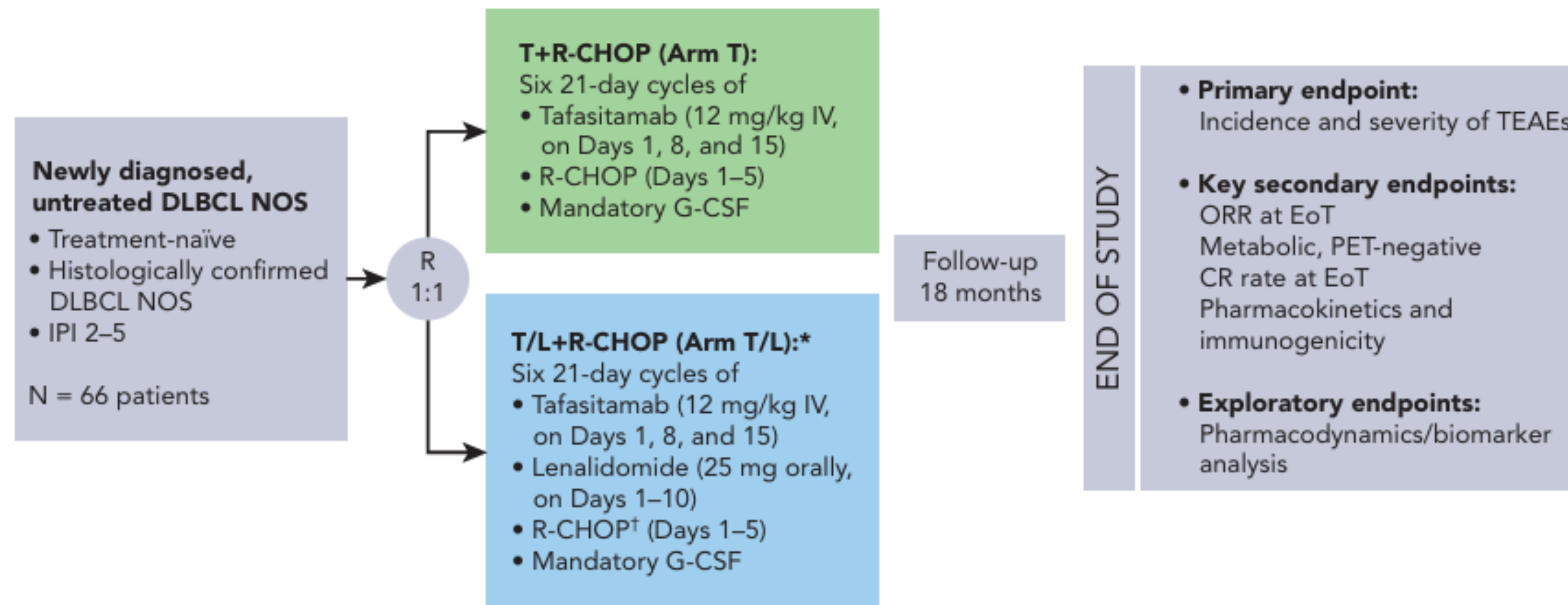
Moving beyond R-CHOP/Pola-R-CHP

- ✓ “Agnostic” approach
- ✓ Biology-driven approach
- ✓ Chemo-free approach

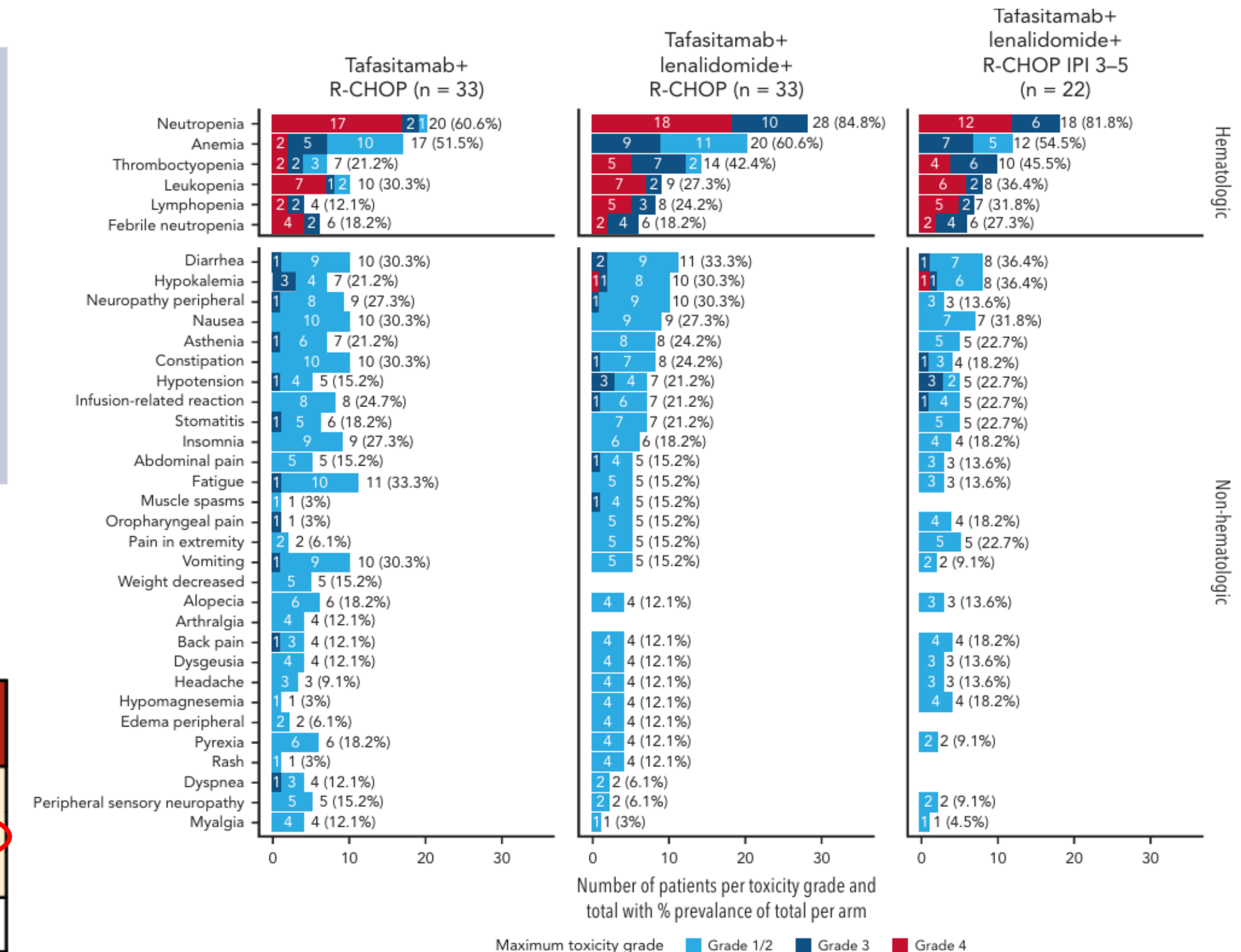
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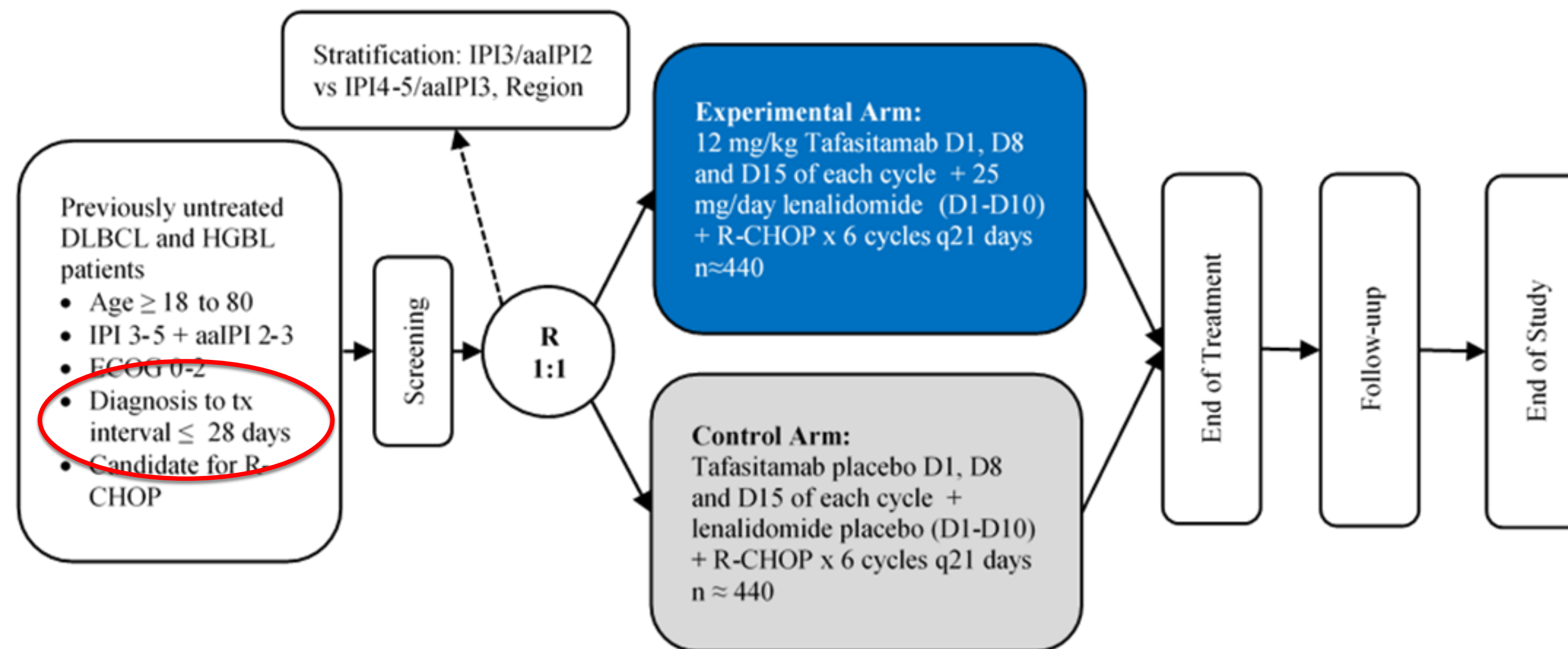
First-MIND study: open-label, randomized phase Ib study



Event	Arm T (n = 33)	Arm T/L (n = 33)	Arm T/L IPI 3–5 (n = 22)
ORR, n (%) (95% CI)			
CR or PR (at EoT)	25 (75.8) (57.7-88.9)	27 (81.8) (64.5-93.0)	18 (81.8) (59.7-94.8)
CR or PR (best response across all visits)	30 (90.9) (75.7-98.1)	31 (93.9) (79.8-99.3)	20 (90.9) (70.8-98.9)
18-mo DoR rate, % (95% CI)	72.7 (52.7-85.3)	78.7 (58.5-89.9)	76.6 (48.8-90.5)
18-mo DoCR rate, % (95% CI)	74.5 (53.8-87.0)	86.5 (63.8-95.5)	80.0 (50.0-93.1)
24-mo PFS rate, % (95% CI)	72.7 (52.7-85.3)	76.8 (57.1-88.3)	73.6 (47.3-88.2)
24-mo OS rate, % (95% CI)	90.3 (72.9-96.8)	93.8 (77.3-98.4)	95.2 (70.7-99.3)



Front-MIND study: phase III, randomized, place-controlled study



Primary endpoint

- PFS* by INV, event driven
 - Primary analysis: 274 events
 - Interim analysis (futility): 100 events

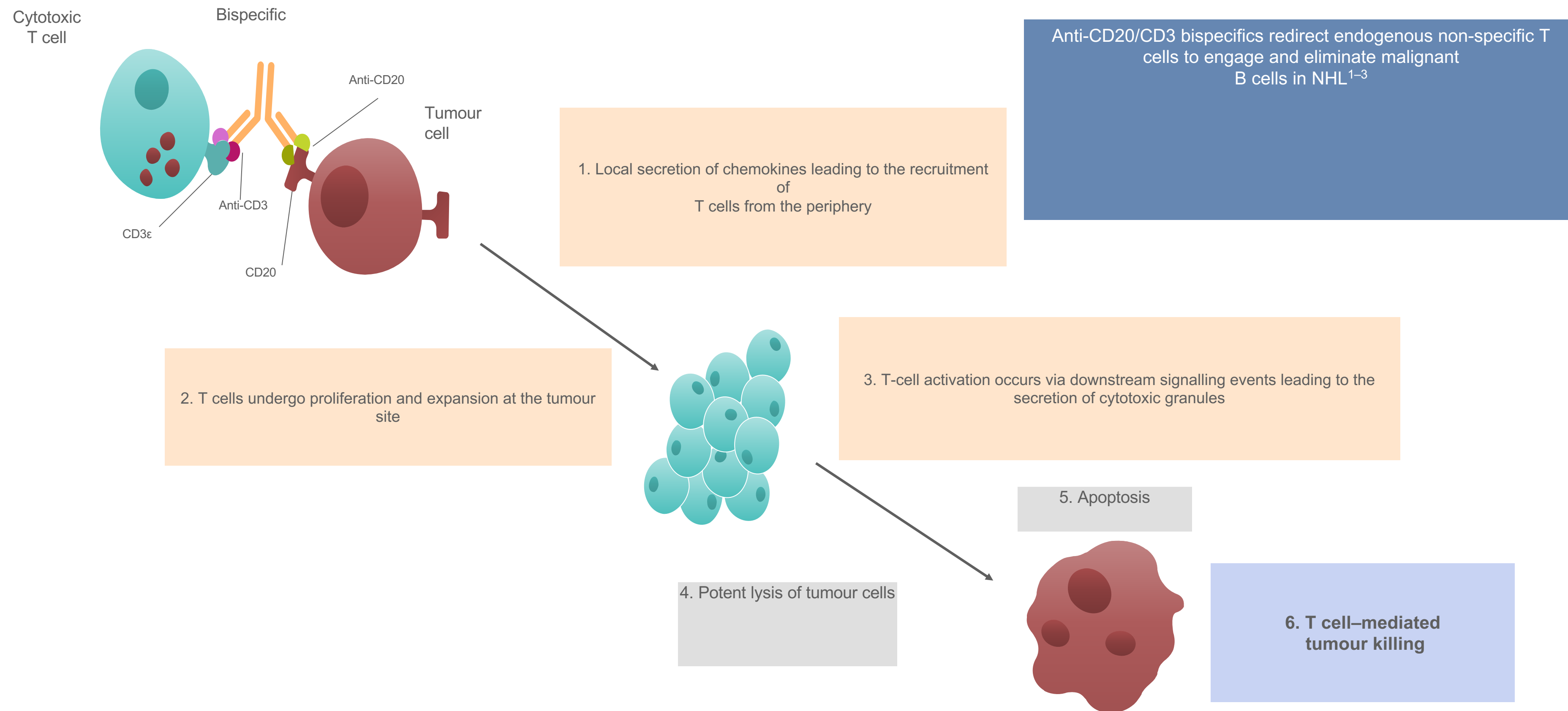
Sample size

- N= 880 incl. drop outs
- Assumptions
 - Projected PFS increase @36 months from ~57% (control) to ~68%
 - HR = 0.70, Power: 83%
 - Accrual: 21 months (350 sites)
 - Annual Drop-out: 15%

Enrollment completed

Results pending..

CD3xCD20 Bispecific Antibodies

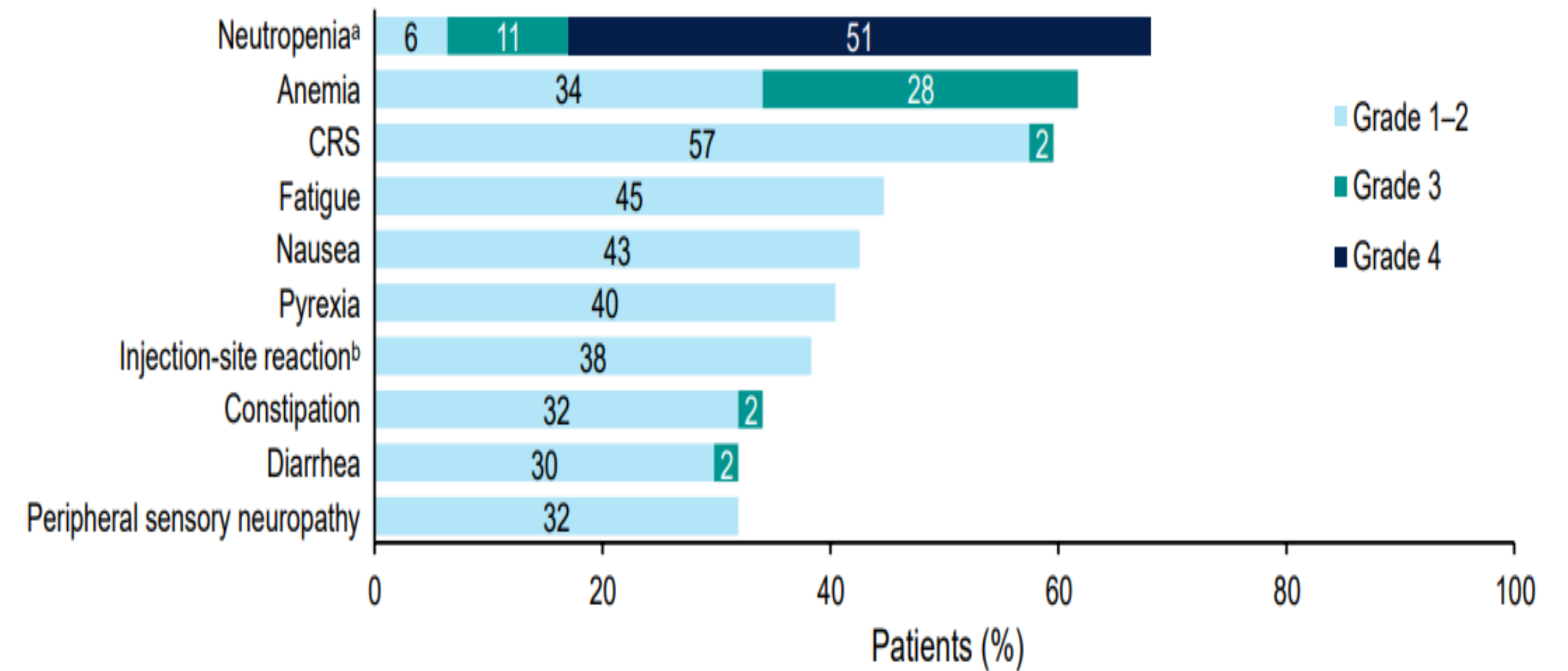


- ✓ Epcoritamab
- ✓ Glofitamab
- ✓ Odronextamab

EPCORE NHL-2 trial: Arm 1**Epcor-R-CHOP**

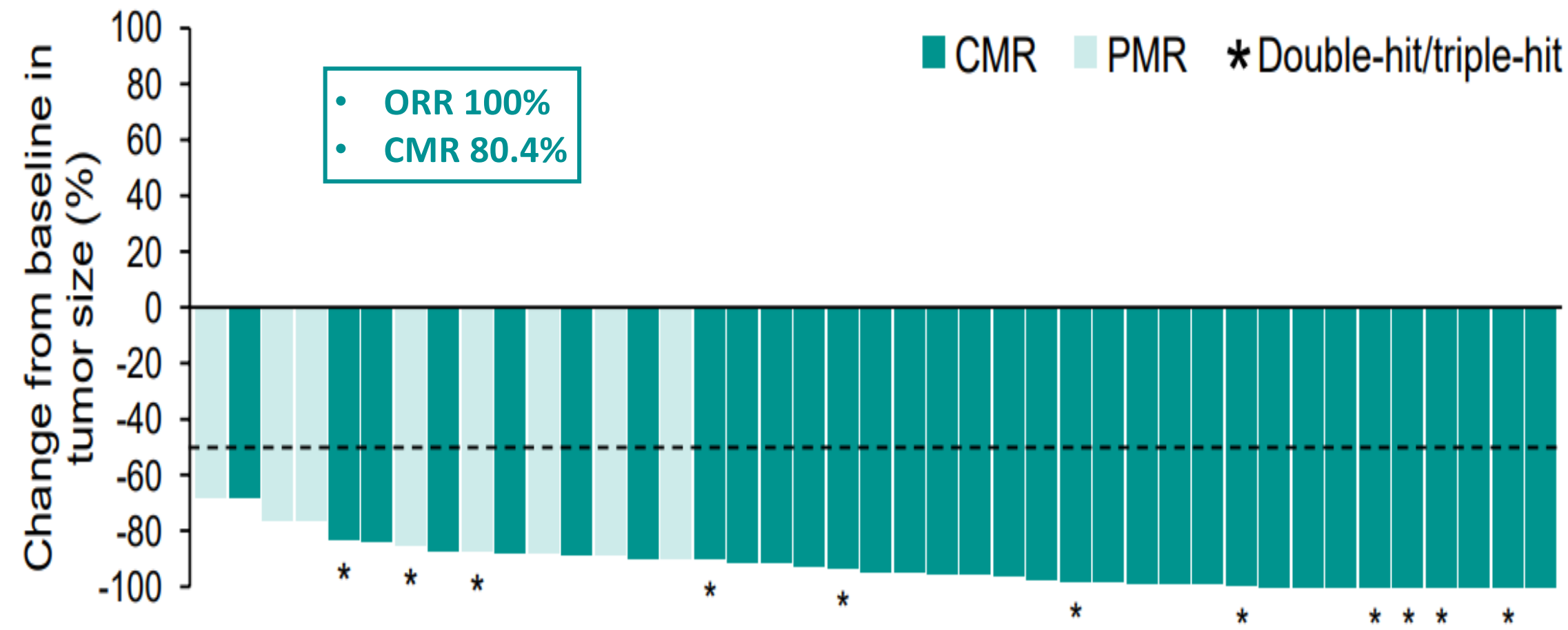
Treatment regimen: Concomitant epcoritamab SC 48 mg + R-CHOP			
Agent	C1–C4	C5–C6	C7+
Epcoritamab SC 48 mg	QW	Q3W	Q4W Up to 1 year
Rituximab IV 375 mg/m ²	Q3W		
Cyclophosphamide IV 750 mg/m ²			
Doxorubicin IV 50 mg/m ²			
Vincristine ^d IV 1.4 mg/m ²			
Prednisone IV or oral 100 mg/d	D1–5 of each cycle		

R-CHOP



- N= 46
- IPI ≥ 3
- median FU 14.2 months

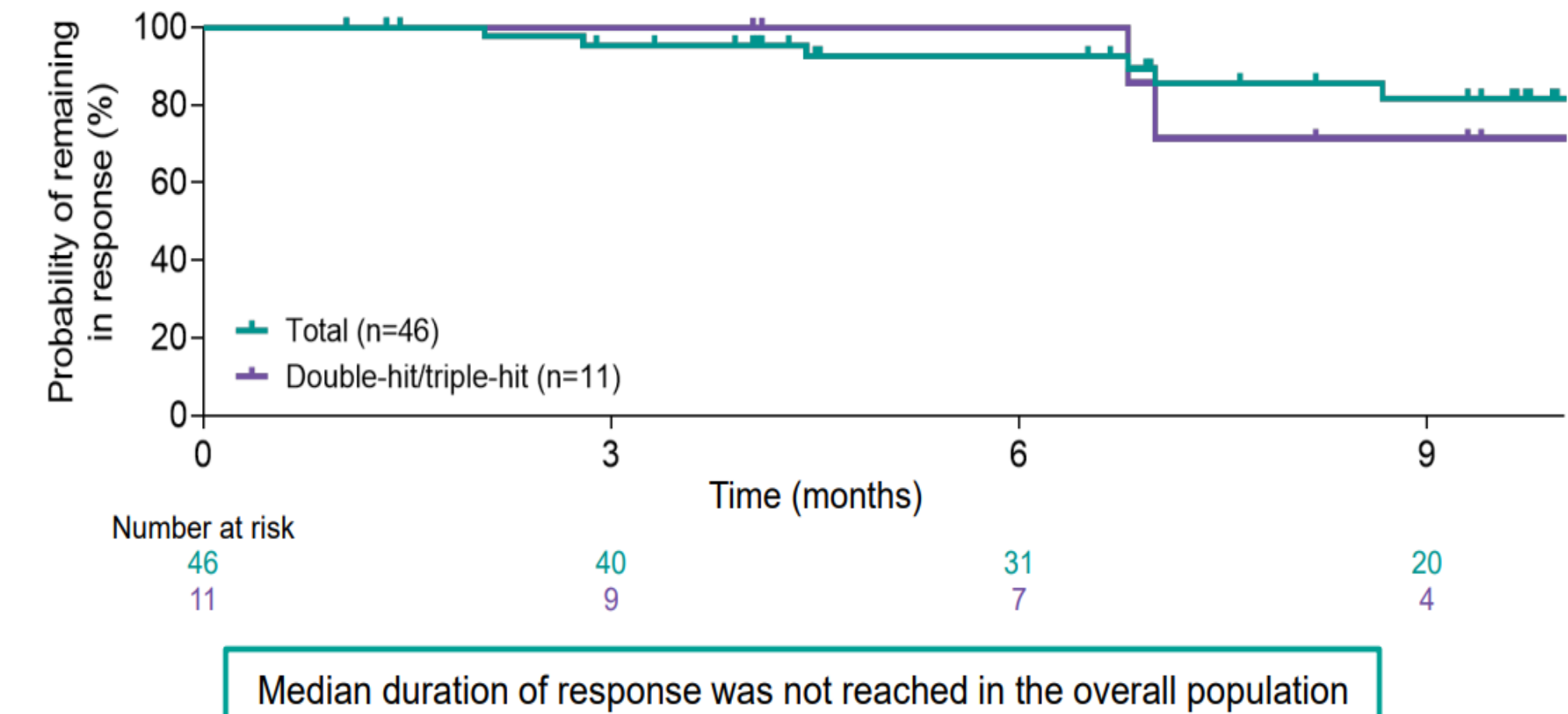
- No TLS
- 2 ICANS (G1, G2)
- CRS C1D15



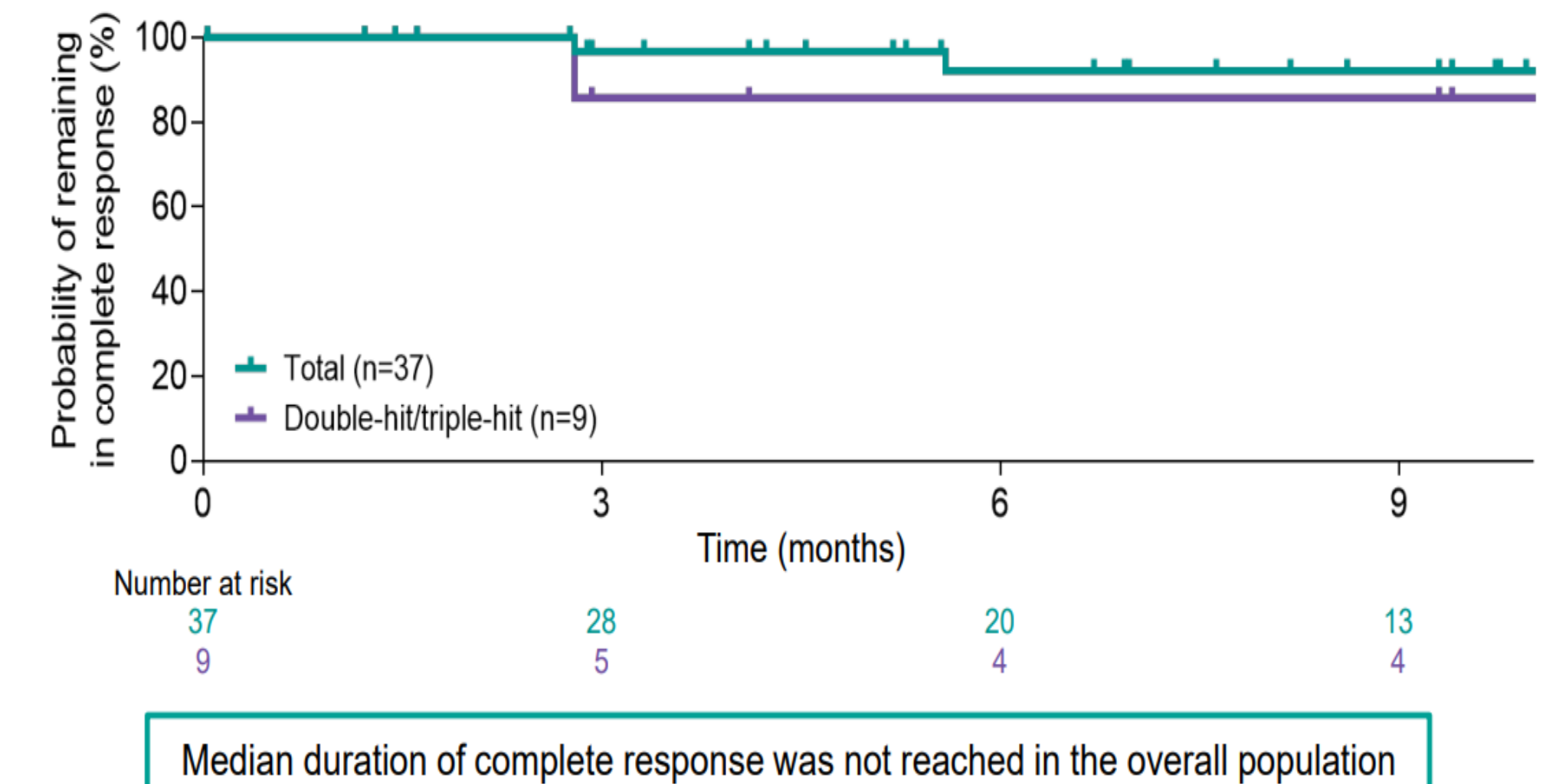
Epcoritamab + R-CHOP induced responses across all patients, including high-risk double-hit/triple-hit patients

EPCORE DLBCL 2: A randomized phase III trial (Epco-R-CHOP vs. R-CHOP) is ongoing

Duration of Response



Duration of Complete Response



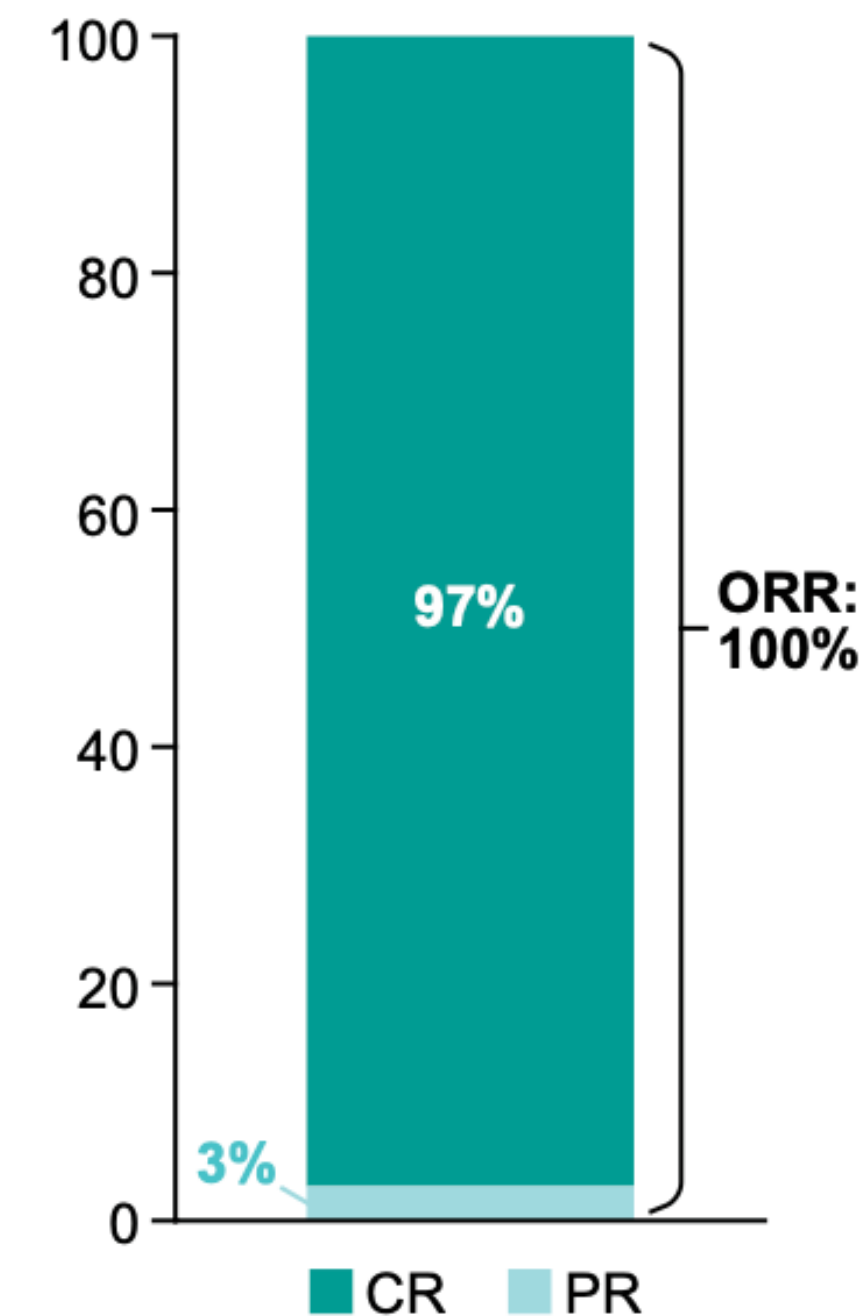
EPCORE NHL-5 trial - Arm 3: phase 1b/2

Epcor-pola-R-CHP

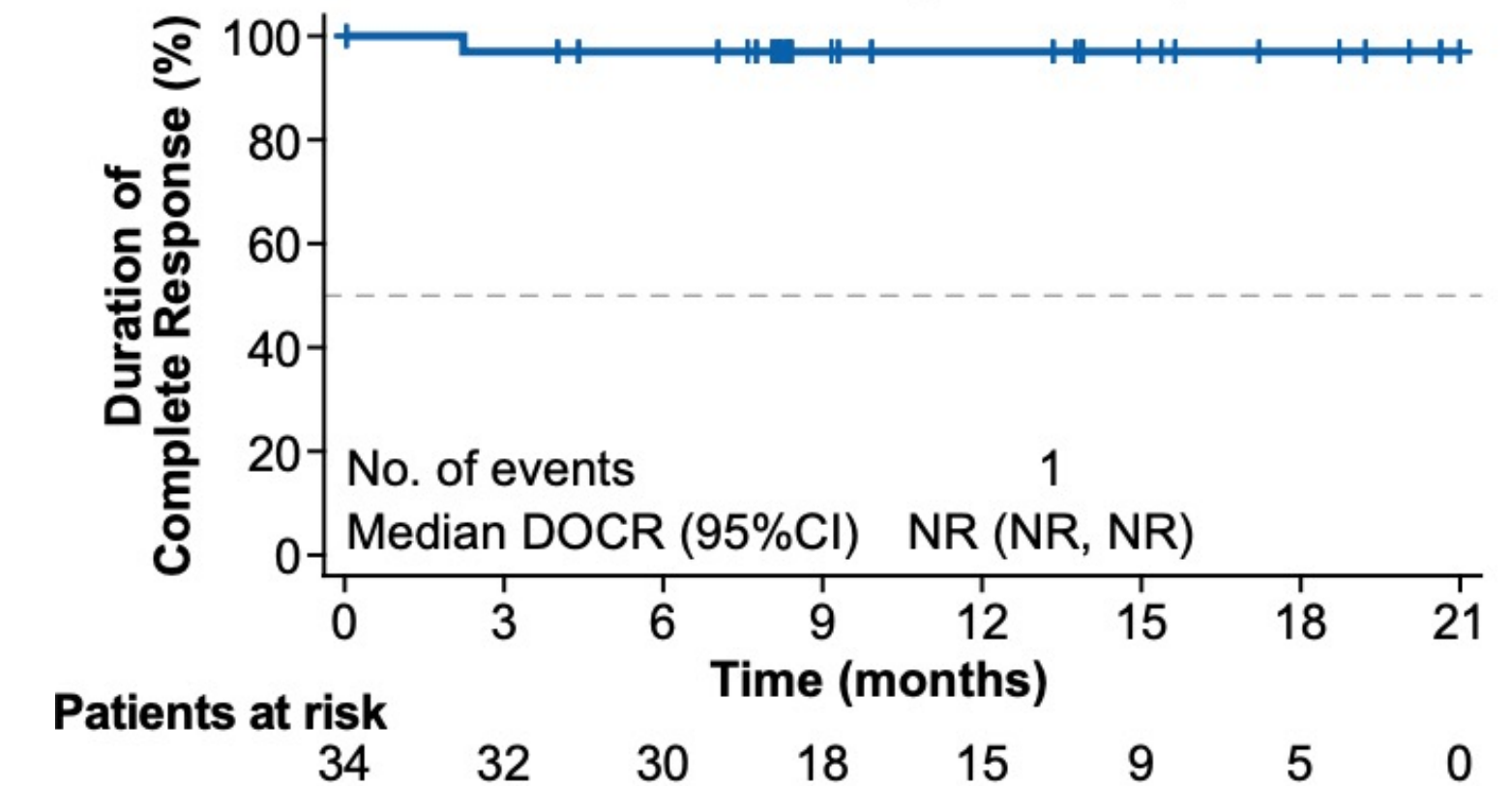
Arm 3: Epcoritamab + pola-R-CHP 1L DLBCL: Dose escalation and dose expansion (21-day cycle) ^b								
Agent	C1	C2	C3	C4	C5	C6	C7	C8
Epcoritamab	Step-up dosing: D1: SUD1 (0.16 mg) D8: SUD2 (0.8 mg) D15: full dose (24 mg or 48 mg)	D1, 8, 15: full dose (24 mg or 48 mg)			D1: full dose (24 mg or 48 mg)			
pola-R-CHP	Polatuzumab vedotin	D1 (1.8 mg/kg)						
	Rituximab	D1 (375 mg/m ²)						
	Cyclophosphamide	D1 (750 mg/m ²)						
	Doxorubicin	D1 (50 mg/m ²)						
	Prednisone	D1–5 (100 mg)						

- N= 37
- IPI ≥ 3
- median FU 16.1 months

Best Overall Response



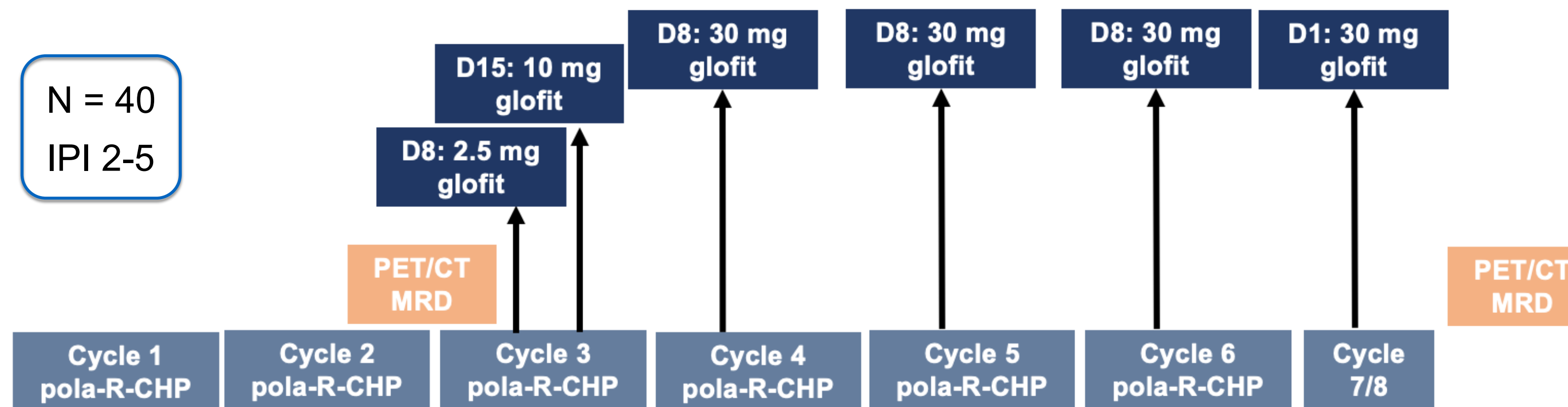
Duration of Complete Response



Glofi-pola-R-CHP

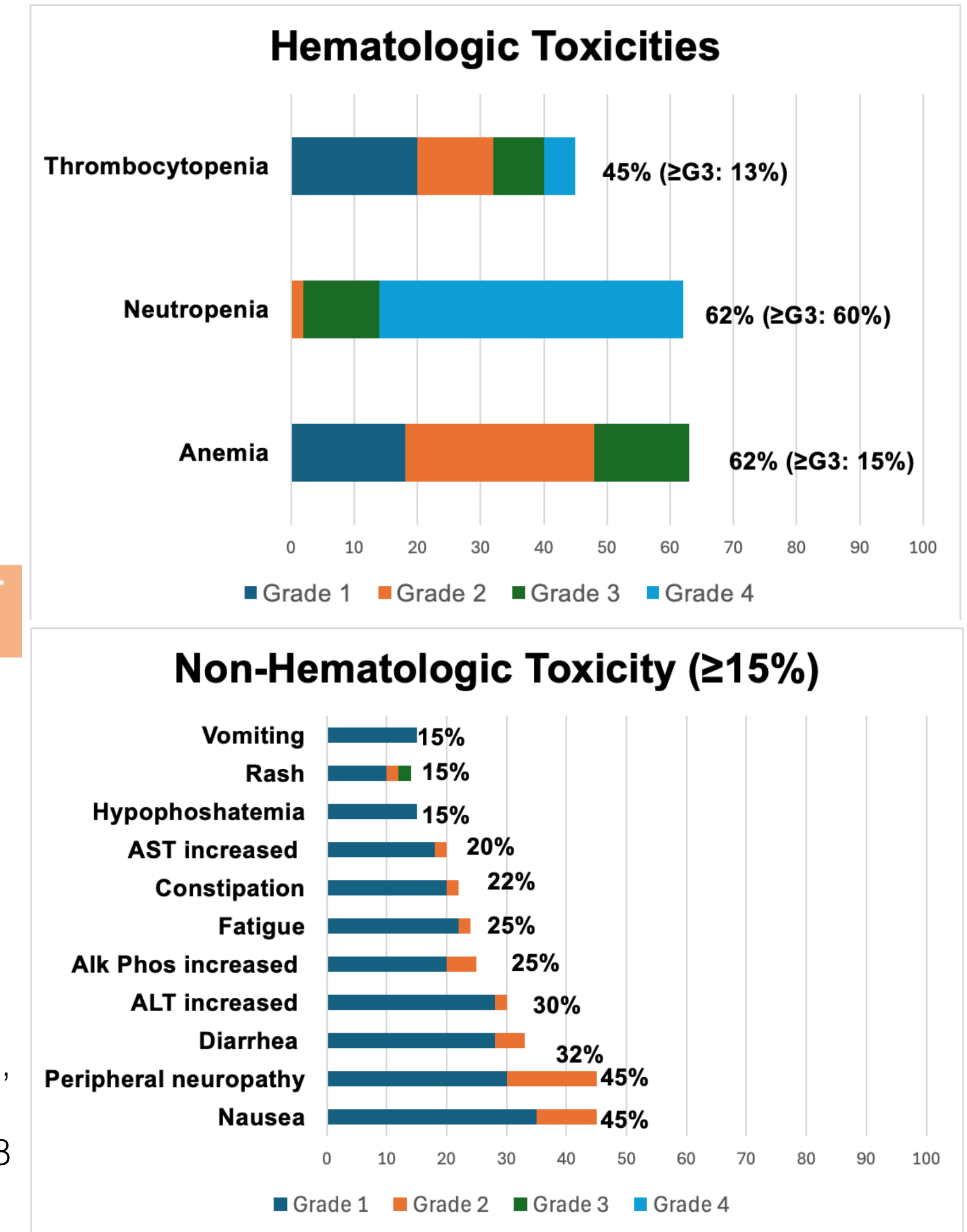
Open label, phase II study

N = 40
IPI 2-5

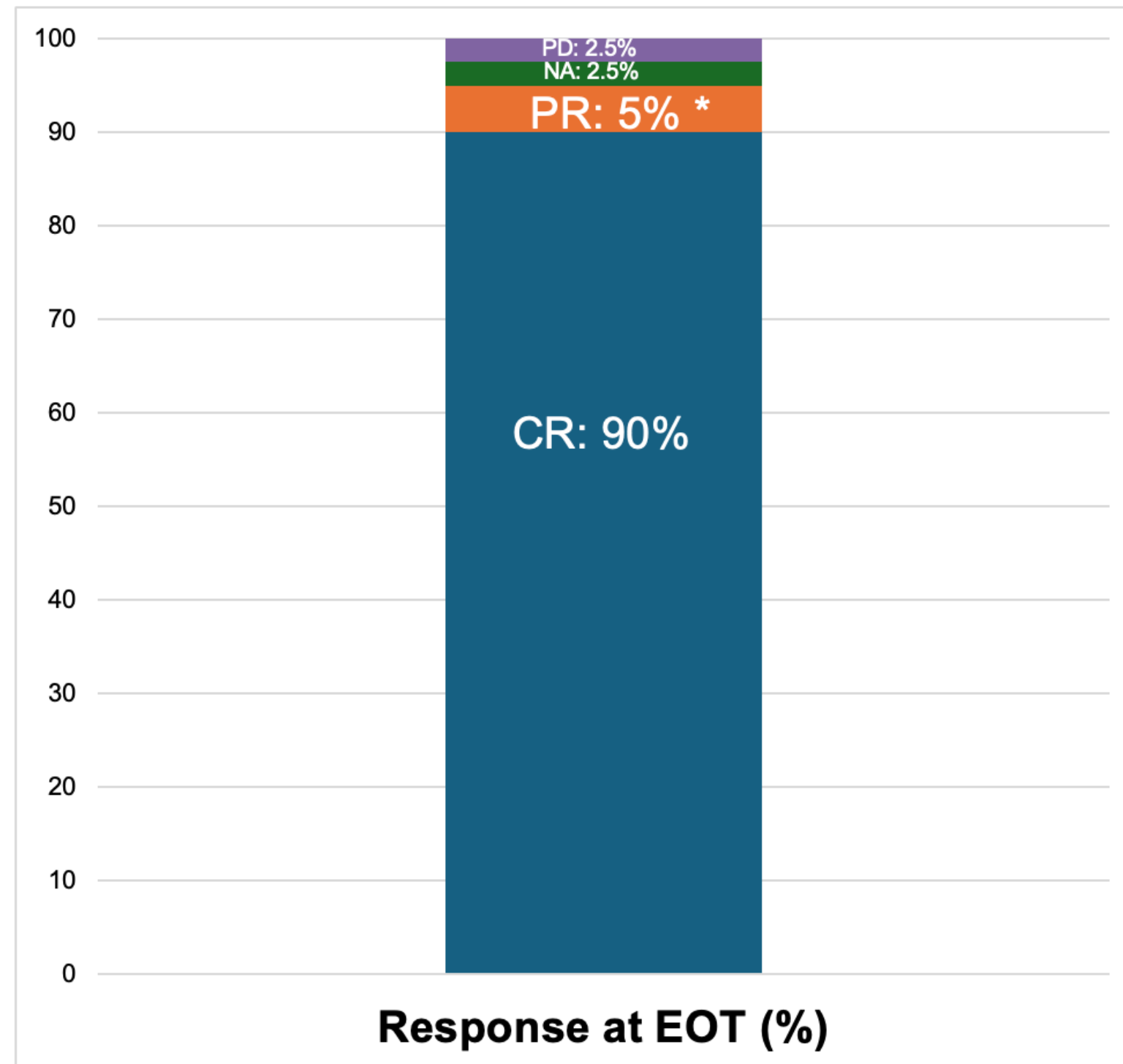


Primary Endpoint: EOT CMR

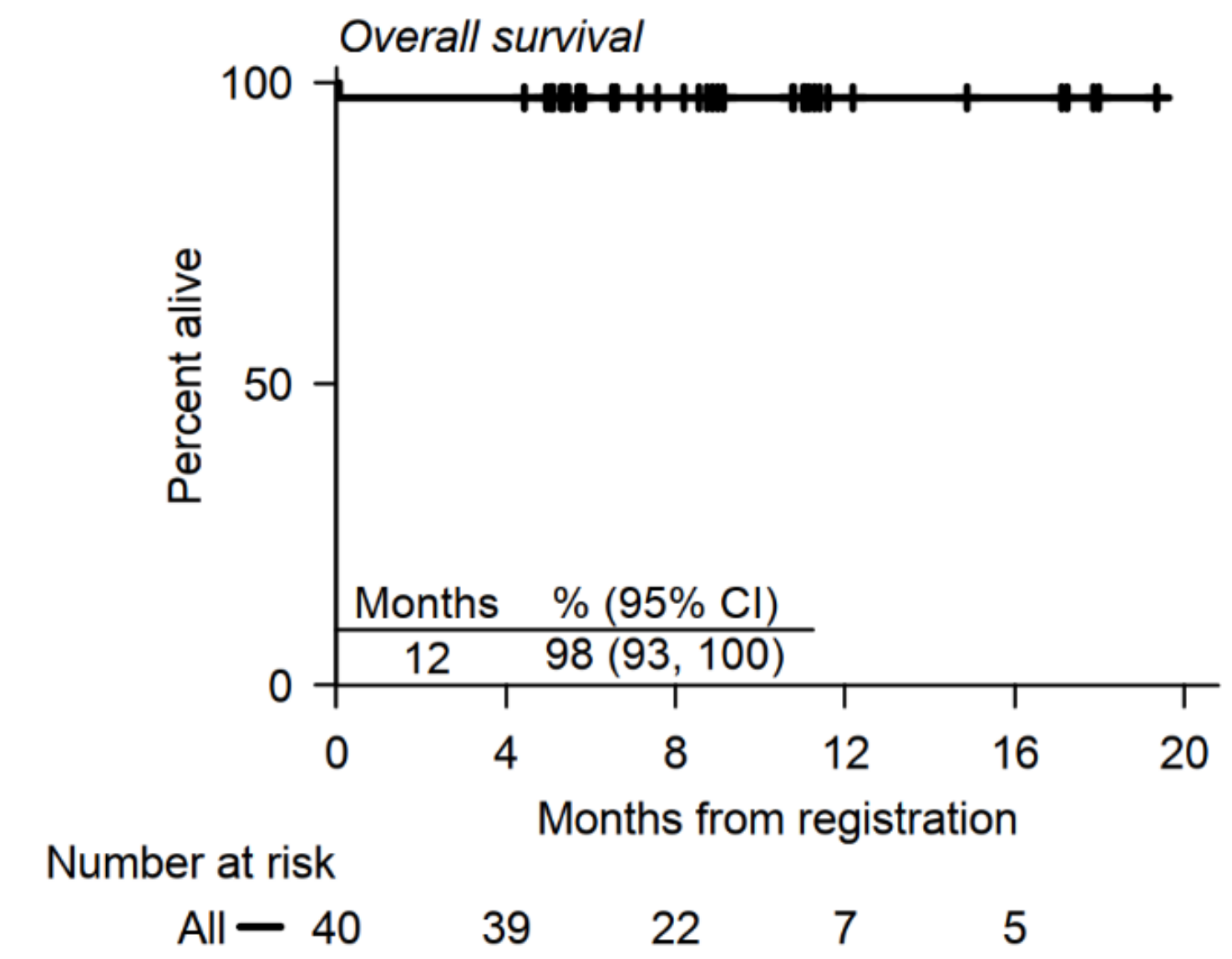
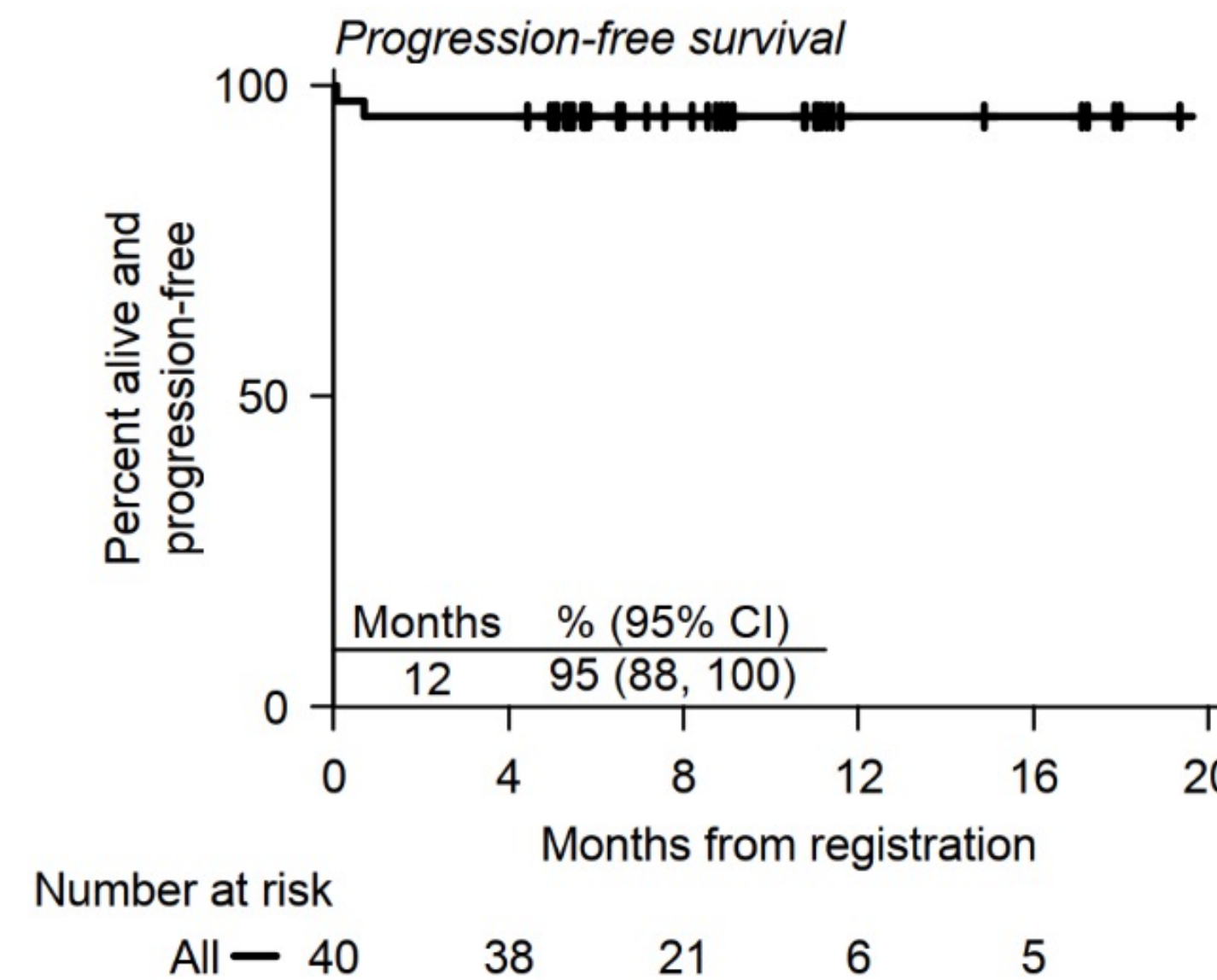
- Grade 1 CRS in 4 patients (10%)
 - 1 patient after 2.5 mg dose, improved with dexamethasone
 - 3 patients with fever after C6D8 (steroid premedication omitted)



Crombie JL et al ICML 2025

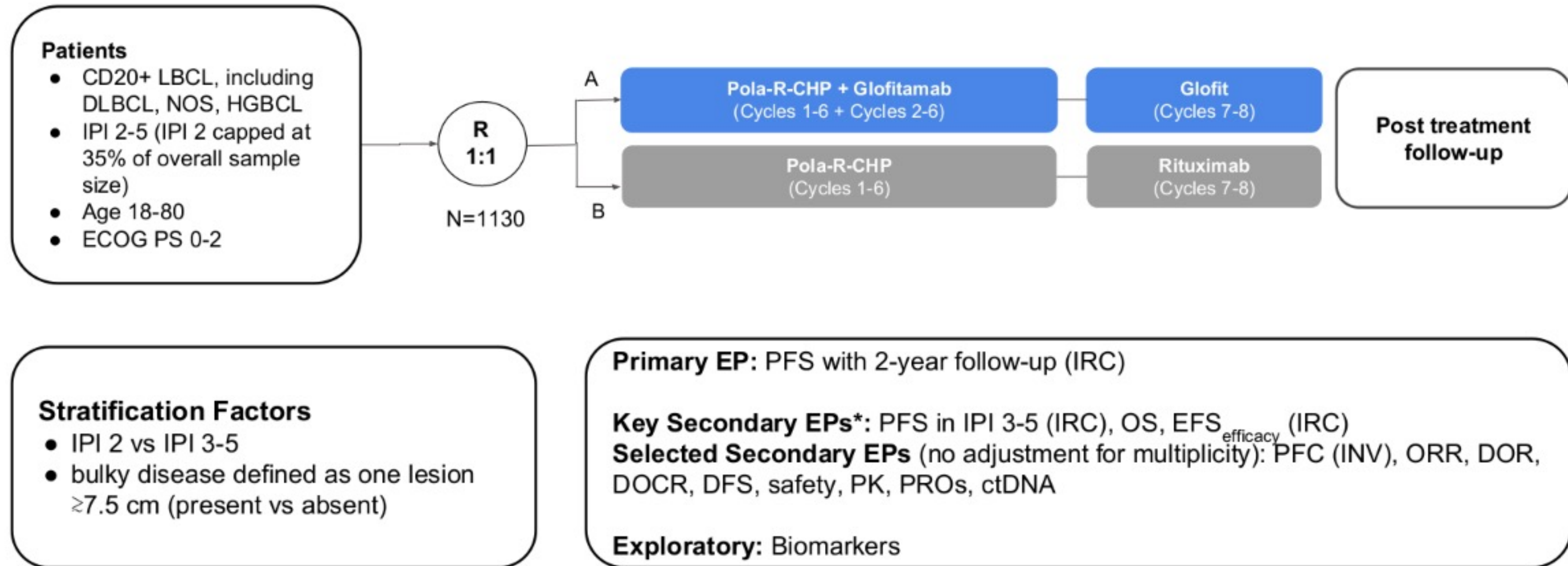


Median follow-up 8.7 months



- Both patients with PR at EOT converted to CR without additional therapy
- 20 patients with EOT MRD testing by ClonoSEQ® (Adaptive): 19 MRD- (95%)

SKYGLO: A randomized phase III trial is ongoing



Recruiting..

Odronextamab

Odronextamab in patients with R/R Diffuse Large B-Cell Lymphoma

Treatment schedule

Cycle 1 (Step-up Dosing)

Odronextamab IV
D1,2: 0.7 mg > D8,9: 4 mg >
D15,16: 20 mg

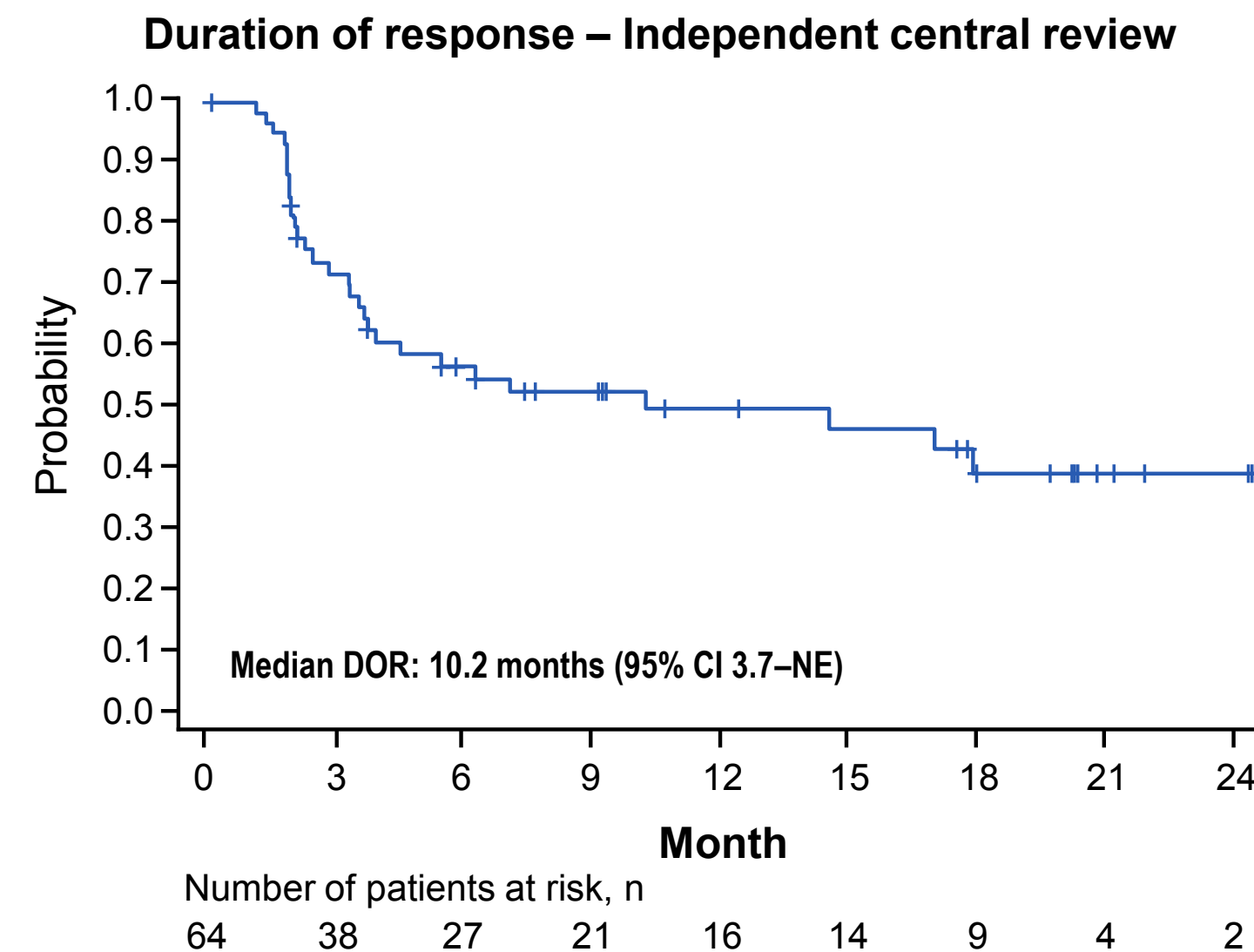
Cycle 2-4

Odronextamab IV
80 mg D1, D8, D15

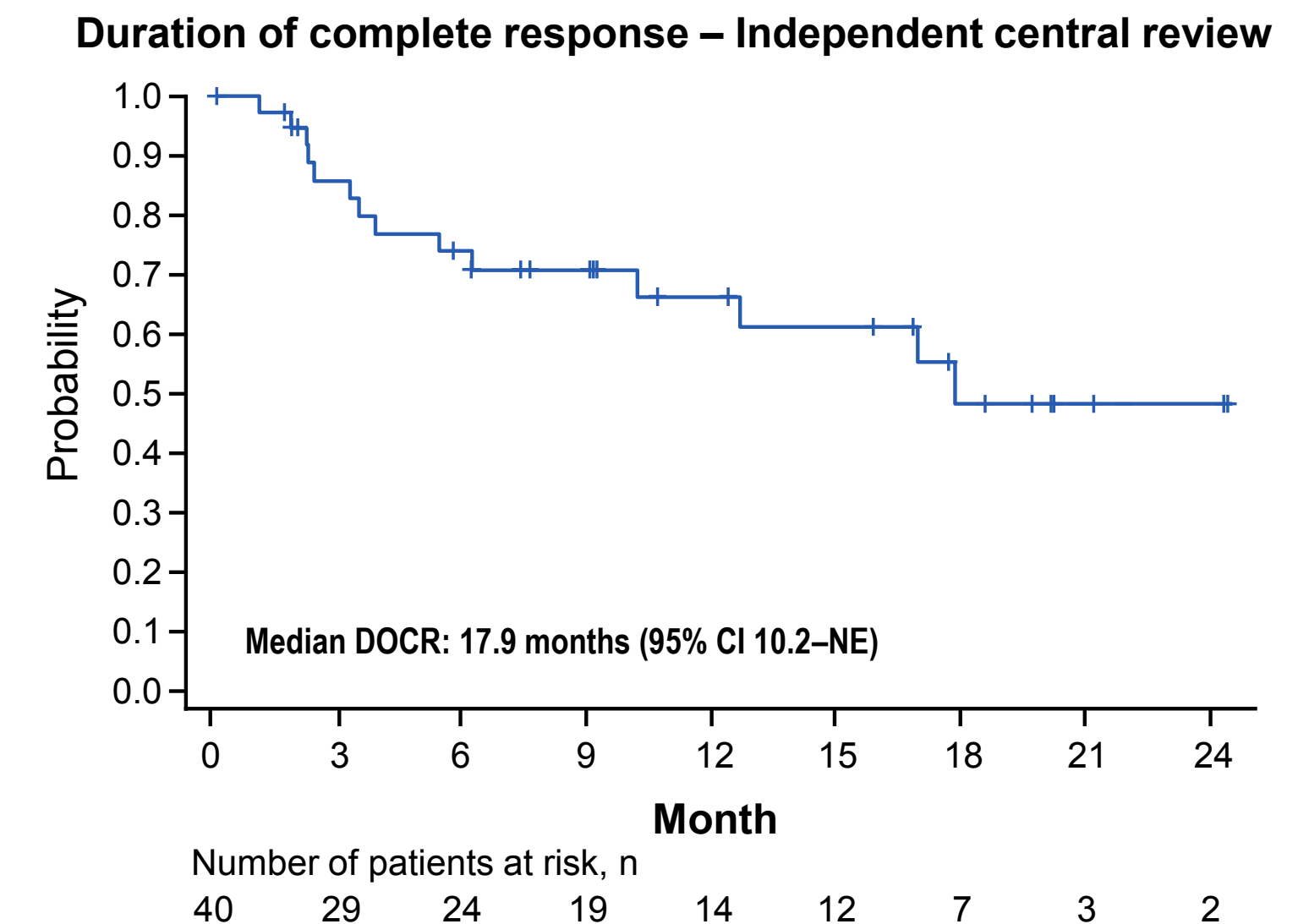
Cycles 5+

Odronextamab IV
160 mg Q2W

*21-day cycles.



- 12-month DOR: 49.4% (95% CI: 35.0–62.2)
- 18-month DOR: 38.9% (95% CI: 23.9–53.6)



- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

Data cut-off date: Sep 15, 2022.
CI, confidence interval; DOCR, duration of complete response; DOR, duration of response; NE, not evaluable.

OLYMPIA-3: Phase III open label study evaluating efficacy and safety of Odro-CHOP vs R-CHOP in 1L DLBCL is ongoing

Kim WS et al. ASH 2022

Verona, 26-27 settembre 2025

Moving beyond R-CHOP/Pola-R-CHP

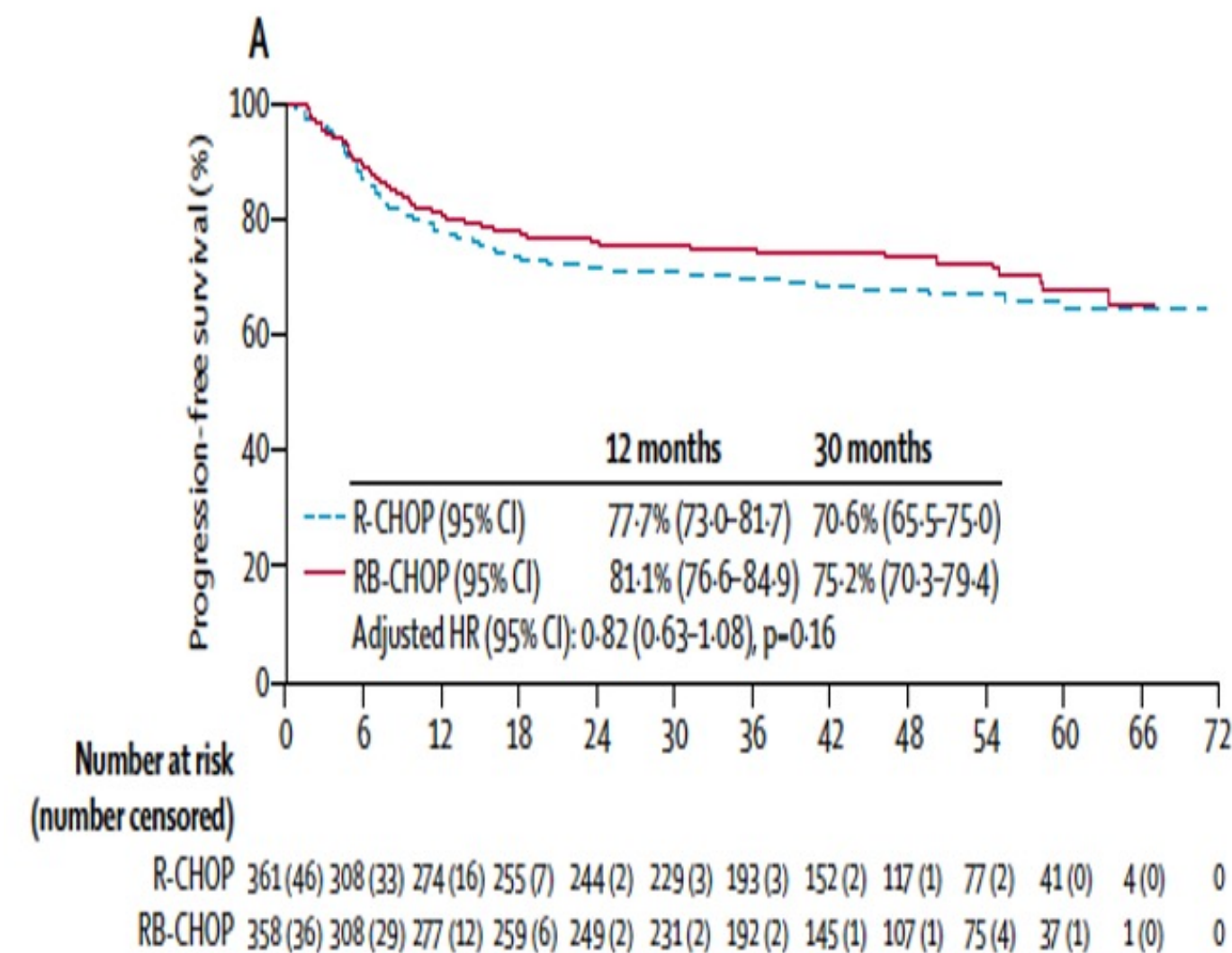
- ✓ “Agnostic” approach
- ✓ Biology-driven approach
- ✓ Chemo-free approach

Moving beyond R-CHOP/Pola-R-CHP

- ✓ “Agnostic” approach
- ✓ **Biology-driven approach**
- ✓ Chemo-free approach

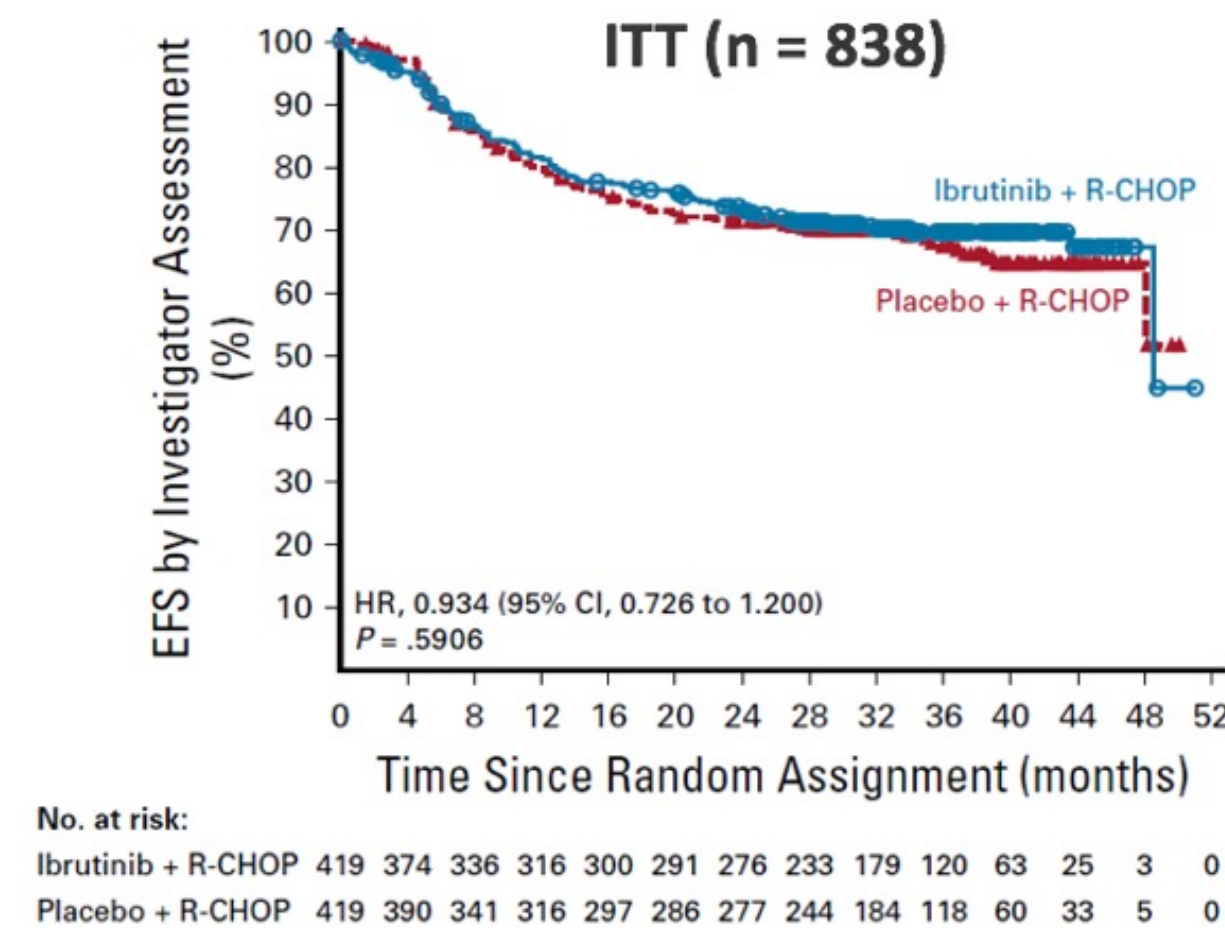
COO-Based approaches

R-CHOP + Bortezomib



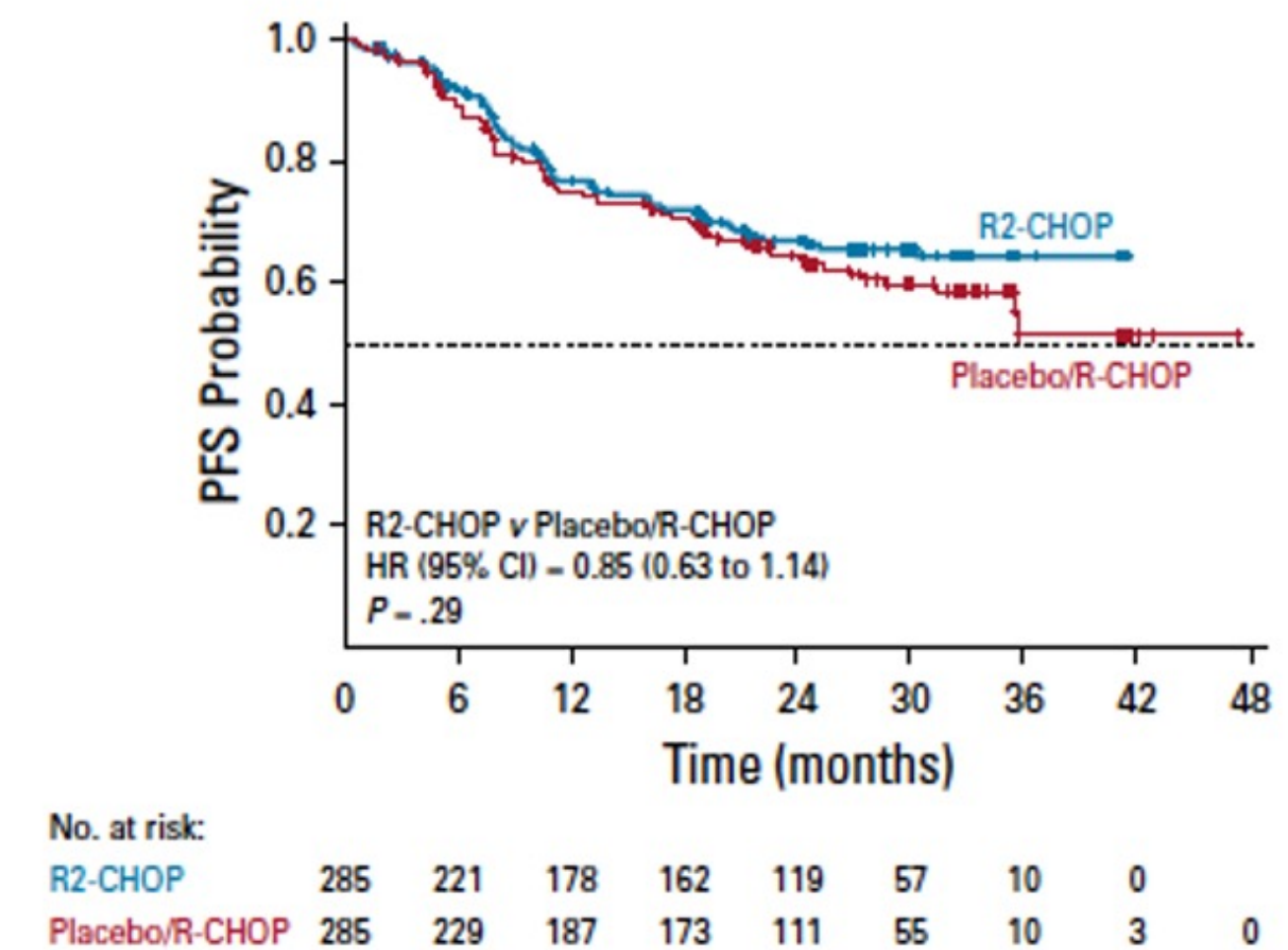
COO by DASL

R-CHOP + Ibrutinib



Non-GCB by IHC

R-CHOP + Lenalidomide



ABC by Lymph2Cx

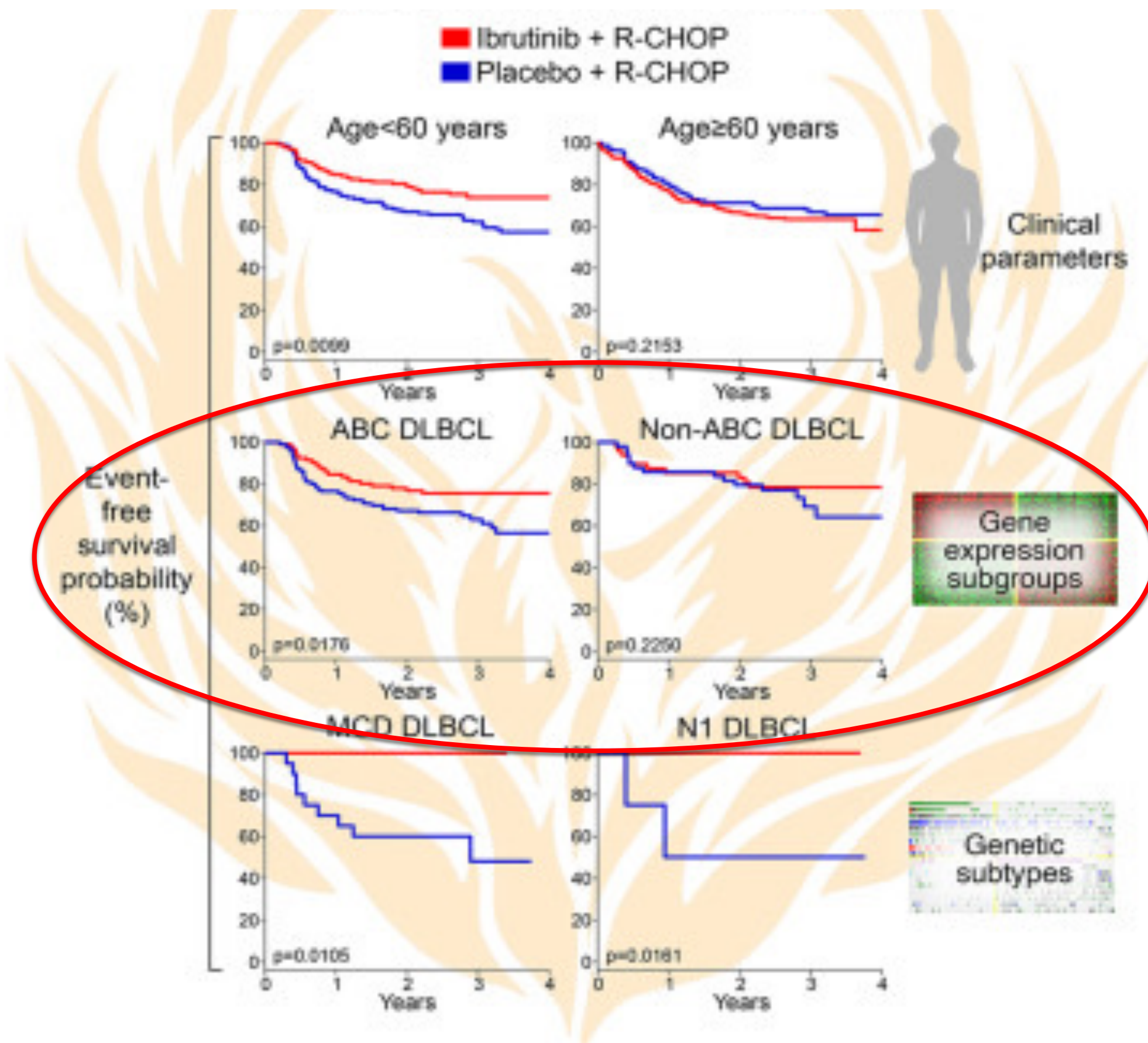
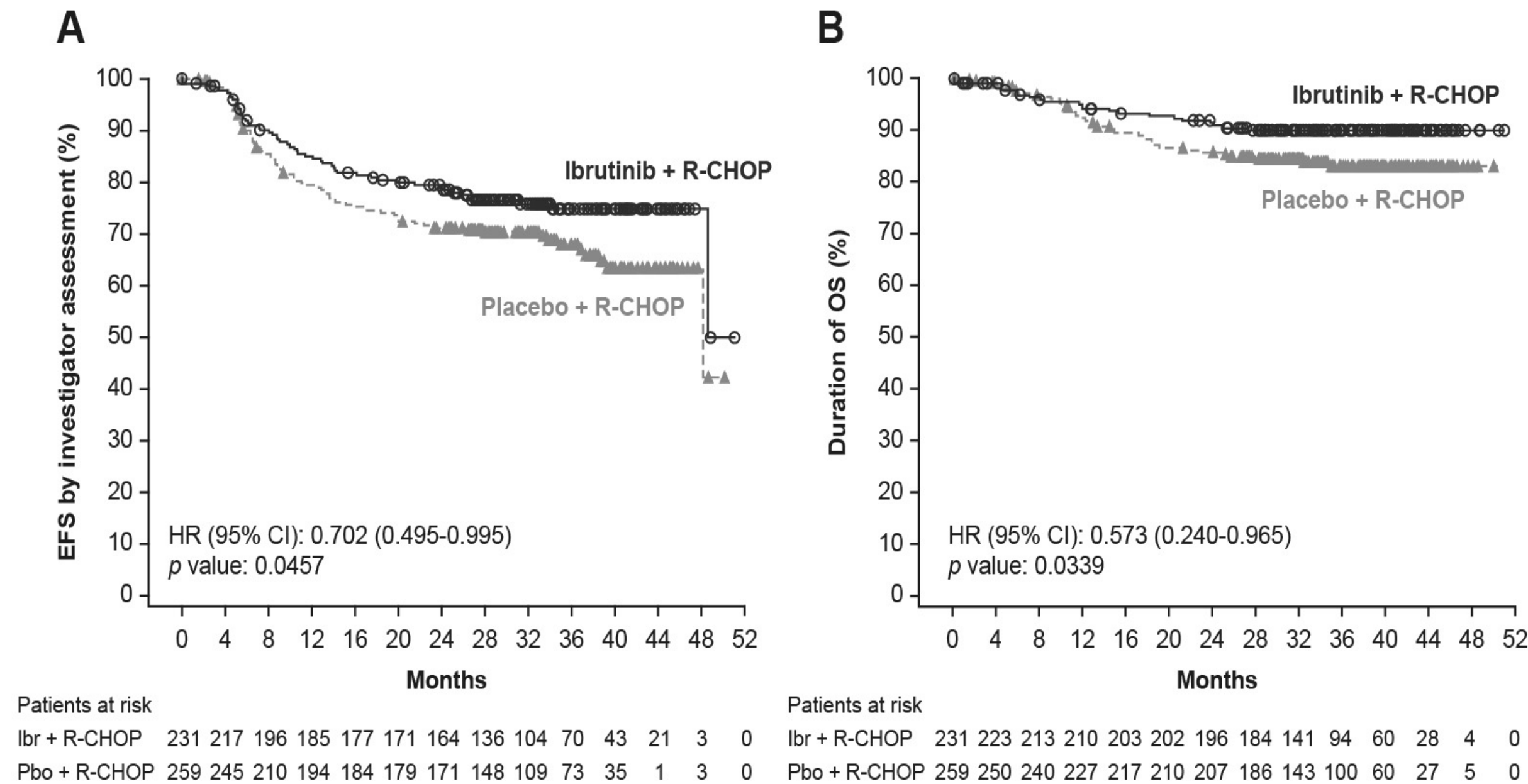


Davies A, et al. Lancet Oncol 2019; Younes A, et al. J Clin Oncol 2019; Nowakowski G, et al. J Clin Oncol 2021.

Phoenix trial: Subgroup analysis

✓EFS and OS in patients < 60 years

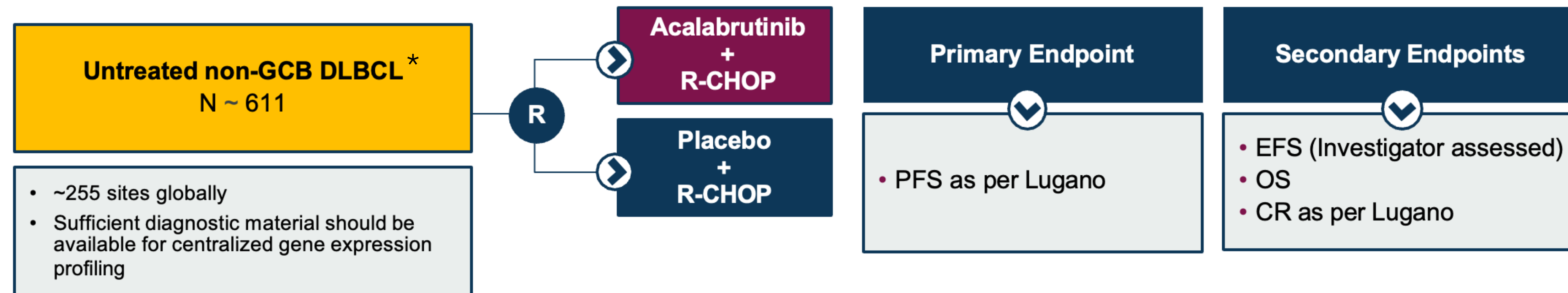
✓By GEP : ABC DLBCL (n = 239, 70.2%)



Johnson P et al, Blood 2019

Wilson W, et al Cancer Cell 2021

ESCALADE (ACE-LY-312): Phase III, Randomized, Double-Blind Study of Acalabrutinib + R-CHOP for 1L Non-GCB Subtype DLBCL



Key Inclusion Criteria	Key Exclusion Criteria	Key Trial Dates
• Adults ≥18 and ≤75 years of age** • Histologically documented DLBCL (confirmation of non-GCB subtype by centralized gene expression profiling) • No prior treatment for DLBCL ** • ECOG performance status of 0 to 2 • Stage II–IV disease • IPI score of 1–5	• Known CNS lymphoma or leptomeningeal disease • Primary mediastinal lymphoma • High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements • History of indolent lymphoma or CLL • History of, or ongoing confirmed PML • Significant cardiovascular disease	Study start date: October 8, 2020 Estimated study completion date: February 5, 2027 Estimated primary completion date: February 5, 2027 Current status: Active, not recruiting

* By GEP

** first design ≤ 65 years, IPI 2-5

Enrollment completed

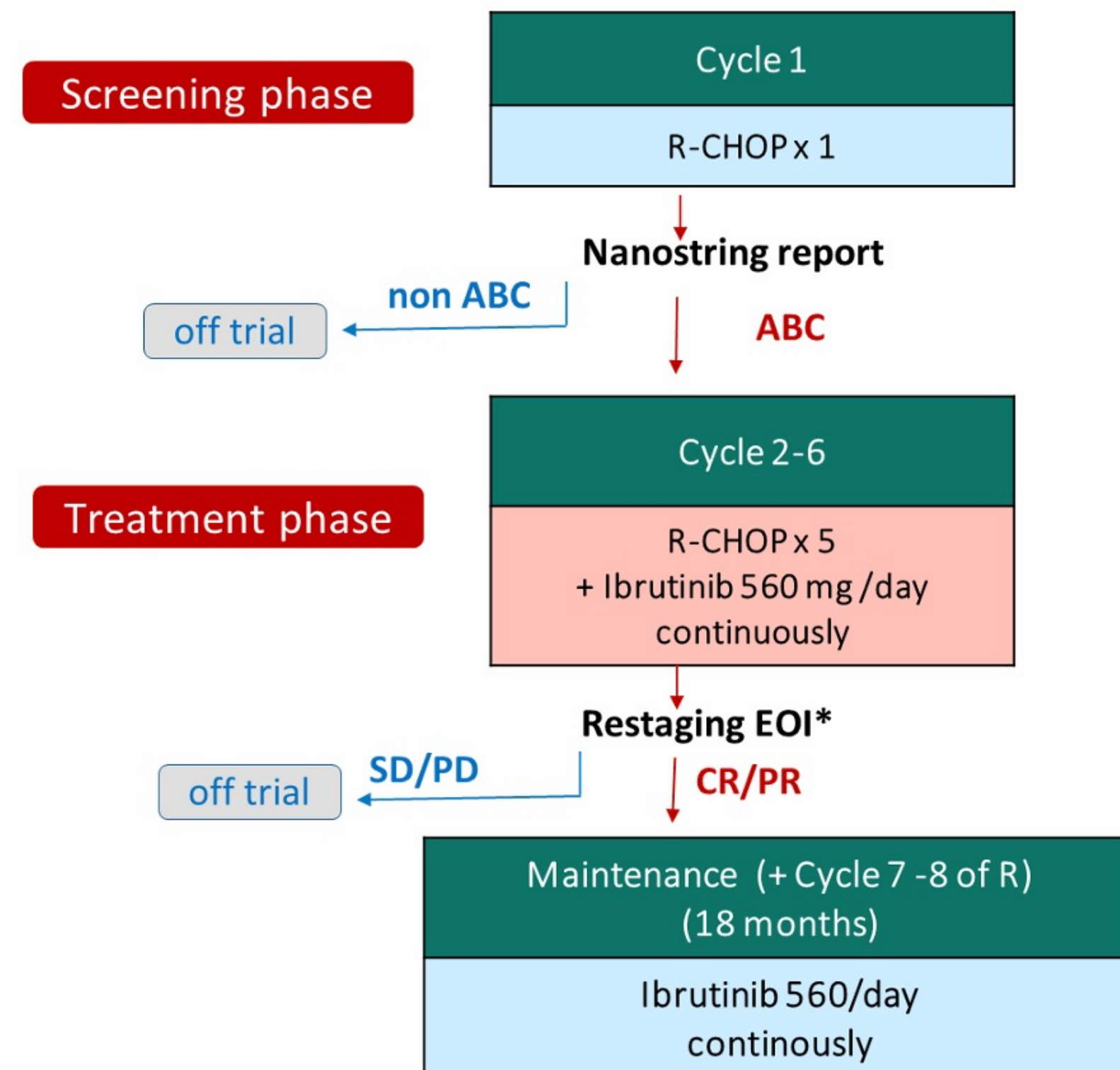
Results pending..

Verona, 26-27 settembre 2025

Phase II multicenter single arm study to evaluate the efficacy and safety of ibrutinib in combination to rituximab-CHOP followed by ibrutinib maintenance in untreated patients ABC-DLBCL at intermediate-high and high risk (IPI ≥ 2)



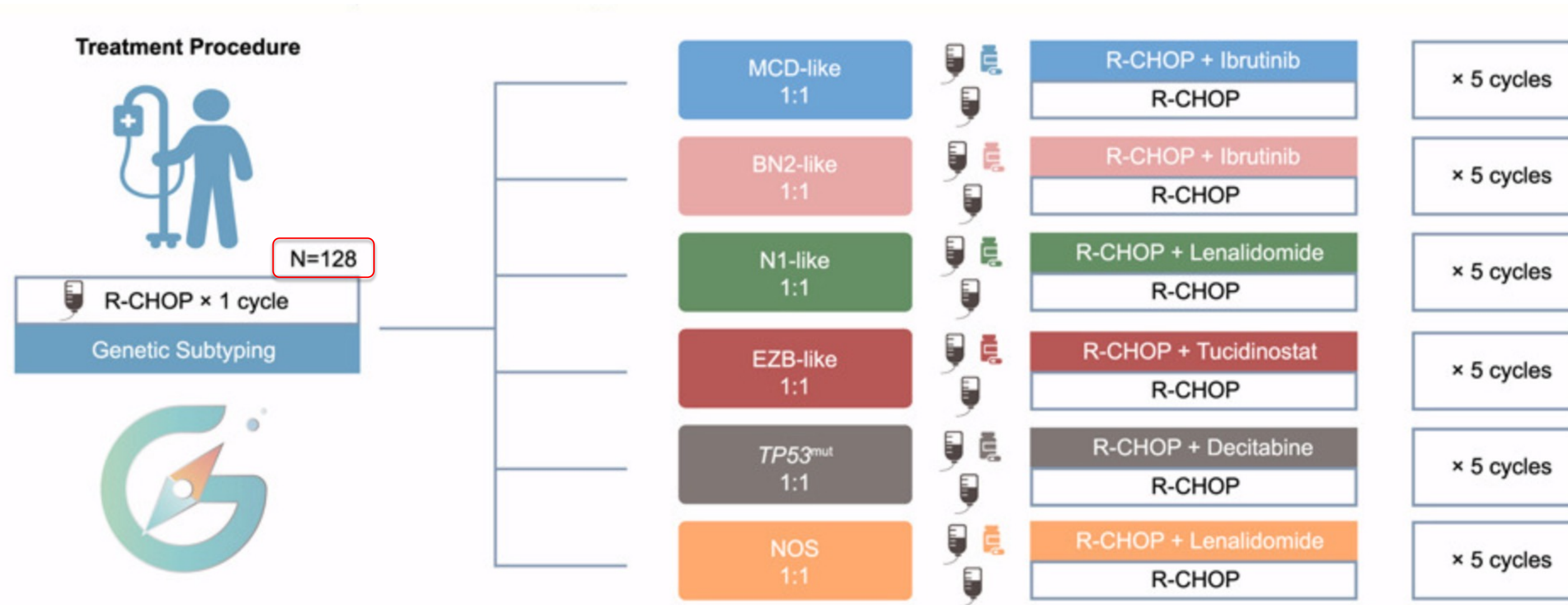
FIL_RI-CHOP



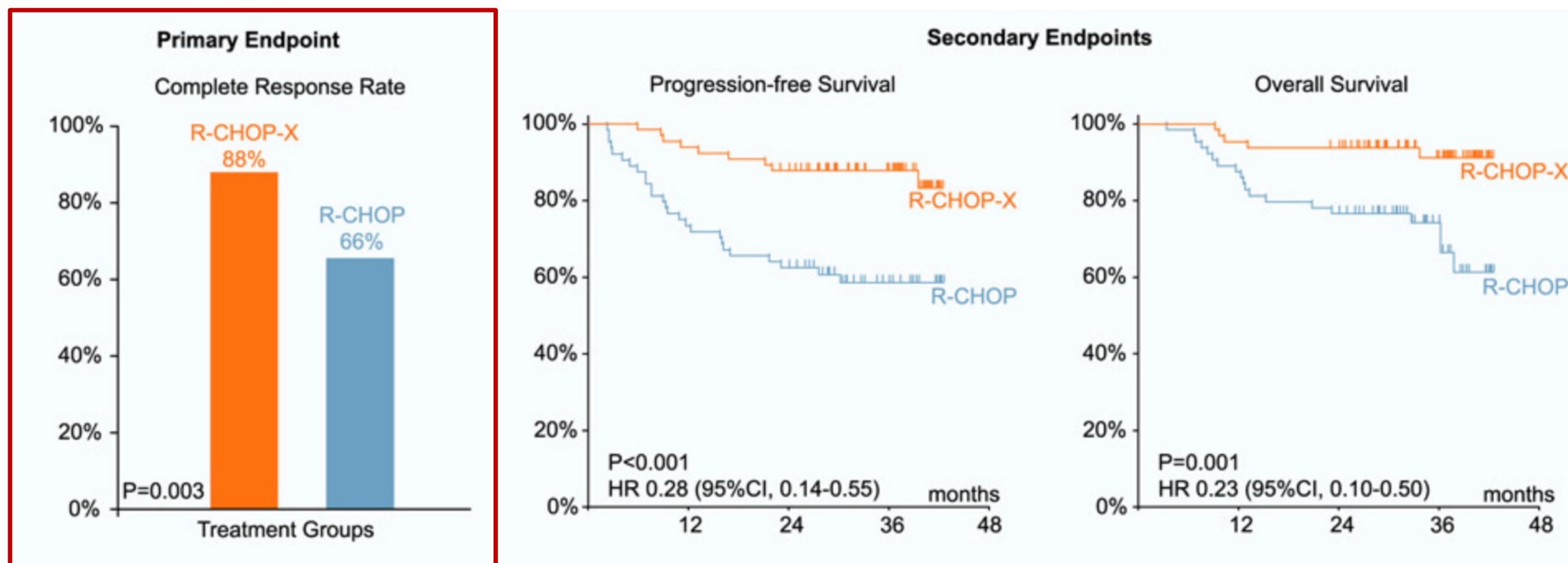
Totale pazienti screenati: **279 pazienti** (**204 screening failure** e **75 DLBCL-ABC**)

Results pending ...

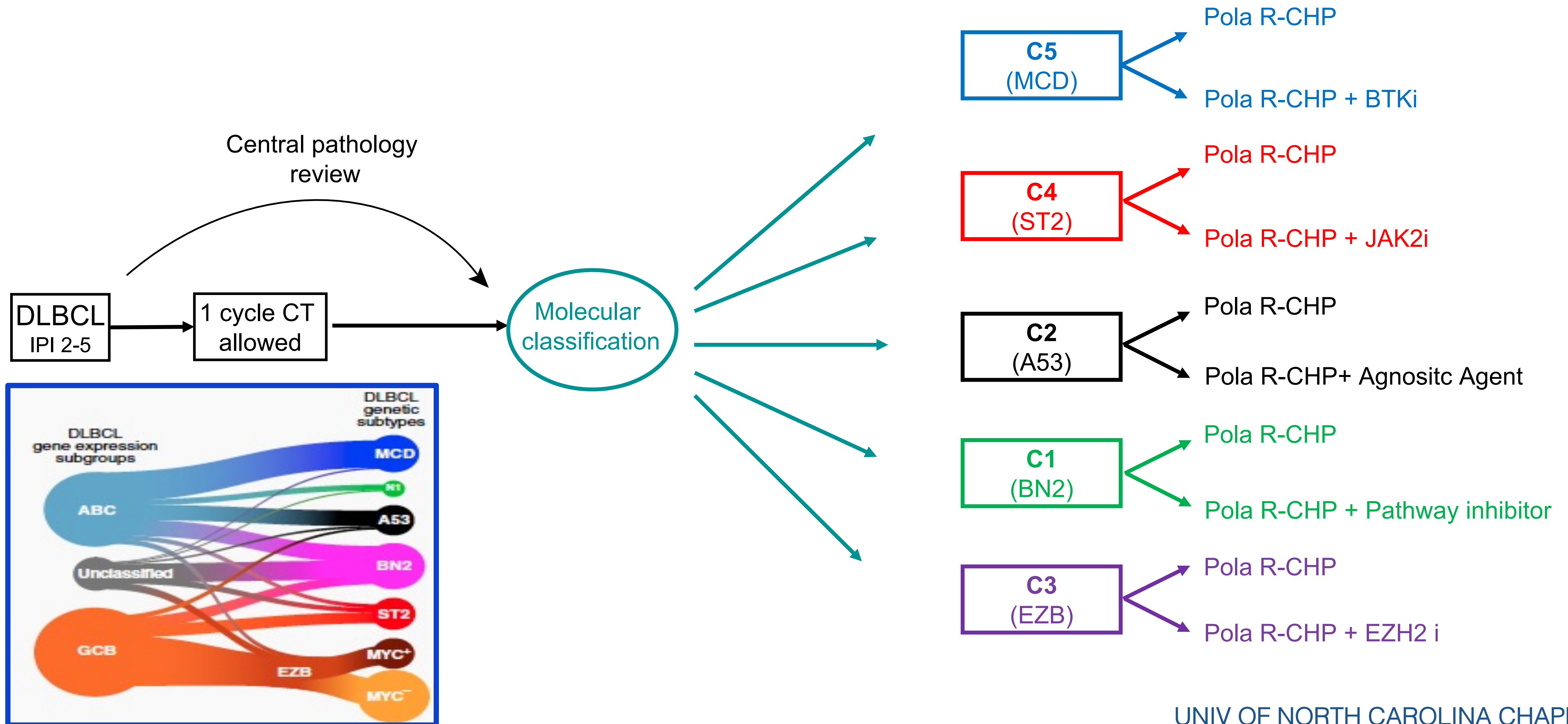
GUIDANCE-01 trial: Genetic subtype-guided immunochemotherapy in DLBCL



GUIDANCE-02: Phase III multicenter study evaluating efficacy of genetic-subtype-guided R-CHOP+X vs R-CHOP in 1L DLBCL is ongoing



LymphoMATCH trial



UNIV OF NORTH CAROLINA CHAPEL HILL

Moving beyond R-CHOP/Pola-R-CHP

- ✓ “Agnostic” approach
- ✓ Biology-driven approach
- ✓ Chemo-free approach

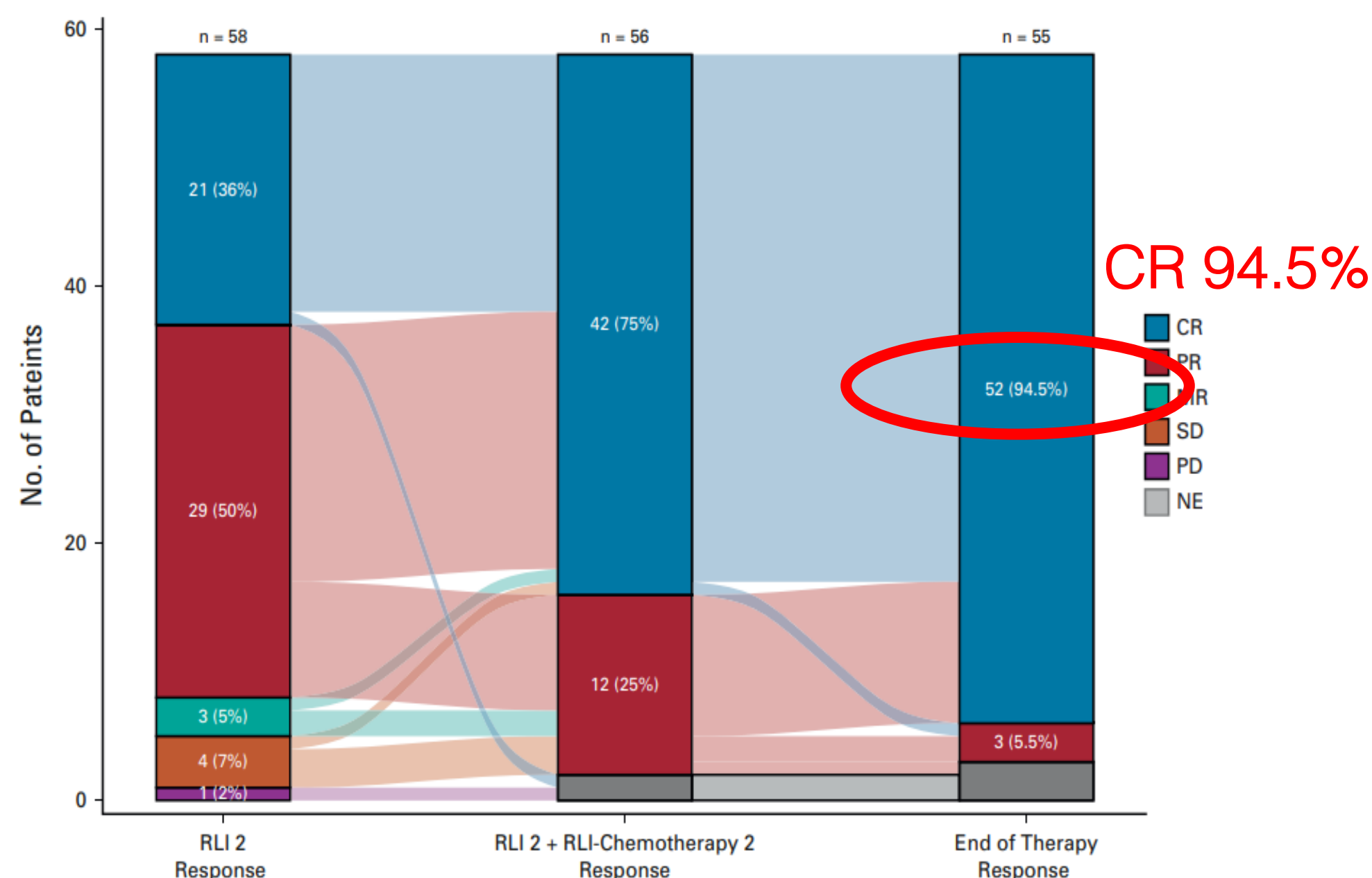
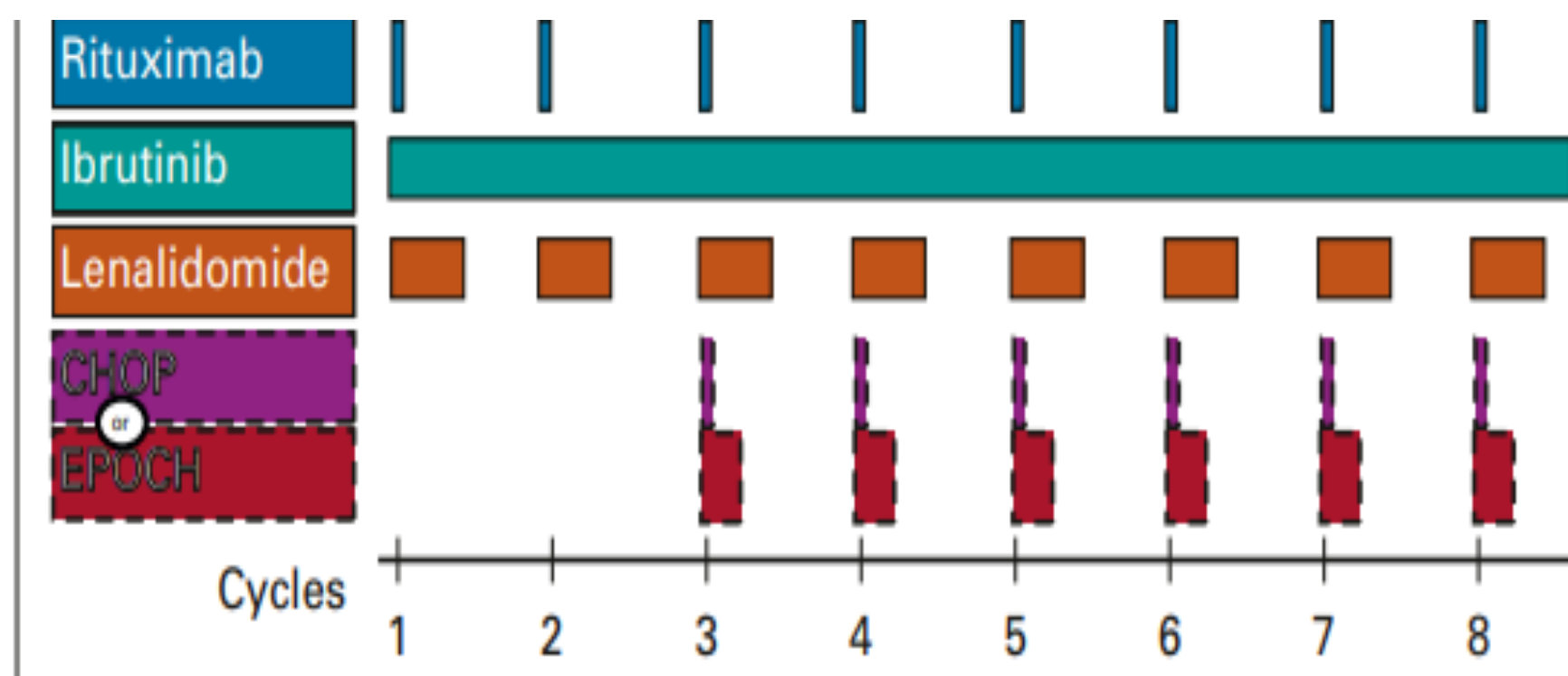
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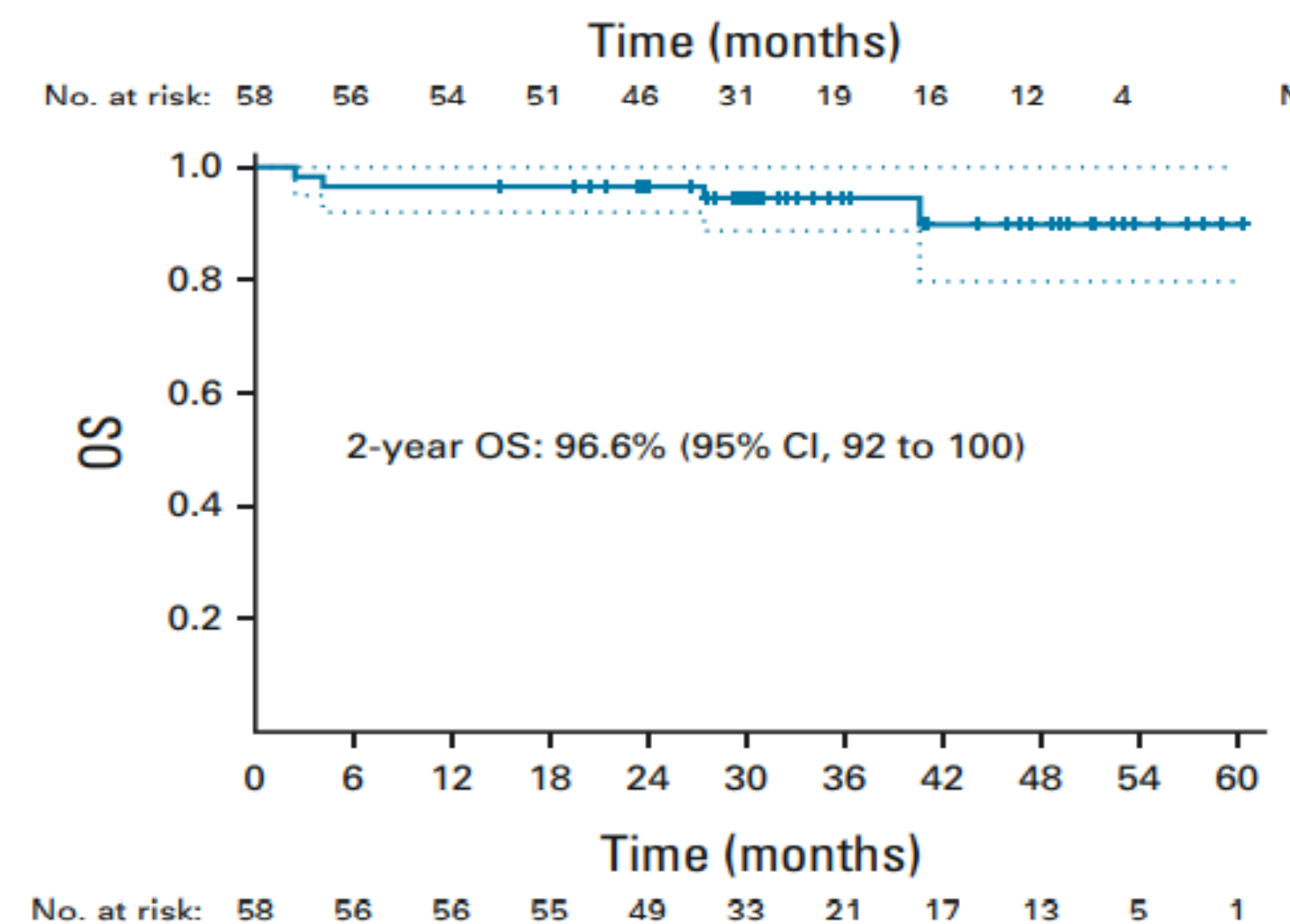
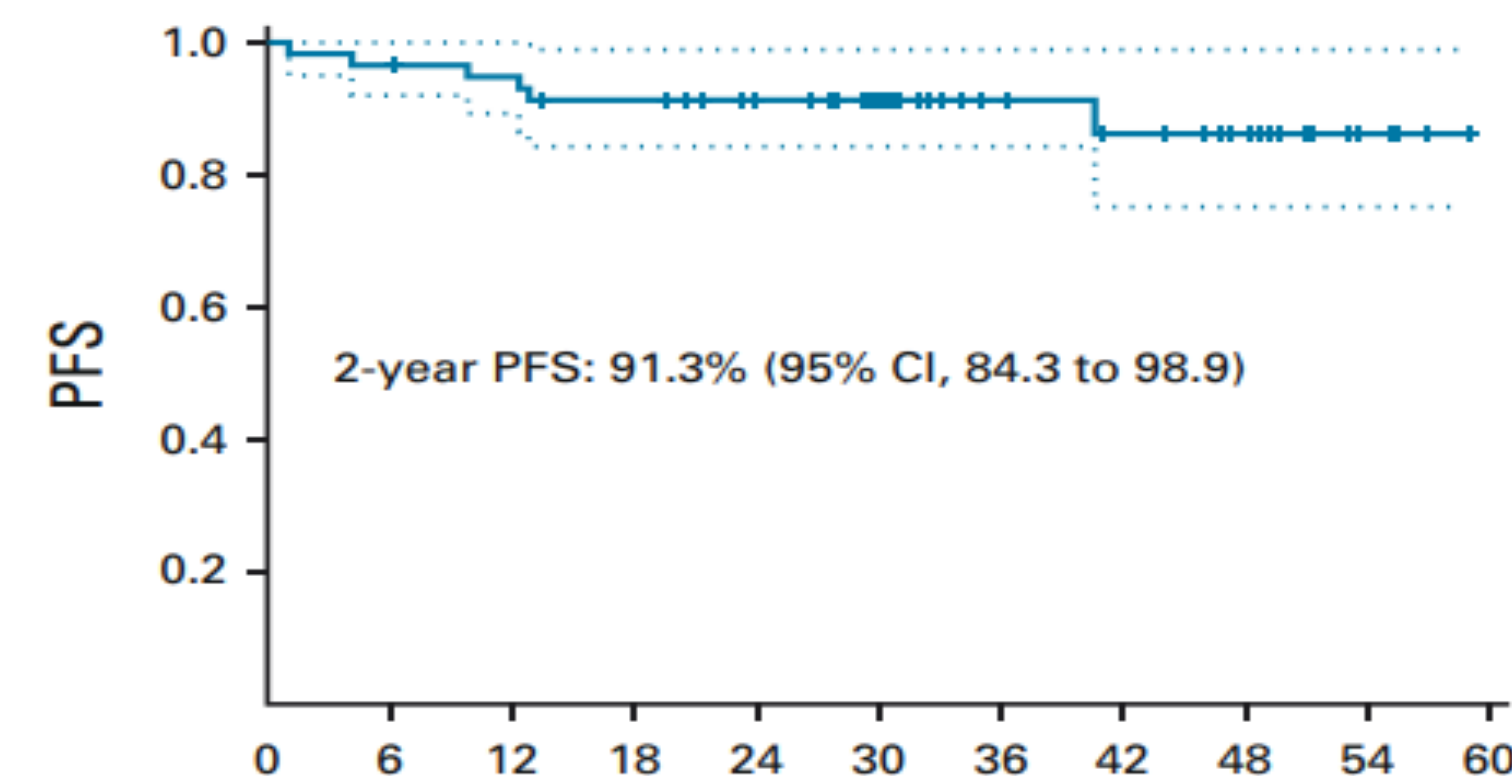
SMART START: R+Len+Ibrutinib (RLI) Lead-in Prior to Addition of Chemotherapy for 1L DLBCL

Phase II,
single center

- N = 60 pts
- Non-GCB (IHC)
- IPI 3-5



Median follow-up 31 months



Westin J et al, J Clin Onc 2022

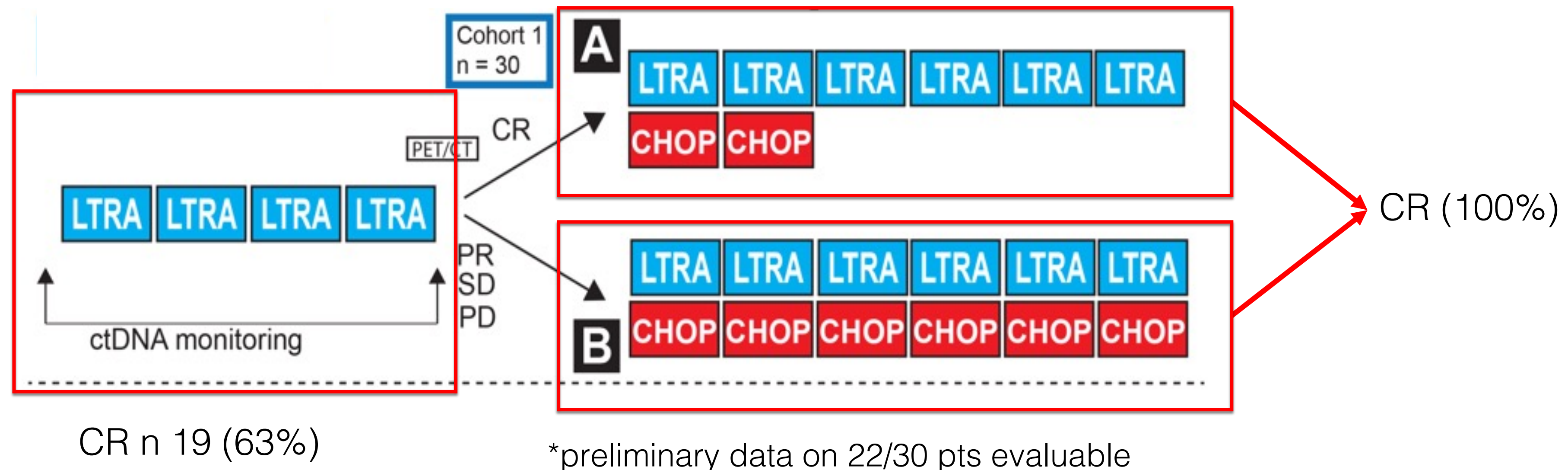
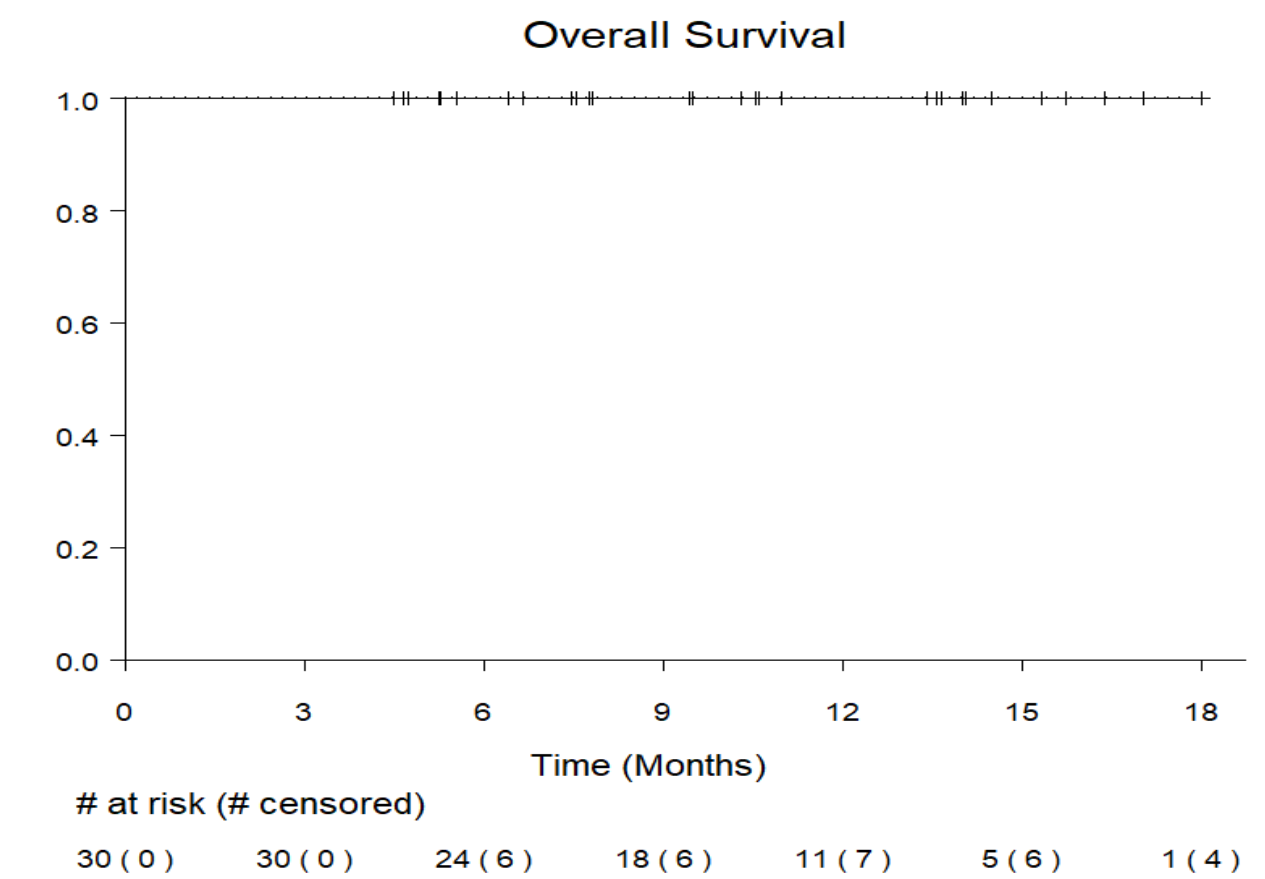
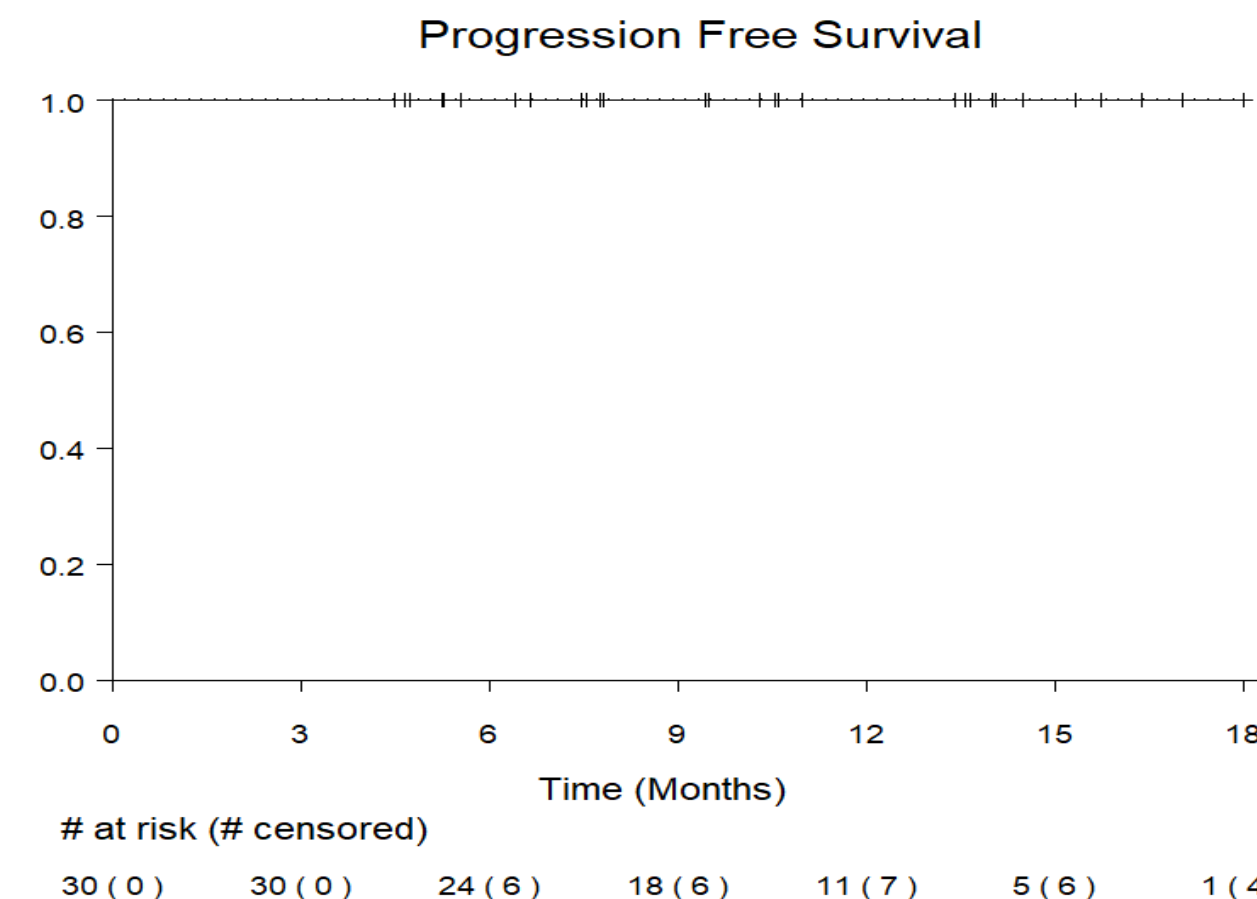
Smart Stop: Len + Tafa + R + Acalabrutinib Alone and with Chemotherapy for 1L DLBCL

Phase II, Single center

Lenalidomide
Tafasitamab
Rituximab
Acalabrutinib

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/m2	IV	Once	1
Acalabrutinib (A)	100mg	PO	BID	1-21

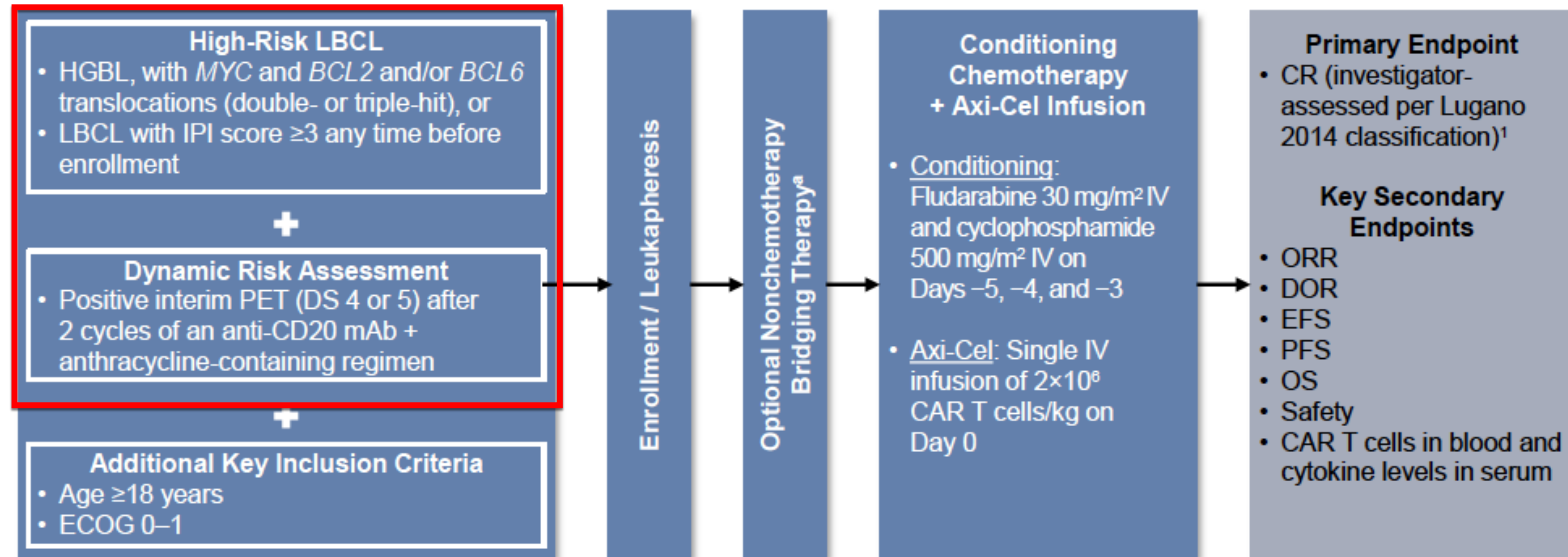
LTRA



Moving beyond R-CHOP/Pola-R-CHP

- ✓ “Agnostic” approach
- ✓ Biology-driven approach
- ✓ Chemo-free approach
- ✓ jumping ahead: CAR-T in front line

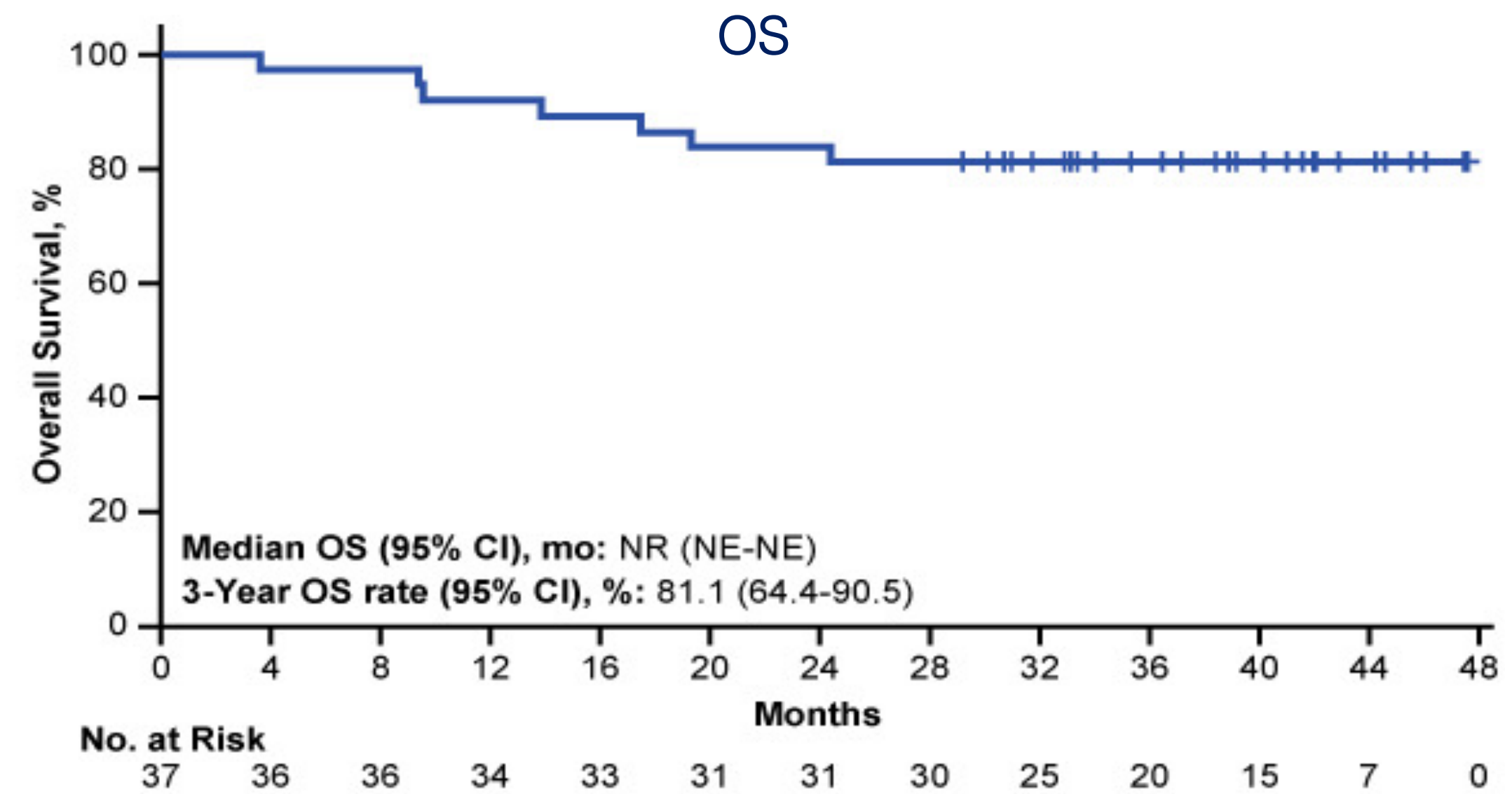
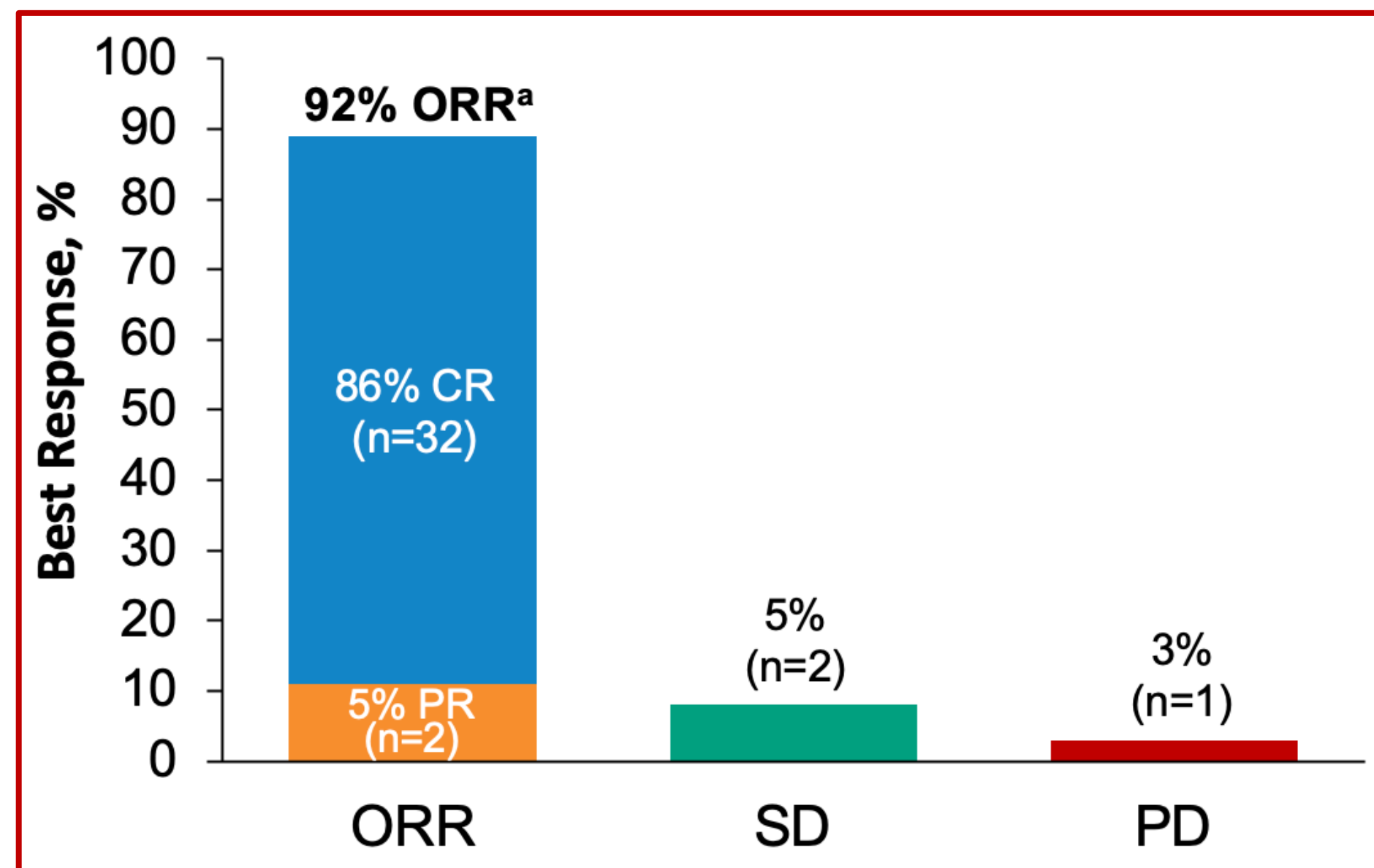
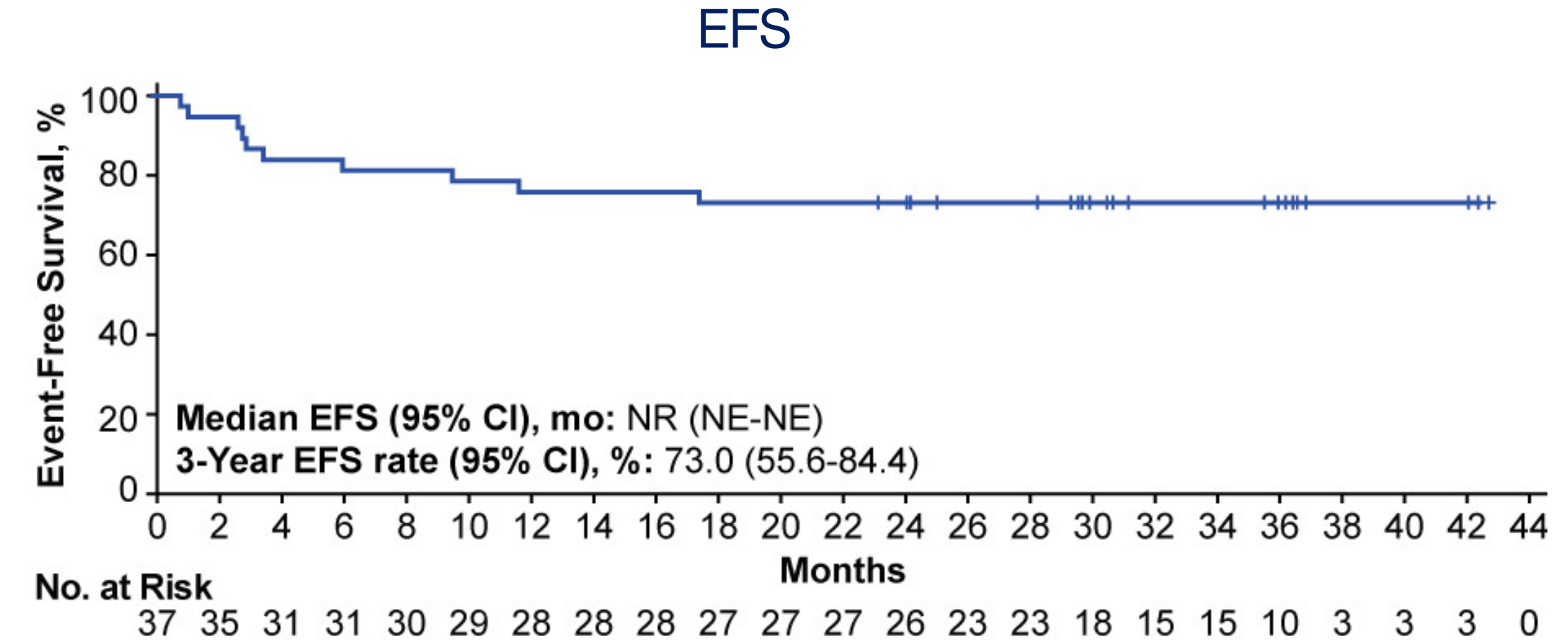
ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as 1L in Patients with High-Risk LBCL



The young side of LYMPHOMA

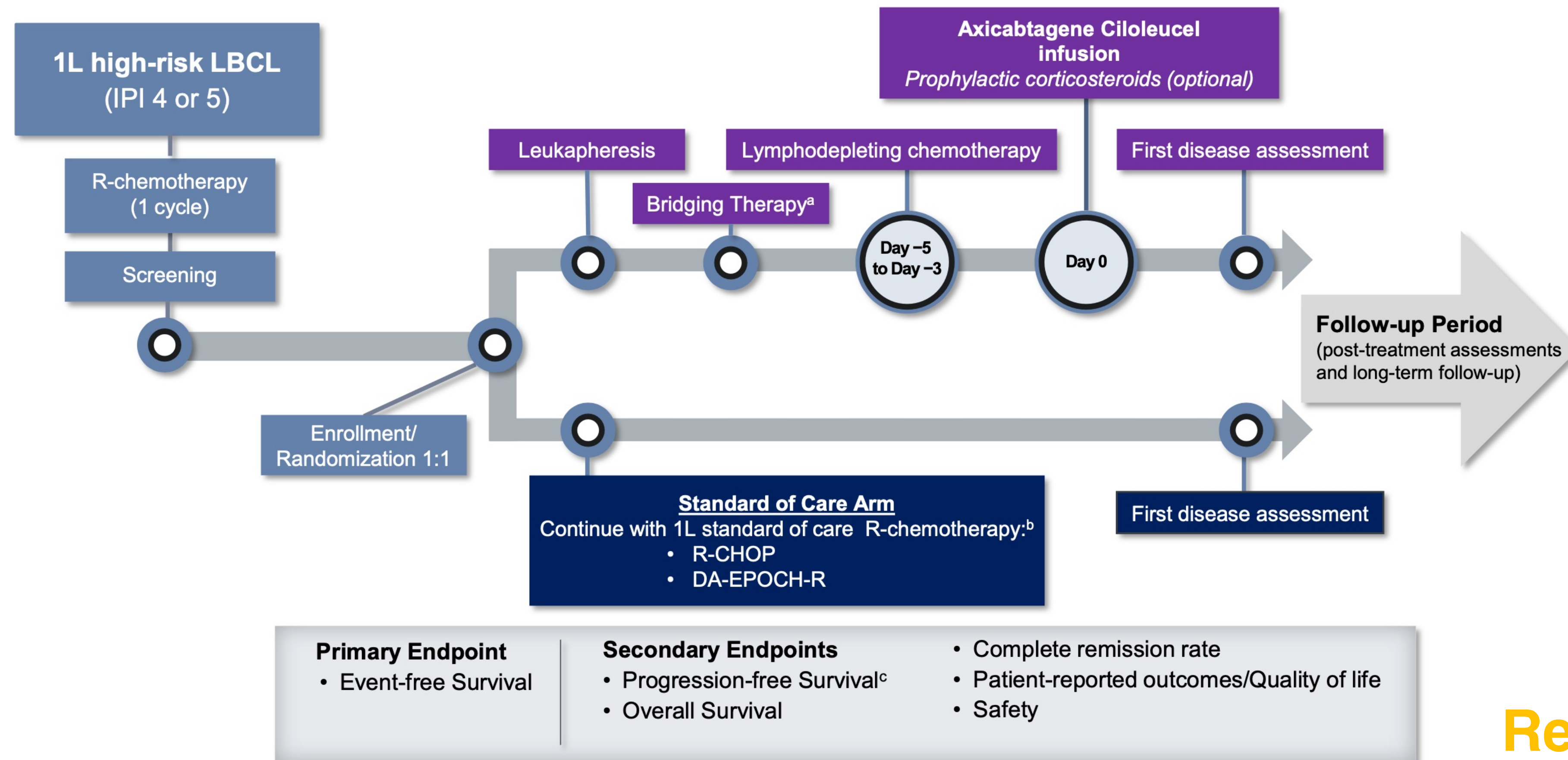
gli under 40 a confronto

Efficacy Evaluable n=37 ^b	
Overall CR rate, % (95% CI)	86 (71-95)
DHL/THL and IPI score ≥ 3 (n/N)	4/4 100 (40-100)
DHL/THL only (n/N)	5/6 83 (36-100)
IPI score ≥ 3 only (n/N)	23/27 85 (66-96)
Patients converted from PR/SD to CR, n (%)	9 (24)
PR to CR	8 (22)
SD to CR	1 (3)



Neelapu SS, et al. Nature Med 2023; Chavez et al, ASH 2023

ZUMA-23: an adaptive phase III, randomized, open-label, multicenter study to compare axi-cel vs SOC as 1L for high-risk LBCL



Recruiting...

^aBridging therapy with R-CHOP or DA-EPOCH-R will be administered during the cell manufacturing period.

^bParticipants will receive the investigator's choice of either R-CHOP or DA-EPOCH-R for a total of 6 cycles (21-day cycle).

^cBy both blinded Central Assessment and Investigator Assessment

1L DLBCL ongoing phase III trials

Agent	Trial	Pts	N	Primary endpoint
Acalabrutinib	ESCALADE	nonGCB, IPI 1-5	600	PFS
Tafasitamab-len	FrontMIND	IPI 3-5	880	PFS
Glofitamab	SKYGLO	IPI 2-5	1130	PFS
Epcoritamab	EPCORE-DLBCL-2	IPI 2-5	900	PFS
Odronextamab	OLYMPIA-3	IPI 2-5	840	PFS
Axi-cel	ZUMA-23	IPI 4-5	300	EFS

DOMANDA n 2

Settembre 2030:

Paziente di 40 aa con diagnosi di DLBCL (non GCB), in stadio IVB (localizzazioni pleuropolmonari, gastrica, peritoneale, surrene), IPI 3, CNS IPI4 (stadio, LDH, sedi extranodali, surrene). Quale terapia 1L?

- a. Pola-R-CHP
- b. Tafa-Lena-R-CHOP
- c. Acala-R-CHOP
- d. Glofi-Pola-R-CHP
- e. EpcO-R-CHOP/(Pola-R-CHP)
- f. Odro-CHOP
- g. CAR-T

The young side of LYMPHOMA

gli under 40 a confronto



Verona, 26-27 settembre 2025

Grazie per l'attenzione !

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