FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Linfomi a grandi cellule in I linea: oltre R CHOP?

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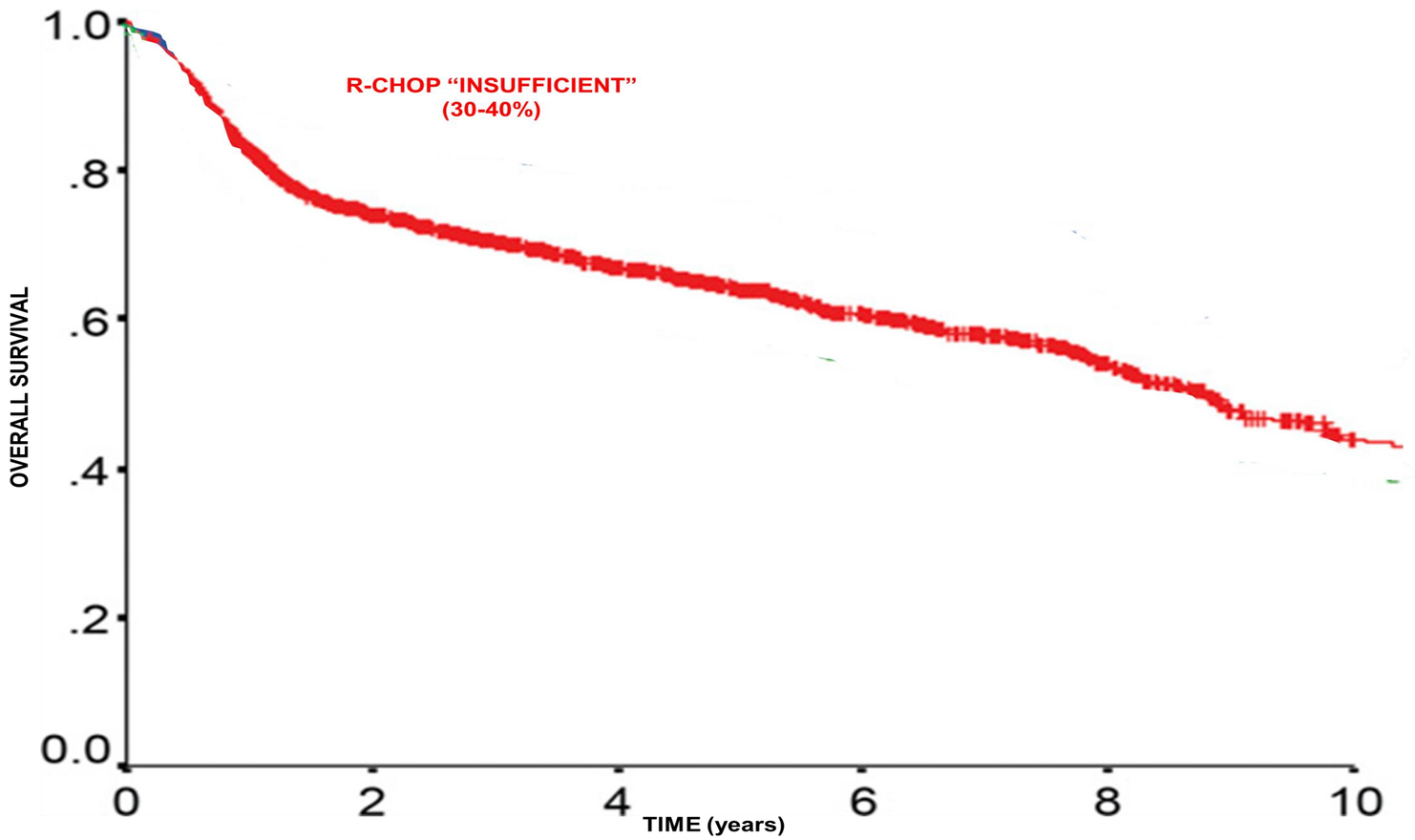
Disclosures of Alice Di Rocco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			x		x	X	
Jannsen			x		X		
Kite-Gilead			x		X	X	
Novartis			x		X	x	
Incyte			x		x		
Roche			X		X	X	
Eli-Lilly					X		
Takeda			x			X	
SOBI					x	x	
ASTRAZENECA						X	
RECORDATI RARE DISEASE					X		

How to improve outcome in first line therapy of DLBCL



Improving R-CHOP21

Better predictive/valuate quality of response

Take into consideration biological diversity of DLBCL

Sehn LH and Salles G, NEJM 2021;

Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the prospective Elderly Project of the Fondazione Italiana Linfomi.

- N=1353, >65y, dec 2013 – dec 2017
  - Mandatory sGA at enrollment
- Treatment choice independent from sGA results

EPI score

N° pts	Age group	Included Variable	Categorisation	OS
1065 pts	Training cohort: 65–94; external validation cohort: 65–9	sGA: fit (0 p), unfit (3 p), frail (4 p); IPI: 1 (0 p), 2 (1 p), 3–5 (3 p); hemoglobin: >12 g/L (0 p), <12 g/L (1 p	Low 0-1 points (23%) Intermediate 2-5 (48%) High Risk 6-8 (29%)	3-y OS 87% 3-y OS 69% 3-y OS 42%

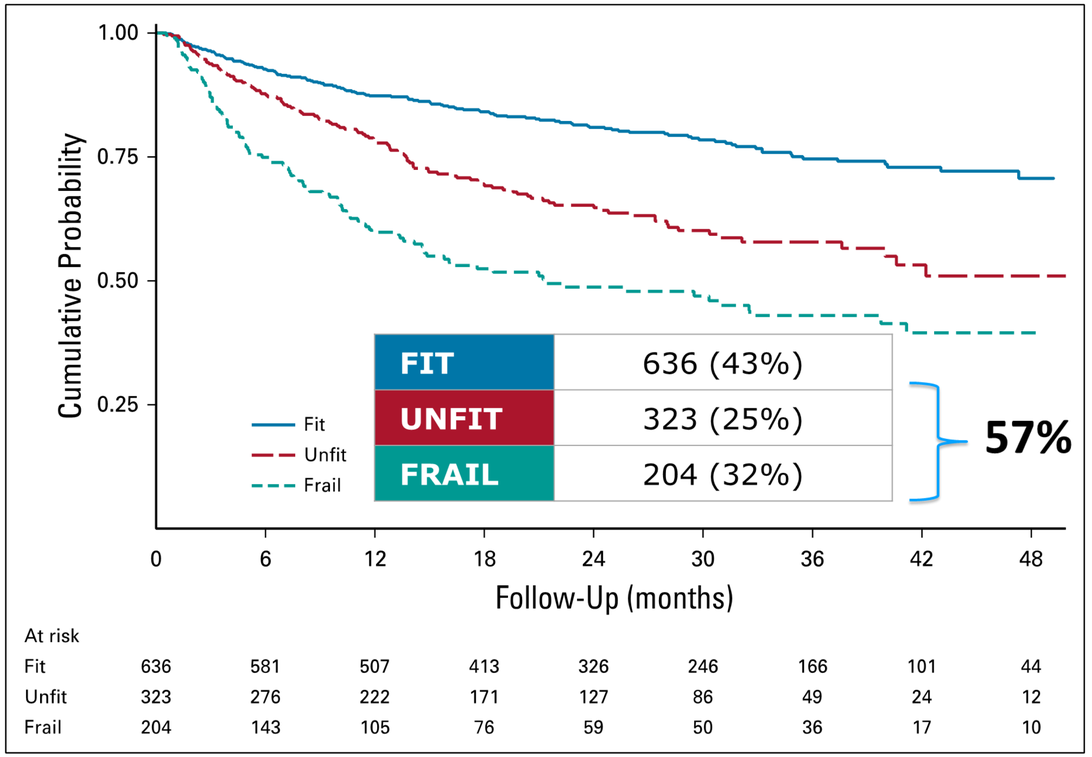
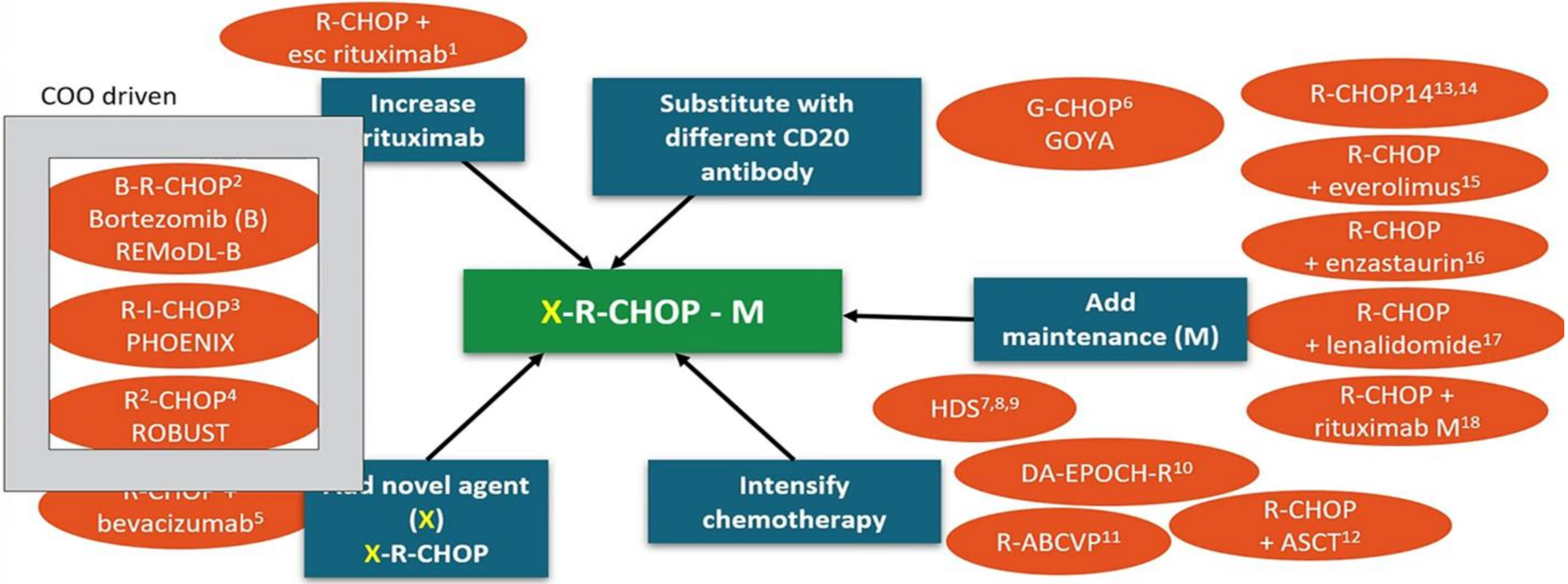


FIG 1. Overall survival by sGA in all patients with treatment details (N = 1,163). sGA, simplified geriatric assessment.

Improving on R-CHOP in DLBCL



1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955.

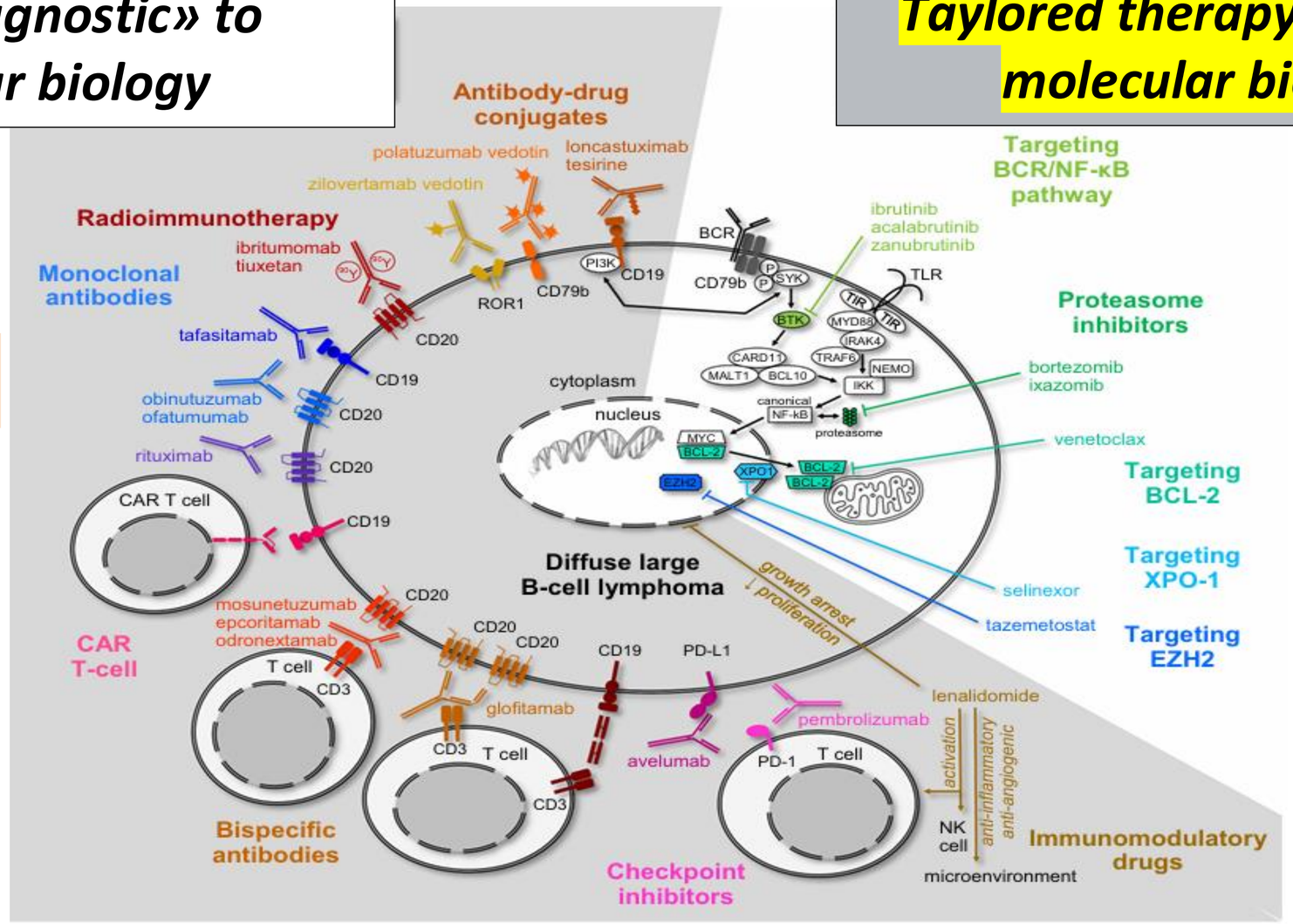
How to move beyond R-CHOP ?

Therapy «agnostic» to molecular biology

Taylored therapy based on molecular biology

Novel Antibodies

Immune system engaging therapy



Targeting BCR/NF-kB pathways

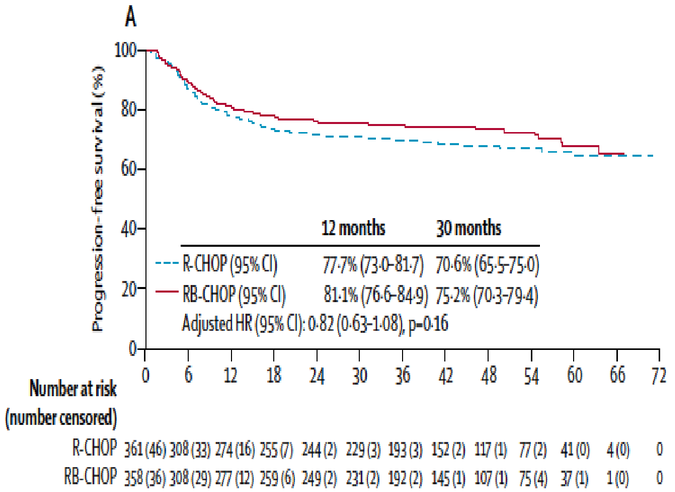
Proteasome Inhibitors

Targeting BCL-2

COO-ABC : targeting high biological risk

R-CHOP + Bortezomib

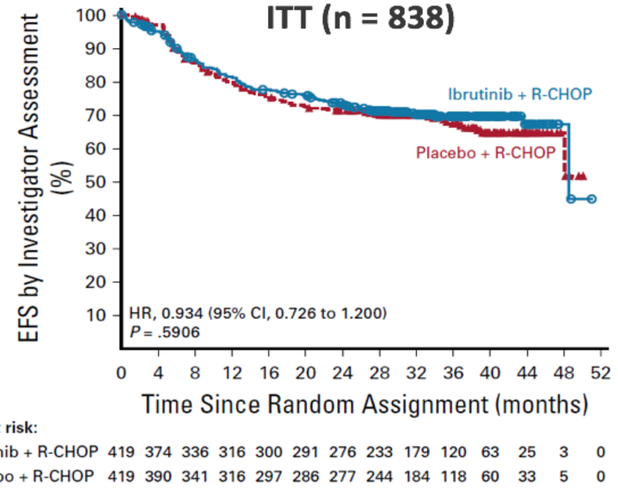
ReMoDL- B



Davies A, et al. Lancet Oncol 2019;

R-CHOP + Ibrutinib

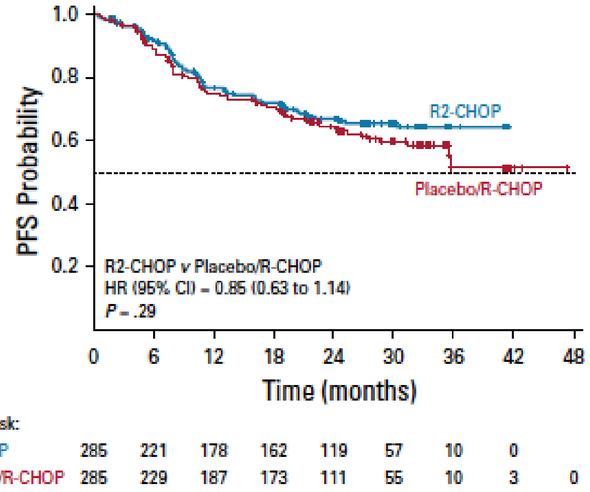
Phoenix



Younes A, et al. J Clin Oncol 2019;

R-CHOP + Lenalidomide

Robust



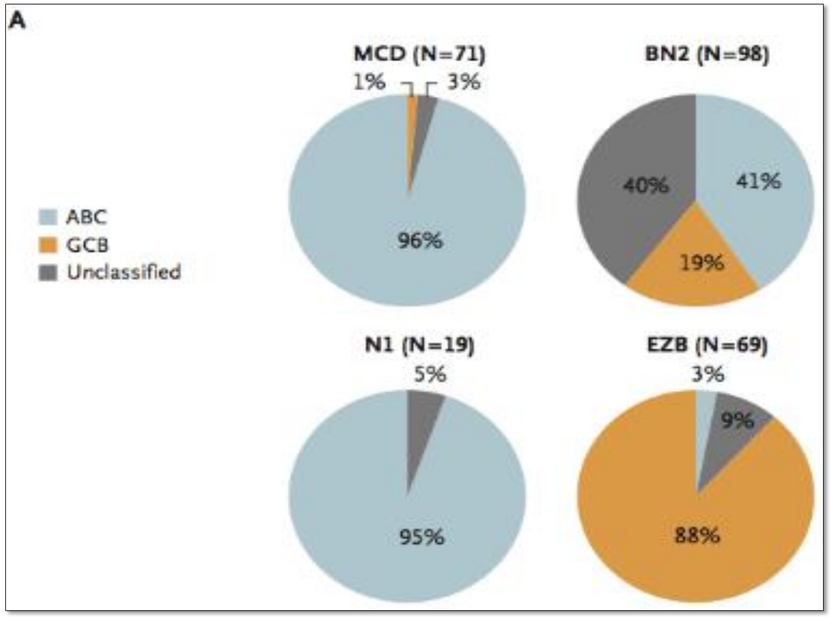
Nowakowski G, et al. J Clin Oncol 2021.

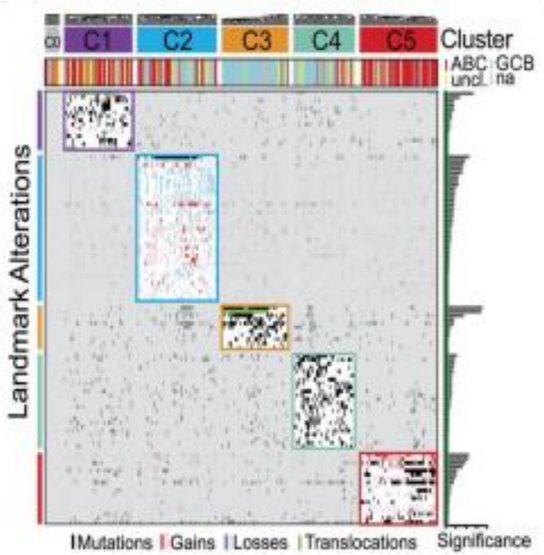
Biological Heterogenity of DLBCL has prognostical implications

ORIGINAL ARTICLE

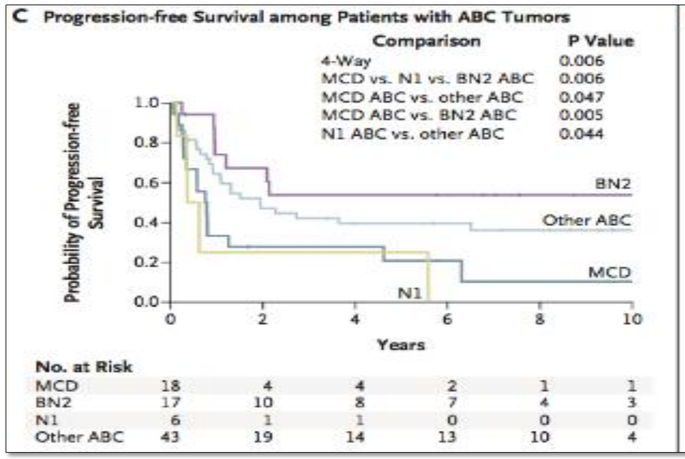
Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

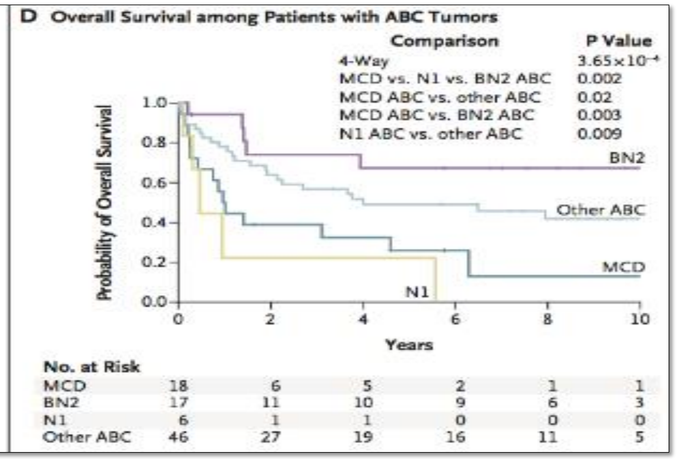
R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt





Genetic Subtype *DFCI*	Genetic Subtype *NCI*	Key Features	Transcriptional Subtype	Prognosis
C1	BN2	*BCL6* and NOTCH2- and NF-κB and immune escape pathway alterations; occulty transfomed MZL	ABC	Favorable
C2	(A53 / TP53)	Biallelic inactivation of *TP53*, 9p21.3/*CDKN2A*; genomic instablity	ABC/GCB independent	Steady rate of progression
C3	EZB	*BCL2* SVs, inactivating *PTEN* alterations and alterations of epigenetic enzymes	GCB	Unfavorable
C4	ST2	BCR/PI3K-, JAK/STAT-, RAS-pathway and histone alterations	GCB	Favorable
C5	MCD	*BCL2* copy gain, activating *MYD88* and *CD79B* mutations; extranodal tropism	ABC	Unfavorable



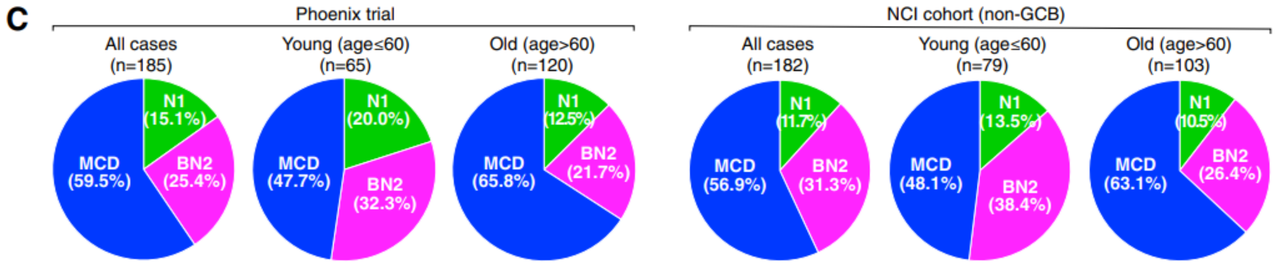


Schimtz et al, N.Engl J Med 2018

Article

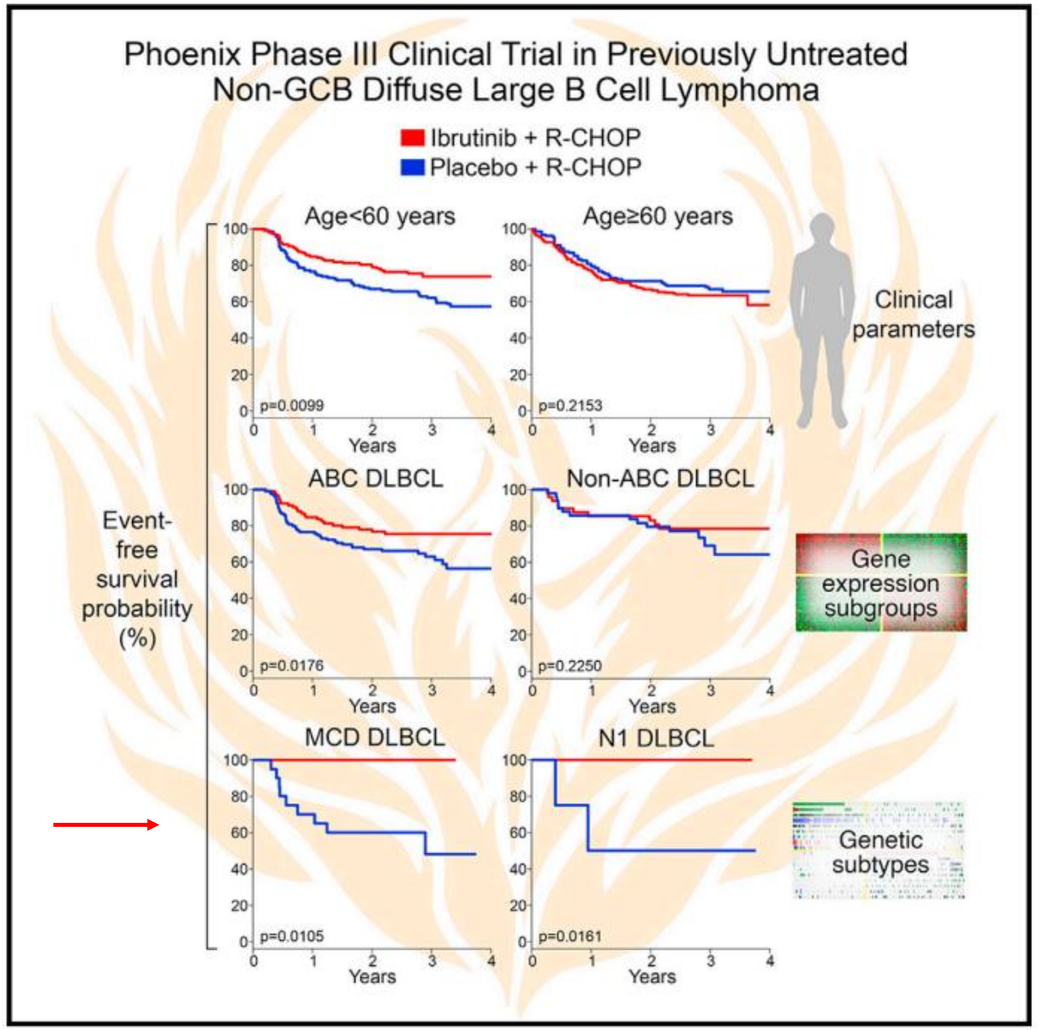
Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL

- ✓ By GEP : **ABC DLBCL (n = 239, 70.2%)**, CD10-negative GCB (n = 72, 21.3%) or Unclassified DLBCL (n = 29, 8.4%)

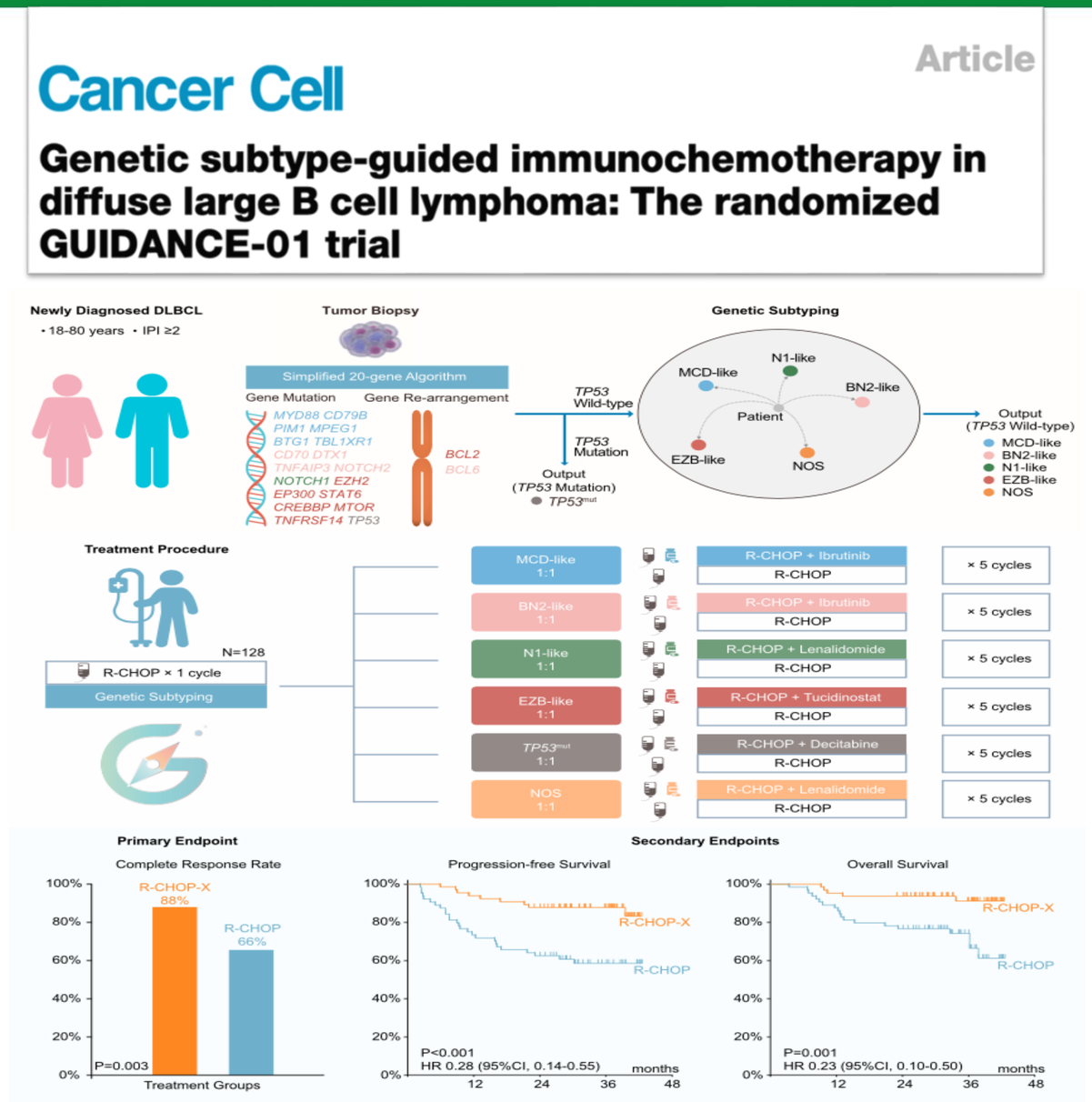


- ✓ MCD had a higher proportion of older patients than BN2 and N1 (p = 0.019)

- ✓ The Phoenix MCD patients had more frequent extranodal involvement than the other subtypes (p = 0.0066)



Wilson W. Et al. Cancer Cell 2021



A SINGLE MODEL OF PRECISION MEDICINE IN DLBCL

- 64 pts in experimental arm
- single Institution, unblinded
- Ongoing multicenter, randomized, phase 3 trial (GUIDANCE-02)

Golcadomide+R-CHOP phase 1 study

Phase 1b study (NCT04884035): Golcadomide dose was optimized to maximize efficacy and tolerability while maintaining delivery of R-CHOP[1]

Patients with previously untreated aggressive B-cell lymphoma

Dose escalation (part 1)

Golcadomide + R-CHOP-21

Golcadomide dose levels

DL-1: 0.2 mg, days 1-7

DL1: 0.4 mg, days 1-7

DL2: 0.4 mg, days 1-10[a]

R* 1:1

Dose expansion (part 2)

Golcadomide + R-CHOP-21 at RP2D-1

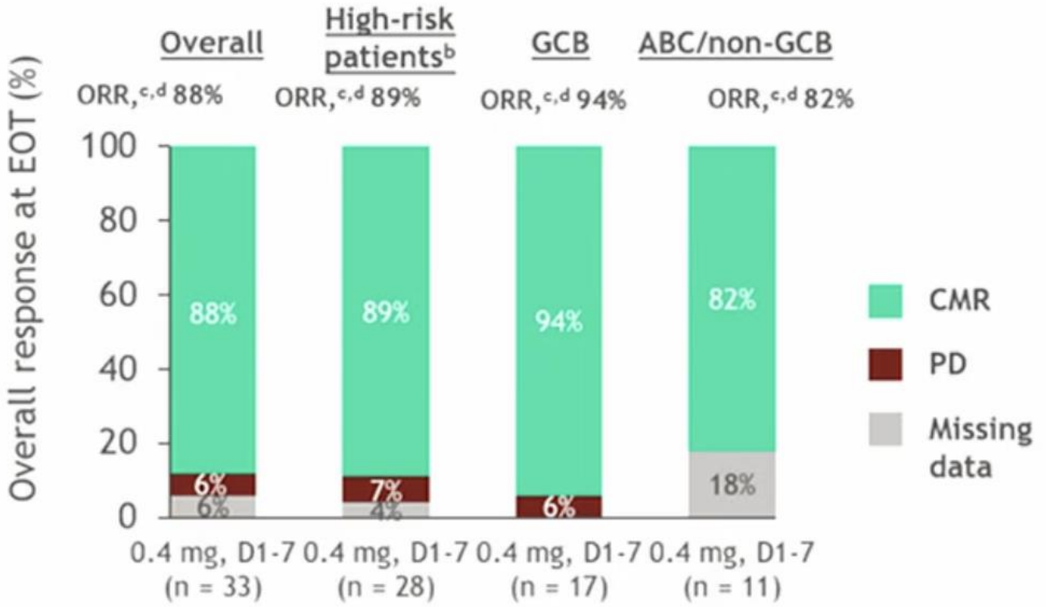
Golcadomide + R-CHOP-21 at RP2D

*Randomization for the purpose of dose optimization (FDA Project Optimus)

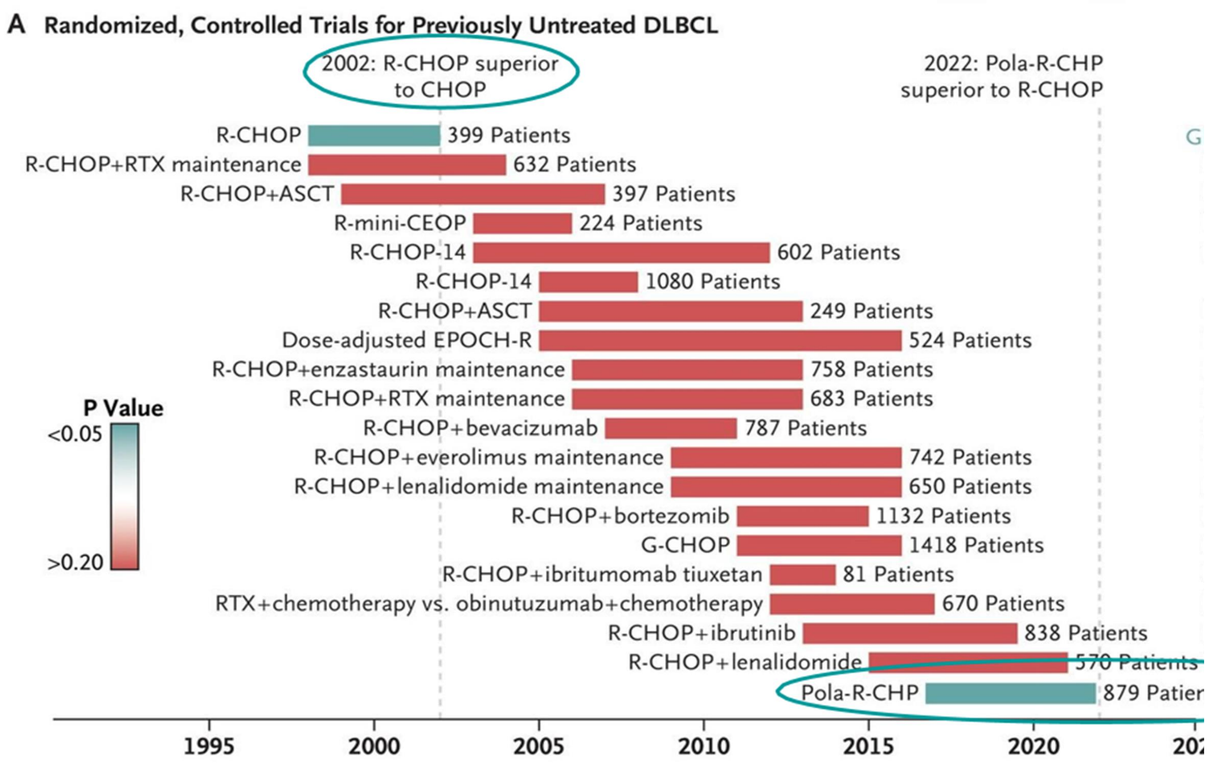
Patients treated for six 21-day cycles unless disease progression occurred, unacceptable toxicity, study withdrawal, or physician decision

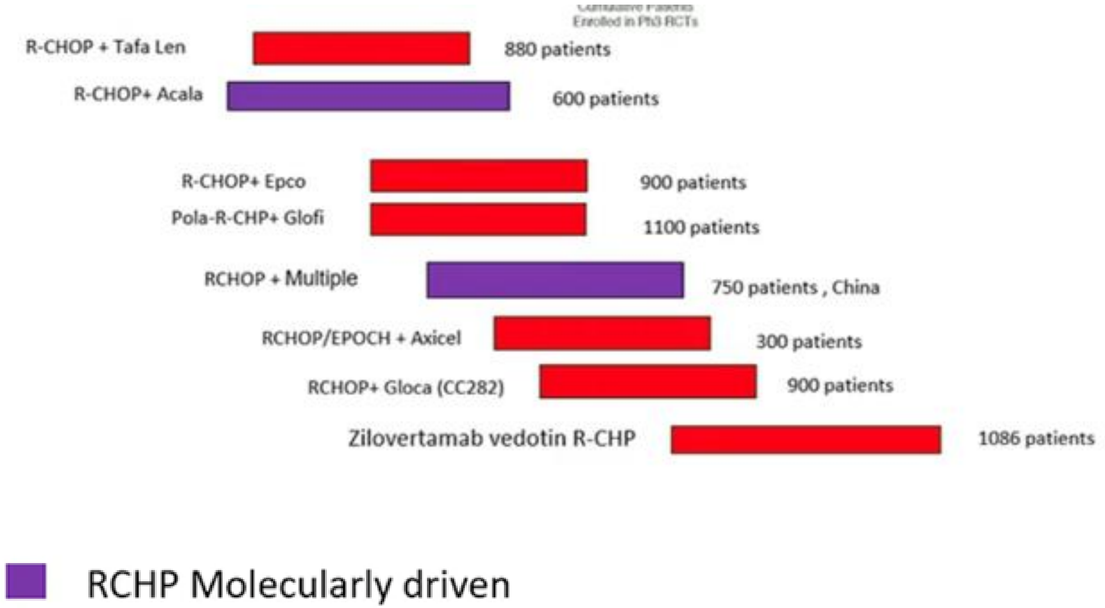
Median relative dose intensity with golcadomide 0.4 mg, D1-7 (n = 37)

Golcadomide, %	Cyclophosphamide, %	Doxorubicin, %	Vincristine, %
97	99	99	99



BEYOND R-CHOP: SUBTYPE DRIVEN vs Agnostic





Palmer AC, et al. N Engl J Med 2023

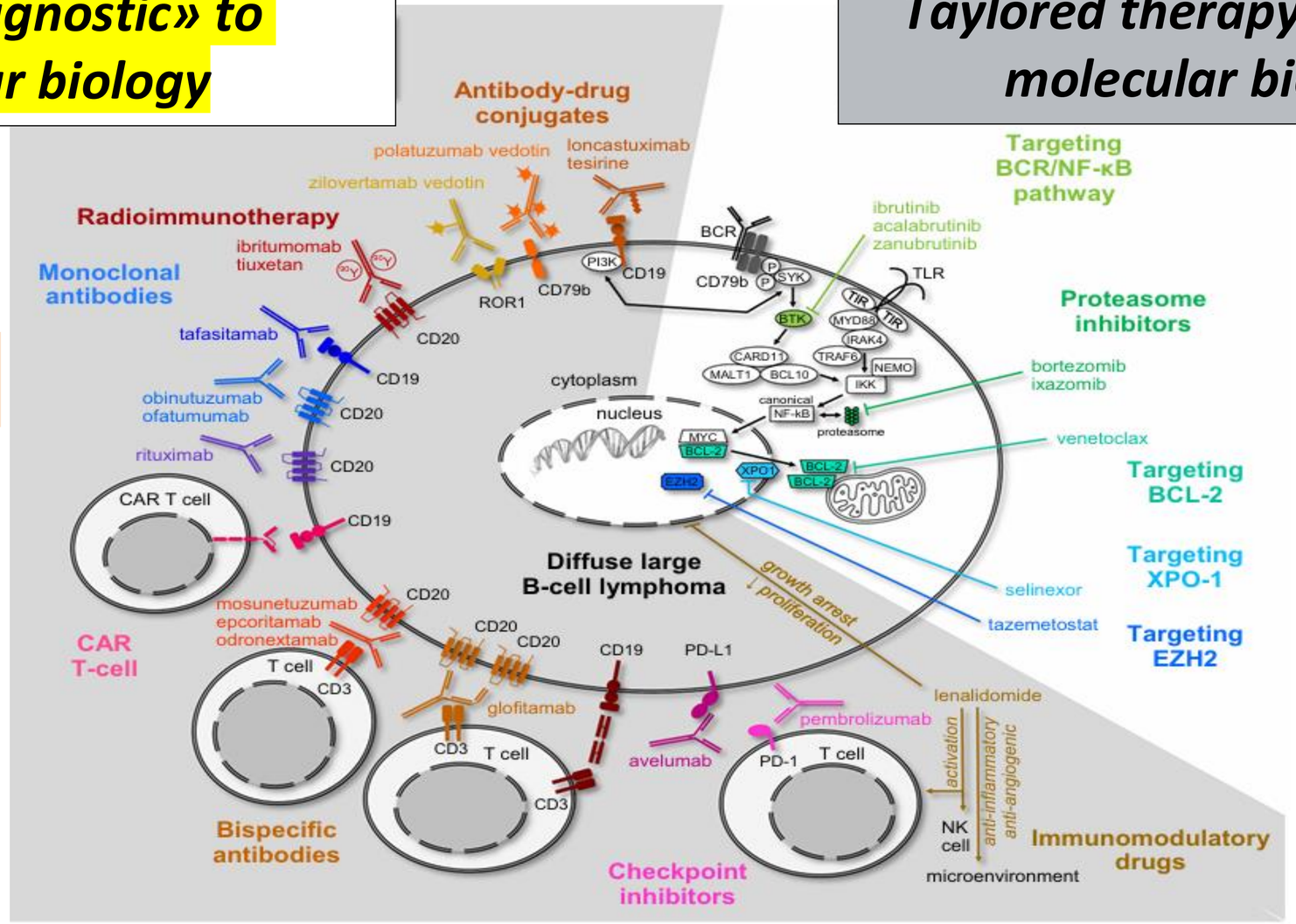
How to move beyond R-CHOP/Pola-R-CHP ?

Therapy «agnostic» to molecular biology

Taylored therapy based on molecular biology

Novel Antibodies

Immune system engaging therapy



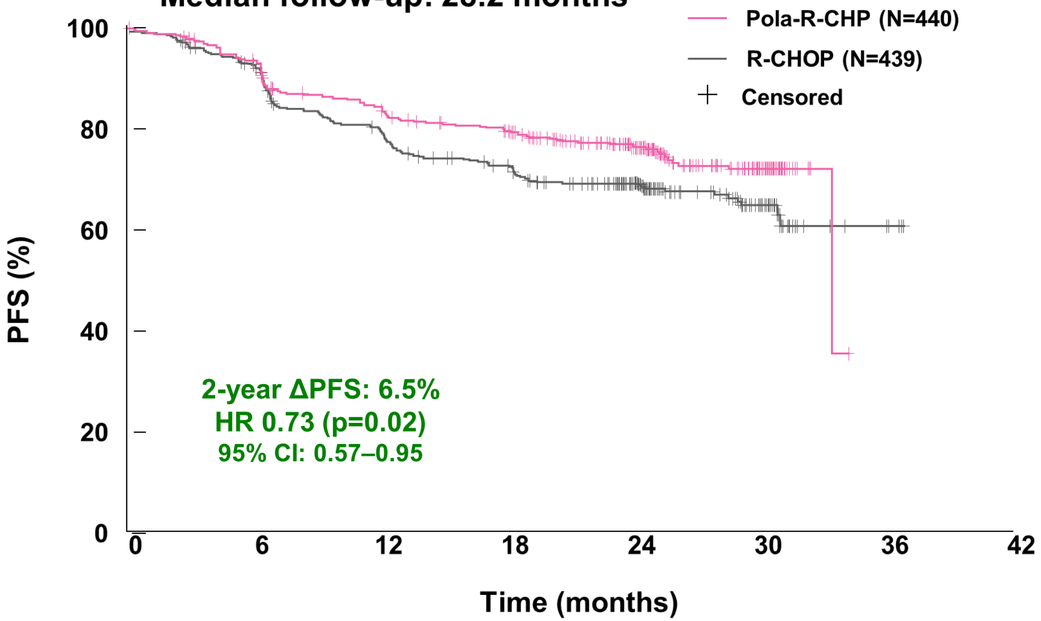
Targeting BCR/NF-kB pathways

Proteasome Inhibitors

Targeting BCL-2

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP
Primary endpoint: PFS

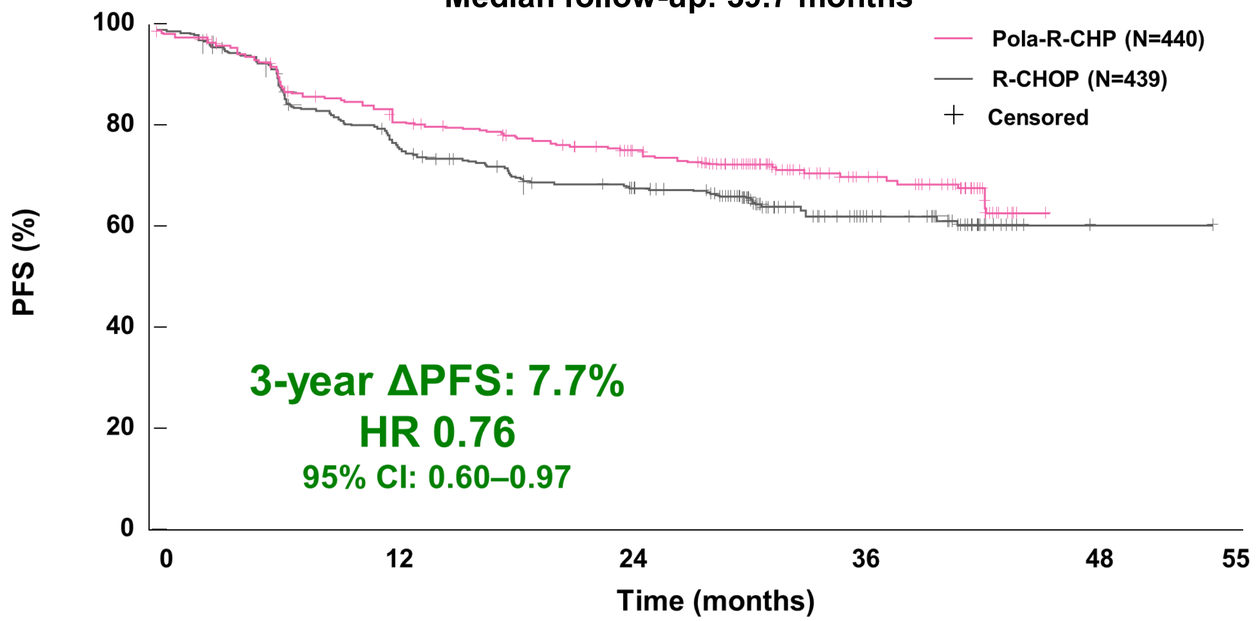
Primary analysis (CCOD: June 28, 2021)[1]
Median follow-up: 28.2 months



No. of patients at risk

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

Updated results (CCOD: June 15, 2022)
Median follow-up: 39.7 months



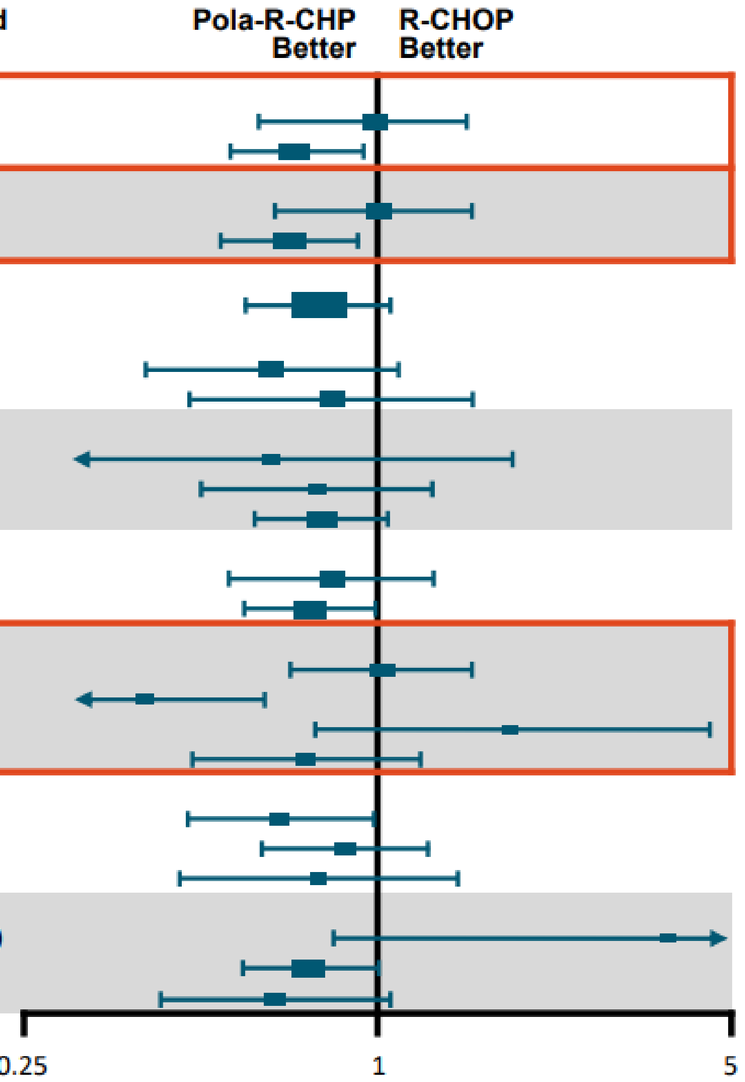
No. of patients at risk

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

Pola-R-CHP demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death versus R-CHOP

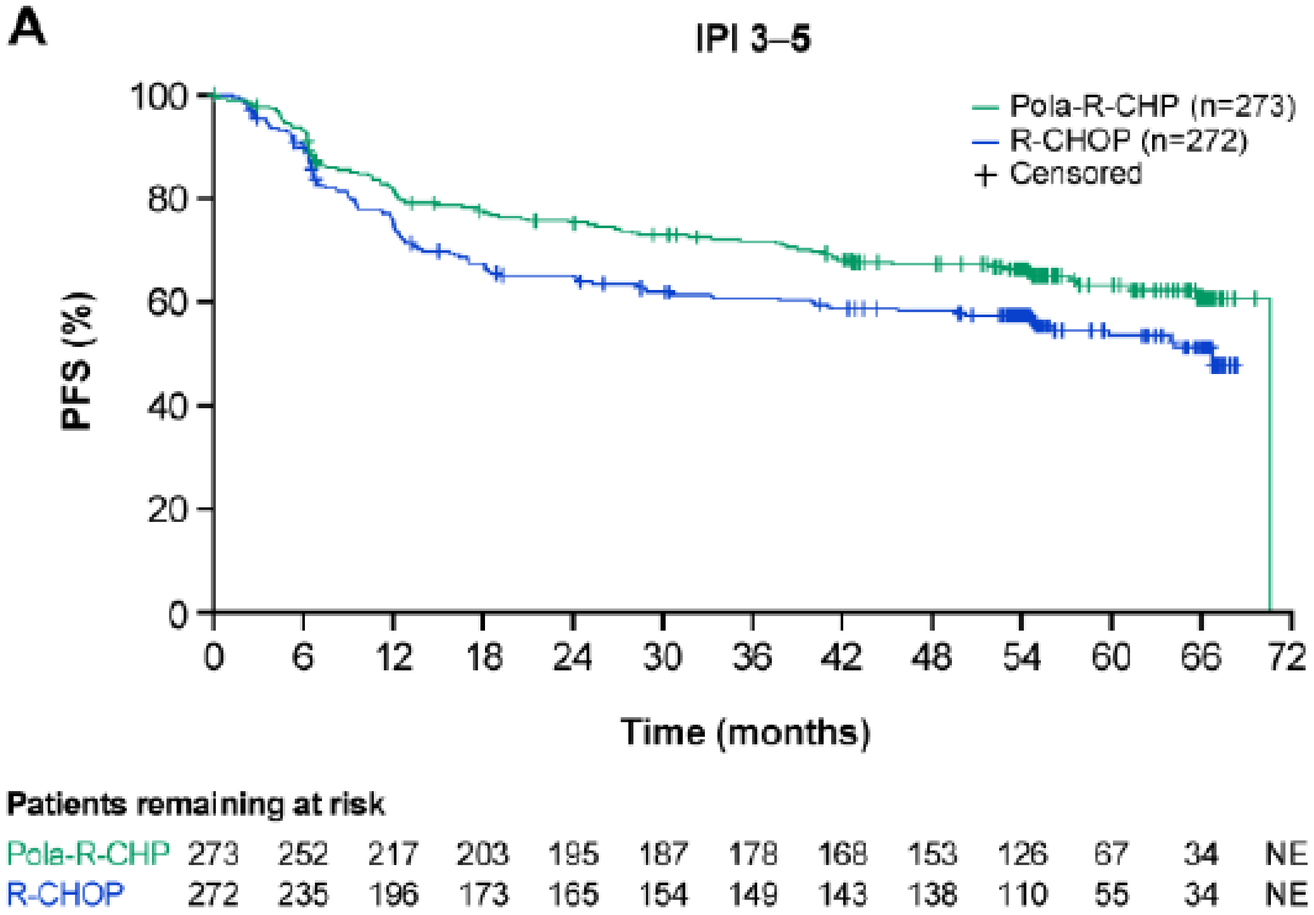
Investigator-assessed PFS by subgroup (unstratified)

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



Tilly H, et al. N Engl J Med 2022;386:351–63.

PFS Efficacy per IPI Score 3-5 (rimborsabilità in italia)



Con un follow up di 5 anni, Polivy mantiene l'importante vantaggio in PFS (endpoint primario) nei pazienti con IPI 3-5: **-29% (HR: 0,71) di rischio vs R-CHOP**

Morschhauser et al. Supplement data JCO, https://doi.org/10.1200/JCO-25-00925

Polatuzumab impact on subsequent lymphoma therapies

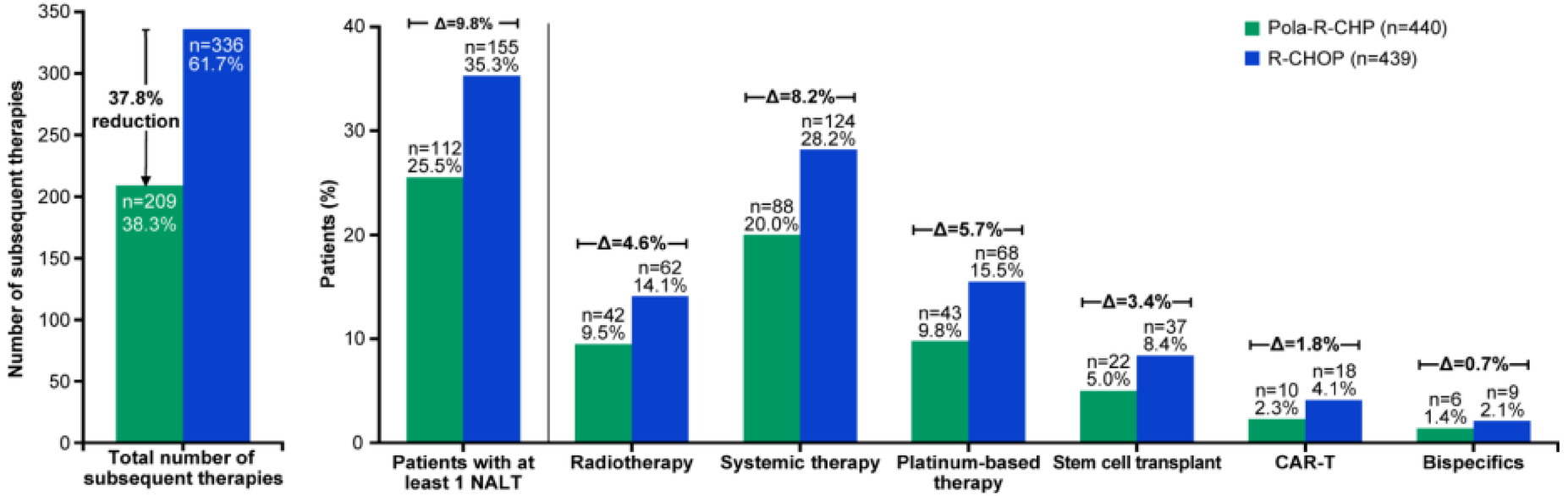


FIG S2. Subsequent lymphoma therapies in the global population. CAR-T, chimeric antigen receptor T-cell therapy; NALT, next anti-lymphoma treatment; Pola-R-CHP, polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

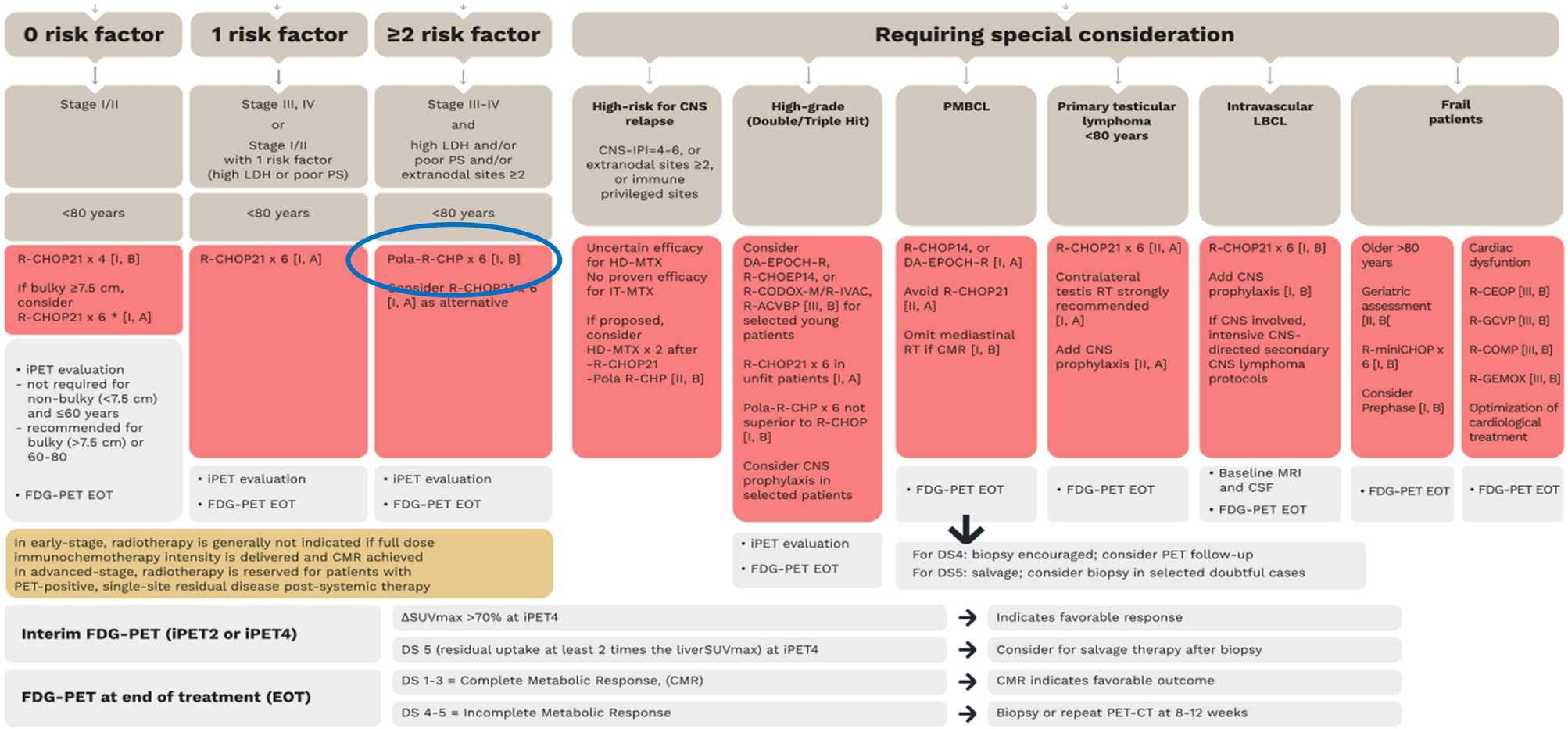
Morschhauser et al. Supplement data JCO, https://doi.org/10.1200/JCO-25-00925

DOI: 10.1002/hem3.70207

GUIDELINES - EXPERT OPINION

HemaSphere eha

Large B-cell lymphoma (LBCL): EHA Clinical Practice Guidelines for diagnosis, treatment, and follow-up



What comes after Pola-R-CHP? ….

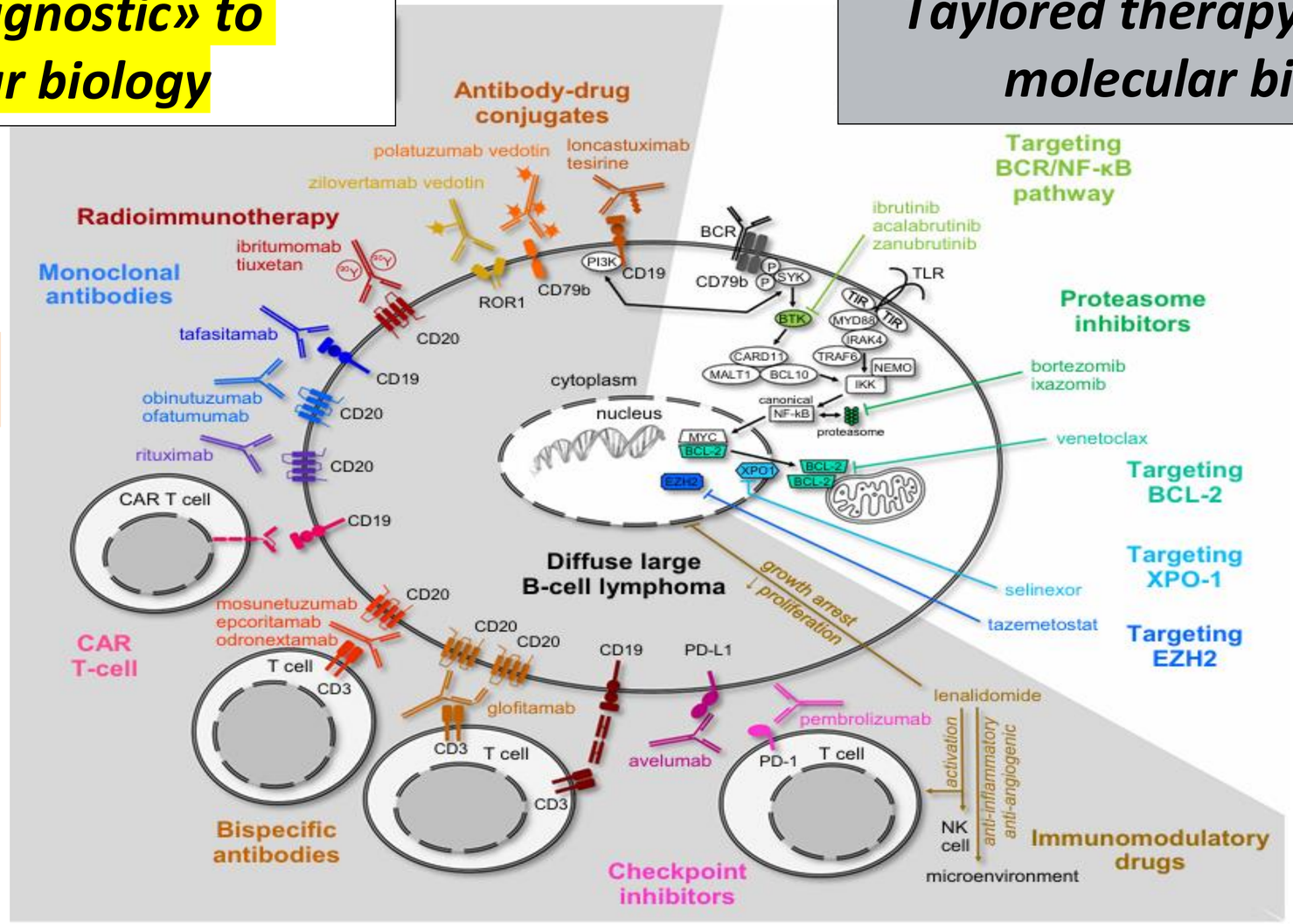
How to move beyond R-CHOP/Pola-R-CHP ?

Therapy «agnostic» to molecular biology

Taylored therapy based on molecular biology

Novel Antibodies

Immune system engaging therapy



Targeting BCR/NF-kB pathways

Proteasome Inhibitors

Targeting BCL-2

CLINICAL TRIALS AND OBSERVATIONS

Three-year follow-up analysis of first-line axicabtagene ciloleucel for high-risk large B-cell lymphoma: the ZUMA-12 study

Julio C. Chavez,[1] Michael Dickinson,[2] Javier Munoz,[3] Matthew L. Ulrickson,[3] Catherine Thieblemont,[4] Olalekan O. Oluwole,[5] Alex F. Herrera,[6] Chaitra S. Ujjani,[7] Yi Lin,[8] Peter A. Riedell,[9] Natasha Kekre,[10] Sven de Vos,[11] Jacob Wulff,[12] Chad M. Williams,[12] Joshua Winters,[12] Ioana Kloos,[12] Hairong Xu,[12] and Sattva S. Neelapu[13]

KEY POINTS

- **First-line axi-cel demonstrated an 86% complete response rate and 3-year PFS rate of 75% in efficacy-evaluable patients with high-risk LBCL.**
- **New malignancies and nonrelapse mortalities were rare, occurring in 4 and 2 patients each, and none was related to axi-cel.**

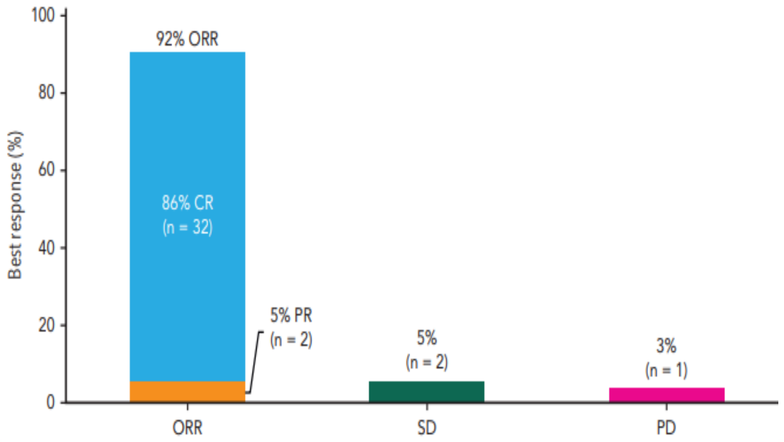
High-Risk LBCL
- HGBL, with *MYC* and *BCL2* and/or *BCL6* translocations (double- or triple-hit), or
- LBCL with IPI score ≥3 any time before enrollment

+

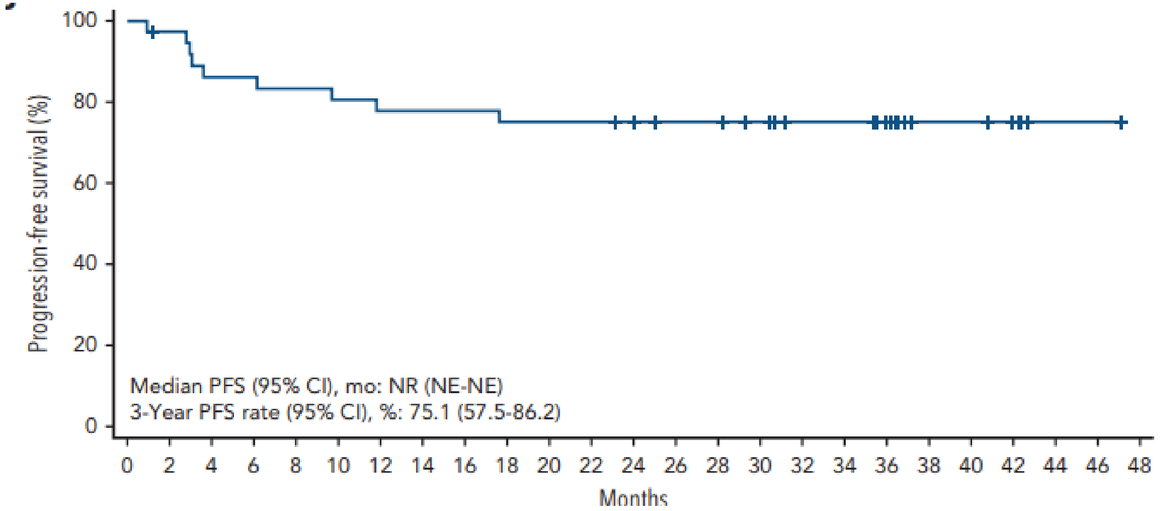
Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5) after 2 cycles of an anti-CD20 mAb + anthracycline-containing regimen

+

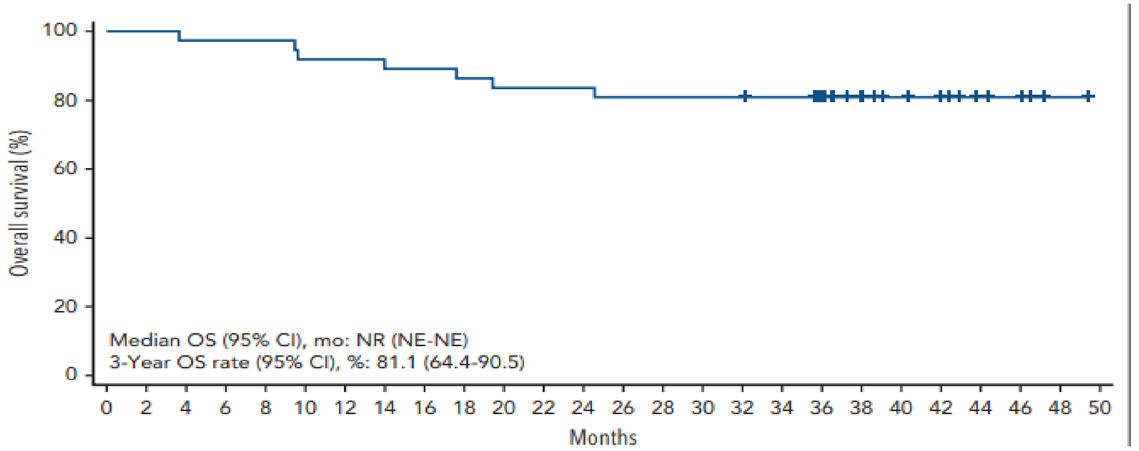
Additional Key Inclusion Criteria
- Age ≥18 years
- ECOG 0–1



Survival assessments in the 3-year analysis.



median follow-up of 47.0 months



New perspectives in 1L DLBCL

Agent	Protocol	Pts	Pts	1ry Endpoint
Acalabrutinib[1]	ESCALADE	nonGCB, IPI 1-5, 18-70 yo	600	PFS
Tafasitamab[2]	FrontMIND	IPI HI and H, 18-80 yo	880	PFS
Glofitamab▼[3]	SkyGLO	IPI 2-5, 18-80 yo	1130	PFS
Mosunetuzumab▼[4]	GO40515	IPI 2-5, > 18 yo	160	PFS
Epcoritamab[5]	EPCORE-DLBCL-2	IPI 2-5, > 18 yo	900	PFS
Odronextamab[6]	OLYMPIA-3	IPI 2-5, > 18 yo	840	PFS
Axi-cel[7]	ZUMA23	IPI 4-5, > 18 yo	300	EFS

1 Davies AJ, et al. Blood 2022;140(Suppl 1):9478–9 2. https://clinicaltrials.gov/study/NCT04824092
3 https://www.clinicaltrials.gov/study/NCT06047080. 4. Olszewski AJ, et al. Presented at ASH 2022. Oral;
5. Sehn LH, et al. Presented at ASCO 2023. Abstract TPS7592; 6. Tessoulin B, et al. Presented at EHA 2023. Abstract PB2335.
7 Westin JR et al, ICML 2023 Abs #OT06

Safety and efficacy of tafasitamab with or without lenalidomide added to first-line R-CHOP for DLBCL: the phase 1b First-MIND study

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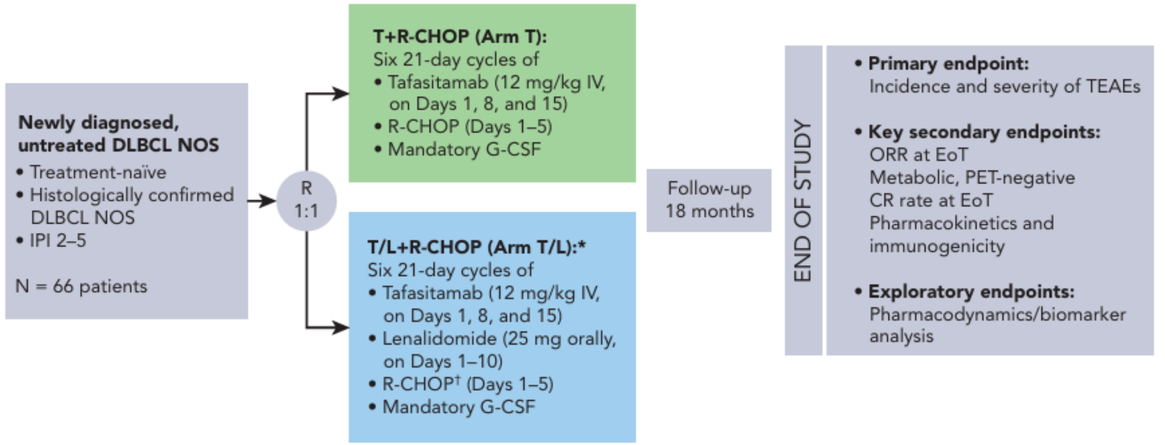
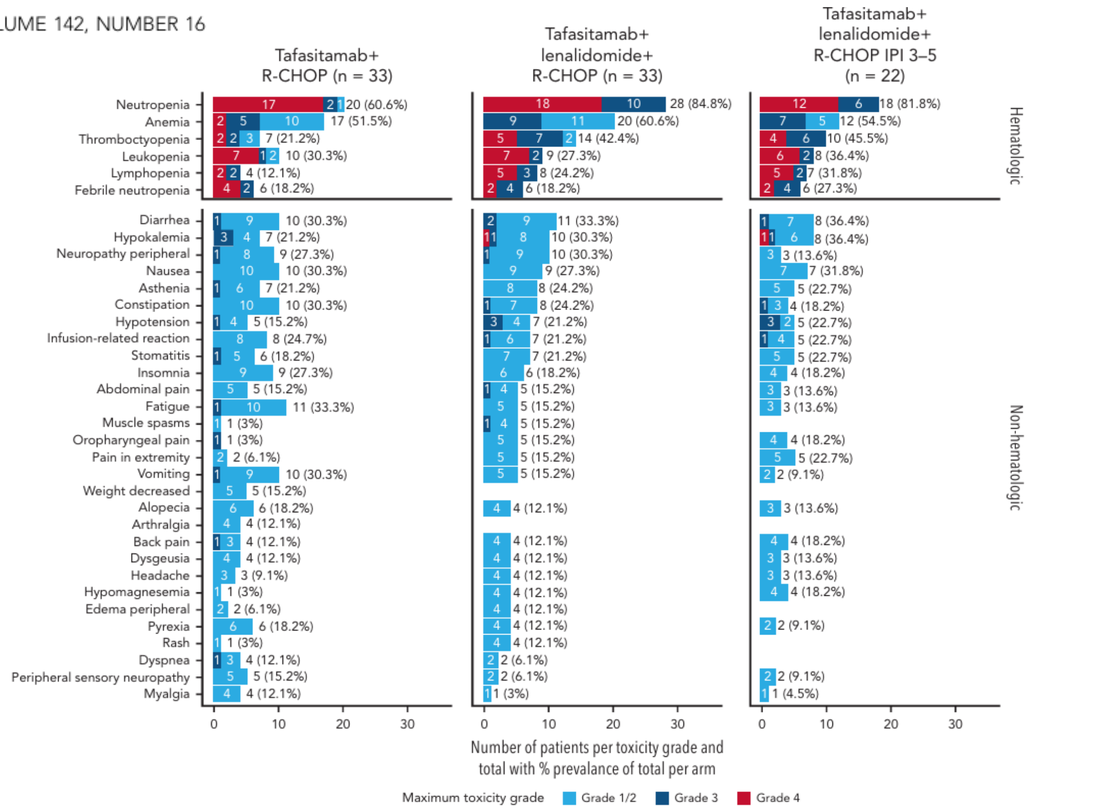


✓ Efficacy outcome after > 18 months of follow up

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)



Trial	Phase	Inclusion criteria	Patients Status	Endpoints
NCT04824092 FRONT-MIND Tafasitamab + lenalidomide + R-CHOP vs R-CHOP	III	18–80 y., IPI 3–5, PS ≤ 2	Recruiting (880 pts)	PFS

Beleda et al. Blood 2023

Glofitamab▼ combined with R-CHOP or Pola-R-CHP in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): final results from the NP40126 study

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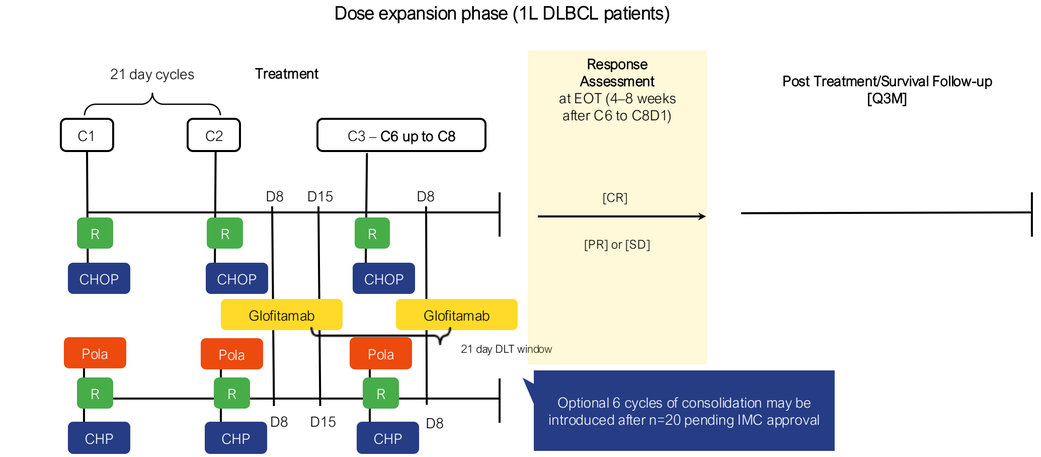


Table 1. Baseline characteristics.

n (%), unless specified	Glofit + R-CHOP (n=56)	Glofit + Pola-R-CHP (n=24)	All treatments (N=80)
Median age, years (range)	68 (21–84)	65 (32–85)	68 (21–85)
Female	29 (51.8)	12 (50.0)	41 (51.3)
Baseline ECOG PS			
0–1	47 (83.9)	22 (91.7)	69 (86.3)
2	8 (14.3)	2 (8.3)	10 (12.5)
3	1 (1.8)	0	1 (1.3)
Cell of origin			
GCB	24 (42.9)	8 (33.3)	32 (40.0)
Non-GCB*	11 (19.6)	10 (41.7)	21 (26.3)
Unclassified	11 (19.6)	3 (12.5)	14 (17.5)
Unknown	10 (17.9)	3 (12.5)	13 (16.3)
Ann Arbor stage III/IV at study entry	54 (96.4)	23 (95.8)	77 (96.3)
IPI risk factors			
1	2 (3.6)	1 (4.2)	3 (3.8)
2	19 (33.9)	8 (33.3)	27 (33.8)
3	20 (35.7)	10 (41.7)	30 (37.5)
4/5	15 (26.8)	5 (20.8)	20 (25.0)
Bulky disease >10 cm	20 (35.7)	3 (12.5)	23 (28.8)

*Includes one patient with ABC cell of origin in the Glofit + Pola-R-CHP arm. ABC, activated B-cell; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell.

Table 2. Efficacy summary.

n (%), unless specified	Glofit + R-CHOP (n=56)	Glofit + Pola-R-CHP (n=24)	All treatments (N=80)
ORR	52 (92.9)	24 (100)	76 (95.0)
CMR	48 (85.7)	23 (95.8)	71 (88.8)
DOR, median months (95% CI)	NE (NE)	NE (NE)	NE (NE)
2-year event free rate, % (95% CI)	84.3 (74.3–94.3)	79.2 (62.9–95.4)	82.6 (74.1–91.2)
DOCR, median months (95% CI)	NE (NE)	NE (NE)	NE (NE)
2-year event-free rate, % (95% CI)	91.2 (83.0–99.5)	80.9 (63.9–97.8)	88.0 (80.1–95.8)

CI, confidence interval.

✓ Most CMRs had been achieved at the first interim assessment (approximately 2 months)

- No grade 5 events of neutropenia, febrile neutropenia, thrombocytopenia, or anemia occurred in either treatment arm.

Topp MS, et al. ICML 2025; poster presentaion (#280)

Adults with previously untreated CD20 DLBCL and IPI ≥3 received SC epco (every week, cycle [C] 1–4; every 3 weeks, C5–6) + R CHOP for 6 cycles (21 d) followed by single-agent epco every 4 weeks up to 1 y (in cycles of 28 d).

- ✓ 33 patients, median age 66,
- ✓ All pts had IPI ≥3 and ≥24% had double- or triple-hit DLBCL.

- ✓ ORR 100%
- ✓ CMR 90%

- ✓ CRS (42% grade [G] 1/ 2, 3% G3) and ICANS (3% G2)
- ✓ Infections 42%

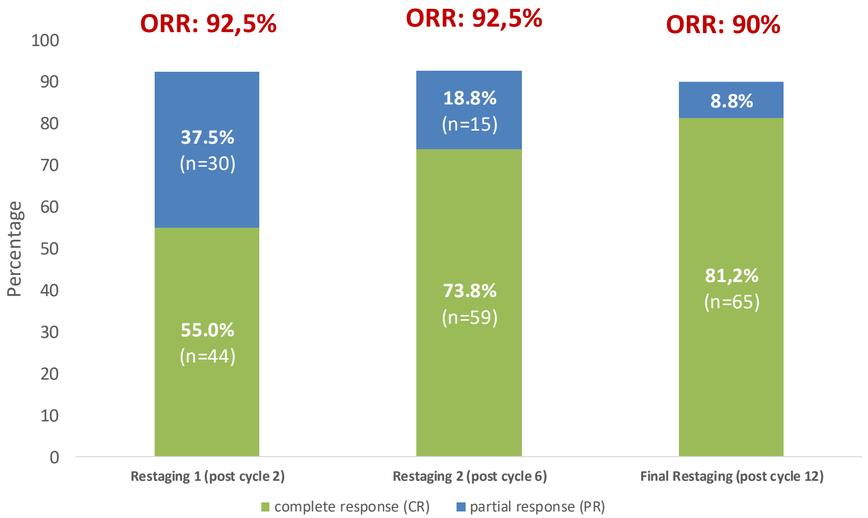
Trial	Phase	Inclusion criteria	Patients Status	Endpoints
NCT4663347 EPCORE NHL-2 Epcoritamab + R-chemotherapy	Ib/II	≥ 18 y., PS ≤ 2, B-NHL	Recruiting (130 pts)	Safety, ORR

… What about very elderly patients?

R-Pola-Glo – Chemo-light Frontline Therapy Induces High Response Rates with a Favorable Safety Profile in Elderly/Frail Patients with Aggressive Lymphoma

	FIT	UNFIT		FRAIL
ADL	≥5*	< 5*	6*	<6*
	and	*and/or*	*and*	*and/or*
IADL	≥6*	<6*	8*	<8*
	and	*and/or*	*and*	*and/or*
CIRS-G	0 score =3-4 *and* ≤8 score =2	≥1 score =3-4 *and/or* > 8 score =2	0 score =3-4 *and* <5 score =2	≥1 score =3-4 *and/or* ≥5 score =2
	and	*and*	*and*	*and*
Age	<80	<80	≥80	≥80
R-Pola-Glo (n=79)	6 (7.5 %)	28 (35.0 %)	15 (18.8 %)	30 (37.5 %)

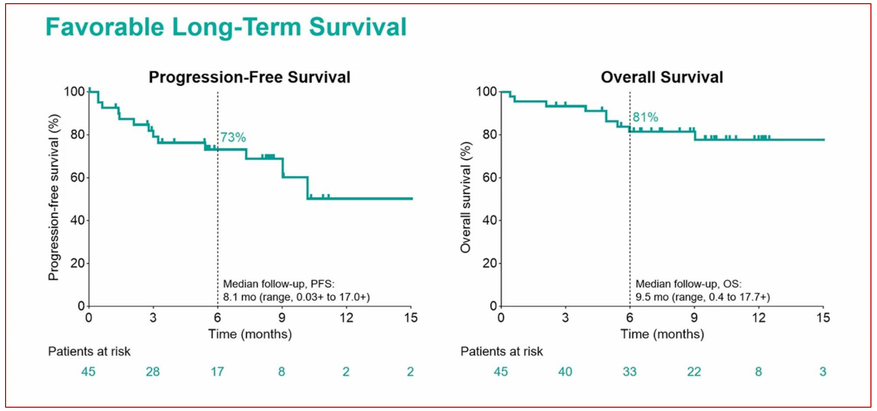
91.3%



- 90% (72/80) of patients are alive at EOT

EPCORE DLBCL-3: Fixed-Duration Epcoritamab Monotherapy in Older (≥75 y), Anthracycline-Ineligible Patients With Previously Untreated Large B-Cell Lymphoma (LBCL)

- N= 45 patients
- ORR: 78%; CR rate: 70%; 89% of complete responses were ongoing
- 8 patients (18%) experienced a serious infection; 4 (9%) had serious COVID-19



Wurm-Kuczera R ; et al ICML 2025 (abstract #159); Belada D et al, ICML 2025

Conclusions and Future directions

- ✓ R-CHOP had been the gold standard for the upfront treatment of DLBCL for almost two decades
- ✓ Novel diagnostic tools including gene expression profiling have shown DLBCL to be a heterogenic disease with recurrent genetic background → *Is it feasible in real life?*
- ✓ Molecularly targeted therapy for DLBCL:
  - -Novel testing approach
  - -Novel trial design
- ✓ *We are in a new wave of immunotherapy*: Pola-R-CHP was the first regimen to show a significant progression free survival (PFS) benefit over R-CHOP in DLBCL patients
- ✓ BsAbs in combination with 1st line regimen are being explored and appear to be safe.
- ✓ Elderly unfit or frail patients with previously untreated DLBCL have distinct needs, and regimens chemo-free may help to improve the future treatment landscape for this understudied population