



POST-NEW ORLEANS 2022

Novità dal Meeting della Società Americana di Ematologia

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Milano

Teatro Dal Verme

2-3-4 Febbraio 2023

COORDINATORI

Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO

Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

2° SESSIONE - LINFOMA II

15.55 Stato dell'arte

16.05 Linfomi indolenti

16.25 Linfomi aggressivi di derivazione B linfocitaria

16.45 Terapie di salvataggio con anticorpi monoclonali

17.05 Discussione

M. MARTELLI

M. MARTELLI

M. LADETTO

A.J.M. FERRERI

L. RIGACCI

Stato dell'arte

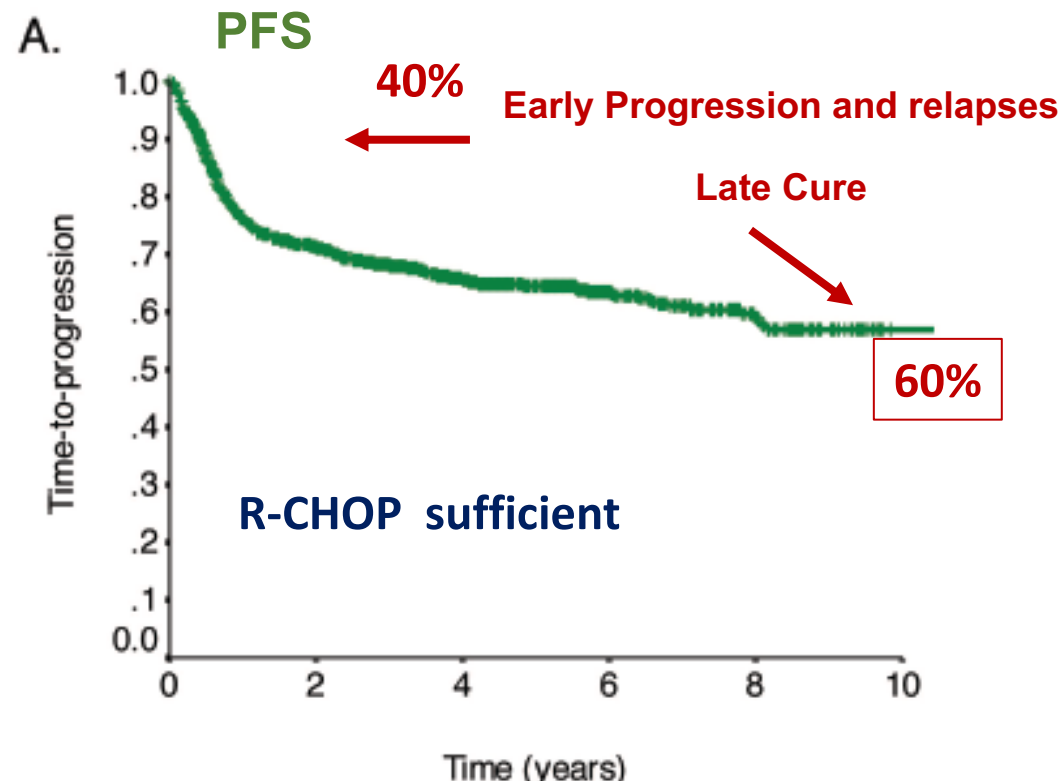
Maurizio Martelli
Ematologia Sapienza Roma



DICHIARAZIONE Maurizio Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Gilead					X	X	
Novartis						X	
Takeda						X	
Eusapharma					X	X	
Incyte					X	X	
Janssen					X	X	
BMS						X	
Beigene					X		
Alexion	x						

Heterogeneity of outcomes in DLBCL treated with R-CHOP

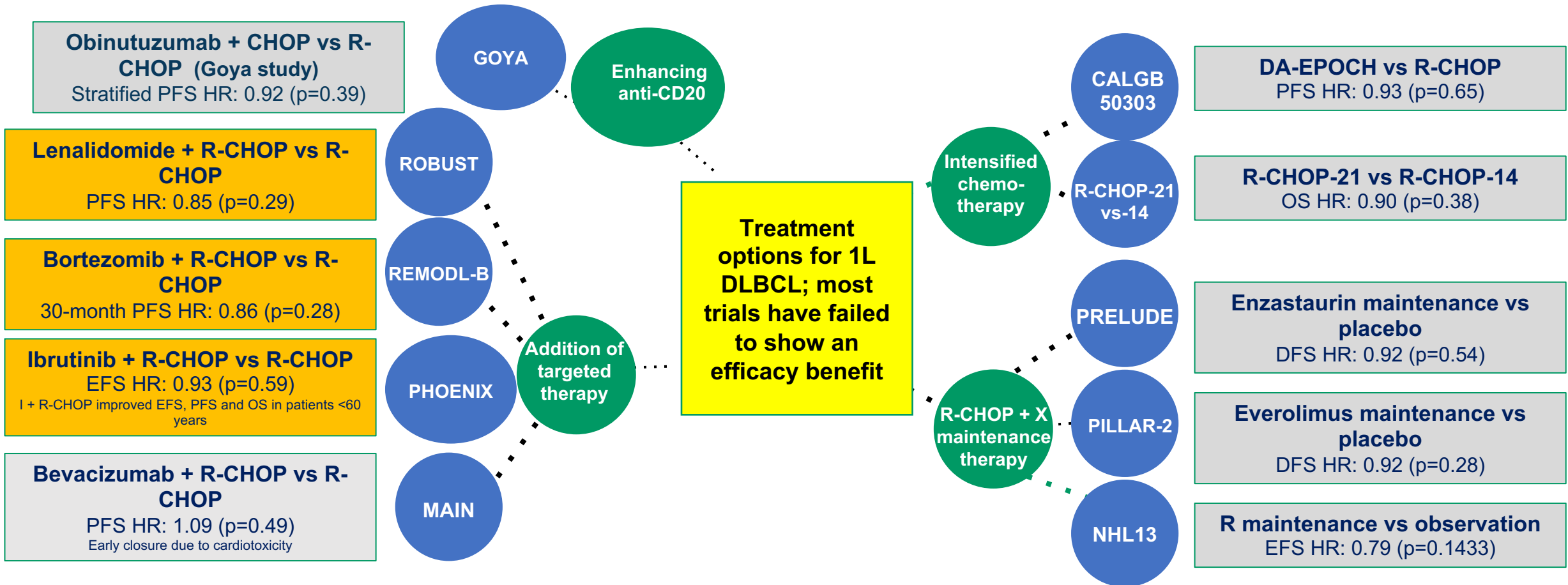


Patients with DLBCL treated with R-CHOP-21 at BCCA (n = 1,476)

R-CHOP is insufficient in 40% of DLBCL:

- Clinical factors
 - IPI (R-IPI)
- GEP
 - ABC vs GCB
- Protein expression
 - MYC and BCL2
- TP-53 expression
- Chromosomal alterations
 - MYC, BCL2, BCL6
- Deep sequencing mutation/combined expression analysis

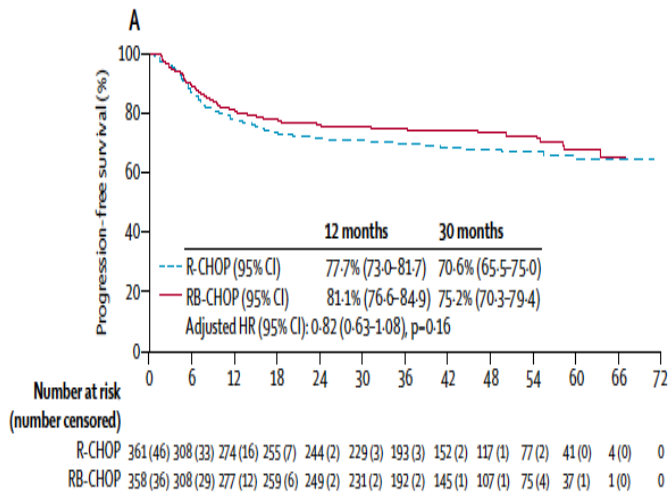
Treatment options to improve first line DLBCL



R-CHOP+ X targeting ABC: results of phase III trial

R-CHOP + Bortezomib

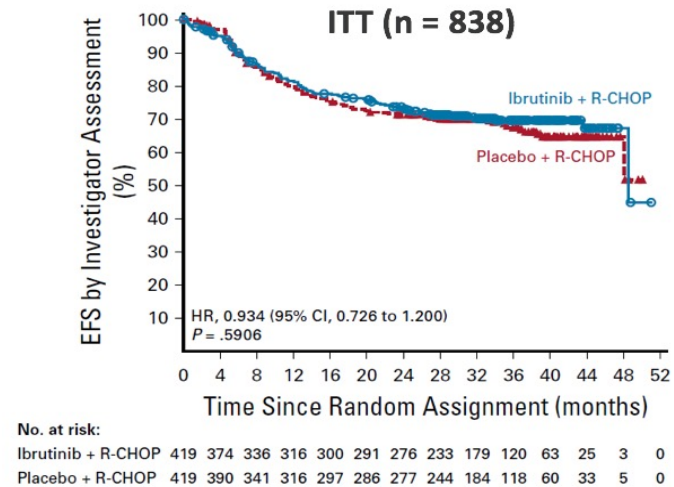
ReMoDL- B



Davies A, et al. Lancet Oncol 2019;

R-CHOP + Ibrutinib

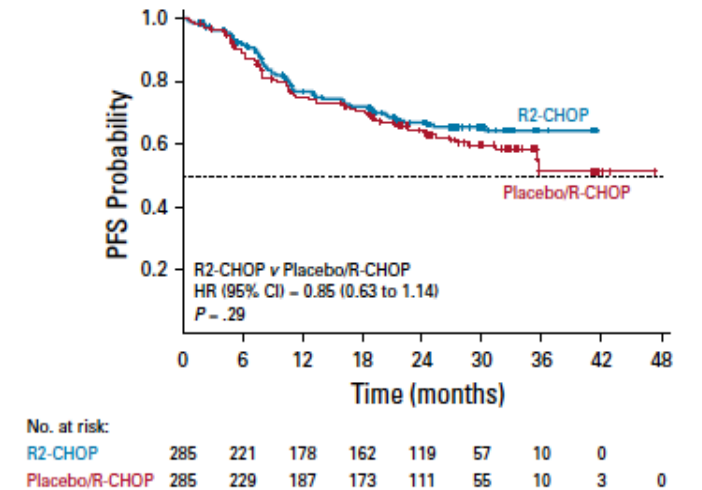
Phoenix



Younes A, et al. J Clin Oncol 2019;

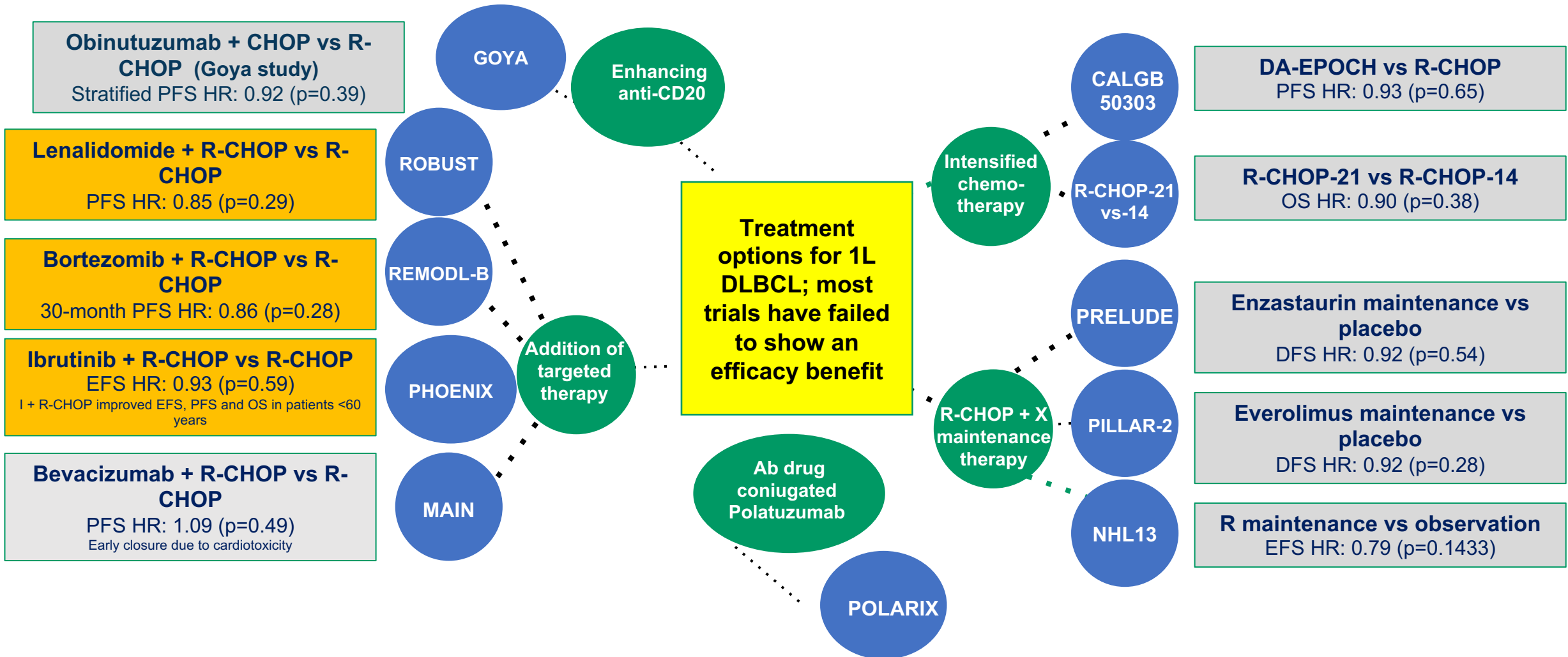
R-CHOP + Lenalidomide

Robust



Nowakowski G, et al. J Clin Oncol 2021.

Treatment options to improve first line DLBCL

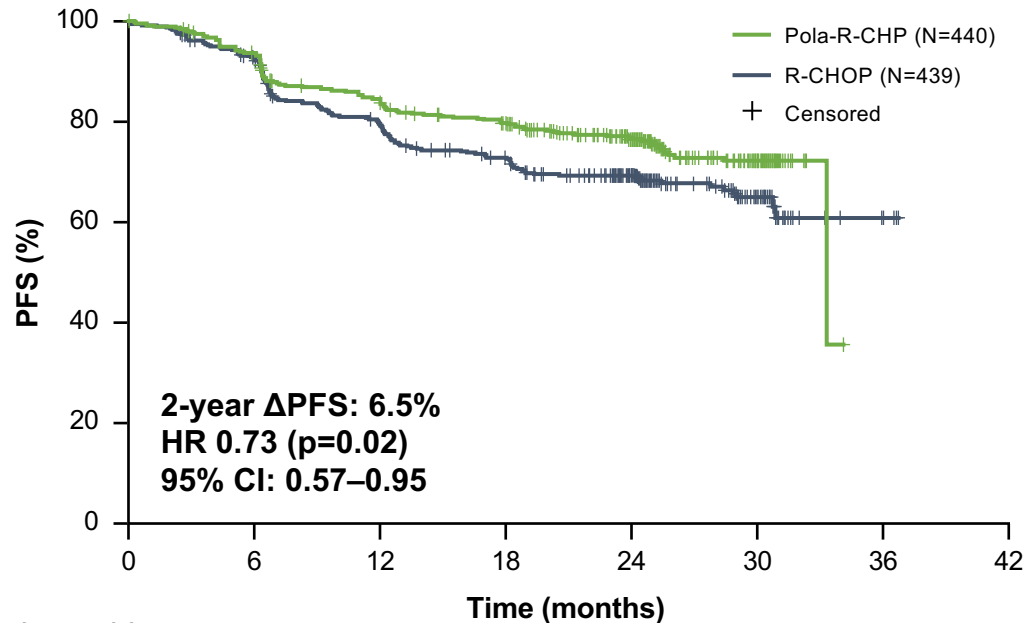


POLARIX: Polatumumab Vedotin + R-CHP vs R-CHOP

Primary endpoint: PFS

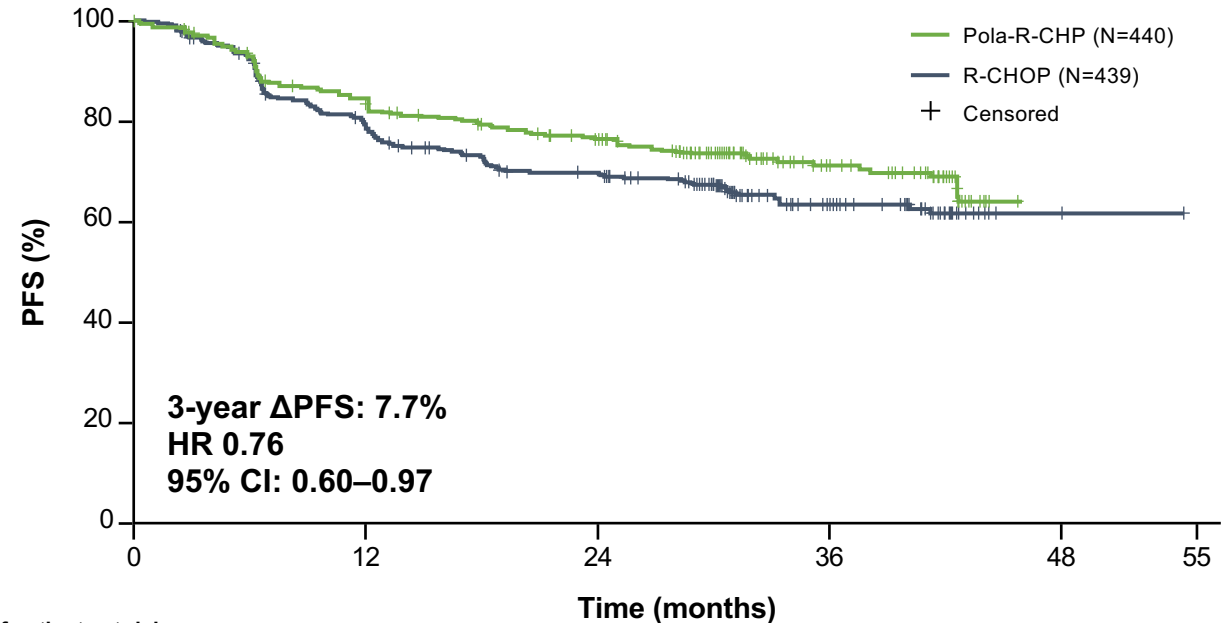
Primary analysis (CCOD: June 28, 2021)¹

Median follow-up: 28.2 months



Updated results (CCOD: June 15, 2022)

Median follow-up: 39.7 months



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	0	0
R-CHOP	439	389	330	296	220	78	3	0

No. of patients at risk

Pola-R-CHP	440	405	354	331	313	242	103	66	0	0
R-CHOP	439	390	331	300	284	222	94	59	2	1

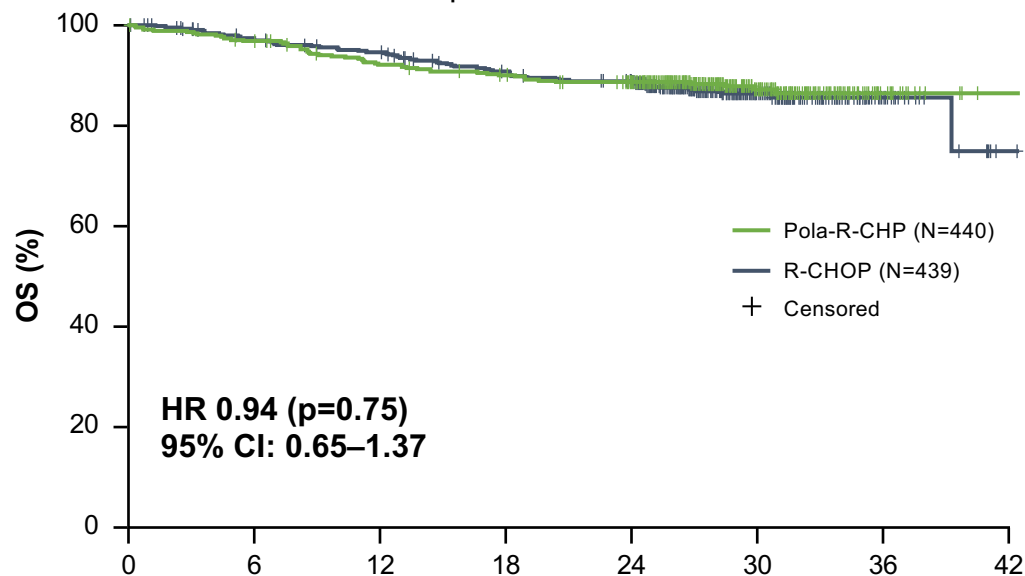
- Best overall response rate: **95.9 %** vs **94.1%**
 - Complete response rate: **86.6%** vs **82.7%**

POLARIX: Polatumumab Vedotin + R-CHP vs R-CHOP

No difference for OS

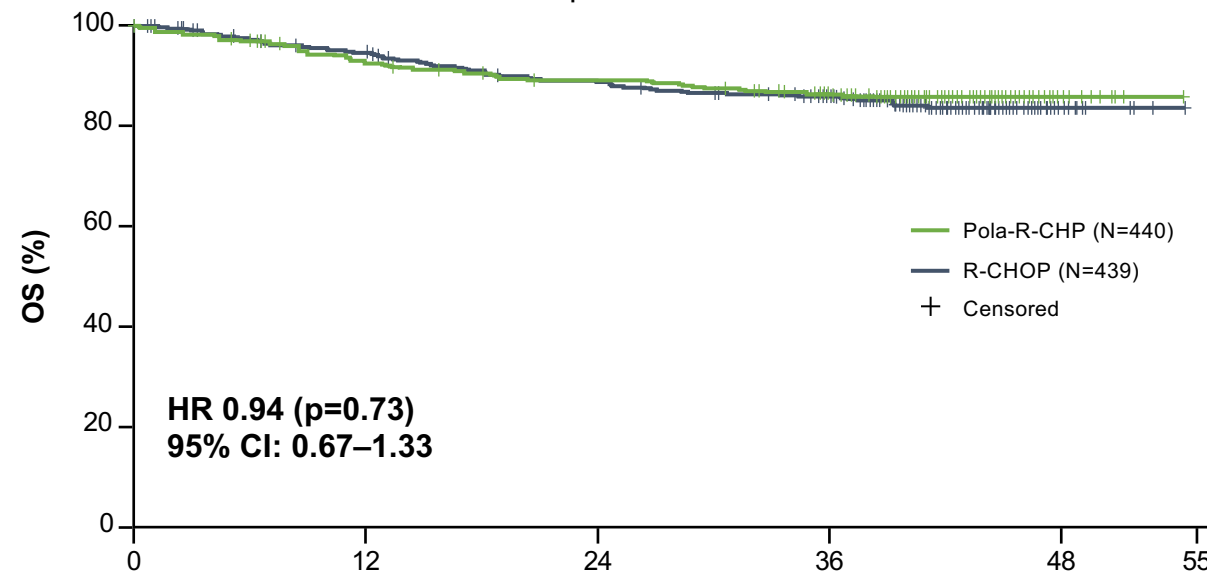
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No. of patients at risk

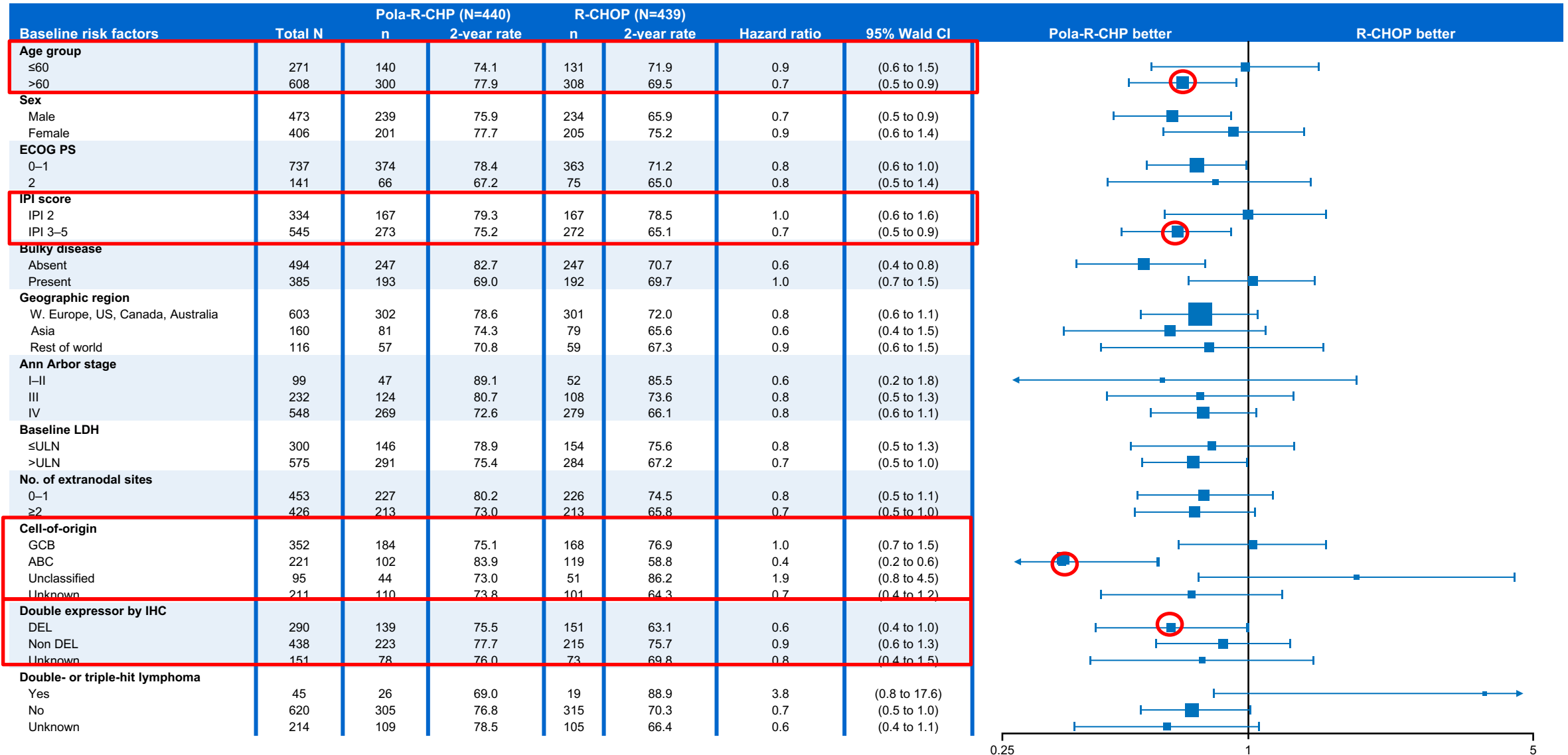
	0	6	12	18	24	30	36	42
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

No. of patients at risk

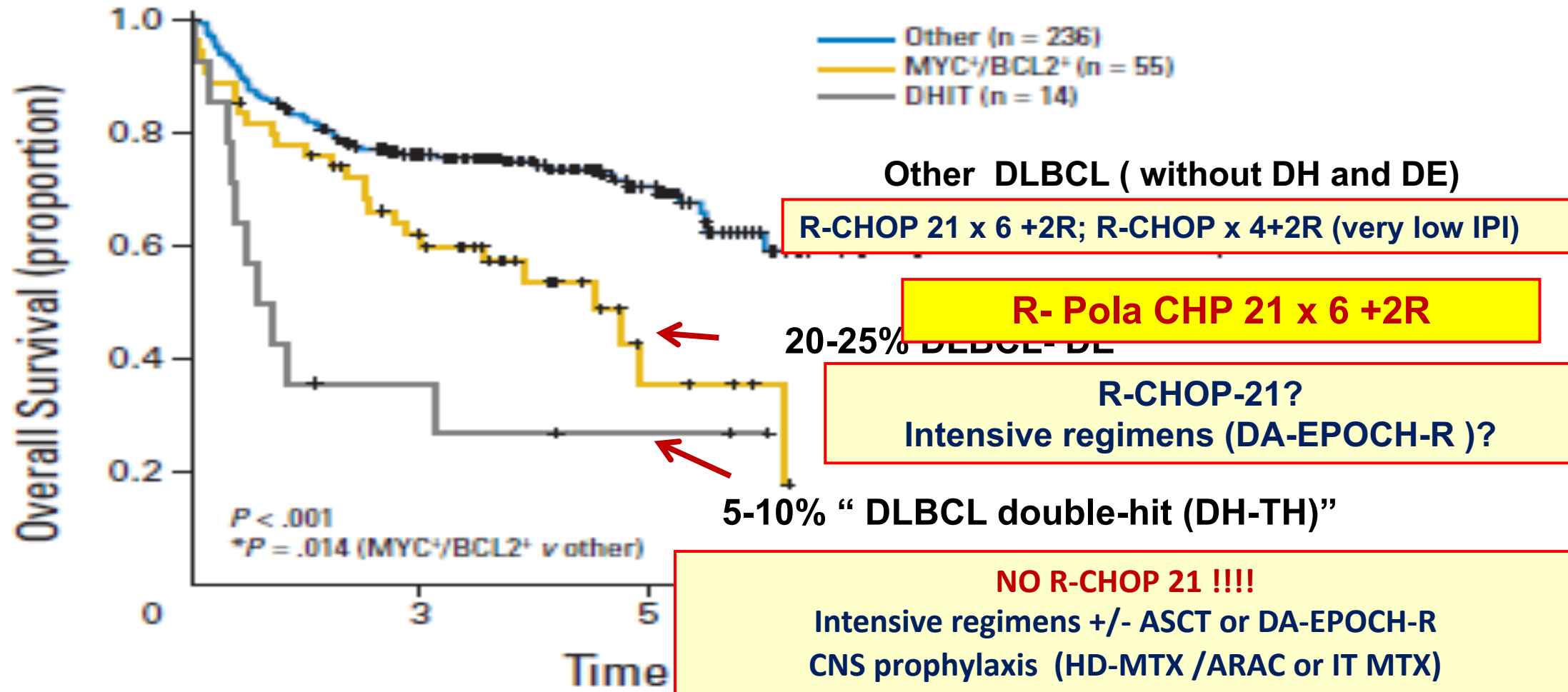
	0	12	24	36	48	55
Pola-R-CHP	440	423	398	387	379	371
R-CHOP	439	415	403	382	372	361

No new safety signals have been identified with longer follow-up compared with the primary analysis

POLARIX : PFS by subgroup (unstratified)

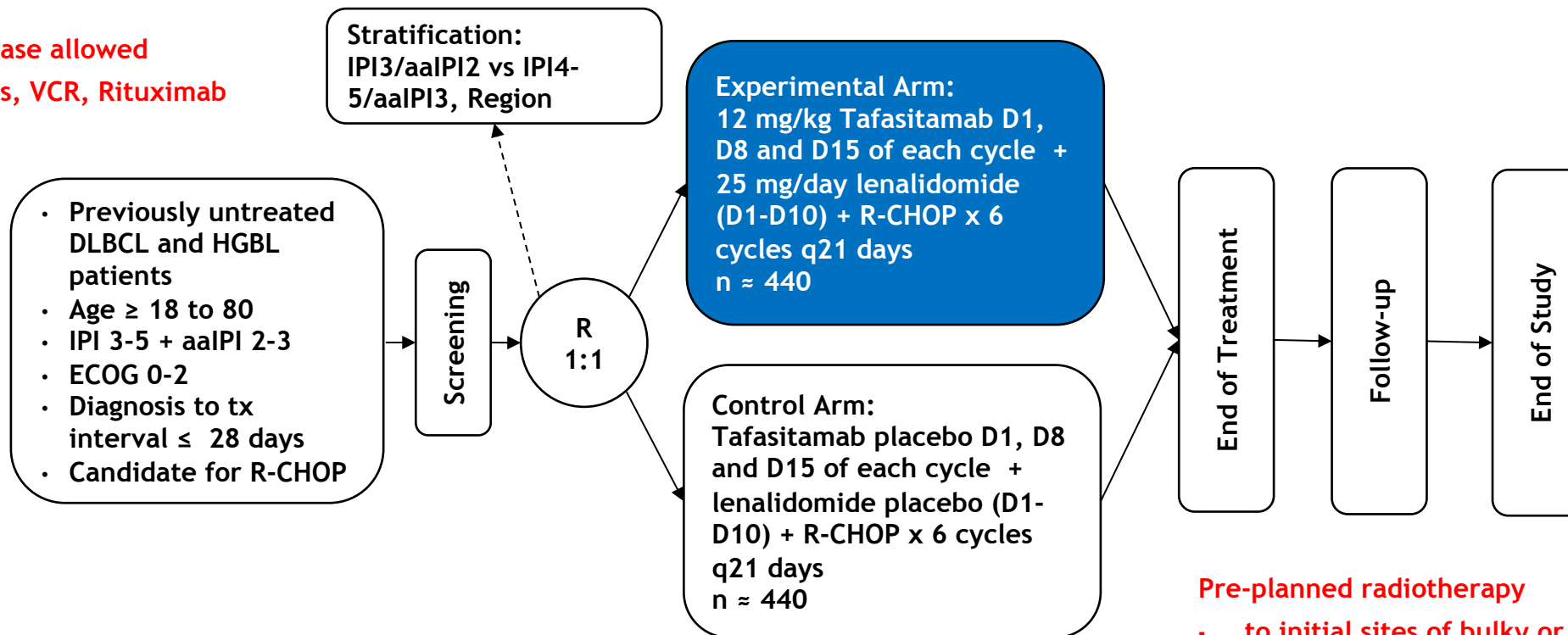


Front-line therapy of DLBCL in 2022-23



FRONTMIND – STUDY DESIGN

Prephase allowed with steroids, VCR, Rituximab



Pre-planned radiotherapy

- to initial sites of bulky or extranodal disease per institutional guidelines

Pre-planned CNS prophylaxis with IV Methothrexate

- Primary endpoint: PFS assessed by investigator (Cheson 2014 criteria)
- Sample size: 880 patients
- Target hazard ratio: 0.70, analysis at 274 PFS events, ~43 months after 1st patient 1st visit (FPFV)
- Power: 83%; Interim analysis for futility at 274 PFS events, 18 months after FPFV; IDMC review; Safety run-in first 40 patients

Novel and Emerging Combinations: Next Wave of R-CHOP “Plus”

- R-CHP + polatuzumab vedotin
- Bispecific antibodies plus:
 - R-CHOP + glofitamab
- R²-CHOP + tafasitamab
- Loncastuximab tesirine + R-CHOP
- R-CHOP + Acalabrutinib

Agnostic

- CAR T-cell therapy
- Tafasitamab/lenalidomide
- Loncastuximab tesirine
- Polatuzumab vedotin



- BTK inhibitors
- PI3K inhibitors
- BCL2 inhibitors
- IRAK4 inhibitors



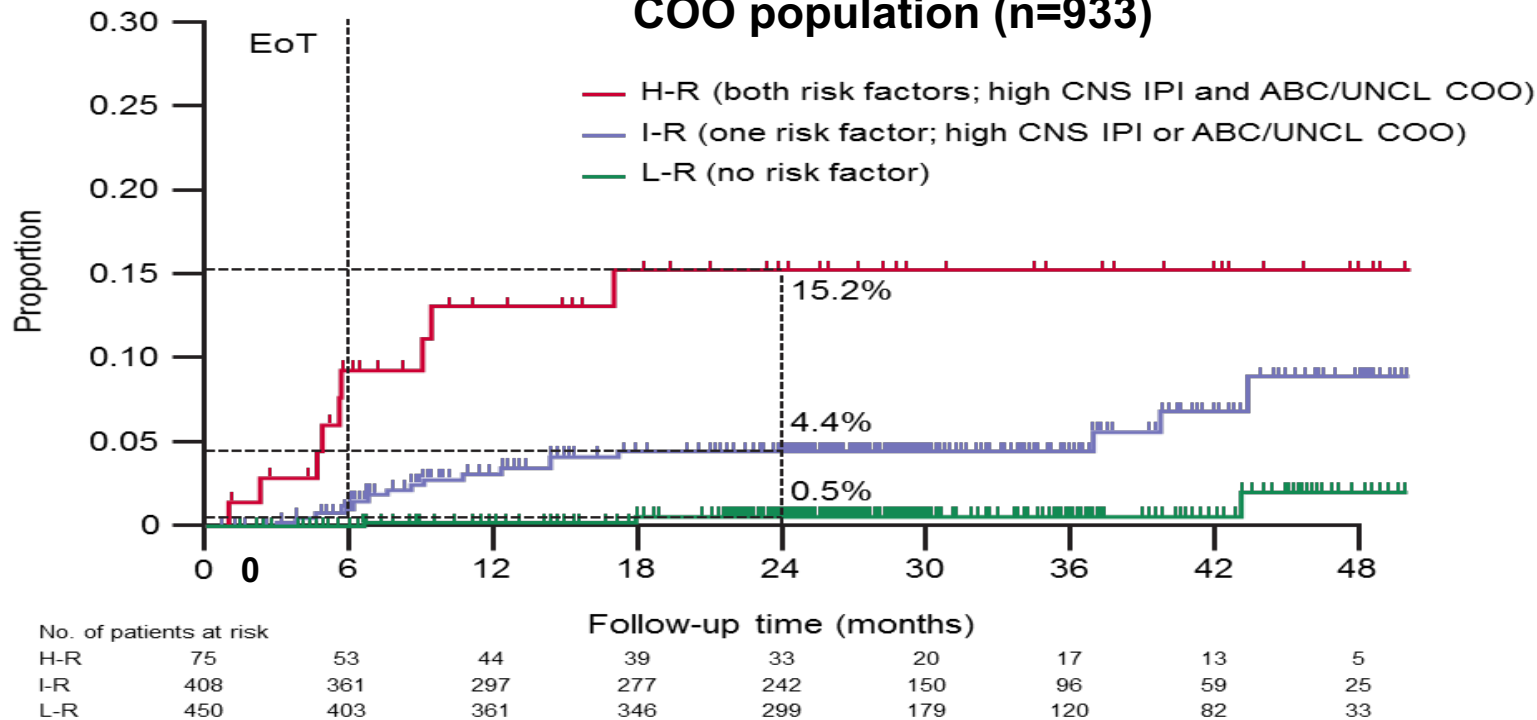
CLINICAL TRIALS AND OBSERVATIONS

Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL

Magdalena Klanova,¹⁻³ Laurie H. Sehn,⁴ Isabelle Bence-Bruckler,⁵ Federica Cavallo,⁶ Jie Jin,⁷ Maurizio Martelli,⁸ Douglas Stewart,⁹ Umberto Vitolo,¹⁰ Francesco Zaja,¹¹ Qingyuan Zhang,¹² Federico Mattiello,¹³ Gila Sellam,³ Elizabeth A. Punnoose,¹⁴ Edith Szafer-Glusman,¹⁴ Christopher R. Bolen,¹⁵ Mikkel Z. Oestergaard,¹⁶ Guenter R. Fingerle-Rowson,³ Tina Nielsen,³ and Marek Tmery¹

GOYA STUDY

Risk of CNS relapse by CNS-IPI-COO, COO population (n=933)



CNS IPI

CNS-IPI-COO

CNS IPI	n (%)	2-year relapse rate	CNS-IPI-COO	2-year relapse rate
H-R	165 (17.7%)	9.6%	75 (8.0%)	15.2%
I-R	596 (63.9%)	2.2%	408 (43.7%)	4.4%
L-R	172 (18.4%)	1.4%	450 (48.2%)	0.5%

Who and What... ?

High CNS IPI (4-6)

Age > 60 years

LDH > normal

ECOG PS > 1

Stage III/IV disease

Extranodal involvement > 1

Kidney and/or adrenal

Testis and Kidney and/or adrenal glands if only involved

Double HIT

Double-expressor and COO ABC according to CNS IPI

CNS-directed prophylaxis should be offered to patients at high-risk of CNS relapse

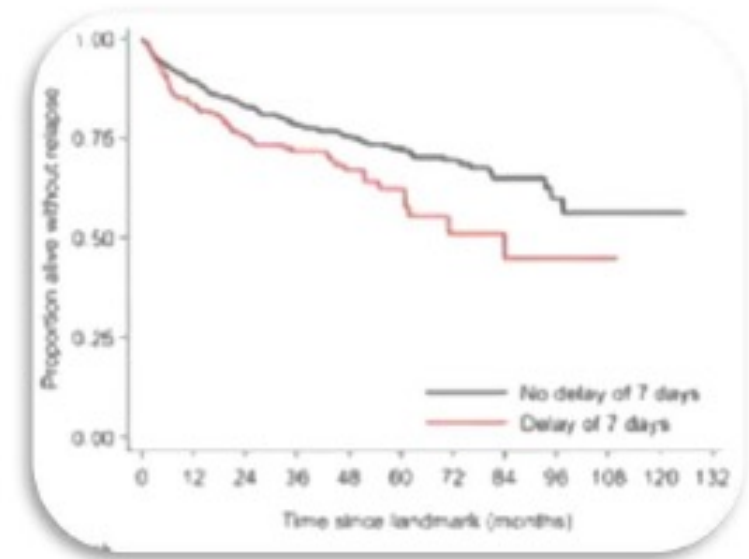
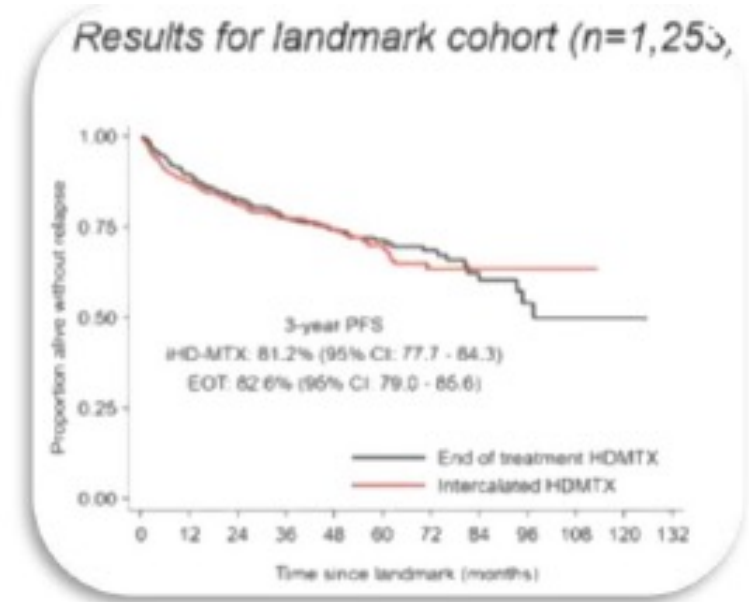
•4-6 cycles of IT prophylaxis (MTX, Ara-C) + 2 courses of MTX 3g/m² or 2-4 courses of MTX 1.5 g/m² in elderly pts and/or comorbidity (dose-adjusted according to creatinine clearance)

Timing of high dose methotrexate CNS prophylaxis in DLBCL: a multicentre international analysis of 1,384 patients

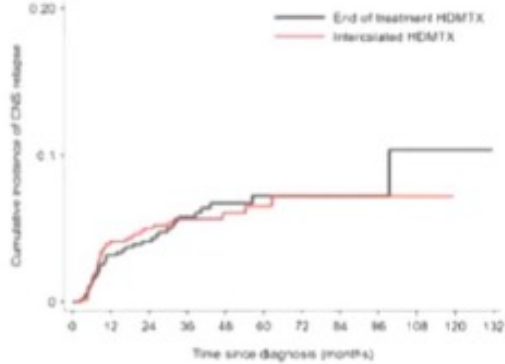
Matthew R. Wilson*, Toby A. Eyre, Amy A. Kirkwood, Nicole Wong Doo, Carole Soussain, Sylvain Choquet, Nicolás Martínez-Calle, Gavin Preston, Matthew Ahearne, Elisabeth Schorb, Marie-Pierre Moles-Moreau, Matthew Ku, Chiara Rusconi, Jahanzaib Khwaja, Mayur Narkhede, Katharine L. Lewis, Teresa Calimeri, Eric Durot, Loic Renaud, Andreas Kiesbye Øvlisen, Graham McIlroy, Timothy J. Ebsworth, Johnathan Elliot, Anna Santarsieri, Laure Ricard, Nimish Shah, Qin Liu, Adam S. Zayac, Francesco Vassallo, Laure Lebras, Louise Roulin, Naelle Lombion, Kate Manos, Ruben Fernández, Nada Hamad, Alberto Lopez-Garcia, Deirdre O'Mahony, Praveen Gounder, Nathalie Forgeard, Charlotte Lees, Kossi Agbetiafa, Tim Strüessmann, Thura Win Htut, Aline Clavert, Hamish Scott, Anna Guidetti, Brett R Barlow, Jeffery Smith, Fiona Miall, Christopher P. Fox, Chan Y. Cheah, Tarek Christoffer El Galaly, Andrés J. M. Ferreri, Kate Cwynarski, Pamela McKay

*Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom

‘Intercalate’ HD-MTX between R-CHOP cycles (i-HD-MTX)	Vs	Deliver HD-MTX at end of R-CHOP therapy (EOT)
Delivers early CNS prophylaxis		May not prevent early CNS progression
Toxicity e.g. renal may compromise R-CHOP delivery		No risk of interruption to R-CHOP therapy

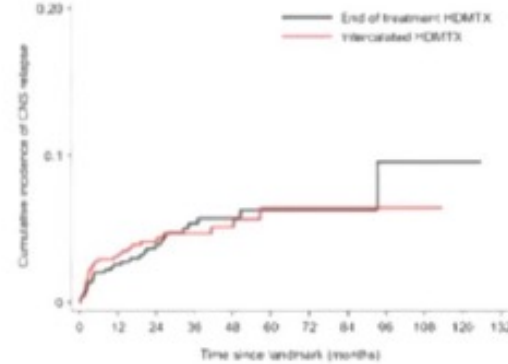


All patients (n=1,384)



3-year CNS relapse rates: 5.8% vs 5.7%
HR: 1.01 (95% CI: 0.65-1.57)
3-year difference: 0.04% (95% CI: -2.0 to 3.1)

Landmark analysis (n=1,253)

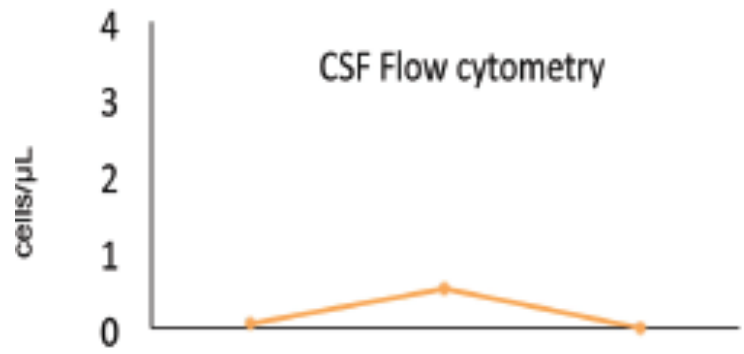
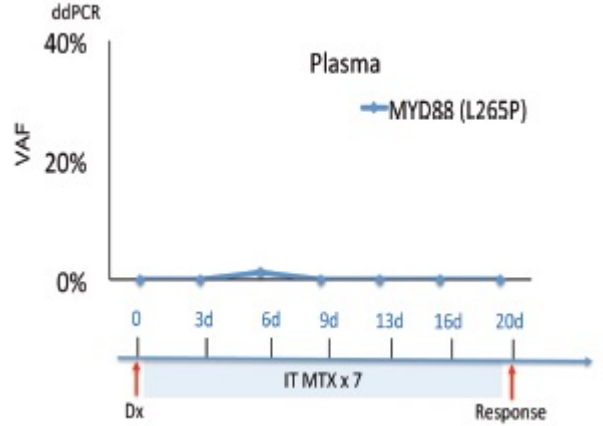
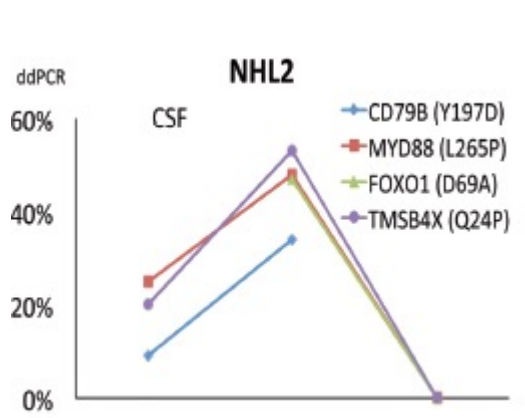
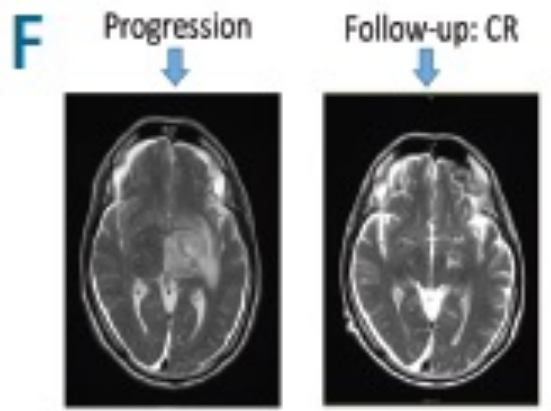


3-year CNS relapse rates: 4.7% vs 4.7%
HR: 0.99 (95% CI: 0.60-1.66)
3-year difference: -0.03% (95% CI: -1.0 to 3.0)

Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas

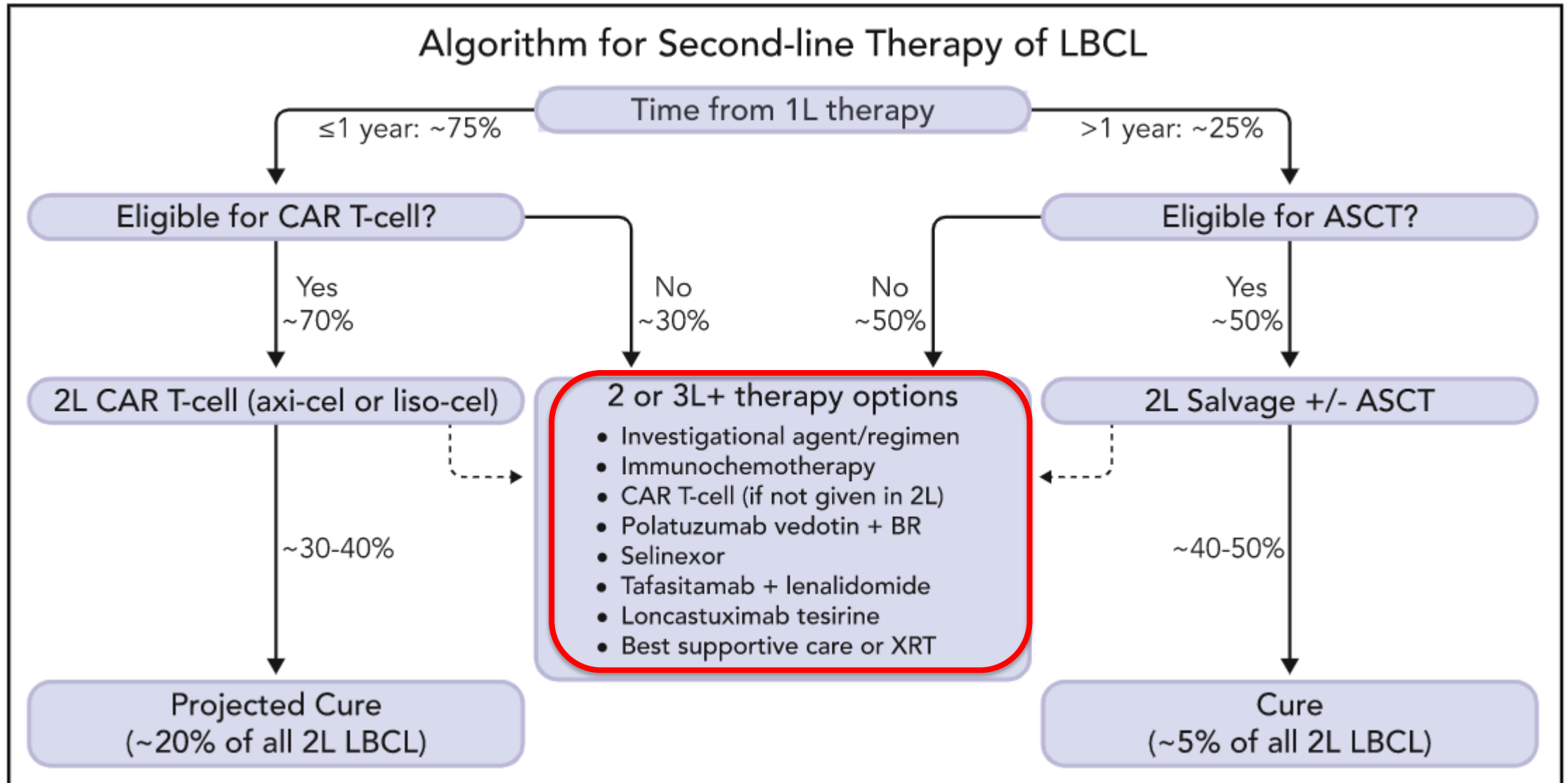
Haematologica 2021
Volume 106(2):513-521

Sabela Bobillo,^{1*} Marta Crespo,^{1*} Laura Escudero,^{2*} Regina Mayor,²
Priyanka Raheja,¹ Cecilia Carpio,¹ Carlota Rubio-Perez,²
Bárbara Tazón-Vega,¹ Carlos Palacio,¹ Júlia Carabia,¹ Isabel Jiménez,¹
Juan. C. Nieto,¹ Julia Montoro,¹ Francisco Martínez-Ricarte,³ Josep Castellví,⁴
Marc Simó,⁵ Lluís Puigdefàbregas,¹ Pau Abrisqueta,¹ Francesc Bosch^{1#}
and Joan Seoane^{2,6#}



- Circulating tumor DNA (CT DNA) in the CSF of patients with CNS Lymphoma is more abundant than in plasma
- CT DNA in the CSF fluid exhibits higher sensitivity than flow cytometry in detecting CNS lesions
- CT DNA in CSF fluid can be used to monitor CNS tumor burden and response to treatment

A new treatment algorithm for patients with R/R DLBCL after first-line therapy



Novel therapies approved in RR-DLBCL

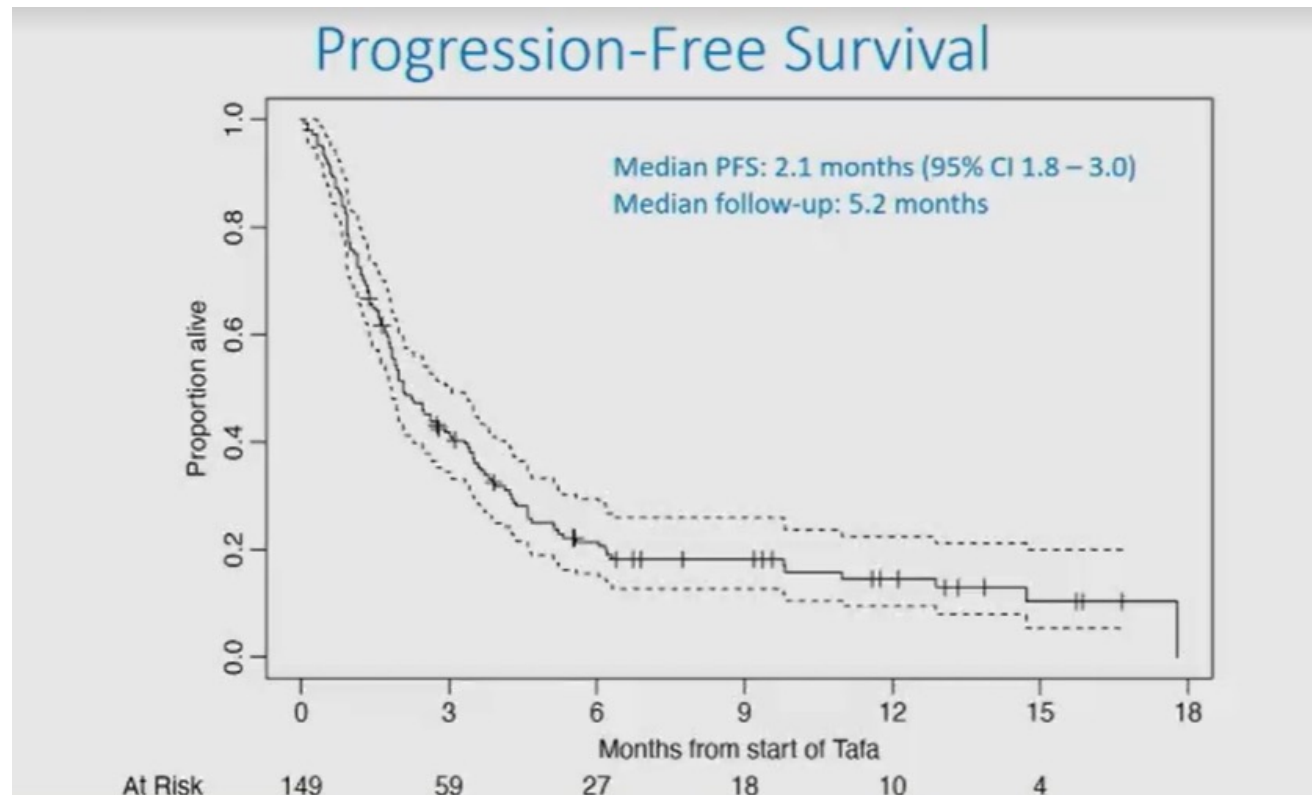
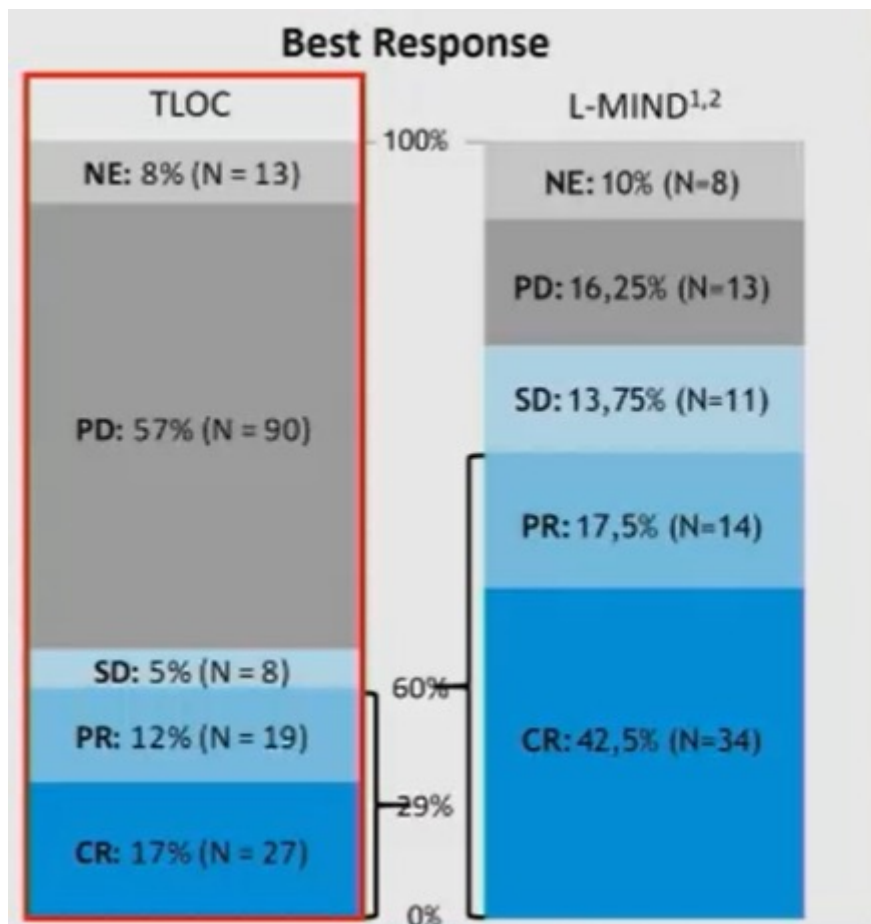
	Pola-BR	Selinexor	Tafasitamab/Lenalidomide	Locastuximab Tesirine
MOA	Anti-CD79b ADC	XPO-1 inhibitor	Anti-CD19 mAb/Immunomodulator	Anti-CD19 ADC
ORR	45%	28%	58%	48%
CR rate	40%	10%	40%	24%
PFS	9.2 m	2.6 m	11.6 m	4.9 m
DOR	12.6 m	9.3 m	43.9 m	10.3 m
OS	12.4 m	NR	33.5 m	9.9 m

Sehn LH et al Blood Adv.2022; Kalakonda Lancet Haematol 2020; Duell J.et al Haematologica 2021.; Caimi PF et al Lancet Oncol. 2021

Pola-BR in real life setting

	n	Refractory to last prior therapy	mOS months	mPFS months	CR rate	ORR	mFUP months
Vodicka et al.	21	76.2	8.7	3.8	23.8	33.3	6.8
Dimou et al.	49*	78.0	8.5	4.0	20.0 25.0 (best)	35.0 43.0 (best)	10.8
Segman et al.	47	23.0	8.3	5.6	40.0	61.0	6.8
Liebers et al.	54*	87	5.5	3.25	14.8 (best)	48.1 (best)	7.5
Northend et al.	133	68.4	8.2	4.8	31.6 (best)	57.0(best)	7.7
Pellegrini et al.	55	81.8	9.0	4.9	18.2 27.3 (best)	32.7 49.1(best)	11

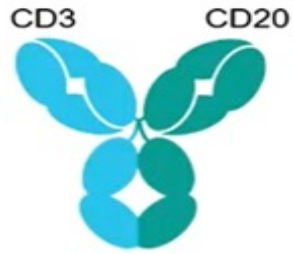
Real-world Tafa-len treatment N= 157 (retrospective study): Responses and Progression-Free Survival



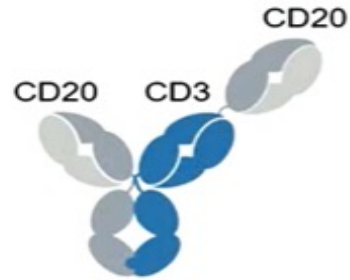
42 patients (28%) had CAR-T before TL
 - 4/19 CD19 not reported , more prior lines of tx, more prior refractory

Worse PFS was seen in patients with refractory disease, ≥ 3 lines of therapy, higher IPI

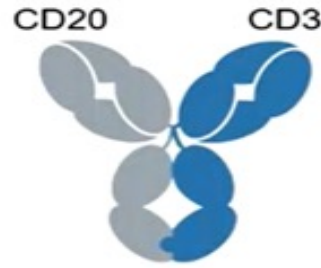
Bispecific antibodies CD3xCD20



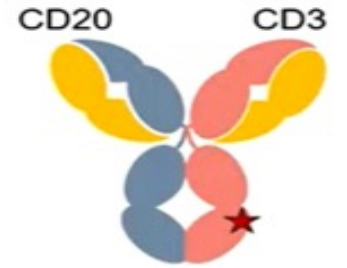
Epcoritamab
DuoBody-CD3xCD20
IgG1



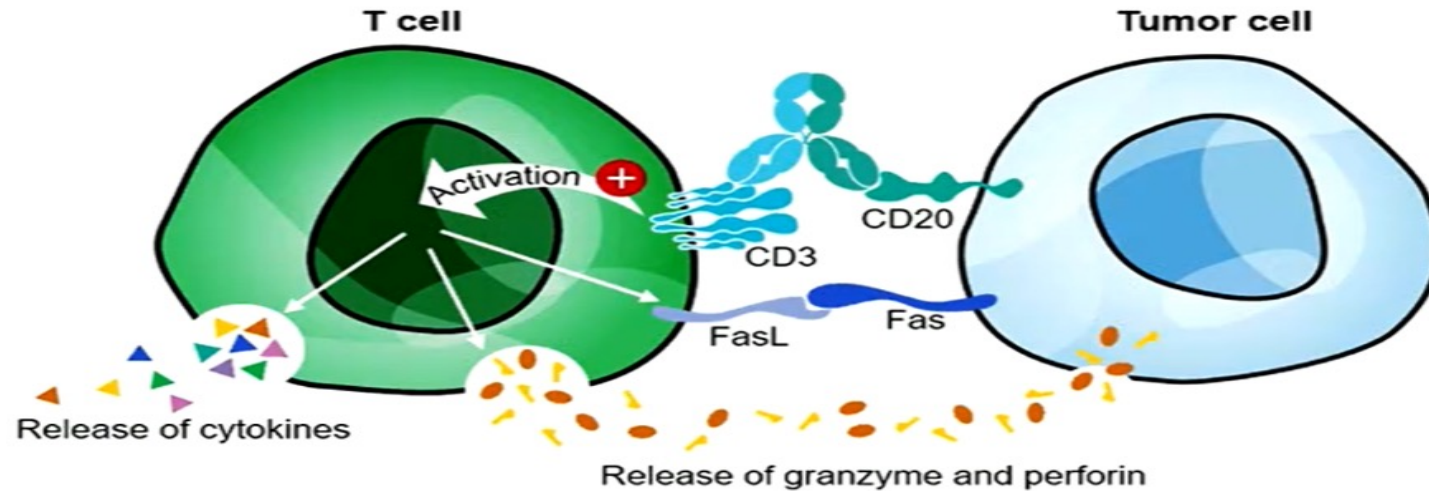
Glofitamab
2+1 CrossMab
IgG1



Mosunetuzumab
Knob-in-hole
IgG1

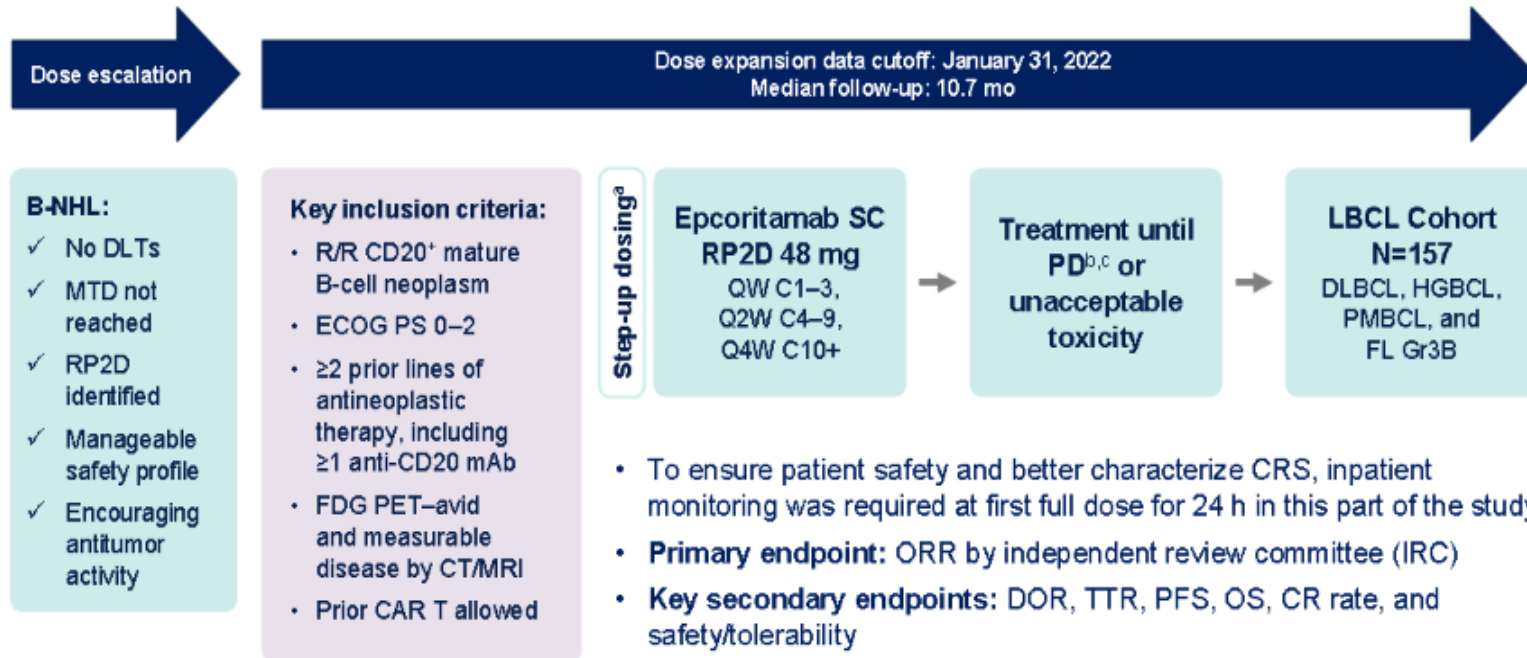


Odronextamab
VELOCI-Bi
IgG4

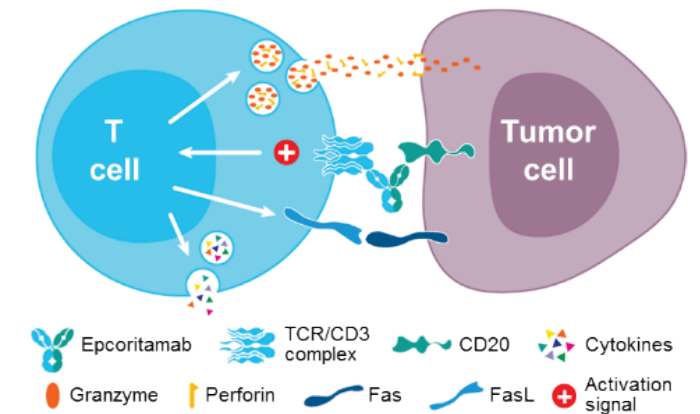


Subcutaneous Epcoritamab in R/R DLBCL: a phase 2 study in 157 patients

EPCORE NHL-1: LBCL Expansion Cohort



- **Induces T-cell activation** by binding to CD3 on T cells and CD20 on malignant B cells
- **Promotes immunological synapse** between bound cells, resulting in apoptosis of B cells
- **Binds to a distinct epitope on CD20**, different from the epitopes of rituximab and obinutuzumab
- **Retains activity** in the presence of CD20 mAbs

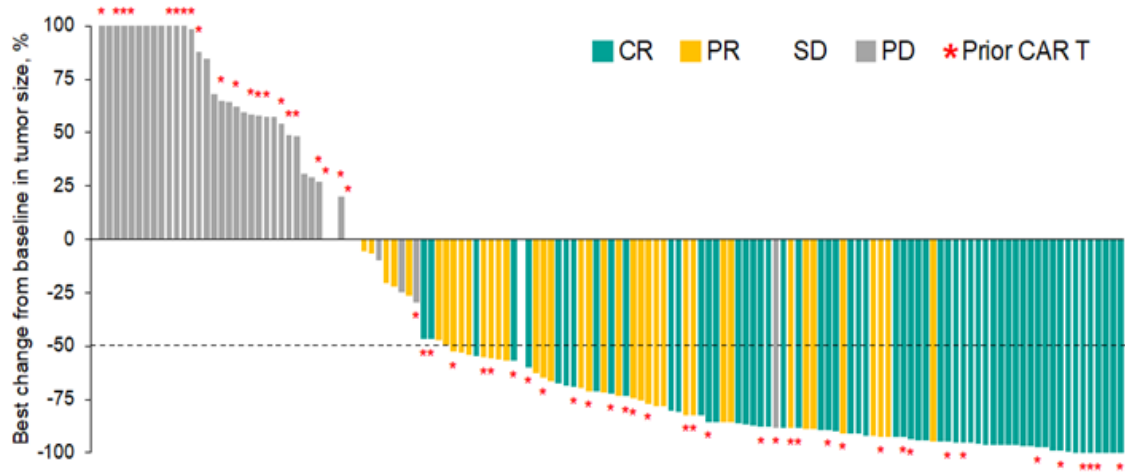


Subcutaneous Epcoritamab in R/R DLBCL:

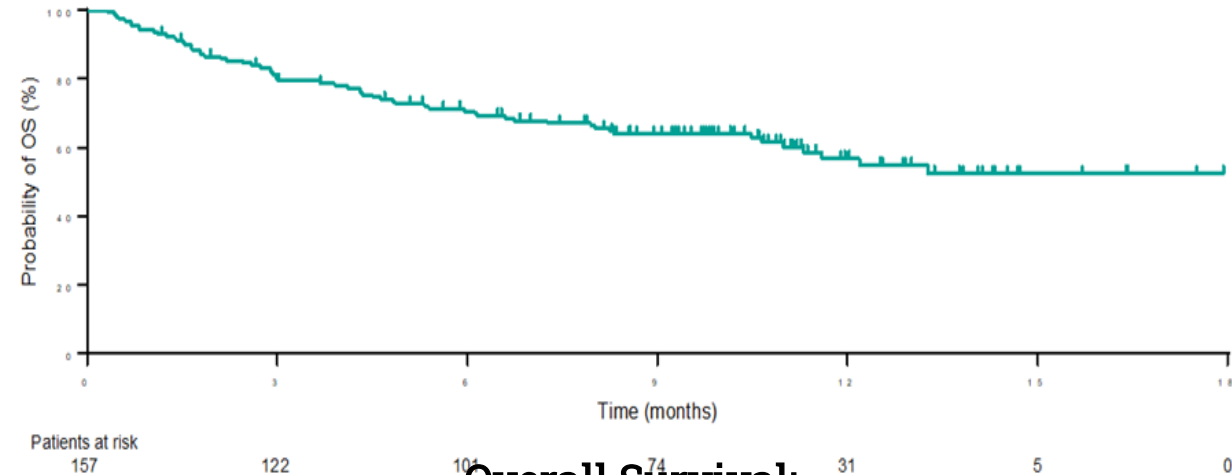
Patients Were Challenging to Treat and Highly Refractory

Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics ^a	LBCL, N=157
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)

Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory ^b disease, n (%)	96 (61)
Refractory ^b to last systemic therapy, n (%)	130 (83)
Refractory ^b to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Progressed within 6 mo of CAR T therapy	46/61 (75)

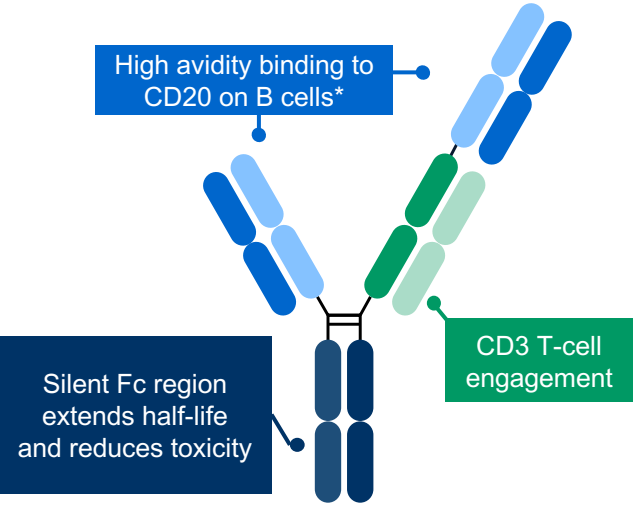


Response rate:
ORR 63%, CR 39%, prior CAR T 34%

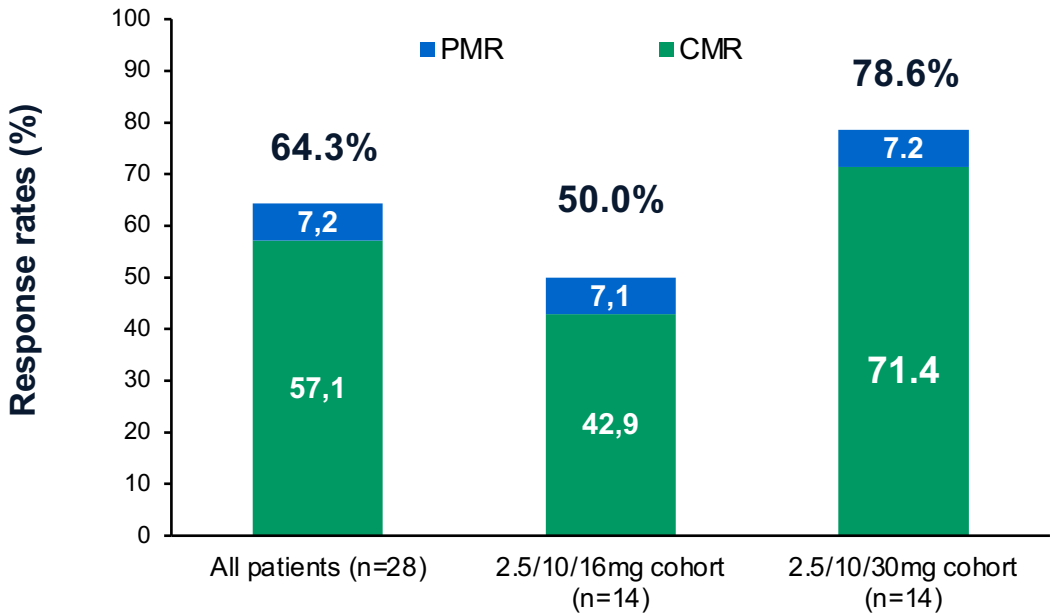


Overall Survival:
Median not reached, 6 mo 71%, 12 mo 57%

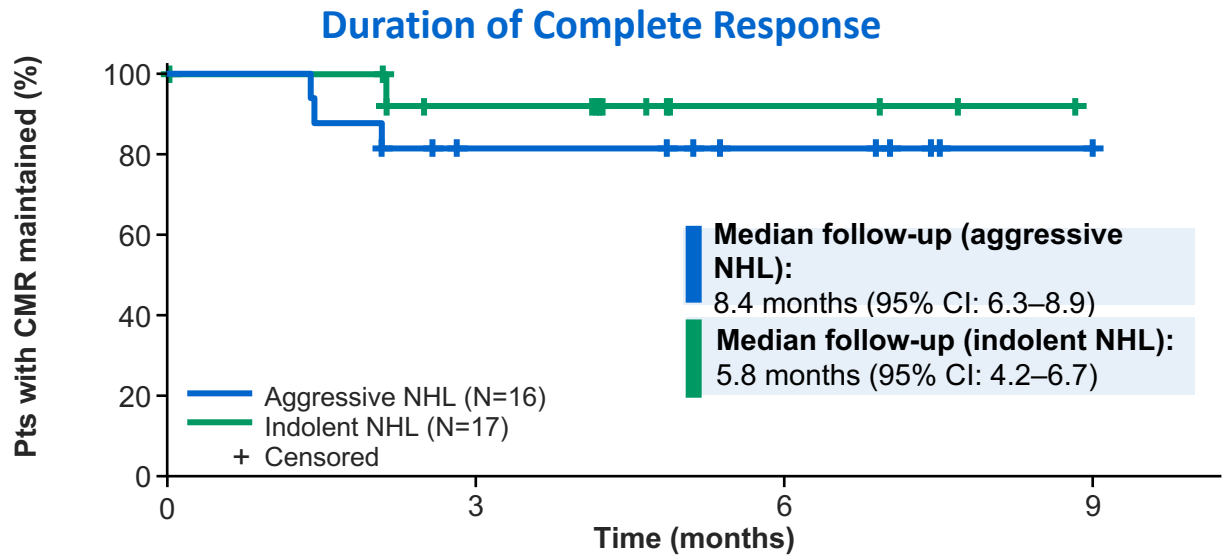
Glofitamab in R/R B-cell lymphoma patients.



Response rate: Aggressive NHL



For aggressive NHL, a trend of improved response was observed at the RP2D (2.5/10/30mg; N=14), with a **CMR rate of 71.4%**



Time (months)	Aggressive NHL (N=16)	Indolent NHL (N=17)
0	16	17
3	8	10
6	5	3
9	1	NE

Median follow-up (aggressive NHL):
8.4 months (95% CI: 6.3–8.9)

Median follow-up (indolent NHL):
5.8 months (95% CI: 4.2–6.7)

- The median duration of response for complete responders have not been reached
- **Aggressive NHL:** 13/16 CMRs are ongoing, 8 CMRs lasting >3 months; 5 CMRs lasting >6 months
- **Indolent NHL:** 16/17 CMRs are ongoing, 10 CMRs lasting >3 months; 3 CMRs lasting >6 months

Hutchings M et al, JCO 2021, Carlo-Stella, ICML-16.

CD20xCD3 bispecific antibodies + SoC

Rational combinations of targeted therapies

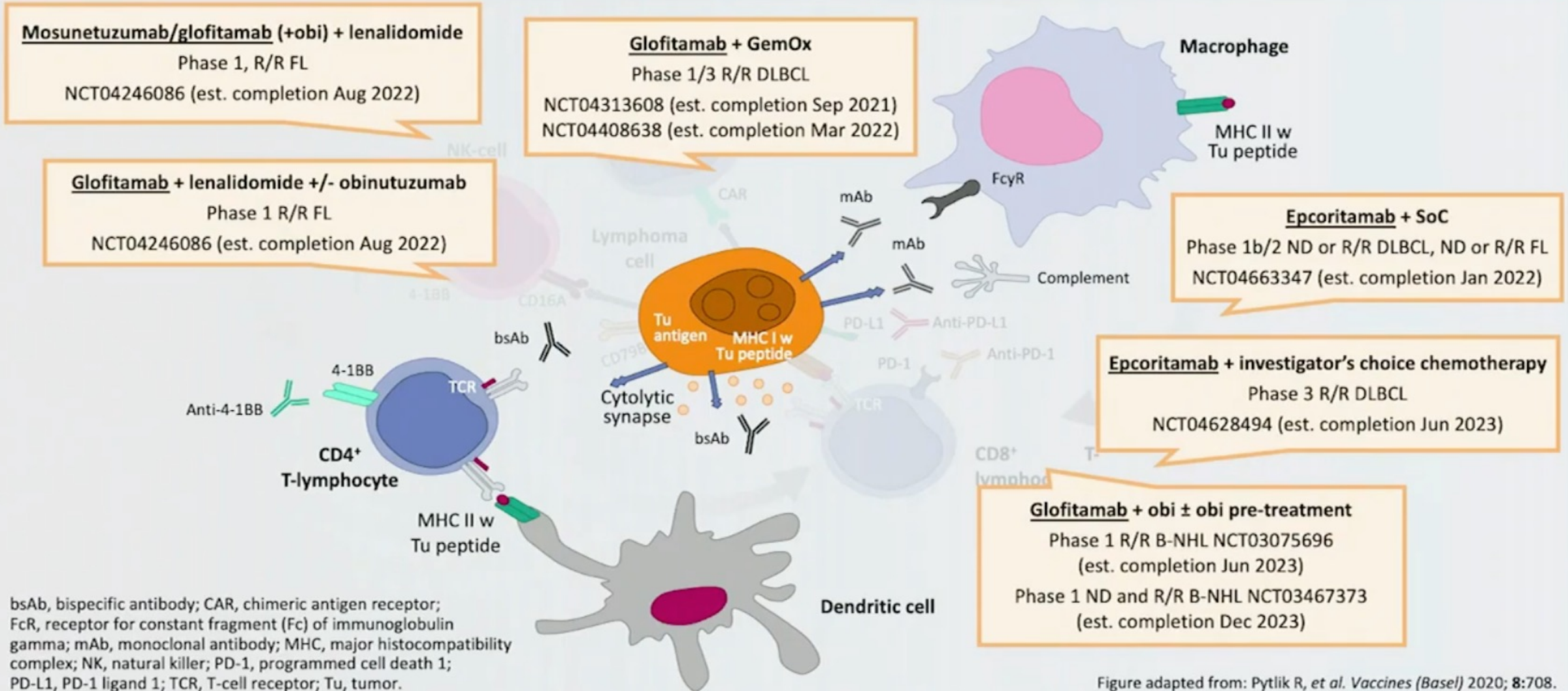
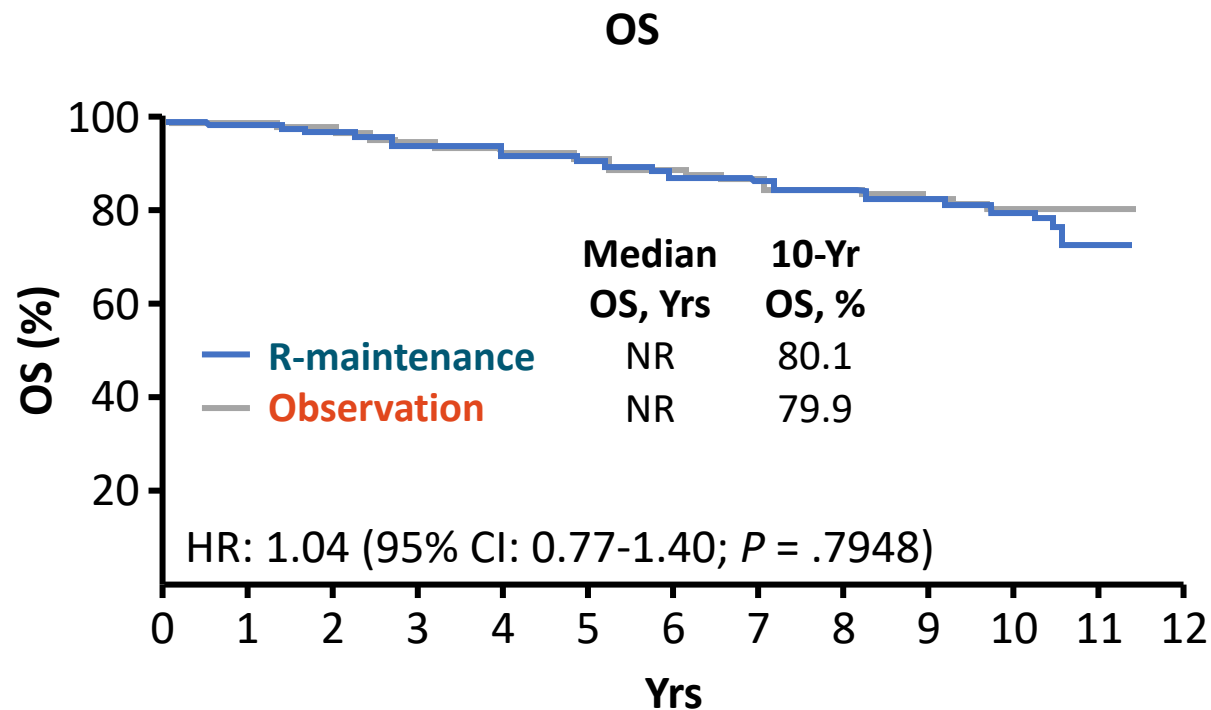
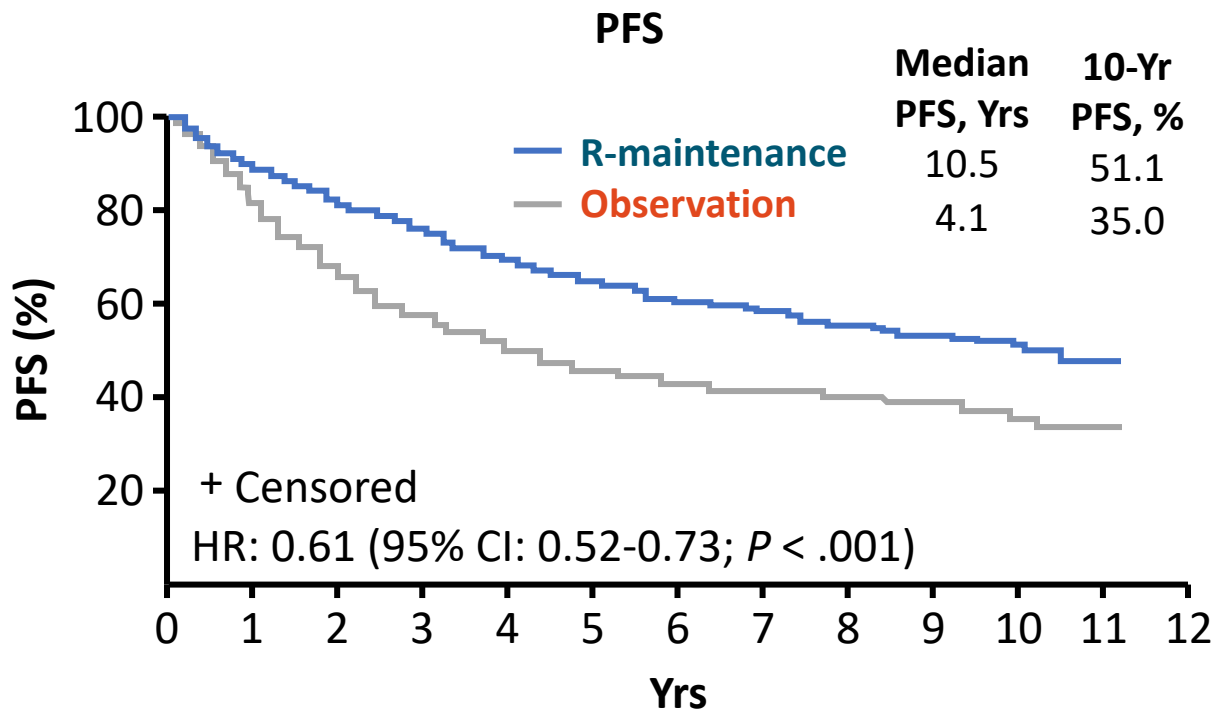


Figure adapted from: Pytlik R, et al. *Vaccines (Basel)* 2020; 8:708.

PRIMA Long-term Follow-up: PFS but Not OS Improved with Maintenance Rituximab vs Observation



Patients at Risk, n

	0	1	2	3	4	5	6	7	8	9	10	11	12
R-maint	505	445	406	372	333	309	284	231	208	170	67	4	0
Obs	513	415	336	290	251	217	200	155	147	122	41	1	0

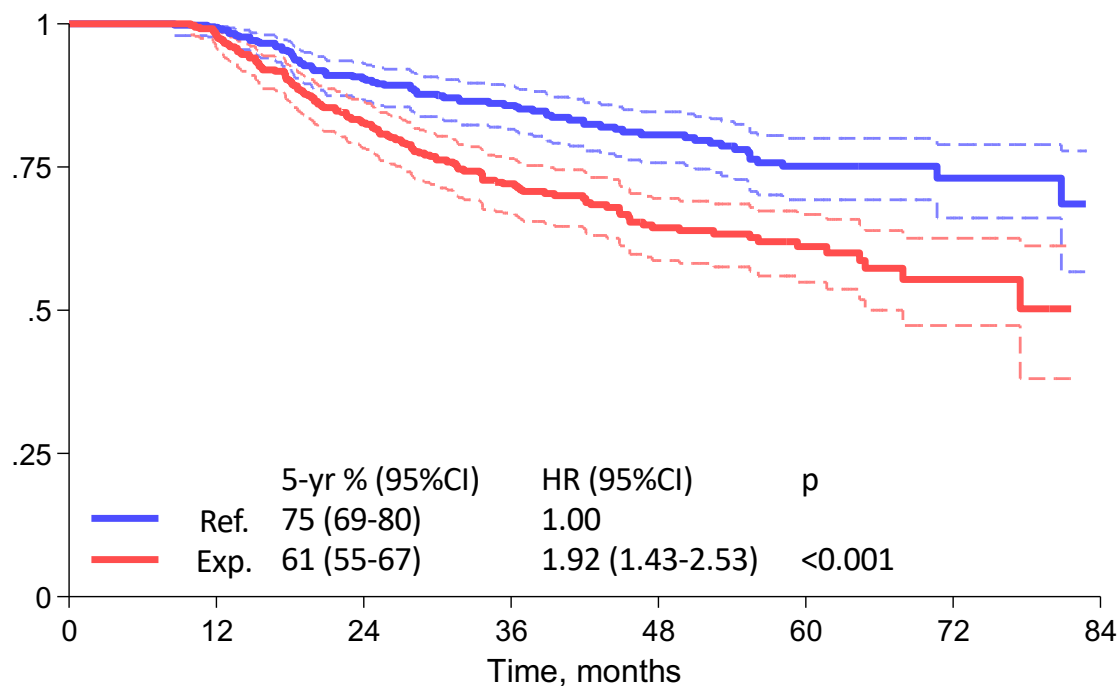
Patients at Risk, n

	0	1	2	3	4	5	6	7	8	9	10	11	12
R-maint	505	492	480	464	449	432	407	341	313	261	107	8	0
Obs	513	501	485	472	460	440	412	319	297	256	91	8	0

Updated results of the FOLL12 trial

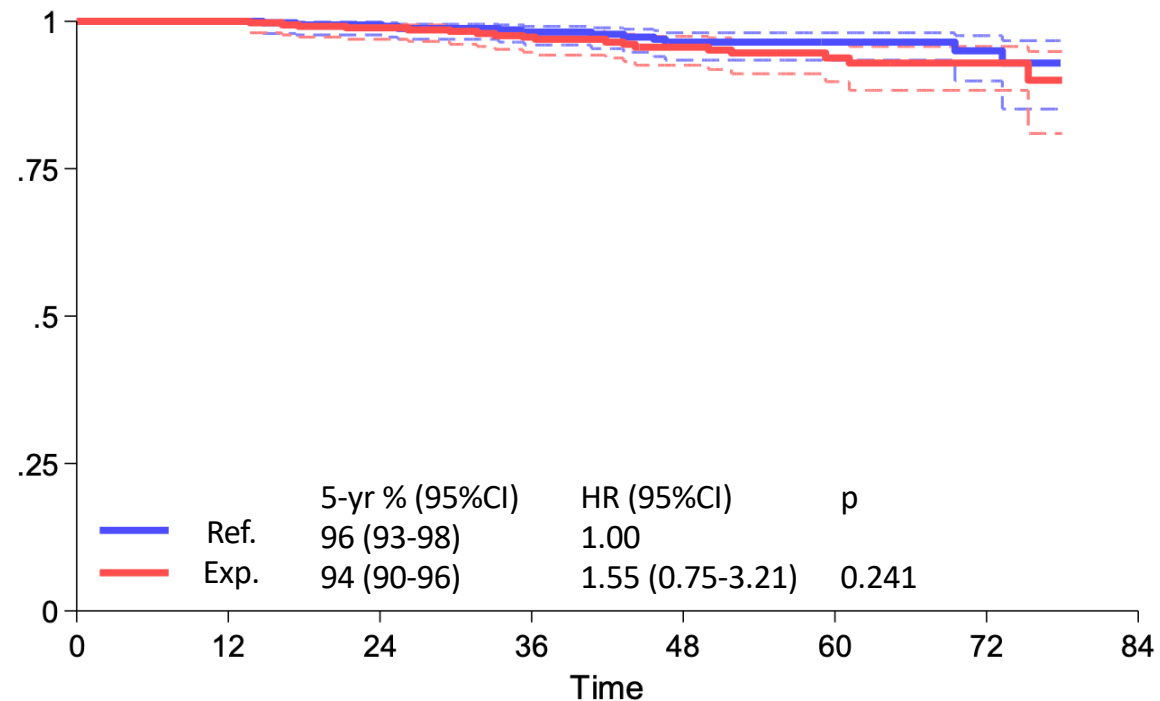
N=712, Med f-up 53m, 197 PFS events, 30 deaths

PFS



At risk	0	12	24	36	48	60	72	84
Ref.	351	345	306	248	173	96	34	5
Exp.	361	344	283	217	135	65	19	4

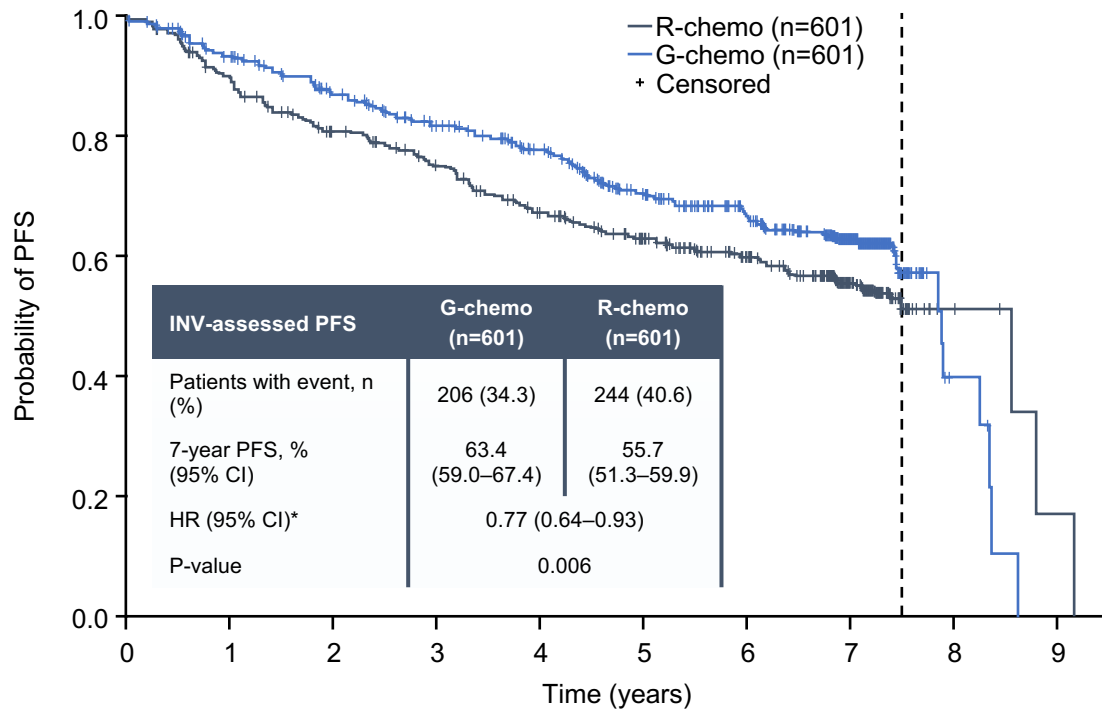
OS



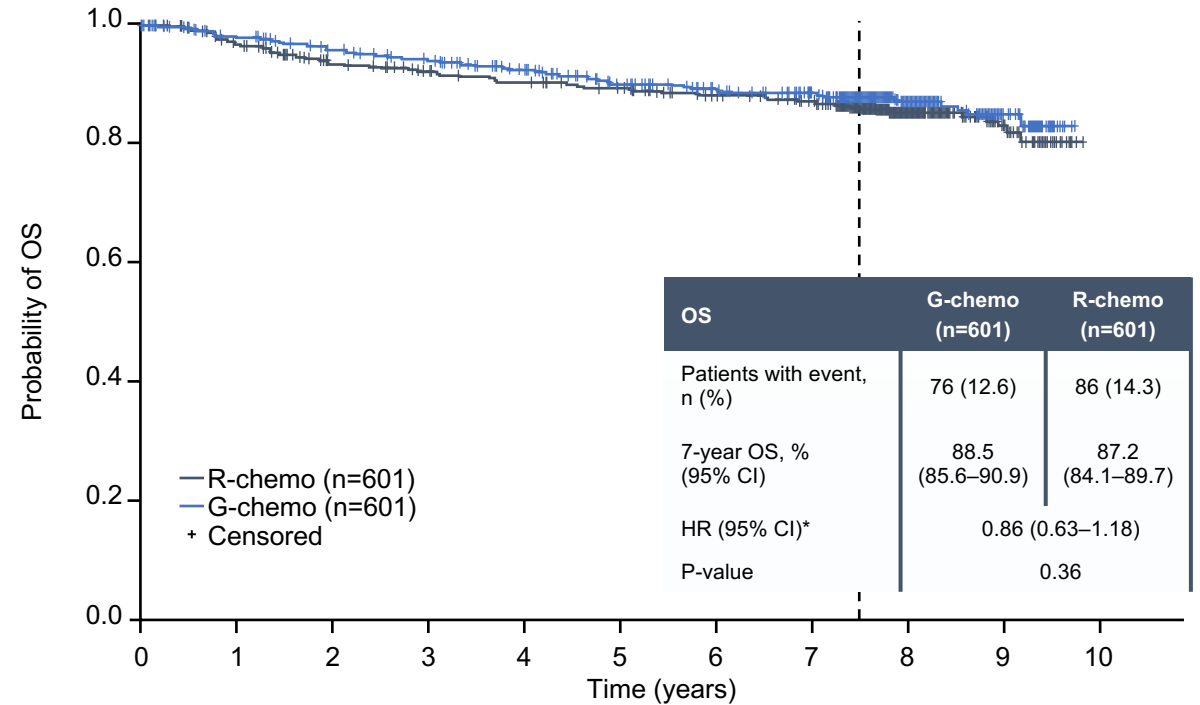
At risk	0	12	24	36	48	60	72	84
Ref.	351	347	337	283	206	125	50	8
Exp.	361	351	337	285	202	111	45	9

GALLIUM study first line follicular lymphoma

PFS



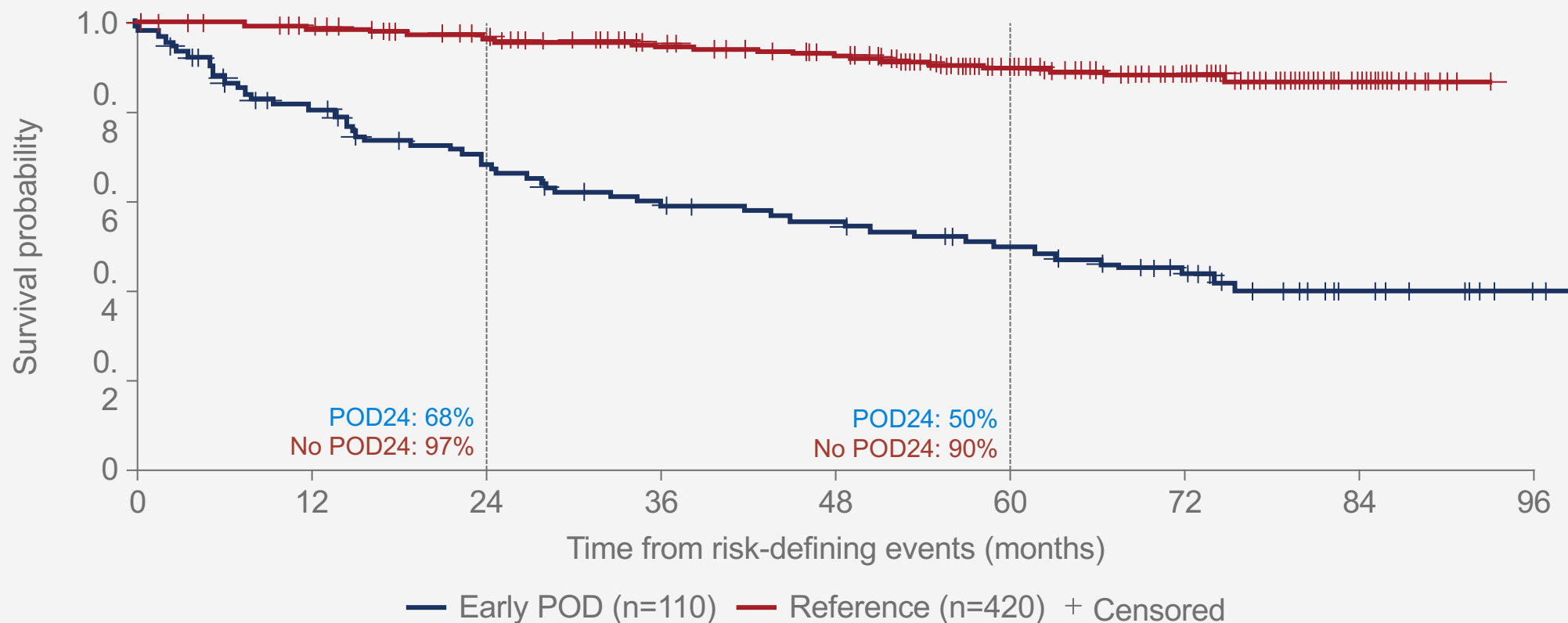
OS

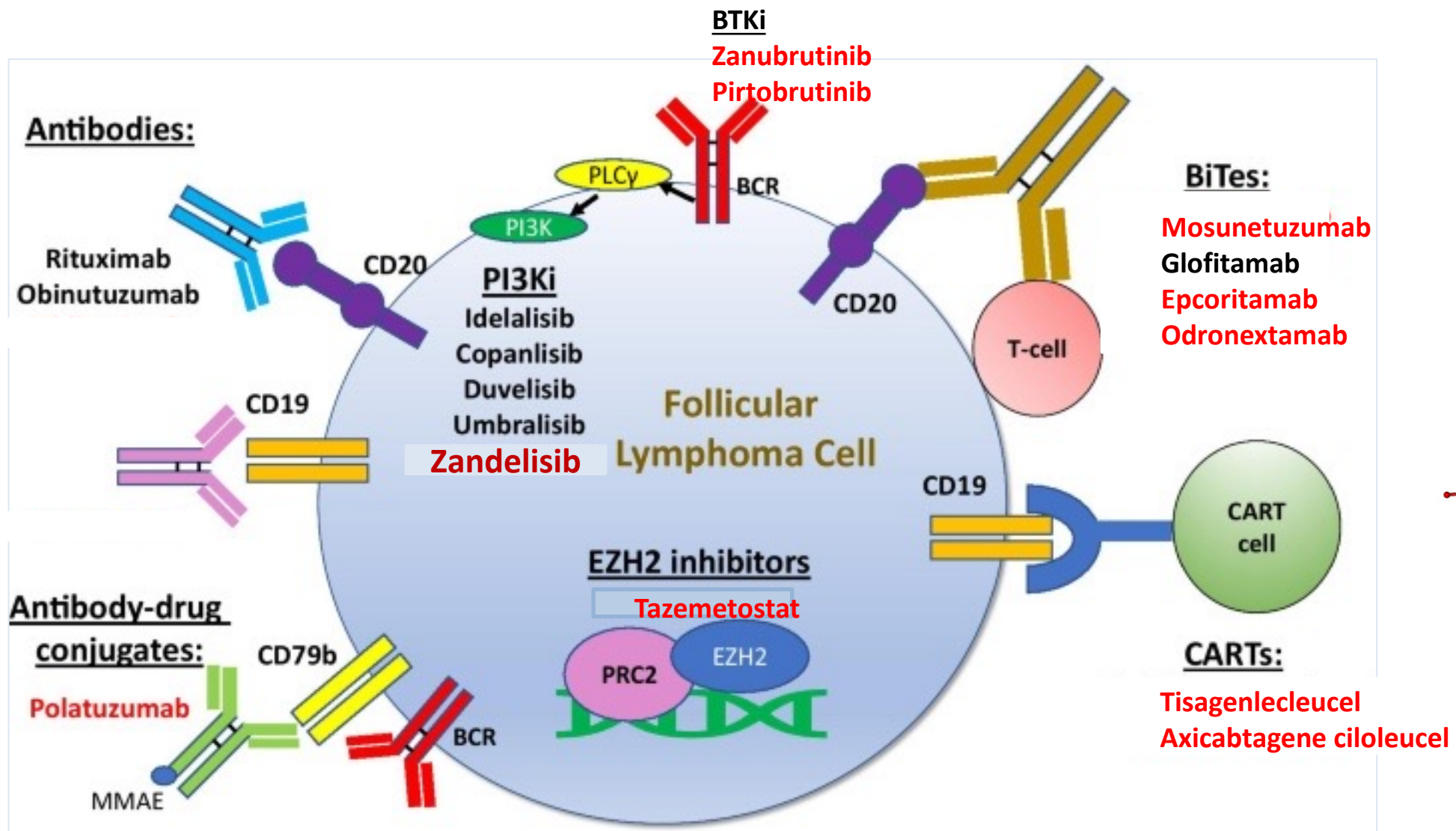


PFS favored G-chemo vs R-chemo in patients with an intermediate-to-high-risk (2–5) FLIPI score

Patients with advanced stage FL who progress in their first or second years of treatment have poorer outcomes

Casulo and colleagues (2015) explored the association between early POD within 24 months and risk of death after R-CHOP





Novel agents investigated in RR-Follicular/Indolent



POST-NEW ORLEANS 2022

Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Milano

Teatro Dal Verme

2-3-4 Febbraio 2023

COORDINATORI

Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO

Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

16.05 Linfomi indolenti

M. LADETTO

16.25 Linfomi aggressivi di derivazione B linfocitaria

A.J.M. FERRERI

16.45 Terapie di salvataggio con anticorpi monoclonali

L. RIGACCI

17.05 Discussione

**Grazie
per la cortese attenzione**