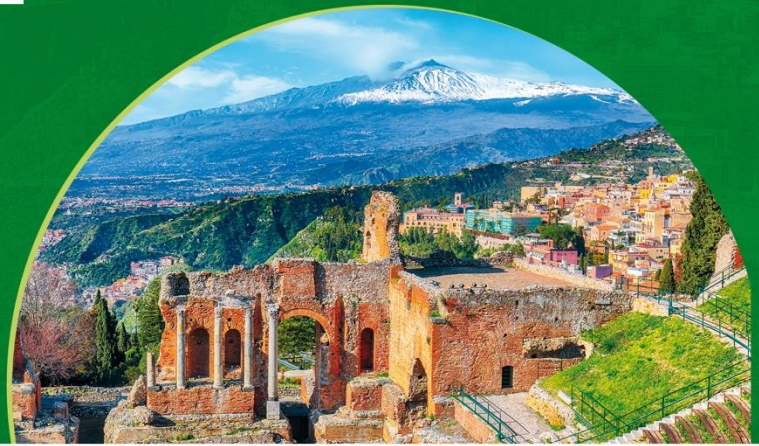
CORSO EDUCAZIONALE COMMISSIONE ANZIANI

XIII EDIZIONE

Giardini Naxos - Marriott Delta Hotels
17-18 aprile 2026



Terapia di I linea dei DLBCL nei pazienti anziani FIT: oltre R-CHOP?

Federica Cavallo

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Disclosures of Federica Cavallo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE	X				X	X	X
ABBVIE					X	X	X
INCYTE					X	X	
ASTRA ZENECA						X	X
SOBI					X	X	
BRISTOL MYERS SQIBB					X	X	
PIERRE FABRE					X	X	X
NOVARTIS					X		X
GILEAD					X		X
TAKEDA					X		X
LILLY					X		
BEONE					X		X
GENTILI						X	

FIT

UNFIT/FRAIL

Dr. Storb, right, helps Jeff Bernard ready the quad for the Sausage Pull race in September 2024.

Photo by Thinkstock on FreeImages

Simplified Geriatric Assessment (sGA)

Criteria	Fit	Unfit		Frail
ADL	≥ 5	< 5	6	< 6
IADL	≥ 6	< 6	8	< 8
CIRS-G	0 score=3-4 ≤ 8 score=2	1 score=3-4 > 8 score=2	0 score=3-4 < 5 score=2	1 score=3-4 ≥ 5 score=2
Age	<80	<80	≥ 80	≥ 80

N= 1163

ADL: activities of daily living; IADL: instrumental ADL: CIRS-G: cumulative illness rating scale for geriatrics

EPI SCORE: sGA, IPI, Hb <12 g/dL

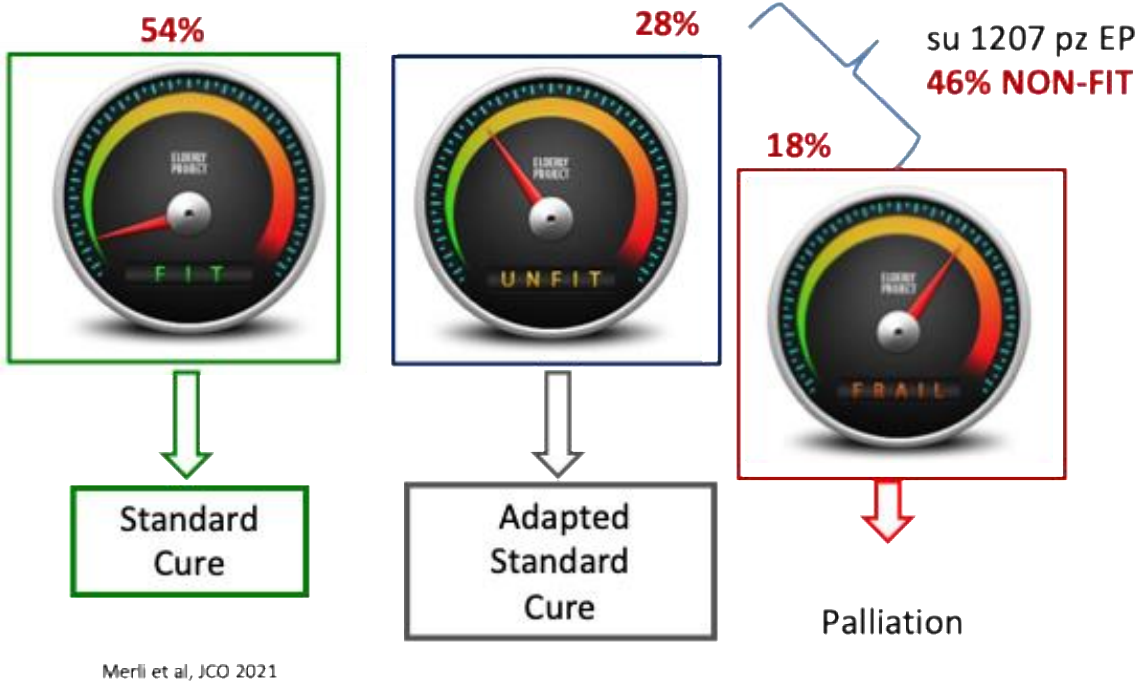
Low (0-1): 3y OS 87%

Intermediate (2-5): 3y OS 69%

High (6-8): 3y OS 42%

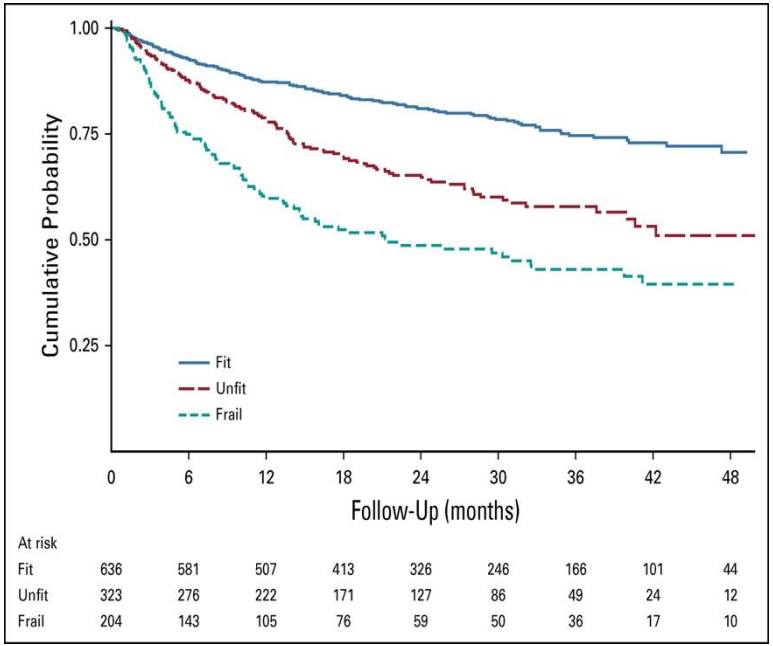
Merli et al, JCO 2021

Simplified Geriatric Assessment (sGA)



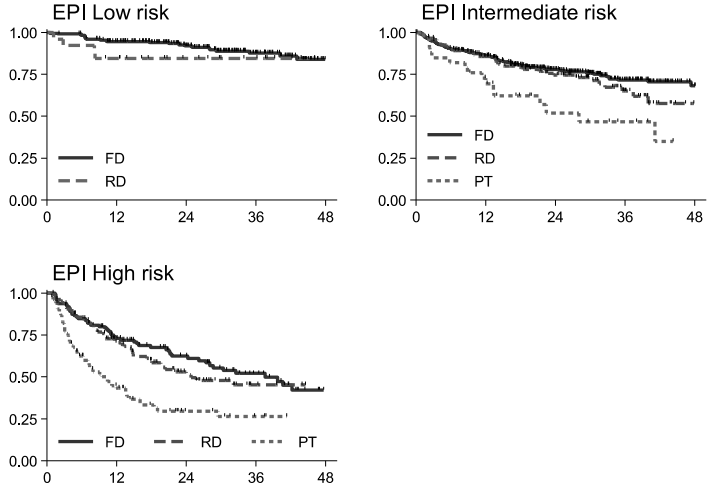
Merli et al, JCO 2021

OS by sGA



At risk									
Fit	636	581	507	413	326	246	166	101	44
Unfit	323	276	222	171	127	86	49	24	12
Frail	204	143	105	76	59	50	36	17	10

OS by EPI and type of therapy



FIT 54%, UNFIT 28%, FRAIL 18%

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Other adverse risk factors in Elderly patients

Hystology:

- DLBCL NOS- activated B-cell (ABC) subtypes
- EBV-positive DLBCL

Low vitamin D levels

Sarcopenia

Nutritional state

Low vitamin D is an unmodifiable adverse prognostic factor in older DLBCL patients: Results from the PREVID randomized trial by Fondazione Italiana Linfomi (FIL).

Annalisa Arcari[1] , Tanja Lazic[2], Alessandra Tucci[3], Benedetta Puccini[4], Federica Cavallo[5], Michele Spina[6], Monica Tani[7], Sonya De Lorenzo[8], Ivana Casaroli[9], Mariantonietta Tafuri[10], Luigi Petrucci[11], Michele Cimminiello[12], Carmine Selleri[13], Elisa Lucchini[14], Guido Gini[15], Barbara Botto[16], Luca Arcaini[17], Manuela Zanni[18], Riccardo Bruna[19], Jacopo Olivieri[20], Elsa Pennese[21], Annarita Conconi[22], Emanuele Cencini[23], Salvatrice Mancuso[24], Chiara Pagani[3], Manuel Ciceri[4], Michele Clerico[5], Caterina Mammi[25], Luigi Marcheselli[26], Valentina Tabanelli[27], Stefano Luminari[2], Francesco Merli[2]

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INTRODUCTION

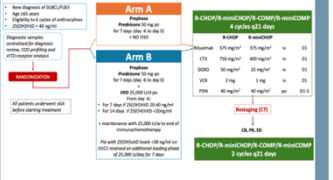
- The median age of Diffuse Large B-cell lymphoma (DLBCL) pts is 66 y.
- **Simplified geriatric assessment** (sGA) and **Elderly Prognostic Index** (EPI) are validated prognostic tools for elderly DLBCL[1]
- **R-CHOP/R-POLA CHP** is the standard first line therapy for fit pts <80 y/o
- **R-COMP** (with liposomal anthracycline) shows similar efficacy with less cardiotoxicity[2]
- Reduced-dose regimens (R-mini-CHOP or R-mini-COMP) are used in unfit/frail pts [3]
- A **corticosteroid pre-phase** improves tolerability and reduces early toxicity[4]
- **Vitamin D deficiency** is highly prevalent in elderly lymphoma patients
- Low serum 25(OH)VitD at diagnosis is associated with **worse prognosis** and **impaired rituximab-mediated cytotoxicity**[5,6]

AIM

To evaluate whether **vitamin D supplementation** during **prephase** improves Progression Free Survival (**PFS**) in elderly patients with newly diagnosed DLBCL

METHODS

Multicentre, randomized, open-labeled, phase III study



Primary endpoint: 2-year PFS
Secondary endpoints: 2-year OS, toxicity, sGA/EPI validation

RESULTS

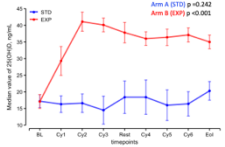
Between 2020 and 2024 a total of **343 patients** were enrolled; after the exclusion of 29 screening failures, **314 were evaluable** (156 reference arm, 158 experimental arm). Median follow-up was **23 months** (range 1-48 months)

Baseline Characteristics	REF – Arm A (N = 156)	EXP – Arm B (N = 158)	Total (N = 314)
Age y, median (IQR)	76 (72-82)	75 (70-80)	76 (71-81)
Sex (M)	77 (49.4%)	89 (56.3%)	166 (52.9%)
ECOG-PS (≥2)	19 (12.2%)	21 (13.3%)	40 (12.7%)
Histology			
DLBCL	152 (97.4%)	154 (97.5%)	306 (97.4%)
FL 3b	4 (2.6%)	4 (2.5%)	8 (2.6%)
Ann Arbor Stage III-IV	120 (76.9%)	124 (78.5%)	244 (77.7%)
Extranodal Sites >1	47 (30.1%)	57 (36.1%)	104 (33.1%)
VitD level (median)	17.1 (IQR 10.4-26.0)	17.0 (IQR 10.7-25.4)	17.0 (IQR 10.7-25.6)
sGA			
FIT	84 (53.8%)	92 (58.2%)	176 (56.0%)
UNFIT	46 (29.5%)	47 (29.7%)	94 (29.9%)
FRAIL	26 (16.7%)	19 (12.0%)	45 (14.3%)
IPI risk group			
Low/interm. (1-2)	68 (43.6%)	62 (39.2%)	130 (41.4%)
High (3-5)	88 (56.4%)	96 (60.8%)	184 (58.6%)
EPI risk group			
Low (0-1)	36 (23.1%)	28 (17.7%)	64 (20.4%)
Intermediate (2-3)	71 (45.5%)	84 (53.2%)	155 (49.4%)
High (≥4)	49 (31.4%)	46 (29.1%)	95 (30.2%)

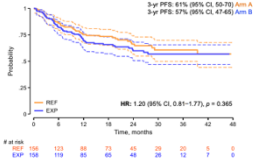
Induction treatment	REF – Arm A (N = 156)	EXP – Arm B (N = 158)	Total (N = 314)
R-CHOP	47 (30.1%)	40 (25.3%)	87 (27.7%)
R-miniCHOP	20 (12.8%)	10 (6.3%)	30 (9.6%)
R-COMP	41 (26.3%)	63 (39.9%)	104 (33.1%)
R-miniCOMP	43 (27.6%)	39 (24.7%)	82 (26.1%)
Not available	5 (3.2%)	6 (3.8%)	11 (3.5%)

Induction treatments were equally distributed among the two arms (Chi^2 p = 0.066).

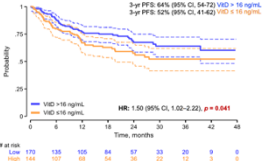
vitD median level in standard arm and in experimental arm (after supplementation)



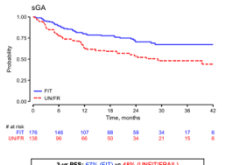
PFS by Treatment Arm



PFS by baseline vitD level

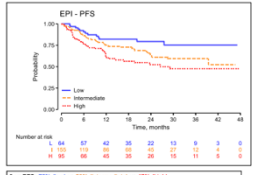


PFS by sGA

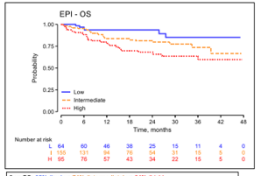


3-yr PFS: 67% (FIT) vs 46% (UNFIT/FRAIL)
UNFIT/FRAIL: HR 1.94 (95% CI 1.31–2.88), p = 0.001

Survival Analysis by EPI



3-yr PFS: 75% (low) vs 59% (intermediate) vs 47% (high)
High-risk EPI: HR 2.61 (95% CI 1.40–4.87), p = 0.003



3-yr OS: 85% (low) vs 74% (intermediate) vs 64% (high)
High-risk EPI: HR 3.69 (95% CI 1.53–8.89), p = 0.004

CONCLUSIONS

- PREVID is the first randomized trial evaluating vitamin D supplementation in older DLBCL patients.
- Vitamin D supplementation corrected biochemical deficiency but **did not improve PFS or OS**.
- **Low baseline vitamin D** remained an **independent adverse prognostic factor**.
- **EPI score** effectively stratified risk for both PFS and OS.
- The biological mechanisms linking vitamin D status and lymphoma outcomes **remain to be clarified**.

Vitamin D retains prognostic, but not predictive, significance in older DLBCL

REFERENCES

1 Merli F et al. Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. J Clin Oncol. 2021 Apr 10;39(11):1214-1222. Arcari A et al. Blood Adv. 2023

2 Arcari et al. A Fondazione Italiana Linfomi cohort study of R-COMP vs R-CHOP in older patients with diffuse large B-cell lymphoma. Blood Adv. 2023 Aug 8;7(15):4160-4169.

3 Baviera et al. Comparative Effectiveness of R-miniCOMP Versus R-miniCHOP in Older Non-Fit Patients With Diffuse Large B-Cell Lymphoma: Insights From a "Fondazione Italiana Linfomi" Cohort Study. Hematol Oncol. 2025 May;43(3):e70099.

4 Lakshmaiah KC et al. Role of prephase treatment prior to definitive chemotherapy in patients with diffuse large B-cell lymphoma. Eur J Haematol. 2018 Jun;100(6):644-648

5 Drake MT et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. J Clin Oncol. 2010 Sep 20;28(27):4191-8.

6 Bittenbring JT et al. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. J Clin Oncol. 2014 Oct 10;32(29):3242-8.

ACKNOWLEDGEMENTS

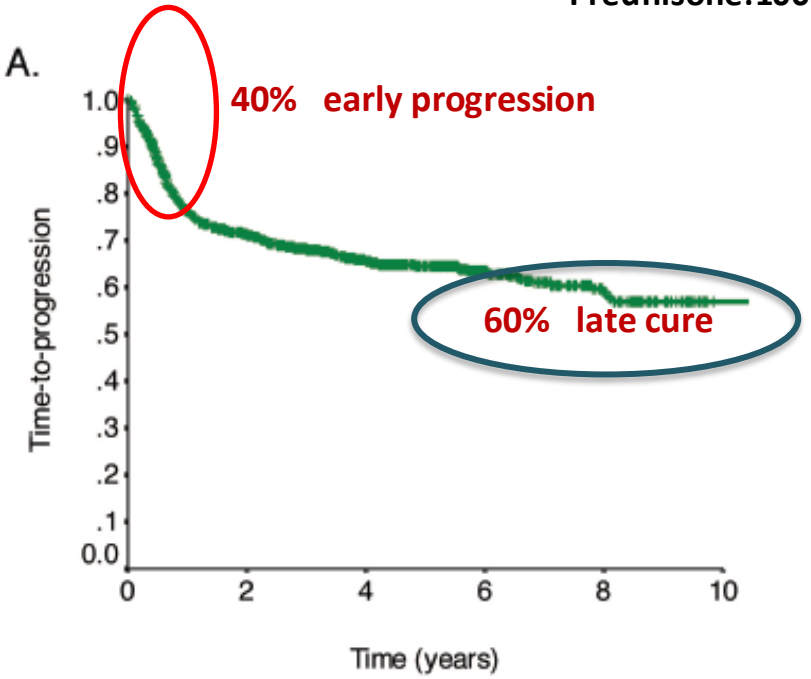
PREVID trial was supported by FIL and funded by GRADE Onlus
A special thank to all participating centers and patients

CONTACT INFORMATION

a.arcari@ausl.pc.it

R - CHOP :

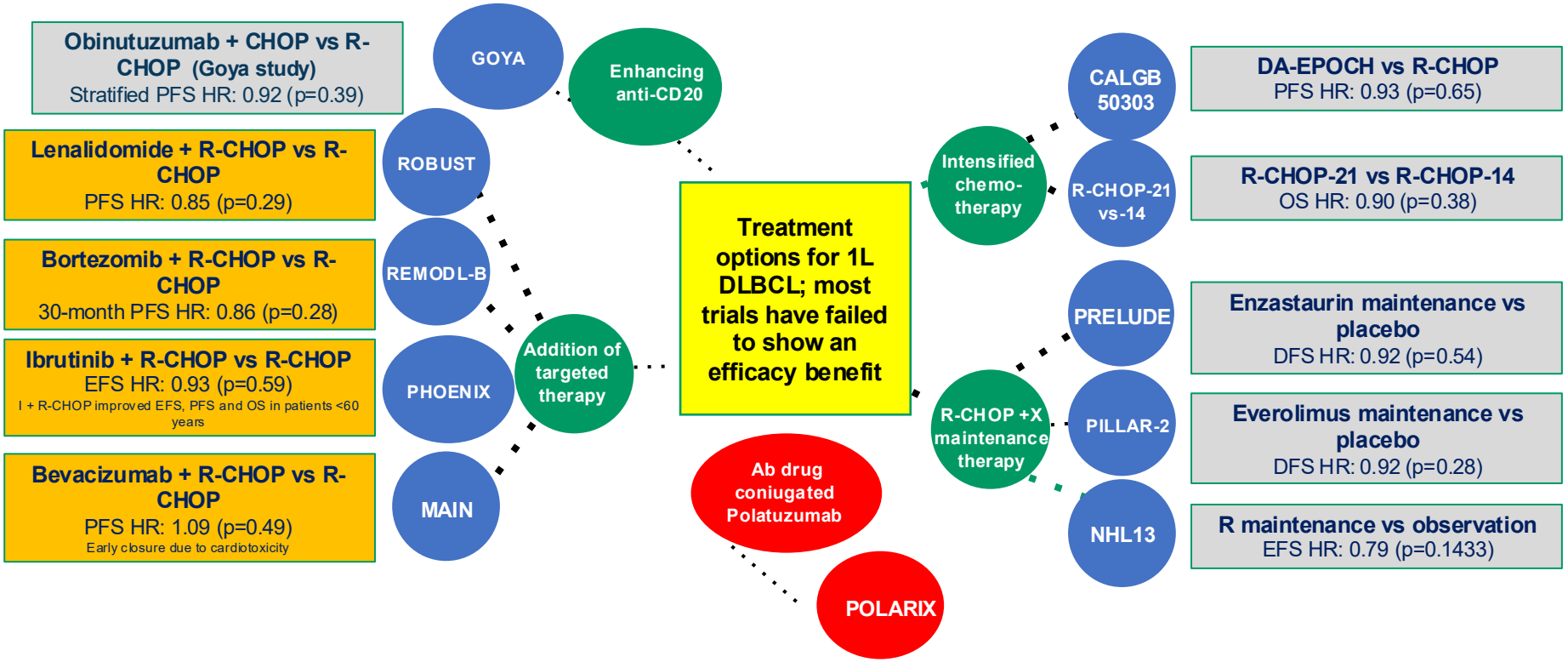
Rituximab: 375 mg/mq gg 1
Ciclofosfamide: 750 mg/mq gg 1
Doxorubicina:50 mg/mq gg 1
Vincristina: 1,4 mg/mq gg 1
Prednisone:100 mg per os gg 1-5



RCHOP first line cured 50-60%

R-CHOP is insufficient in 40% of DLBCL:

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


Obinutuzumab + CHOP vs R-CHOP (Goya study)
Stratified PFS HR: 0.92 (p=0.39)
GOYA
Enhancing anti-CD20
Lenalidomide + R-CHOP vs R-CHOP
PFS HR: 0.85 (p=0.29)
ROBUST
Bortezomib + R-CHOP vs R-CHOP
30-month PFS HR: 0.86 (p=0.28)
REMODL-B
Ibrutinib + R-CHOP vs R-CHOP
EFS HR: 0.93 (p=0.59)
I + R-CHOP improved EFS, PFS and OS in patients <60 years
PHOENIX
Addition of targeted therapy
Bevacizumab + R-CHOP vs R-CHOP
PFS HR: 1.09 (p=0.49)
Early closure due to cardiotoxicity
MAIN
Treatment options for 1L DLBCL; most trials have failed to show an efficacy benefit
Ab drug coniugated Polatuzumab
POLARIX
Intensified chemo-therapy
CALGB 50303
DA-EPOCH vs R-CHOP
PFS HR: 0.93 (p=0.65)
R-CHOP-21 vs-14
R-CHOP-21 vs R-CHOP-14
OS HR: 0.90 (p=0.38)
R-CHOP +X maintenance therapy
PRELUDE
Enzastaurin maintenance vs placebo
DFS HR: 0.92 (p=0.54)
PILLAR-2
Everolimus maintenance vs placebo
DFS HR: 0.92 (p=0.28)
NHL13
R maintenance vs observation
EFS HR: 0.79 (p=0.1433)

The NEW ENGLAND JOURNAL of MEDICINE

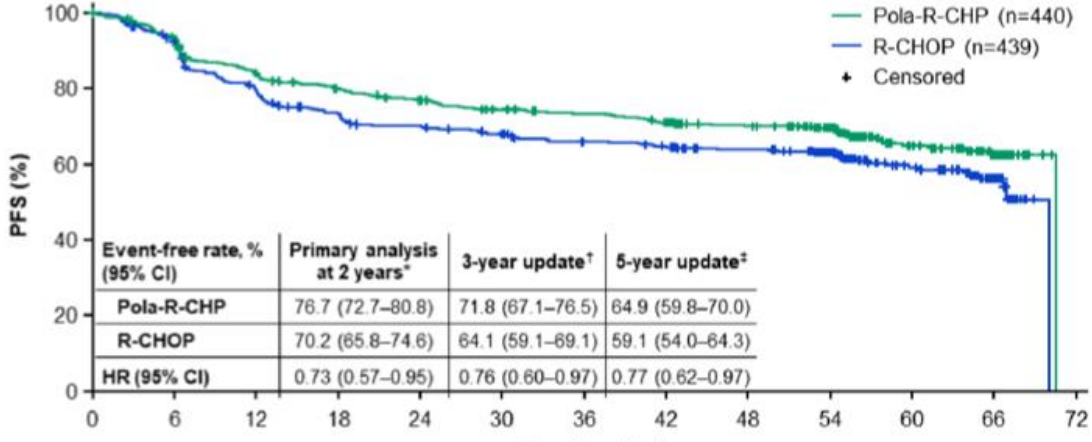
ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

N.Engl.J .Med December 14, 2021

Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

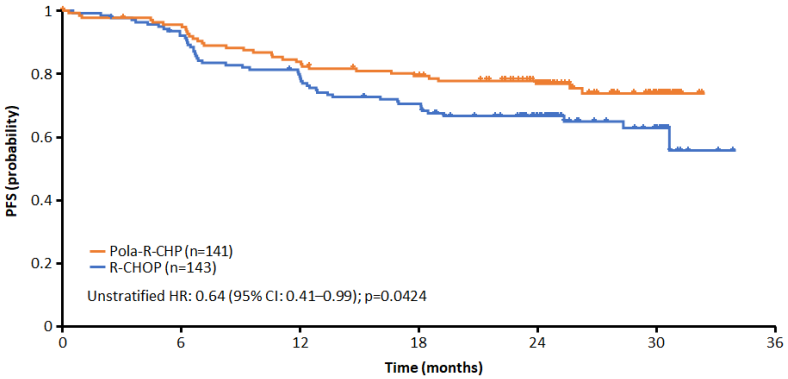
Patients remaining at risk

Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).[1]

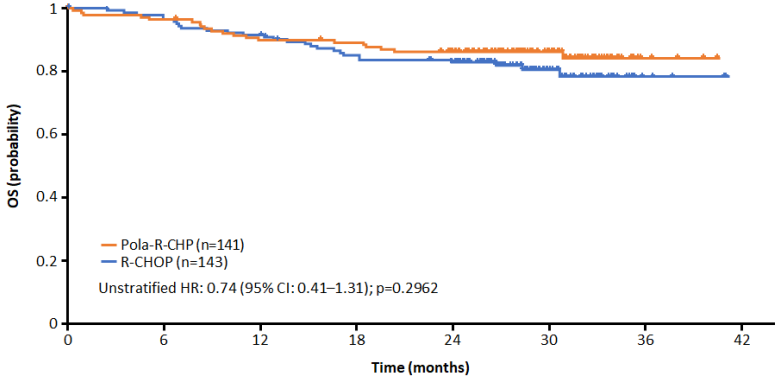
PFS and OS efficacy data in older DLBCL patients

PFS for Pola-R-CHP vs R-CHOP



Number at risk						
Pola-R-CHP	141	131	115	106	82	29
R-CHOP	143	129	110	97	70	26

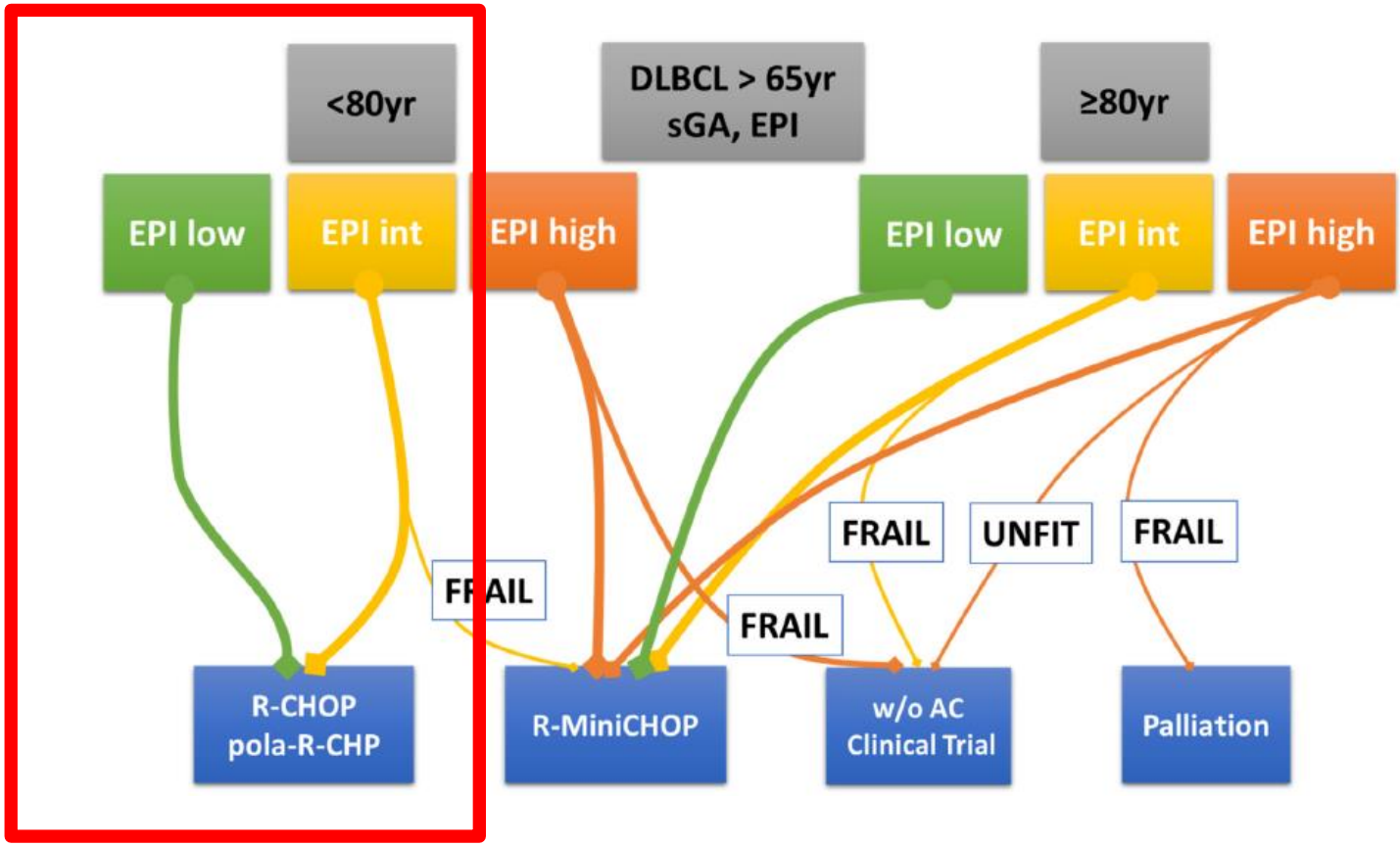
OS for Pola-R-CHP vs R-CHOP



Number at risk							
Pola-R-CHP	141	134	124	122	113	50	4
R-CHOP	143	136	129	117	111	41	5

The risk of **progression, relapse or death** was **lower with Pola-R-CHP** vs R-CHOP (unstratified HR 0.64; 95% CI: 0.41–0.99); **OS data** were immature but **showed trend for reduction** in the risk of death with **Pola-R-CHP** versus R-CHOP (unstratified HR 0.74; 95% CI: 0.41–1.31)

Hu et al:. J.Clinl Oncol suppl.7518



Merli F et al, Cancer 2023

Real-World Outcomes of Frontline Polatuzumab-R-CHP and Impact of Frailty in Older Adults with Diffuse Large B-Cell Lymphoma

- Results from the Multicenter POLAROID Study

- **Varun Iyengar***, **Jomel Meeko Manzano***, Lu Chen, Jessica Chicola, Michelle Okwali, Seth Buller, Guido Pelaez, Vincenzo Pizzuti, Ajay Major, Youssef Youssef, Yazeed Sawalha, Danielle Wallace, Monica Masterson, Nicole Birrer, Allison M. Bock, Adrienne Nedved, Yucai Wang, Thomas Lucido, Joanna M. Rhodes, Siang T. Dim, Jennifer Crombie, Denisse Montana, Michele Stanchina, Juan Pablo Alderuccio, Alyssa Gibson, Peter A. Riedell, Tanim Jain, Benjamin Heyman, Heather Rasmussen, Chaitra Ujjani, Patrick Gould, Hua-Jay J. Cherng, Ahmed Bahnasy, Talal Hilal, Joseph Brandon Parker, Muhamad Alhaj Moustafa, Stacy Pak, Christine Goth, David Russler-Germain, Alex Herrera, **Swetha Kambhampati Thiruvengadam****, **Pallawi Torka****

ASH 2025 Annual Meeting

December 8, 2025

Memorial Sloan Kettering Cancer Center

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Iyengar V, et al; oral presentation ASH 2025, Blood (2024) 144 (Supplement 1): 2336.

Baseline Characteristics (n=535)

OA had higher ECOG and IPI scores, but similar rates of treatment completion

	Younger Adults Age < 70 (N = 325)	Older Adults Age ≥ 70 (N = 210)	P-value
Age	62 (53, 66)	75 (72, 77)	
Sex – no. (%)			0.6
Male	189 (58%)	128 (61%)	
ECOG Score			**<0.001**
0-1	274 (86%)	156 (77%)	
2+	44 (14%)	46 (23%)	
Stage			0.8
I	8 (2.5%)	5 (2.4%)	
II	31 (9.5%)	15 (7.1%)	
III	46 (14%)	37 (18%)	
IV	238 (73%)	152 (72%)	
Extranodal Dx			0.5
Yes	243 (76%)	163 (78%)	
LDH			0.7
< ULN	121 (37%)	73 (35%)	
> ULN	203 (63%)	135 (65%)	
IPI Score			**<0.001**
0 to 2	145 (45%)	49 (23%)	
3 to 5	180 (55%)	161 (77%)	

	Younger Adults Age < 70 (N = 325)	Older Adults Age ≥ 70 (N = 210)	P-value
Bulky Disease	110 (35%)	64 (31%)	0.4
CNS Involvement	7 (2.2%)	10 (4.9%)	0.2
Double Expressor	95 (33%)	62 (36%)	0.6
Double Hit	13 (4.6%)	8 (4.5%)	>0.9
Cell of Origin			0.3
Non-GCB	189 (62%)	130 (67%)	
GCB	116 (38%)	64 (33%)	
Pola-R-mini-CHP	5 (1.5%)	38 (18%)	**<0.001**
Treatment Completion	289 (89%)	178 (85%)	0.2

16

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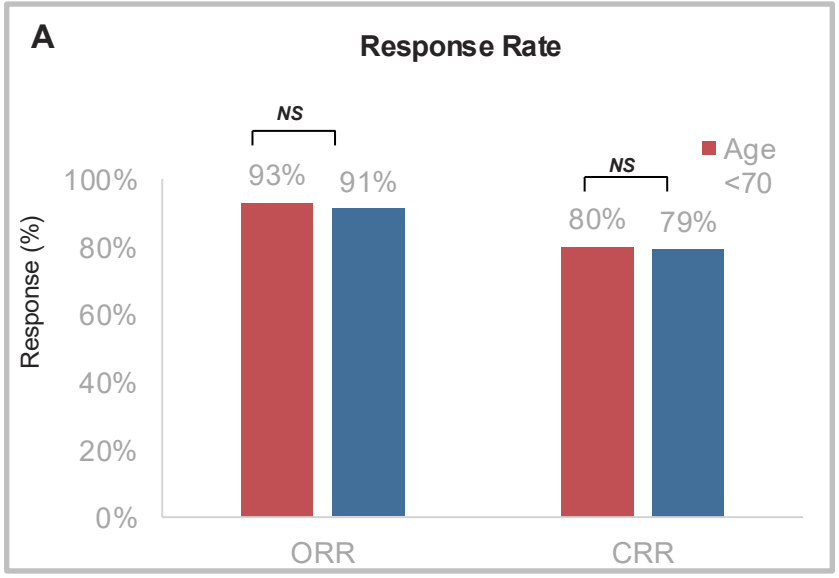
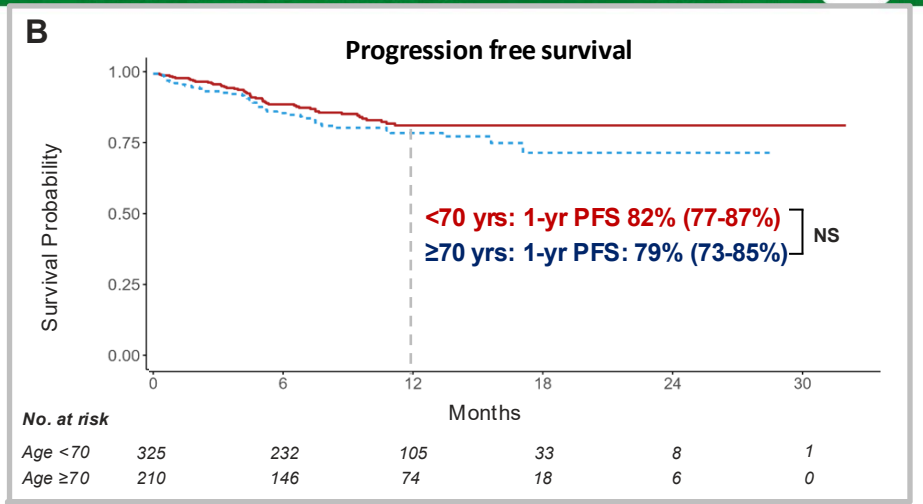
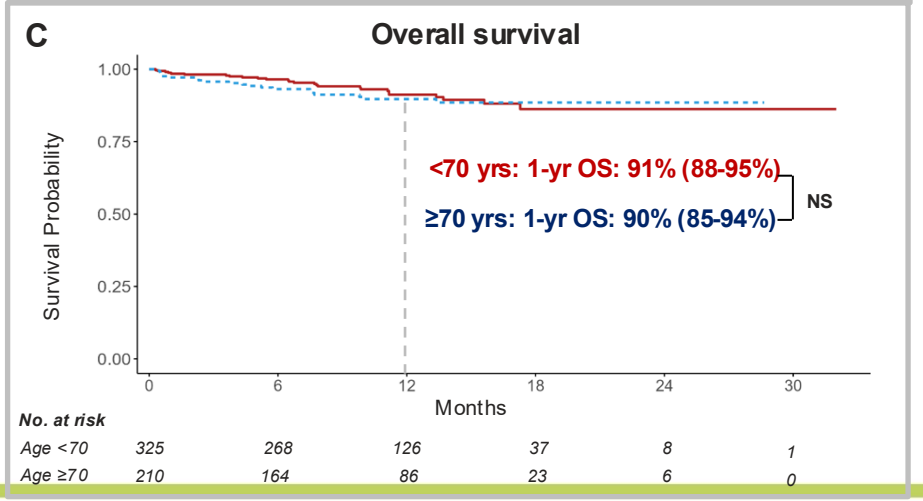
Results - Efficacy

Response rates and PFS/OS are comparable in older vs younger adults



Median follow-up: 11.8 months





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Results - Safety

OA experienced more cytopenias but similar rates of febrile neutropenia and infection

	Younger Adults Age < 70 (N = 325)	Older Adults Age ≥ 70 (N = 210)	P-value
Neutropenia, Grade 3+	88 (27%)	78 (38%)	**0.017**
Febrile neutropenia, Grade 3+	49 (15%)	31 (15%)	>0.9
Thrombocytopenia, Grade 3+	36 (11%)	45 (22%)	**0.002**
Peripheral Neuropathy – no. (%)	107 (34%)	86 (42%)	0.086
Grade 3+	3 (2.8%)	3 (3.5%)	>0.9
Cardiomyopathy	5 (1.6%)	13 (6.2%)	**0.008**
Infection, Grade 3+	65 (20%)	43 (21%)	0.8
Hospitalization	85 (26%)	79 (38%)	**0.006**
ICU Admission	16 (4.9%)	16 (7.7%)	0.3
Treatment Completion			0.2
Yes	289 (89%)	178 (85%)	
Discontinued	36 (11%)	32 (15%)	
Reason for Discontinuation			0.2
Progression	13 (36%)	6 (19%)	
Toxicity	10 (28%)	14 (44%)	
Other	13 (36%)	12 (38%)	

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Results – Fitness Characteristics (OA)

Older adults tended to be fit (ECOG PS 0-1) with few impairments in ADLs though scored ≥6 on CIRS-G

Variable	Older Adults (N=210)
Age, median (range)	75 (70, 90)
ECOG	
0	37 (18%)
1	119 (59%)
2	31 (15%)
3	14 (7%)
4	1 (1%)
CIRS-G	
<6	23 (11%)
≥6	177 (84%)
Median CIRS-G (range)	10 (4, 24)
Impairments in ADLs	17 (8%)
Presence of GS	29 (14%)

	Comorbidities (No. of patients)			
	Minor	Moderate	Severe	Very Severe
Cardiac	12 (6%)	44 (21%)	13 (6%)	0 (0%)
Vascular	39 (19%)	95 (45%)	2 (1%)	2 (1%)
Respiratory	27 (13%)	15 (7%)	6 (3%)	3 (1%)
ENT	40 (19%)	10 (5%)	1 (1%)	1 (1%)
Upper GI	20 (10%)	57 (27%)	2 (1%)	0 (0%)
Lower GI	40 (19%)	28 (13%)	0 (0%)	6 (3%)
Liver/Pancreas	18 (9%)	4 (2%)	2 (1%)	5 (2%)
[19] Renal	10 (5%)	14 (7%)	6 (3%)	4 (2%)
Genitourinary	27 (13%)	33 (15%)	7 (3%)	11 (5)
MSK/Derm	55 (26%)	26 (12%)	1 (1%)	0 (0%)
Neurologic	5 (2%)	14 (7%)	8 (4%)	1 (1%)
Endocrine	35 (17%)	36 (17%)	4 (2%)	12 (6%)
Psychiatric	23 (11%)	8 (4%)	10 (5%)	0 (0%)

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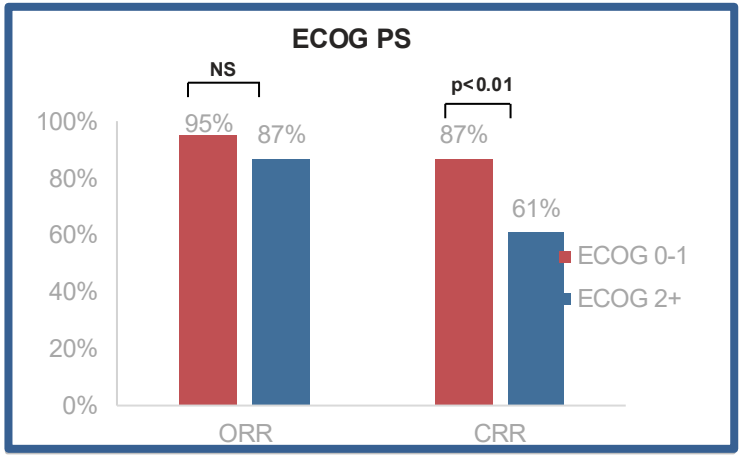
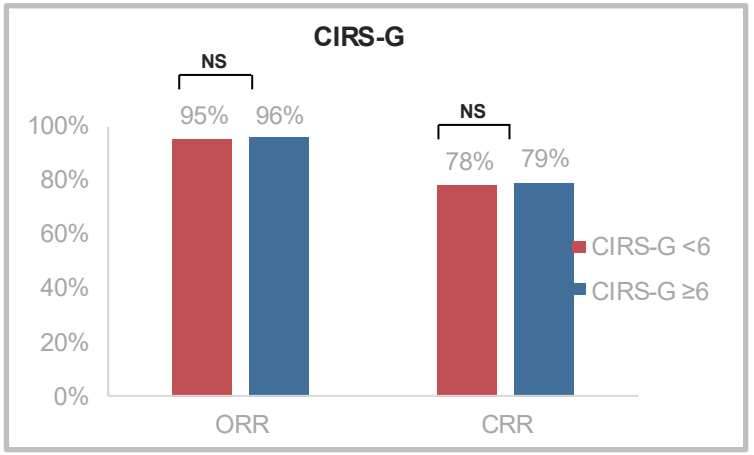
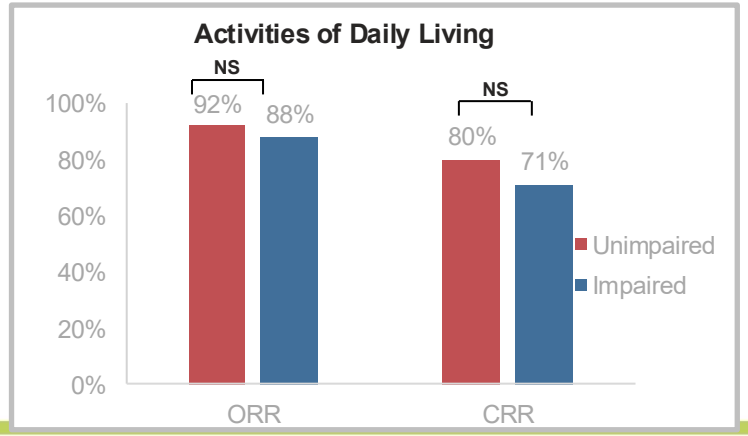
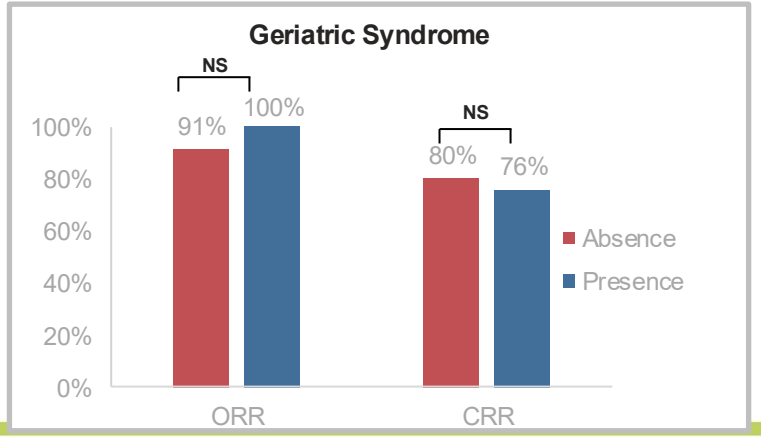
Baseline performance status in older adults correlates with response









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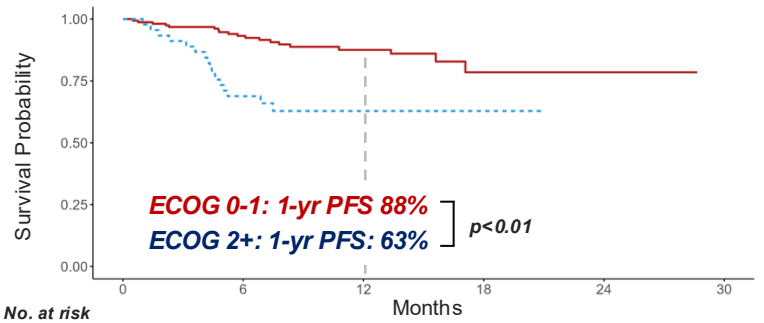
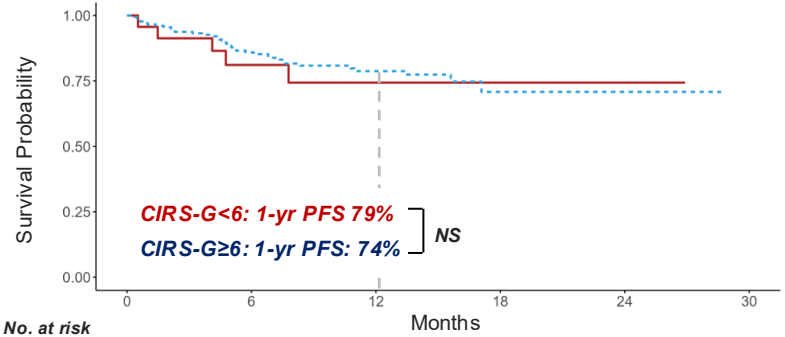
Baseline performance status in older adults correlates with response

ECOG PS



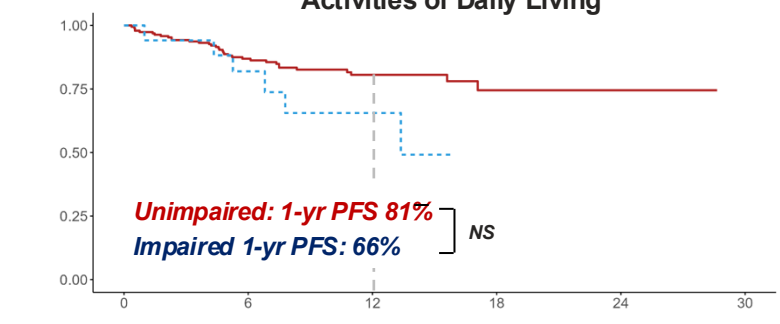
No. at risk						
ECOG 0-1	156	117	63	15	6	0
ECOG 2+	46	25	10	3	0	0

CIRS-G



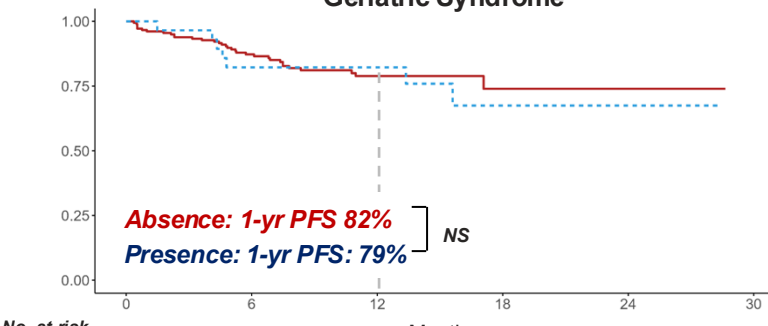
No. at risk						
CIRS-G<6	23	14	8	2	1	0
CIRS-G≥6	177	127	66	16	5	0

Activities of Daily Living



No. at risk						
Unimpaired	191	135	69	18	6	0
Impaired	17	10	5	0	0	0

Geriatric Syndrome



No. at risk						
Absence	180	126	60	14	4	0
Presence	29	20	14	4	2	0

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Frailer patients – measured by ECOG PS – had higher rates of cytopenias with lower rates of treatment completion

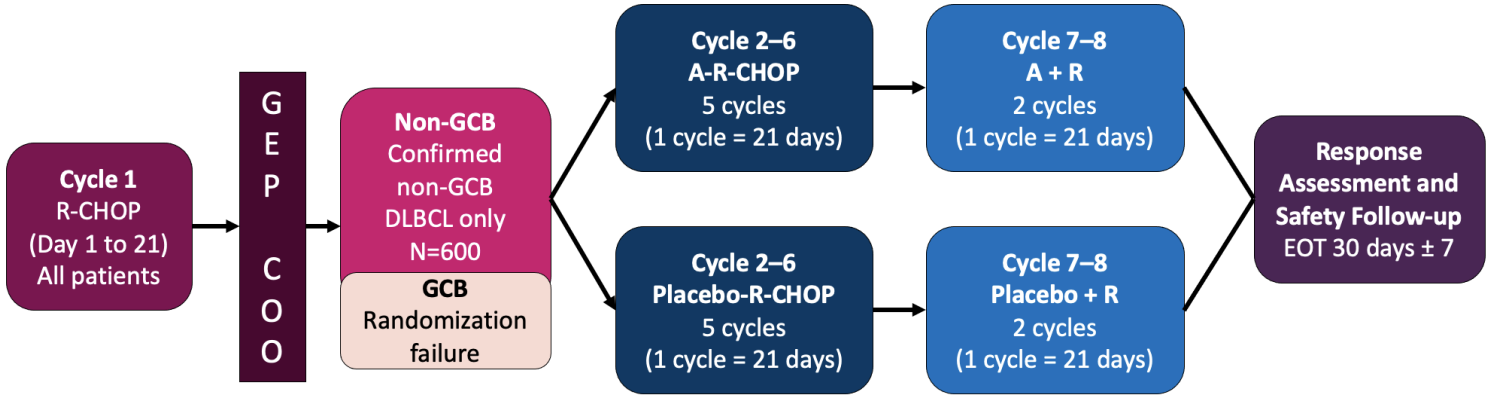
	ECOG PS		CIRS-G		Impairments in ADLs		Presence of GS	
	0-1 (N = 156)	2+ (N = 46)	<6 (N=23)	≥6 (N = 177)	No (N = 191)	Yes (N = 17)	No (N = 180)	Yes (N = 29)
Neutropenia, Grade 3+	52 (34%)	22 (49%)	9 (43%)	66 (38%)	68 (36%)	10 (59%)	67 (38%)	11 (38%)
Febrile neutropenia	20 (13%)	10 (22%)	3 (14%)	26 (15%)	26 (14%)	5 (29%)	27 (15%)	4 (14%)
Thrombocytopenia, Grade 3+	**24 (15%)**	**17 (38%)**	8 (38%)	36 (20%)	38 (20%)	7 (41%)	36 (20%)	9 (31%)
Peripheral Neuropathy, All	66 (43%)	18 (40%)	8 (38%)	72 (41%)	79 (42%)	7 (41%)	73 (41%)	13 (45%)
Grade 3+	3 (4.6%)	0 (0%)	0 (0%)	3 (4%)	3 (4%)	0 (0%)	3 (4%)	0 (0%)
Cardiomyopathy	8 (5.1%)	5 (11%)	0 (%)	13 (7%)	12 (6%)	1 (6%)	11 (6%)	2 (7%)
Infection, Grade 3+	22 (14%)	19 (42%)	3 (14%)	39 (22%)	**36 (19%)**	**7 (44%)**	39 (22%)	4 (14%)
Hospitalization	**47 (30%)**	**30 (65%)**	4 (18%)	72 (41%)	71 (37%)	8 (47%)	68 (38%)	11 (38%)
ICU Admission	8 (5.1%)	6 (13%)	1 (5%)	14 (8%)	15 (8%)	1 (6%)	15 (8%)	1 4%)
Treatment Completion	**140 (90%)**	**34 (74%)**	21 (91%)	147 (83%)	164 (86%)	13 (76%)	154 (86%)	24 (83%)

Iyengar V, et al; oral presentation ASH 2025, Blood (2024) 144 (Supplement 1): 2336.

Strategies Under Investigation in Frontline in DLBCL

Study	Patient Population	Treatment Arms	Estimated N	Trial Status	Primary Endpoint(s)
ESCALADE (NCT04529772)	Non-GCB DLBCL; 18-75 yr	Acalabrutinib + R-CHOP	600	Closed	**PFS** Per Lugano classification (up to 60 mo)
frontMIND (NCT04824092)	High-intermediate and high-risk DLBCL; 18-80 yr	R-CHOP ± tafasitamab and lenalidomide	880	Closed	**PFS** by investigator (up to 43 mo)
SKYGLO	DLBCL IPI 2 vs 3--5; ≥18 yr	Glofi + pola R- CHP vs pola R-CHP	1130	Recruiting	**2-yrs PFS** by investigator
NCT05578976	DLBCL; IPI=2-5; ≥18 yr	Epco + R-CHOP vs R-CHOP	900 Random 2:1	Closed	**2-yrs PFS** by investigator
R1979-ONC-2105 (OLYMPIA 3)	DLBCL; IPI=2-5; ≥18 yr	Odro + CHOP vs R-CHOP	840	Recruiting	**PFS** Per Lugano classification

ESCALADE Study: AR-CHOP vs. R-CHOP



Key inclusion criteria

- 18–75 years
- Histologically documented DLBCL
  - Central laboratory confirmation by GEP of non-GCB subtype of DLBCL*
- No prior treatment for DLBCL
- ECOG PS 0–2
- IPI 1–5
- Stage II–IV
- FDG-avid measurable lesion by CT with diagnostic quality (or MRI)

Primary objective:

- Investigator assessed PFS

Key secondary objective:

- Investigator assessed EFS
- BICR assessed CR rate
- OS

*COO was analyzed using Gene Expression Profiling (GEP), using an investigational LymphMark assay, based on the Lymph2Cx assay. The LymphMark assay analyzes formalin-fixed, paraffin-embedded (FFPE) samples using the nCounter® Analysis System/platform.

REMoDL-A TRIAL CONFIRMS SAFETY AND UNIMPAIRED TREATMENT DELIVERY OF R-CHOP + ACALABRUTINIB IN DLBCL

Louise Stanton, Geoffrey Saunders, Sharon Barrans, Joshua Caddy, Katy McLaughlin, Pam McKay, Antonina Zhelyazkova, Graham Collins, Christopher Fox, Jamie Wilson, Abigail Morgan-Fox, Jackie Raftery, Julie Richardson-Abraham, Oliver Seymour, Katie Mansell, Tracey Mell, Moniek Van Hoppe, Alessandra Serra, Gareth Griffiths, Victoria Warbey, Vivek Radhakrishnan, Pavel Mozgunov, Sally Barrington, Cathy Burton, Peter Johnson, Andrew Davies

REMoDL-A | UK Blood Cancer Research Network | CANCER RESEARCH UK | Southampton Clinical Trials Unit | University of Southampton

INTRODUCTION

- The phase Ib/II **ACCEPT study** (NCT03571308) assessed acalabrutinib (A), a second generation Bruton's tyrosine kinase inhibitor with enhanced kinase selectivity, in combination with R-CHOP in a single arm study for patients (pts) with de novo DLBCL
- At the **recommended phase II dose of A 1000mg bd** R-CHOP+A resulted in a **95% 24-month progression free survival**
- In older patients there was no difference in safety and no compromise of R-CHOP, in contrast to the PHOENIX trial of ibrutinib +R-CHOP

AIM

Primary objective of the REMoDL-A trial

To establish if combining acalabrutinib with R-CHOP improves efficacy, compared to R-CHOP alone, for the treatment of previously untreated patients with DLBCL to a degree that justifies further development of this approach.

Aim of this analysis

To evaluate the treatment delivery of R-CHOP when delivered in combination with A and safety of the combination by arm and age

METHOD

Design - REMoDL-A is a stratified open-label UK multicentre randomised phase II study

Population - newly diagnosed diffuse large B-cell lymphoma requiring full course R-CHOP

Intervention - After the first cycle of treatment patients were randomised 2:1 between R-CHOP+A or R-CHOP for a further 5 cycles. Randomisation was stratified by molecular subtype, International prognostic index (IPI) & age

Re-design - In March 2023 Pola-R-CHP was commissioned in the UK for patients with a IPI score of 2-5. REMoDL-A was amended such that patients with IPI 0-1 continued to be randomised but those with IPI 2-5 were all assigned to R-CHOP+A

Primary Outcome – Progression free survival (PFS). Bayesian dynamic borrowing of historical information via a Meta-Analytic Prior approach will be used to incorporate R-CHOP patients' data from REMoDL-B trial into the efficacy analysis.

RESULTS

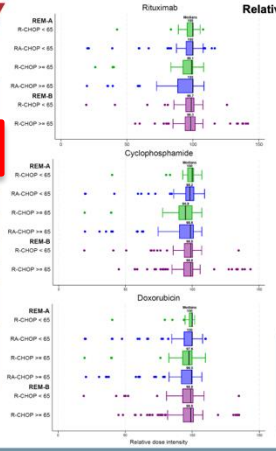
Baseline Characteristics

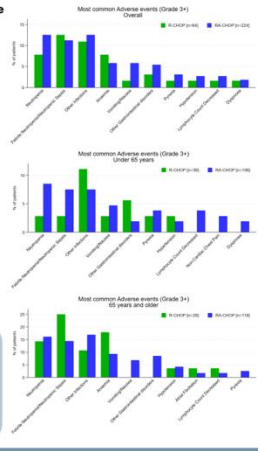
	R-CHOP (n=64)	R-CHOP + acalabrutinib (n=224)
Age – median (range)	62.5 (19 to 82)	65.0 (17 to 83)
Age ≥ 65 years	28 (43.8%)	118 (52.7%)
Gender – male	39 (60.9%)	136 (60.7%)
Stage – III/IV	42 (65.6%)	174 (77.7%)
Elevated LDH	31 (53.4%)	140 (66.0%)
B symptoms	20 (31.3%)	67 (29.9%)
Bulk	26 (40.6%)	100 (44.6%)
IPI score 0-1	25 (39.1%)	49 (20.1%)
2	11 (17.2%)	64 (28.6%)
3-5	28 (43.8%)	115 (51.3%)
GEP ABC	18 (28.1%)	68 (30.4%)
GCB	30 (46.9%)	100 (44.6%)
MHG	2 (3.1%)	17 (7.6%)
Unclassifiable	8 (12.5%)	37 (16.5%)
GEP fail	6 (9.4%)	2 (0.9%)

Recruitment to the trial finished on the 30TH June 2025.

Data cut off October 2025.

Relative dose intensity and adverse events by arm and age





Treatment Delivery

- 93% of patients on both R-CHOP and R-CHOP + acalabrutinib(A) completed all 6 cycles of treatment
- 28% had dose reduction on R-CHOP and 28% R-CHOP + A
- RDI was not significantly different by arm or age

Adverse events

- 48% of patients had a grade 3+ AE on R-CHOP vs 54% on R-CHOP +A. 11 fatal AEs across all arms, three considered possibly related to acalabrutinib - bronchial pneumonia and neutropenic sepsis, subdural haematoma

CONCLUSIONS

The addition of acalacbrutinib to R-CHOP does not impact upon dose delivery of R-CHOP across all age groups.

Some additional GI toxicity was observed in older pts but overall, the AE profile was similar by arm and age.

The final PFS trial results will be available in 2027.

R-CHOP+A is also being assessed in the randomised ESCALADE (NCT04529772) trial for younger patients with non-GC DLBCL

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3. Younes A, Sehn LH, Johnson P, et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. J Clin Oncol 2019;37(15):1285-95.
4. NICE approval https://www.nice.org.uk/guidance/ta874/chapter/1-Recommendations
5. The REMoDL-B trial - ISRCTN51837425

ACKNOWLEDGEMENTS

REMoDL-A is a UK Blood Cancer Research Network multicentre trial coordinated by Southampton Clinical Trials Unit and endorsed by CRUK (C30423/A29680) and funded by AstraZeneca.
Trial registration: NCT04546620.
Thank you to all the patients taking part in the trial, staff working on the trial and the members of the trial committees.

CONTACT INFORMATION

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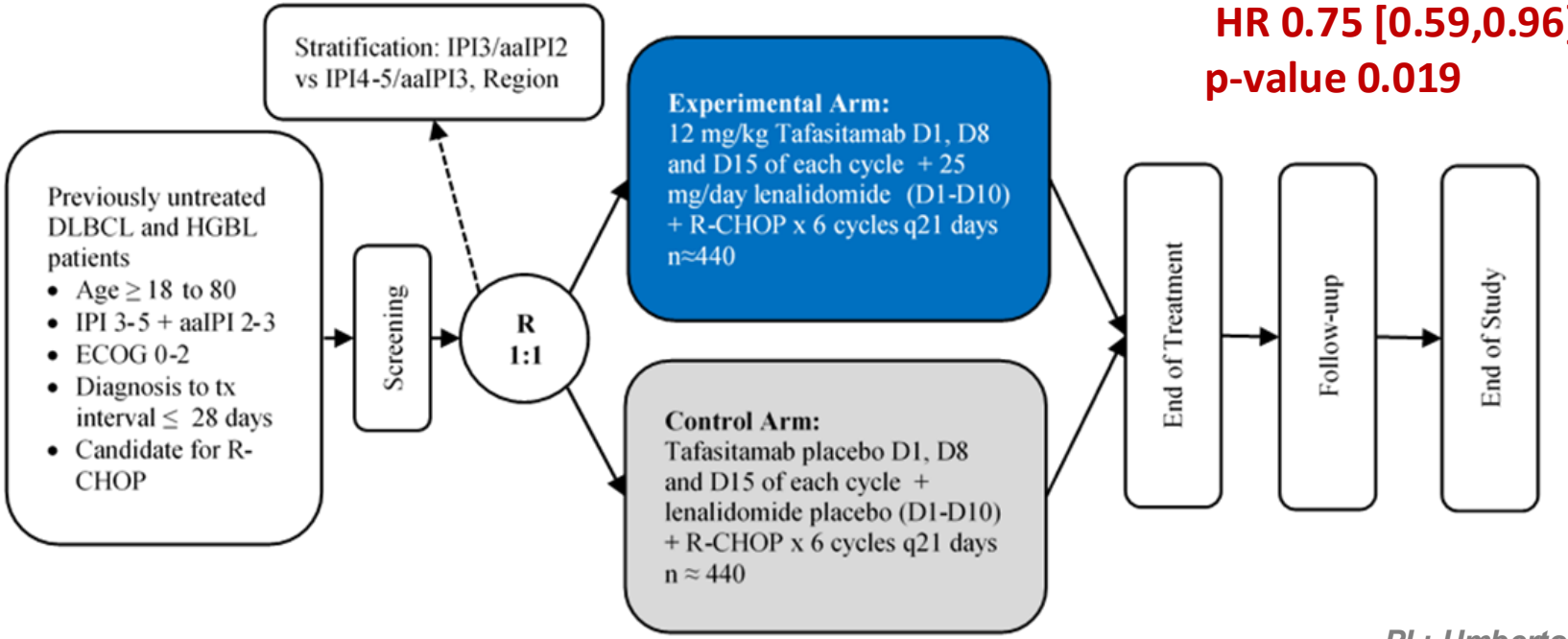
Louise Stanton - l.Stanton@soton.ac.uk .

A Phase 3, multicenter, randomized, trial comparing the efficacy and safety of Tafasitamab plus Lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated high-intermediate and high-risk patients DLBCL



HR 0.75 [0.59,0.96]
p-value 0.019

PI : Umberto Vitolo

18th ICML International Conference on Malignant Lymphoma Lugano 17–21 June 2025

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

Max S. Topp,[1*] Monica Tani,[2] Michael Dickinson,[3] Nilanjan Ghosh,[4] Armando Santoro,[5] Antonio Pinto,[6] Francesc Bosch,[7] Christopher P. Fox,[8] Armando Lopez Guillermo,[9] Thomas Gastinne,[10] Andreas Viardot,[11] William Townsend,[12] Raul Cordoba,[13] Hervé Tilly,[14] Pauline Baumlin,[15] Aurelien Berthier,[15] Sarah Kirk,[16] Chun Wu,[17] Martin Barrett,[16] Franck Morschhauser[18]
*Presenting author e-mail: Topp_M@ukw.de

Part II: dose expansion phase

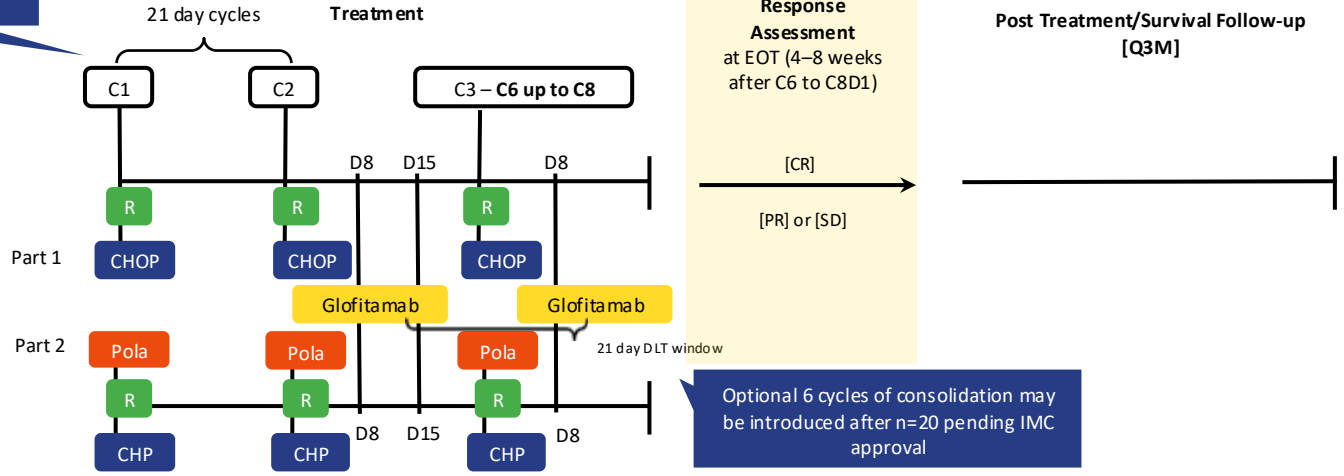
- The aim of Part II of this study is to obtain additional safety, tolerability, pharmacokinetics and preliminary clinical activity data and bridge the OBD determined for R/R NHL patients to 1L DLBCL patients
- Enrolment will be as follows:
  - Safety run-in or cohort (n=6–24, 1L DLBCL patients)
  - Single arm dose expansion phase (n=40, 1L DLBCL patients)

Patients who discontinue prior to Cycle 3 for reasons other than toxicity will be replaced

1L DLBCL safety run-in

- Patients (ECOG PS 0–3) received Glofit 30mg plus standard R-CHOP or R-CHP for 6–8 cycles (each 21-day)

Dose expansion phase (1L DLBCL patients)



•C, cycle; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; D, day; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; G, obinutuzumab; IMC, independent monitoring committee; OBD, optimal biological dose; PR, partial response; Q3M, every 3 months; R, rituximab; SUD, step-up dosing.

NP40126 protocol (v3), updated July 2019;
Topp MS, et al. ASH 2022; oral presentation (abstract #737).
Topp MS, et al. ICML 2025; poster presentaion (#280)

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.

As of January 21, 2025, 80 patients were enrolled

- Fifty (89.3%) patients in the Glofit + R-CHOP arm and 22 (91.7%) patients in the Glofit + Pola-R-CHP arm completed treatment.
- Six (10.7%) patients discontinued treatment in the Glofit + R-CHOP arm due to an AE (n=2; 3.6%), death (n=3; 5.4%) and progressive disease (PD; n=1; 1.8%), and two (8.3%) patients discontinued treatment in the Glofit + Pola-R-CHP arm, both due to an AE.

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

High response rates and durable remissions were achieved after a median follow up of 34.4 months

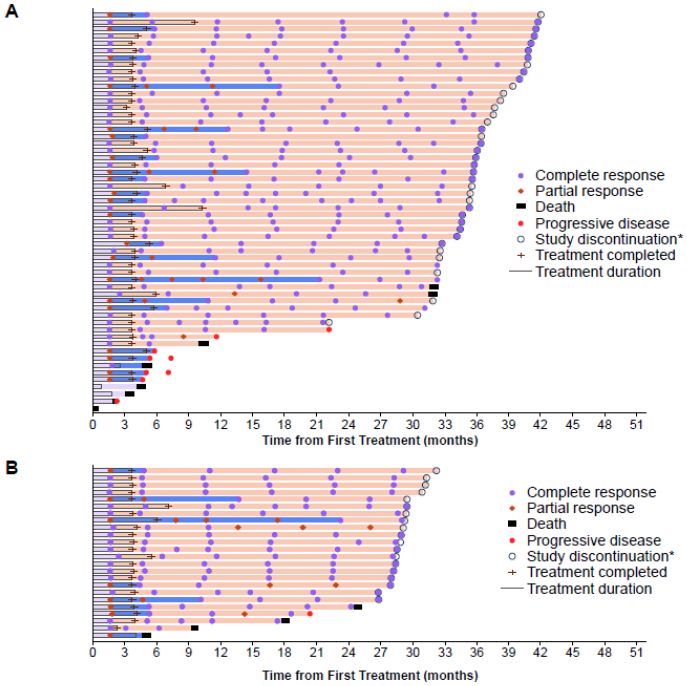
Table 2. Efficacy summary.

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.

- At end-of-treatment, the ORR and CMR rates were high (**Table 2**).
- Most CMRs had been achieved at the first interim assessment (approximately 2 months; **Figure 2**).
- Median PFS was not estimable (NE) for all patients.

Figure 2. Summary of time on treatment for A) the Glofit + R-CHOP arm and B) the Glofit + Pola-R-CHP arm.



*Study discontinuation also includes patients in survival follow-up after the last response assessment at the clinical cut-off date.

Table 3. Safety summary.

n (%)	Glofit + R-CHOP (n=56)	Glofit + Pola-R-CHP (n=24)	All treatments (N=80)
Any AE	56 (100)	24 (100)	80 (100)
Any grade 3–4 AE	40 (71.4)	16 (66.7)	56 (70.0)
Any SAE	20 (35.7)	14 (58.3)	34 (42.5)
Any grade 5 (fatal) AE*	4 (7.1)	1 (4.2)	5 (6.3)
Any AE leading to withdrawal from Glofit	1 (1.8)	2 (8.3)	3 (3.8)
AE related to Glofit leading to withdrawal from Glofit	0	0	0
AE related to Glofit leading to withdrawal from R-CHOP	0	0	0
AE of special interest			
Infections	28 (50.0)	12 (50.0)	40 (50.0)
Grade 3/4	8 (14.3)	5 (20.8)	13 (16.3)
Neutropenia	26 (46.4)	14 (58.3)	40 (50.0)
Grade 3/4	24 (42.9)	14 (58.3)	38 (47.5)
Febrile neutropenia	8 (14.3)	2 (8.3)	10 (12.5)
Grade 3/4	8 (14.3)	2 (8.3)	10 (12.5)
Thrombocytopenia	11 (19.6)	8 (33.3)	19 (23.8)
Grade 3/4	2 (3.6)	4 (16.7)	6 (7.5)
Anemia	27 (48.2)	12 (50.0)	39 (48.8)
Grade 3/4	13 (23.2)	4 (16.7)	17 (21.3)
Peripheral neuropathy	14 (25.0)	6 (25.0)	20 (25.0)
Grade 3/4	0	0	0

Fatal AEs were COVID-19 pneumonia (n=3) and infusion-related reaction (n=1) in the Glofit + R-CHOP arm and acute respiratory distress syndrome (n=1) in the Glofit + Pola-R-CHP arm.
COVID-19, coronavirus disease; SAE, serious AE.

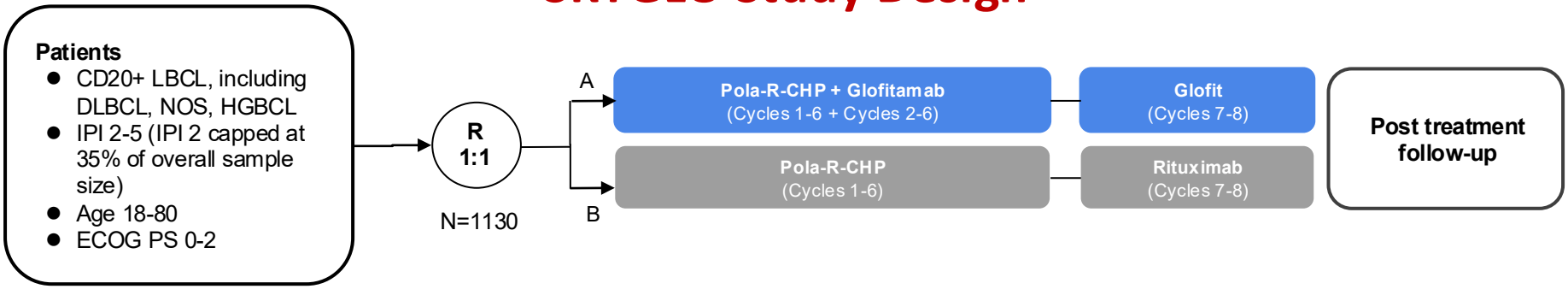
Table 4. CRS summary.

n (%)	Glofit + R-CHOP (n=56)	Glofit + Pola-R-CHP (n=24)	All treatments (N=80)
CRS	6 (10.7)	3 (12.5)	9 (11.3)
Grade 1	4 (7.1)	3 (12.5)	7 (8.8)
Grade 2	2 (3.6)	0	2 (2.5)
SAE of CRS	2 (3.6)	1 (4.2)	3 (3.8)
CRS management	2 (33.3)	0	2 (22.2)
Tocilizumab	2 (33.3)	0	2 (22.2)
Fluids	1 (16.7)	0	1 (11.1)
Low flow oxygen			

- No AEs related to glofitamab led to treatment withdrawal (**Table 3**).
- The most common AEs were anemia in the Glofit + R-CHOP arm (n=27; 48.2%) and neutropenia in the Glofit + Pola-R-CHP arm (n=14; 58.3%).
- No grade 5 events of neutropenia, febrile neutropenia, thrombocytopenia, or anemia occurred in either treatment arm.
- **No immune effector cell-associated neurotoxicity syndrome events (ICANS) were reported after administering glofitamab.**
- Median treatment dose intensity was 100% for all components.

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

SKYGLO Study Design



Stratification Factors
- IPI 2 vs IPI 3-5
- bulky disease defined as one lesion ≳7.5 cm (present vs absent)

Primary EP: PFS with 2-year follow-up (IRC)

Key Secondary EPs*: PFS in IPI 3-5 (IRC), OS, $EFS_{efficacy}$ (IRC)
Selected Secondary EPs (no adjustment for multiplicity): PFC (INV), ORR, DOR, DOCR, DFS, safety, PK, PROs, ctDNA

Exploratory: Biomarkers

Study Design: EPCORE® NHL-2 Arm 1

Key inclusion criteria

- Newly diagnosed CD20+ DLBCL[a]
  - DLBCL, NOS
  - T-cell/histiocyte-rich DLBCL
  - Double-hit or triple-hit DLBCL[b]
  - FL grade 3B
- IPI score ≥3
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: May 15, 2024
Median follow-up: 27.4 mo

Treatment regimen: concomitant fixed-duration epcoritamab 48 mg + R-CHOP[c]

	Agent	C1–4	C5–6	C7+
	Epcoritamab SC 48 mg	QW	Q3W	Q4W Up to 1 year
R-CHOP	Rituximab IV 375 mg/m^2	Q3W		
R-CHOP	Cyclophosphamide IV 750 mg/m^2			
R-CHOP	Doxorubicin IV 50 mg/m^2			
R-CHOP	Vincristine[d] IV 1.4 mg/m^2			
R-CHOP	Prednisone IV or oral 100 mg/d	D1–5 of each cycle		

- **Primary endpoint:** Overall response rate[e]
- **Key secondary endpoints:** CR rate, time to response, time to CR, DOR, DOCR, PFS, OS, MRD negativity, and safety/tolerability
  - MRD was assessed using the exploratory AVENIO ctDNA method

Falchi et al ASH 2024 oral presentation (abstract #581).

All Patients Were High Risk With IPI 3–5 at Screening

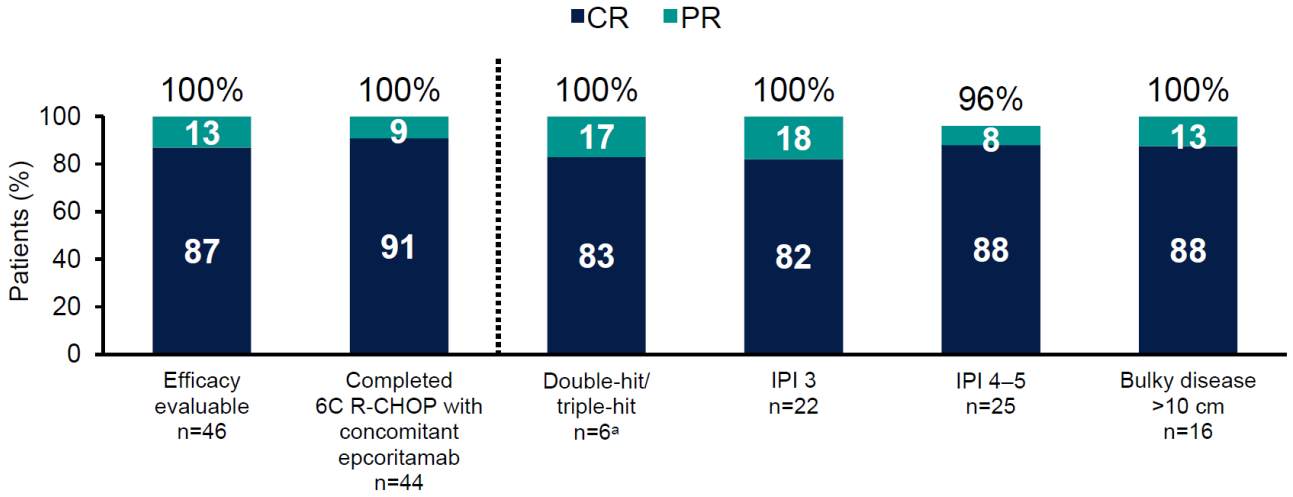
Characteristic	N=47
Median age, y (range)	64 (19–82)
≥75 y, n (%)	7 (15)
Male sex at birth, n (%)	23 (49)
Race, n (%)[a]	
White	37 (79)
Asian	6 (13)
Ethnicity, n (%)[b]	
Not Hispanic or Latino	19 (40)
Hispanic or Latino	1 (2)
ECOG PS, n (%)	
0–1	41 (87)
2	6 (13)
Ann Arbor stage, n (%)	
III	10 (21)
IV	37 (79)
IPI at screening, n (%)	
3	22 (47)
4–5	25 (53)

Characteristic	N=47
DLBCL, n (%)	47 (100)
De novo	39 (83)
Transformed	8 (17)
Double-hit/triple-hit by central lab, n/n (%)[c,d]	6/28 (21)
Bulky disease, n (%)[e]	
>10 cm	16 (34)
LDH, n (%)	
High	32 (68)
Extranodal disease at screening, n (%)	36 (77)
Cell of origin, n (%)	
Germinal center B-cell	28 (60)
Activated/non–germinal center B-cell	15 (32)
Unknown	4 (9)
Median time from initial diagnosis to first dose, wk (range)	4.0 (1.3–60.4)

Falchi et al ASH 2024 oral presentation (abstract #581).

Epcoritamab + R-CHOP in 1L DLBCL

High Complete Response Rates Including Across High-Risk Subgroups

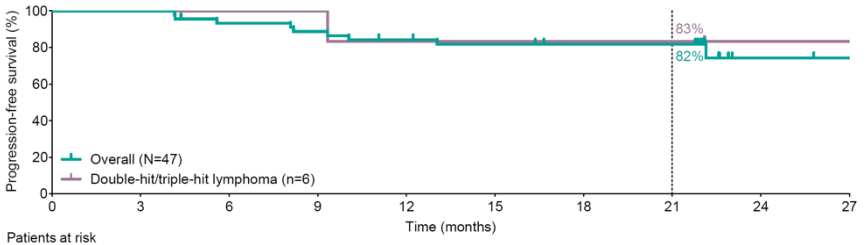


Exposure:

- Median duration of 11.5 mo of epcoritamab (range, 0.6–13.2)
- Median relative dose intensity of R-CHOP 95%–98% for all individual components
  - Three patients did not complete 6C due to withdrawal of consent, PD, and an AE (grade 5 COVID-19)

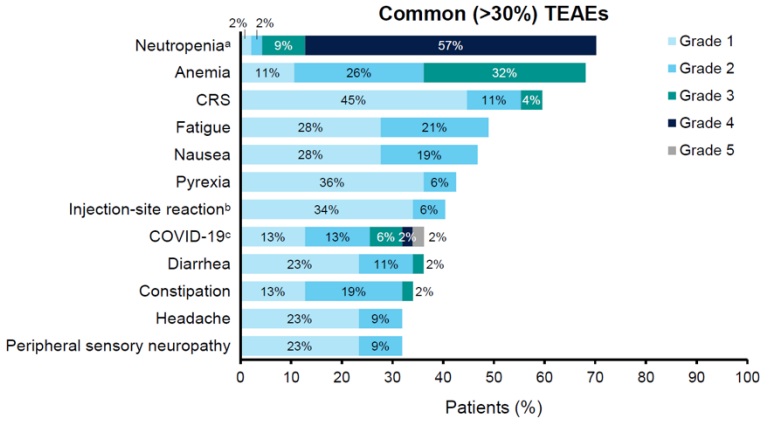
Falchi et al ASH 2024 oral presentation (abstract #581).

High Rates of Progression-Free Survival

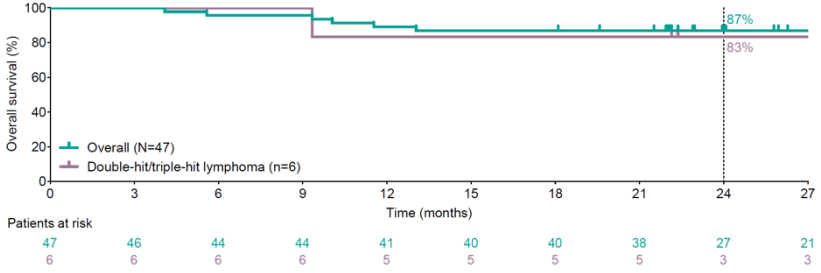


Median follow-up for PFS: 22.9 months. Kaplan–Meier estimated probability of remaining progression free.

Manageable Safety Profile



Encouraging 2-Year Overall Survival

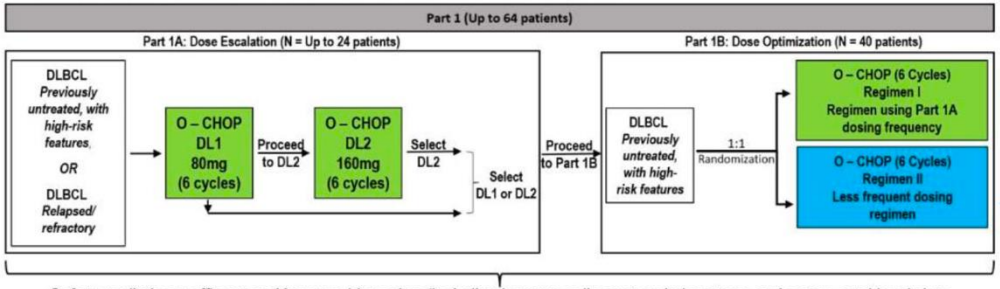


- 8 pts (18%) experienced severe infectious including 4(9%) COVID
- 8 pts (18%) discontinued Epcoritimab for severe TEAEs
- 5 pts had a fatal TEASs (2 COVID)

Falchi et al ASH 2024 oral presentation (abstract #581).

OLYMPIA-3: Odronextamab + CHOP in 1L DLBCL

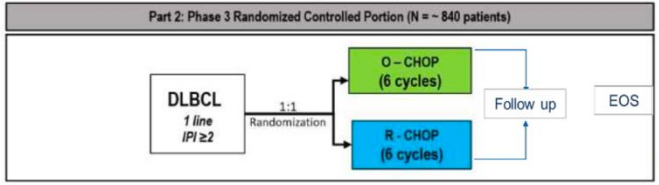
Part 1 – Safety Lead-in



Primary endpoint: DLT and incidence TEAEs.
Secondary endpoint: Efficacy: BOR, CR,DOR

Proceed to Part 2

Part 2 – RCT



- *CHOP treatment starts on Cycle 1 Day 1*
- *Odronextamab treatment begins on Cycle 1 Day 8;*
- *Ph3 Randomization Stratified by:*
  - *Age (<65 vs >= 65)*
  - *IPI Score (2 vs 3 vs 4 to 5)*
- **Primary endpoint: PFS by ICR**
- **Secondary endpoint: EFS,CR by ICR**

Take home messages

- sCGA evaluation is mandatory to define fitness in older DLBCL
- FIT patients should receive curative treatments
- Pola-R-CHP efficacy is confirmed also in older DLBCL
- New combo will be available in the near future
- Accurate management of AEs related to new combo
- Accurate selection of patients for new combo

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