20° EDIZIONE DEL CONVEGNO TREVIGIANO

ALGORITMO TERAPEUTICO

LINFOMI B DIFFUSI A GRANDI CELLULE

Dr PIERO MARIA STEFANI

STRUTTURA COMPLESSA DI EMATOLOGICA PRESIDIO OSPEDALIERO DI TREVISO

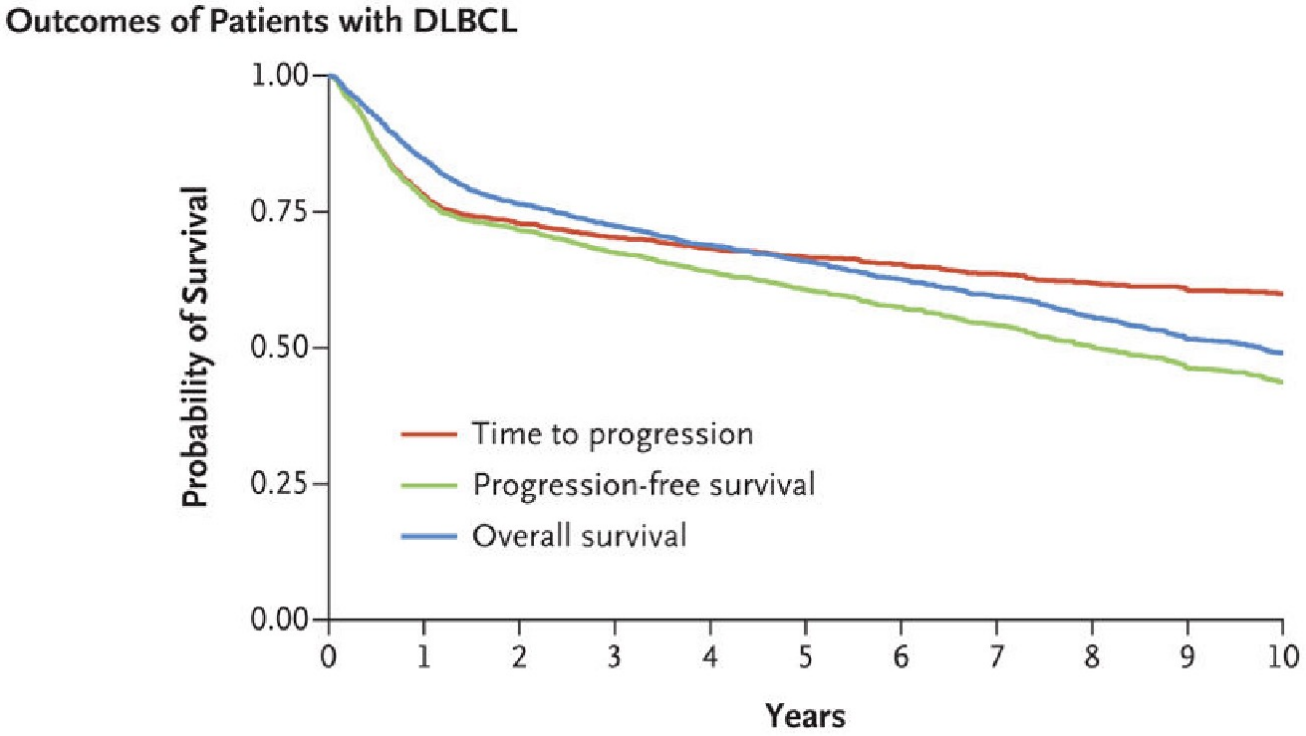
HIGHLIGHTS IN EMATOLOGIA

TREVISO, 22-23 NOVEMBRE 2024

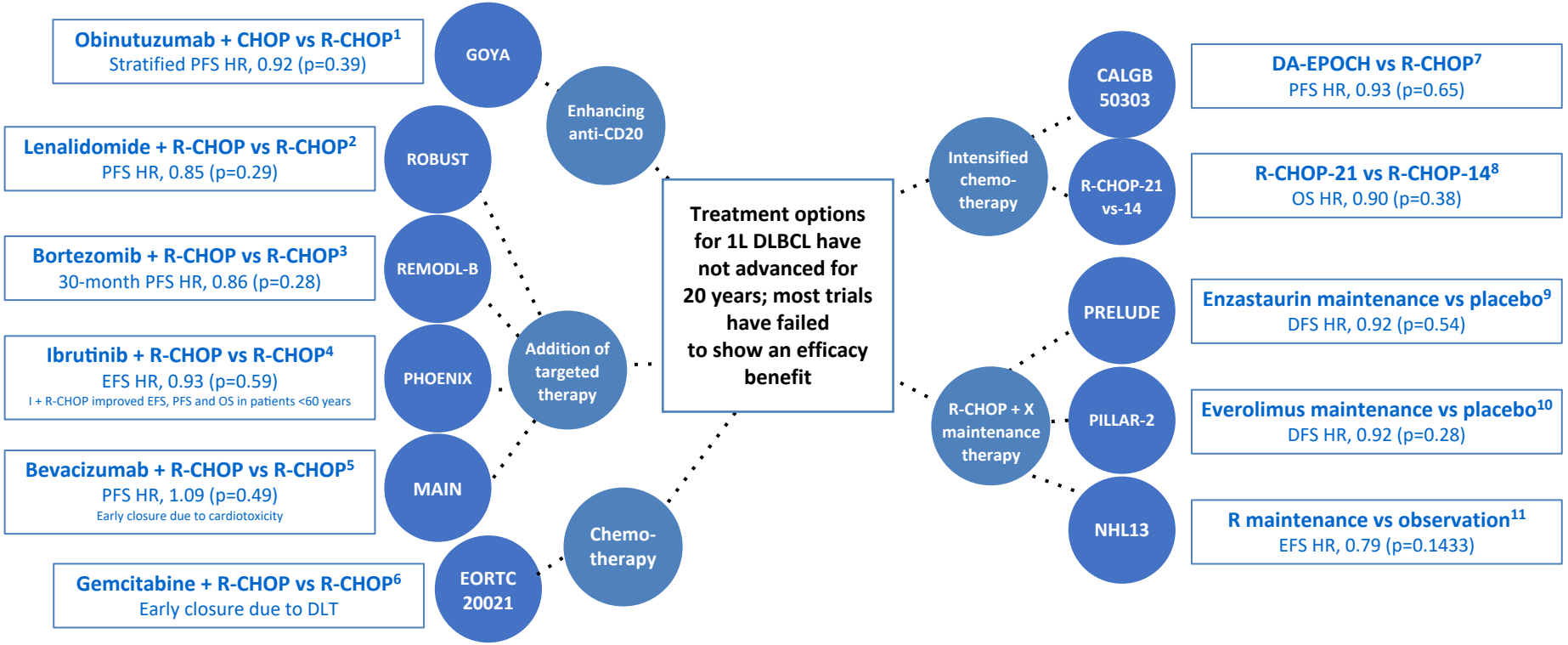
Disclosures of Piero Maria Stefani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
INCYTE					X		
GENTILI					X		
JANSSEN					X		
GILEAD					X		
EUSAPHARMA					X		
TAKEDA					X	X	
ROCHE					X	X	

Diffuse Large B-Cell Lymphoma. LH. Sehn, G. Salles. N Engl J Med. 2021 March 04; 384(9): 842–858.



R-CHOP: ANCORA LO STANDARD?



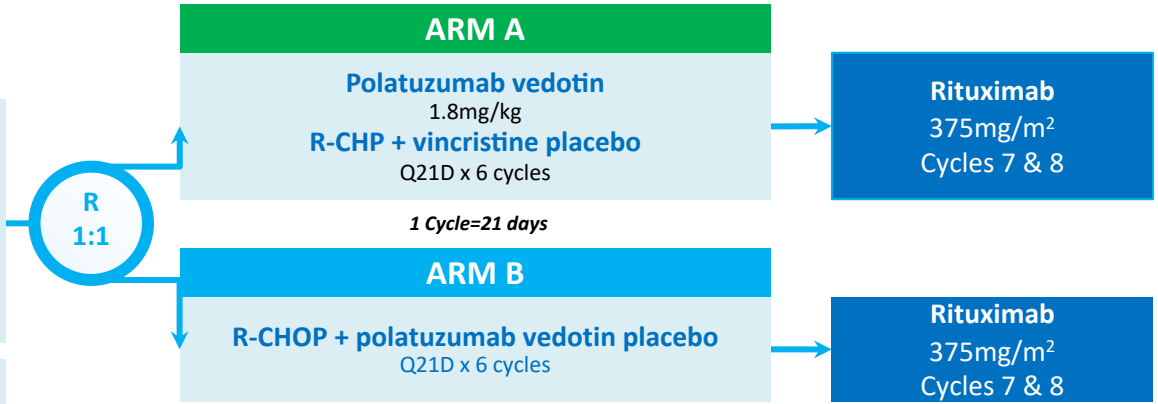
POLARIX Study design overview

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

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

N=879

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



Primary endpoint	PFS by INV
Key secondary endpoints	$EFS_{efficacy}$ by INV, PET CR at EOT by BICR, OS, and safety

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

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

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

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

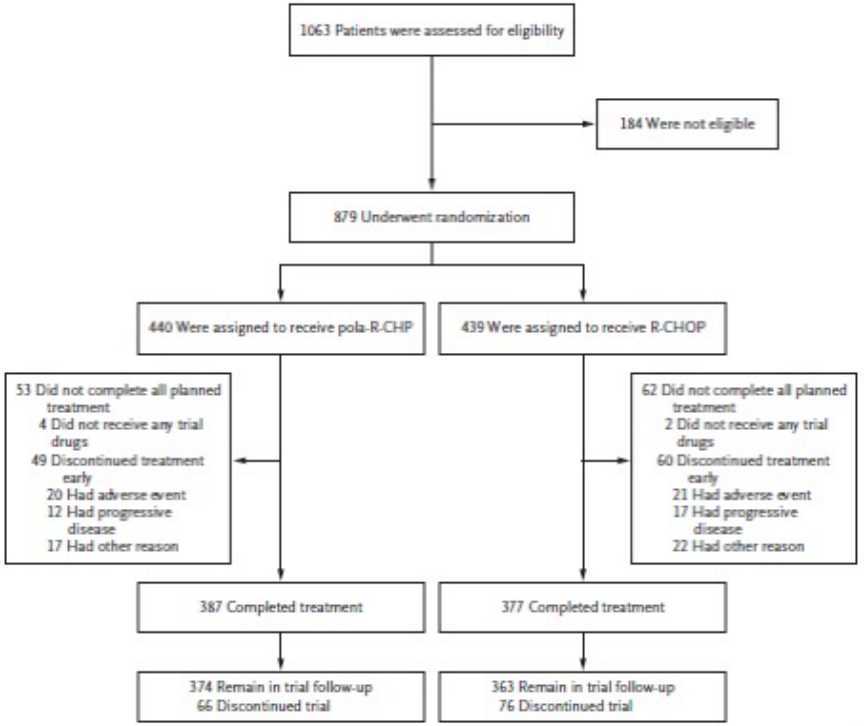


Table 2. Efficacy (Intention-to-Treat Population).

Variable	Pola-R-CHP (N=440)	R-CHOP (N=439)	Hazard Ratio (95% CI)	P Value
Progression-free survival*				
Patients who died or had progression or relapse — no. (%)	107 (24.3)	134 (30.5)	0.73 (0.57–0.95)	0.02
Earliest event — no.				
Death	19	20		
Progression or relapse	88	114		
Estimate at 1 year (95% CI) — %	83.9 (80.4–87.4)	79.8 (75.9–83.6)		
Estimate at 2 years (95% CI) — %	76.7 (72.7–80.8)	70.2 (65.8–74.6)		
Event-free survival*				
Patients who died, had progression or relapse, or had other events — no. (%)†	112 (25.5)	138 (31.4)	0.75 (0.58–0.96)	0.02
Earliest event — no.				
Death	18	20		
Progression or relapse	86	106		
Other†	8	12		
Estimate at 2 years (95% CI) — %	75.6 (71.5–79.7)	69.4 (65.0–73.8)		
Response status at treatment completion‡				
Overall response — no. (%)	376 (85.5)	368 (83.8)		
Complete response	343 (78.0)	325 (74.0)		
Partial response	33 (7.5)	43 (9.8)		
Stable disease — no. (%)	8 (1.8)	6 (1.4)		
Progressive disease — no. (%)	22 (5.0)	28 (6.4)		
Not evaluated or data missing — no. (%)	34 (7.7)	37 (8.4)		
Overall survival				
Patients who died — no. (%)	53 (12.0)	57 (13.0)	0.94 (0.65–1.37)	0.75
Estimate at 2 years (95% CI) — %	88.7 (85.7–91.6)	88.6 (85.6–91.6)		
Disease-free survival§				
No. of patients who could be evaluated¶	381	363		
Patients who died or had relapse — no. (%)	62 (16.3)	79 (21.8)	0.70 (0.50–0.98)	
Earliest event — no.				
Death	8	13		
Relapse	54	66		

* Events of progression or relapse were assessed by the investigator.
† Other events are subsequent therapy for lymphoma or biopsy-confirmed residual disease after treatment.
‡ Response was assessed by an independent central review committee.
§ Events of relapse were assessed by the investigator.
¶ Patients who had a best response of complete response at any time during the trial could be evaluated for disease-free survival; see Table S3.

Safety: common adverse events

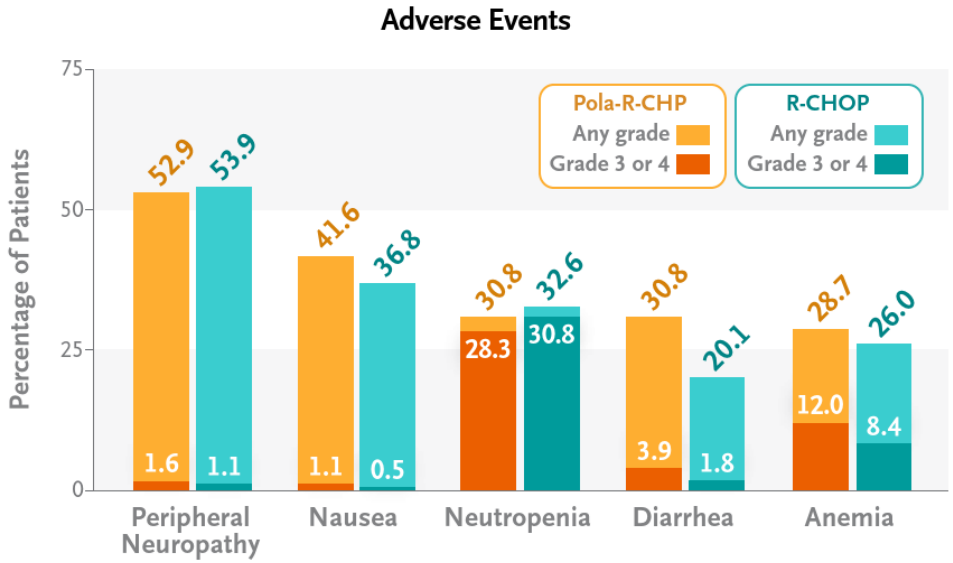


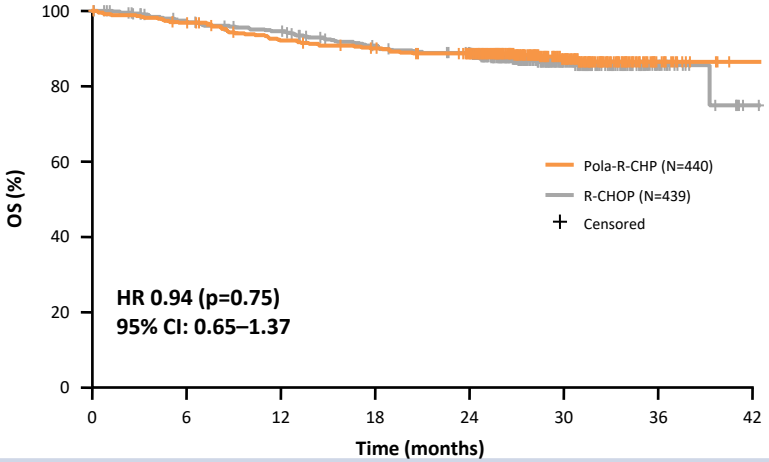
Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

Tilly H, et al. New Engl J Med 2022

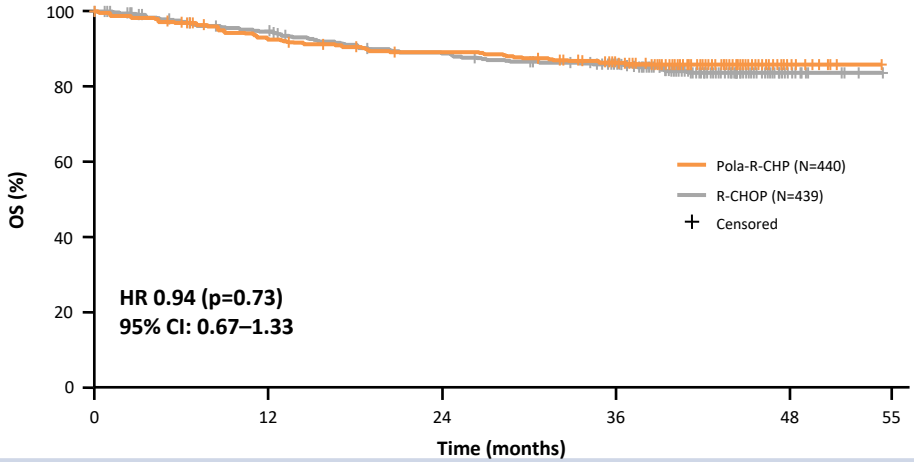
OS remained similar between treatment arms

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



No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

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



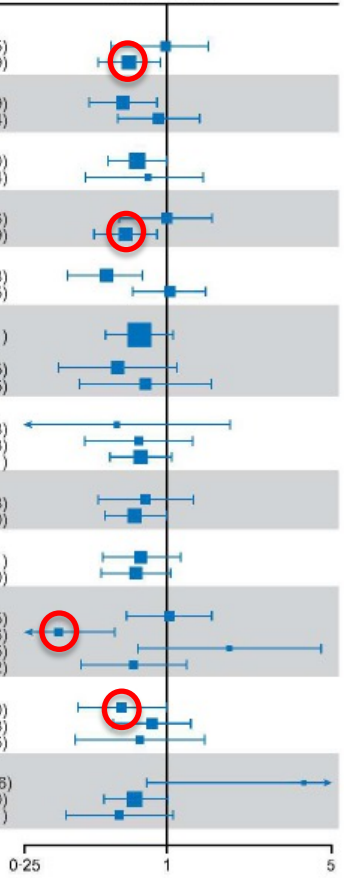
No. of patients at risk										
Pola-R-CHP	440	423	398	387	379	371	338	129	13	1
R-CHOP	439	415	403	382	372	361	329	124	18	1

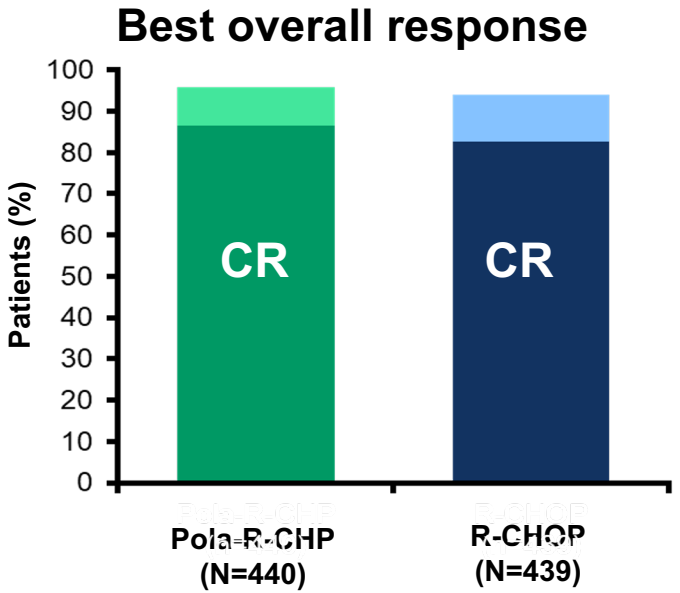
No new safety signals have been identified with longer follow-up compared with the primary analysis

Tilly H, et al. N Engl J Med 2022;386:351–63.
Herrera AF, et al. ASH 2022. Oral presentation 542.

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



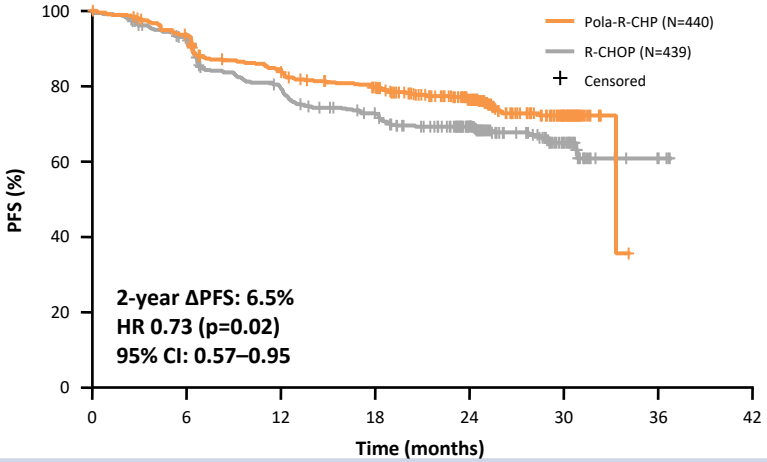


Subgroup Analysis of Investigator-assessed PFS (ITT Population).

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

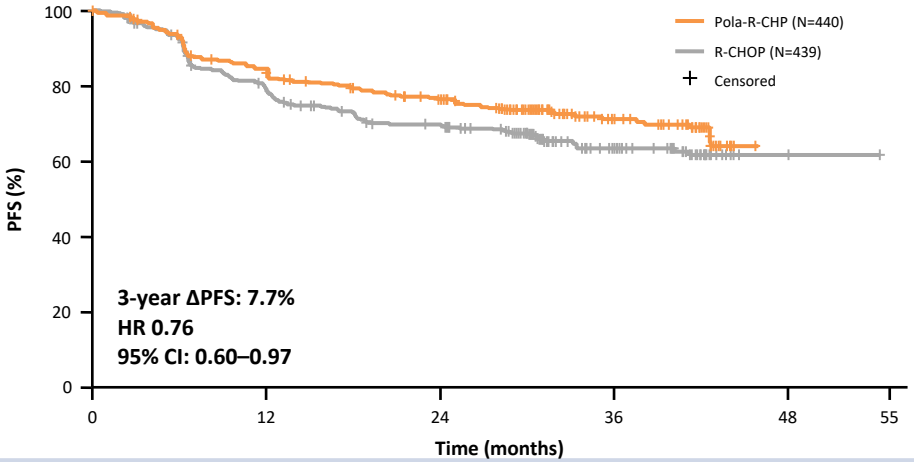
PFS benefit with Pola-R-CHP vs R-CHOP was maintained with longer follow-up

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	0
R-CHOP	439	389	330	296	220	78	3	0

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

Analysis based on the ITT population.
ITT, intention-to-treat; NE, not evaluable; no., number.

Tilly H, et al. N Engl J Med 2022;386:351–63.
Herrera AF, et al. ASH 2022. Oral presentation 542.

Five-Year Analysis of the POLARIX Study: Prolonged Follow-up Confirms Positive Impact of Polatuzumab Vedotin Plus Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) on Outcomes. Gilles Salles. Oral Presentation ASH 2024 abstract #469

ITT population. Pola-R-CHP: 440; R-CHOP: 439.
Expanded population. Pola-R-CHP: 500; R-CHOP: 500.
In the global ITT population (mFU 60.9 months):
5-year PFS: 64.2% vs. 59.1% with Pola-R-CHP vs R-CHOP.
5-year OS: 82.2% vs. 79.6%
5-year DFS: 71.3% vs 65.5%.

In the expanded population (mFU 60.5 m): 5-year PFS 63.1% vs. 59.1% with Pola-R-CHP vs R-CHOP.
5-year OS 82.2% vs. 79.0% with Pola-R-CHP vs R-CHOP, with no statistically significant difference.
5-year DFS 69.4% vs 65.1%.
Safety profiles were comparable with Pola-R-CHP vs R-CHOP.

The number of pts requiring subsequent systemic lymphoma therapy was 106 (21%) vs 145 (29%) with Pola-R-CHP vs R-CHOP.
The cumulative incidence of lymphoma-related death at 5 years was 9.1% vs 12.2% for Pola-R-CHP vs R-CHOP.
Conclusions: Extended 5-year follow-up of POLARIX demonstrated sustained and significant PFS and DFS benefits for pts receiving Pola-R-CHP vs R-CHOP.
These outcomes confirm Pola-R-CHP as a standard of care for pts with previously untreated intermediate- or high-risk DLBCL.

Pola-RCHP scheda AIFA

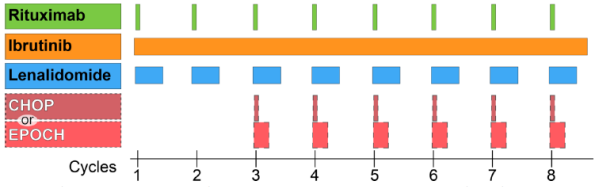
DLBCL IPI 3

BLOCCHI:

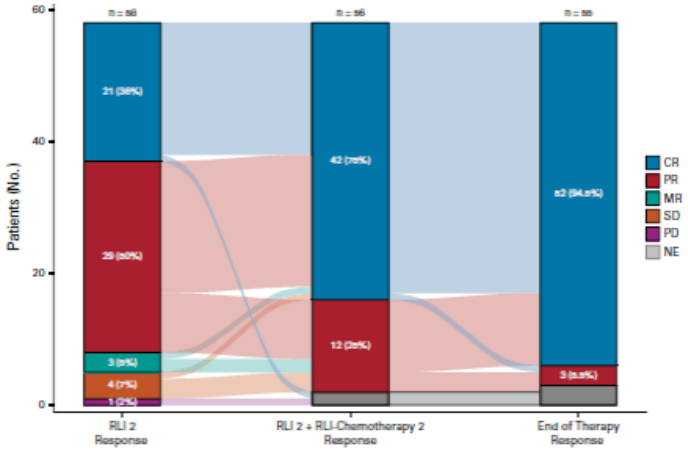
- **ECOG >3**
- **NEUROPATIA G>1**
- **Coinvolgimento SNC**
- **FL G3b**
- **Indolente trasformato**
- **Epatopatia: Child-Pugh B e C**
- **Presenza di malattia cardiovascolare o polmonare clinicamente grave**

Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma

Jason Westin, MD, MS[1]; R. Eric Davis, MD[1]; Lei Feng, MS[2]; Fredrick Hagemeister, MD[1]; Raphael Steiner, MD[1]; Hun Ju Lee, MD[1];



Supplemental Figure 1 Legend: A cycle of therapy was 21 days. Therapy on cycle 1 and 2 consisted of rituximab 375mg/m2 IV on day 1, ibrutinib 560mg orally daily (amended to 420mg orally daily if >65 years old), and lenalidomide 25mg orally days 1-10 (RLI). Therapy on cycles 3 – 8 consisted of RLI with either CHOP (cyclophosphamide 750mg/m^2 IV on day 1, doxorubicin 50mg/m^2 IV on day 1, Vincristine 2mg IV on day 1, and Prednisone 100mg orally days 1-5) or EPOCH (etoposide 50mg/m^2/day IV continuous days 1-4, Prednisone 100mg orally days 1-5, vincristine 0.4mg/m^2/day IV continuous days 1-4, cyclophosphamide 750mg/m2 IV on day 5, and Doxorubicin 10mg/m^2/day IV continuously days 1-4).



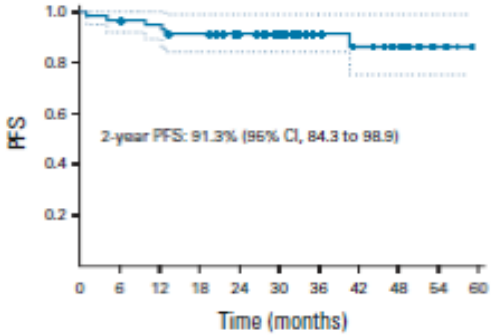
60 patients non-GCB DLBCL

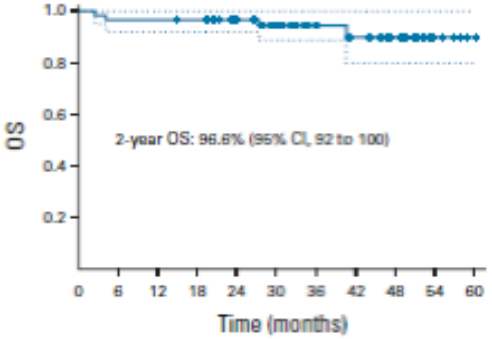
single-arm phase II trial of rituximab, lenalidomide, and ibrutinib (RLI) with the sequential addition of chemotherapy

RESULTS The median age was 63.5 years (range, 29-83 years) with 28% age 70 years or older. R-IPI identified 42% as HR, and 62% were DE.

The ORR after two cycles of RLI was 86.2%, and the complete response rate at the end of RLI- chemotherapy was 94.5%.

With a mFU of 31 months, the PFS and OS were at 91.3% and 96.6% at 2 years, respectively.

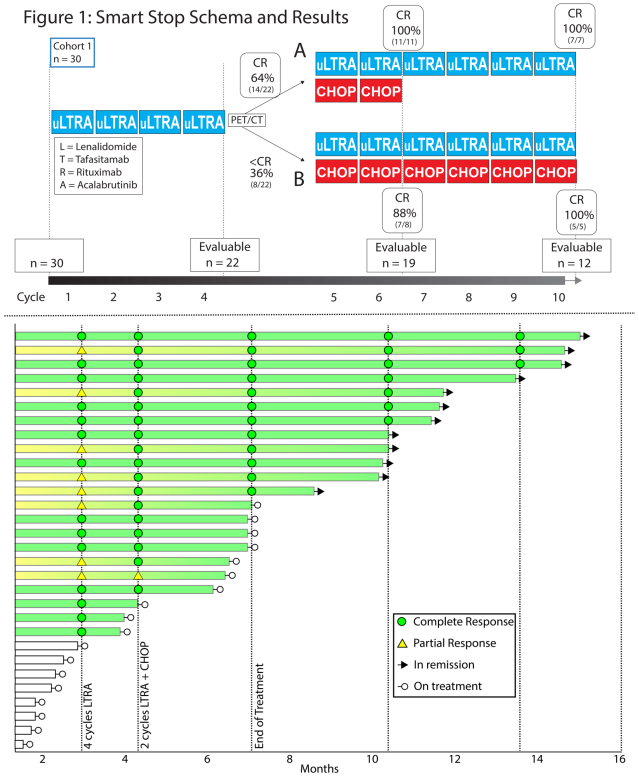




J Clin Oncol 41:745-755. © 2022 by American Society of Clinical Oncology

Smart Stop: Lenalidomide, Tafasitamab, Rituximab, and Acalabrutinib Alone and with Combination Chemotherapy for the Treatment of Newly Diagnosed Diffuse Large B-Cell Lymphoma, Jason Westin, (ASH 2023 oral presentation #856)

Figure 1: Smart Stop Schema and Results



52 patients
The median age was 61 years (range: 32-85)
67% of patients have poor risk R-IPI,
77% had advanced stage
83% had the non-GCB subtype and 17% had the GCB subtype of DLBCL.

After 4 cycles of LTRA, the ORR is 100% and the CRR is 64%.
After an additional 2 cycles of LTRA-CHOP, the ORR is 100% and the CRR is 95%.
At end of all therapy, the CRR is 100%
To date, no patient has progressive lymphoma-
47% of patients experienced rash (13% grade 3), and 40% of patients required a dose reduction of lenalidomide.

Conclusions: The Smart Stop trial demonstrates that combination of lenalidomide, tafasitamab, rituximab, and acalabrutinib is highly effective as an initial chemotherapy-free combination in patients with newly diagnosed DLBCL, and may allow for a response adapted reduction in chemotherapy.

ESCALADE (ACE-LY-312): Phase 3, Randomized, Double-Blind Study of Acalabrutinib With R-CHOP in Subjects With Previously Untreated Non-GCB Subtype DLBCL (NCT04529772)

Untreated non-GCB DLBCL

N≈ 600

- ≈270 sites globally
- Sufficient diagnostic material should be available for centralized gene expression profiling

R

- **Acalabrutinib + R-CHOP**
- **Placebo + R-CHOP**

Primary Endpoint

- PFS per Lugano[a]

Secondary Endpoints

- EFS (Investigator assessed)
- OS
- CR per Lugano[a]

Key Inclusion Criteria

- Adults ≥18y and ≤75y
- Histologically documented DLBCL (confirmation of non-GCB subtype by centralized gene expression profiling)
- No prior treatment for DLBCL
- ECOG PS 0–2
- Stage II–IV disease
- IPI score of 1–5

Key Exclusion Criteria

- Known CNS lymphoma or leptomeningeal disease
- Primary mediastinal lymphoma
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- History of indolent lymphoma or CLL
- History of, or ongoing confirmed PML
- Significant cardiovascular diseas

Key Trial Dates

Study start date: October 8, 2020

Estimated study completion date:

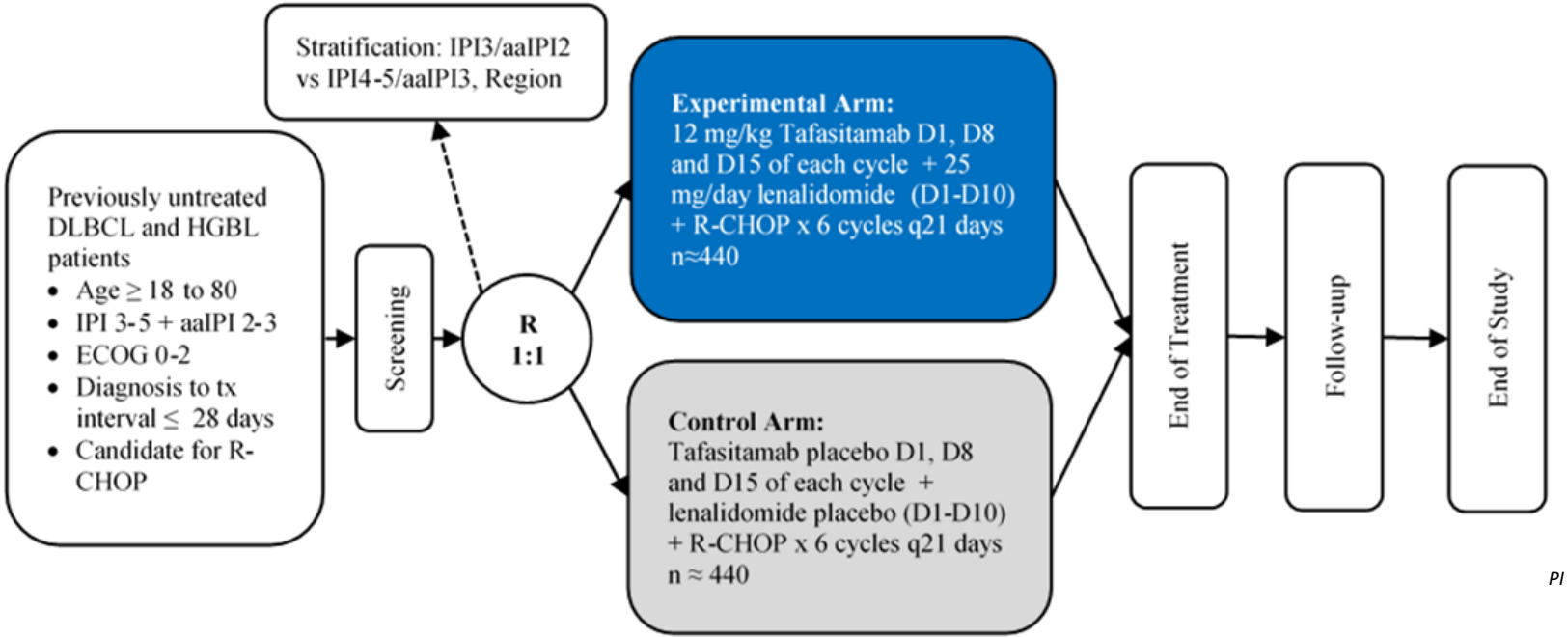
February 5, 2027

Current status: Recruiting

EHA Library. Sehn L. 06/09/21; 324114; PB1434

FRONTMIND

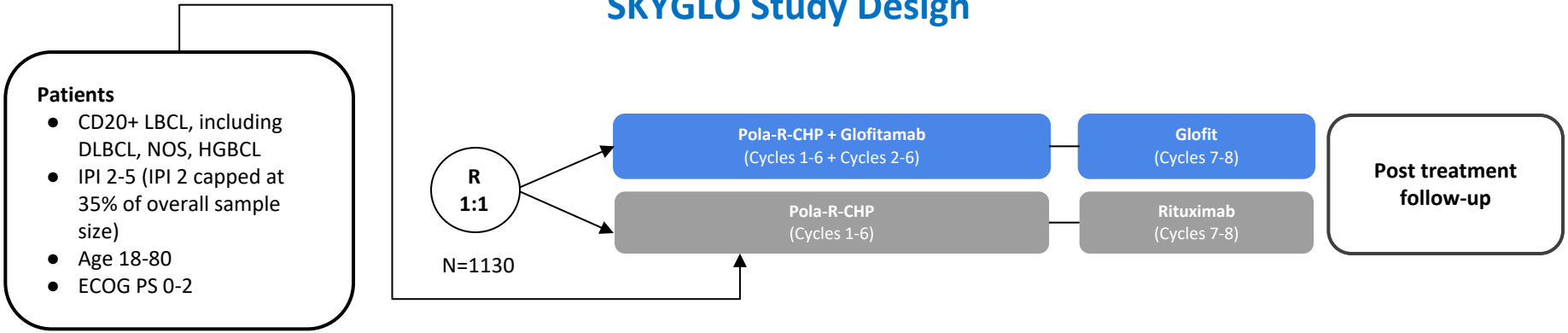
A Phase 3, multicenter, randomized, trial comparing the efficacy and safety of Tafasitamab plus Lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated high-intermediate and high-risk patients DLBCL



PI : Umberto Vitolo

Vitolo U, et al,2022 TPS7590 Poster Session

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 NCT06047080. ClinicalTrials.gov website

Dickinson M, et al. ASCO 2023, doi:10.1200/JCO.2023.41.16_suppl.7549
https://classic.clinicaltrials.gov/ct2/show/study/NCT06047080

Epcoritamab + R-CHOP as first line therapy in High-Risk DLBCL

Study design: EPCORE NHL-2 arm 1

Arm 1 of EPCORE NHL-2, a phase 1b/2, open-label, multicenter trial, is evaluating the safety and antitumor activity of SC epcoritamab + standard R-CHOP for 6 cycles of 21 days, followed by epcoritamab monotherapy for a total of 1 year, in adults with previously untreated DLBCL with high-risk features[a]

Key inclusion criteria

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

Data cutoff: March 25, 2022
Median follow-up: 6.9 mo

Dose escalation, n=10

Step-up dosing

Epcoritamab (SC)
24 mg (n=4) or
48 mg (n=6)
QW C1–4,
Q3W C5–6,
Q4W C7+

+ R-CHOP
C1–6

Primary objectives: DLT/Safety and tolerability
Key secondary objective: Antitumor activity[d]

Expansion, n=23

Step-up dosing

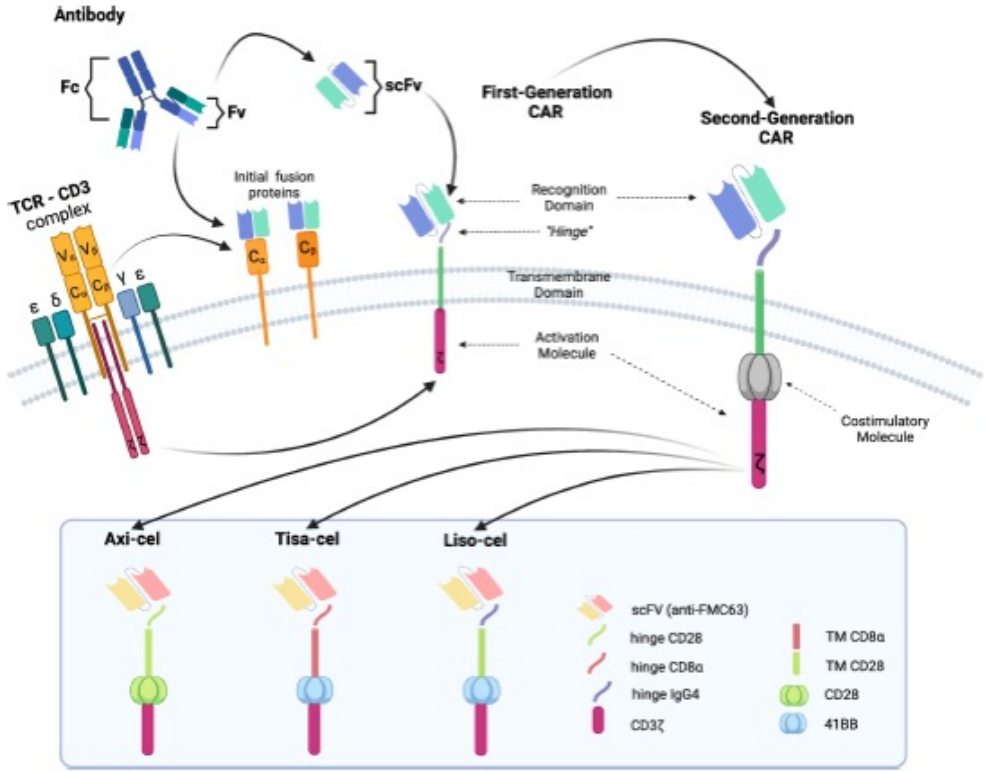
Epcoritamab (SC)
48 mg
QW C1–4,
Q3W C5–6,
Q4W C7+

+ R-CHOP
C1–6

Primary objective: Antitumor activity[d]
Treatment up to 1 year

Falchi L., et al,2022 7523 Poster Session

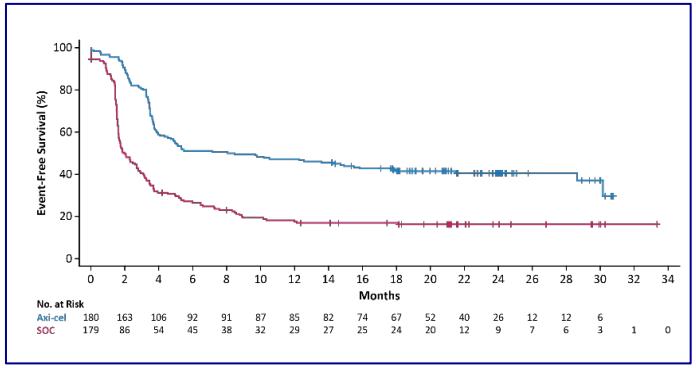
IMMUNOTERAPIA CELLULARE



CAR T vs. SoC in 2ª linea per i DLBCL R/R - EFS

Axi-Cel

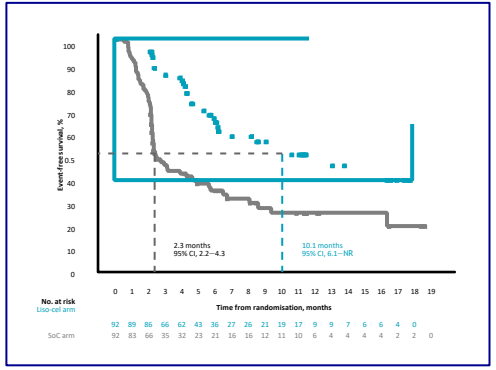
ZUMA-7[1,2]



Median follow-up: 24.9 m
HR: 0.40 (0.31–0.51)

Liso-Cel

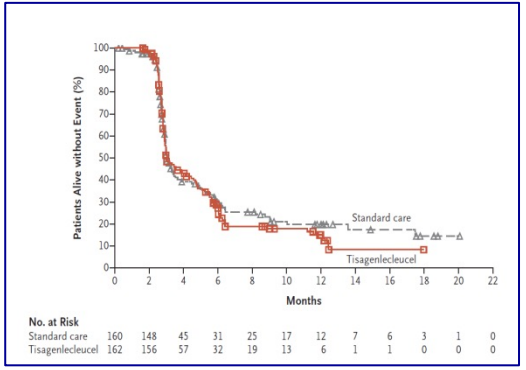
TRANSFORM[3]



Median follow-up: 6.2 m HR: 0.35 (0.23-0.53)

Tisa-Cel

BELINDA[4,5]



Median follow-up: 10.0 m
HR: 1.07 (0.82–1.40)

Cross-study comparisons cannot be made due to differences in study designs, endpoint definitions and patient populations

1.Locke FL, *et al.* ASH 2021 (Abstract 2). 2. Locke FL, *et al. N Engl J Med* 2022; 3. Abramson R, et al. Blood 2022. 4. Bishop MR, *et al.* ASH 2021 (Abstract LBA6). 5. Bishop MR, *et al. N Engl J Med* 2022. Axicabtagene ciloleucel è rimborsato in italia per il trattamento di pazienti adulti con DLBCL e linfoma primitivo del mediastino a grandi cellule B (PMBCL) refrattari o recidivanti, dopo due o più linee di terapia sistemica

CAR T-cell therapy vs. SoC in 2L DLBCL - Safety

	ZUMA-7		TRANSFORM		BELINDA	
	SoC	**Axi-Cel**	SoC	**Liso-cel**	SoC	**Tisa-cel**
N	168	170	91	92	160	162
Grade 3–5 AEs	83%	91%	87%	92%	84%	90%
Grade 3–5 haematological toxicity						
Anaemia	39%	30%	49%	49%	57%	33%
Thrombocytopenia	57%	15%	64%	49%	47%	32%
Neutropenia	41%	69%	51%	80%	39%	40%
Febrile neutropenia	27%	2%	24%	15%	25%	13%
Grade 3–5 infections	11%	14%	21%	15%	15%	17%
Prolonged cytopenias	19%	29%	3%	43%	N/A	N/A
CRS						
Grade 1–2	---	86%	---	48%	---	53.7%
Grade 3–5	---	6%	---	1%[b]	---	4.9%
Onset / Duration (median)	---	3 / 7 d	---	5 / 4 d	---	N/A
Neurological events						
Grade 1–2	19%	39%	---	7%	---	8.4%
Grade 3–5	1%	21%	---	4%	---	1.9%
Onset / Duration (median)	23 / 23 d	7 / 9 d	---	11 / 6 d	---	N/A
Toxic deaths (due to AEs)	**2 (1%)**	**7[a] (4%)**	2 (2%)	1 (1%)	**13 (8.1%)**	**10 (6.2%)**

ZUMA 7: Axi vs. SOC in first relapse

Survival Benefit Favoring Axi-Cel Was Similar Across Key Prespecified Subgroups

	Axi-Cel No. of Patients	Axi-Cel With Events/Total No.	SOC No. of Patients	SOC With Events/Total No.	Hazard Ratio	(95% CI) LCI	(95% CI) UCI
Overall[a]	82/180	95/179			0.726	0.540	0.977
Age							
<65 y	56/129	64/121			0.779	0.541	1.120
≥65 y	26/51	31/58			0.691	0.401	1.190
Response to first-line therapy at randomization							
Primary refractory disease	66/133	72/131			0.773	0.553	1.080
Relapse ≤12 mo after initiation or completion of first-line therapy	16/47	23/48			0.586	0.308	1.116
Second-line age-adjusted IPI							
0 or 1	37/98	40/100			0.842	0.538	1.317
2 or 3	45/82	55/79			0.647	0.436	0.962
Prognostic marker according to central laboratory							
HGBL, double-hit	14/32	14/25			0.716	0.330	1.553
Double-expressor lymphoma	26/57	33/62			0.729	0.435	1.221

0.1 0.2 0.5 1 2

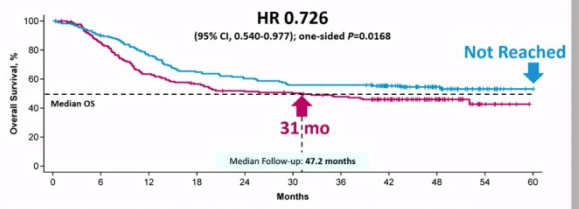
Axi-Cel Better Standard Care Better

[a] Dashed vertical line is shown at 0.726, which is the overall survival hazard ratio for death among all patients in the axi-cel arm versus the SOC arm.

Axi-cel, axicabtagene ciloleucel; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LCI, lower confidence interval; SOC, standard of care; UCI, upper confidence interval.

Westin et al ICML 2023 Abstract 22 15

Axi-Cel Improved Overall Survival Versus Standard of Care



- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Historical SOC trials had lower OS rates in early R/R LBCL, including median OS of ~10 months in ORCHARRD[a]

[a] van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551.

Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; OS, overall survival; R/R, relapsed/refractory; SOC, standard of care.

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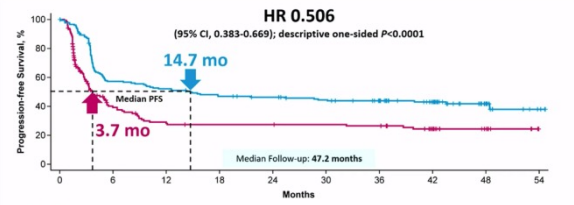
PFS By Investigator Confirmed Benefit of Axi-Cel Over SOC



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; PFS, progression-free survival; SOC, standard of care.

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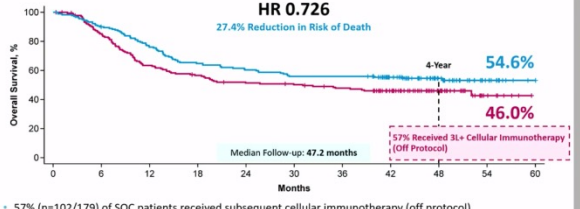
Axi-Cel Improved Overall Survival Versus Standard of Care



- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] ~40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).

3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

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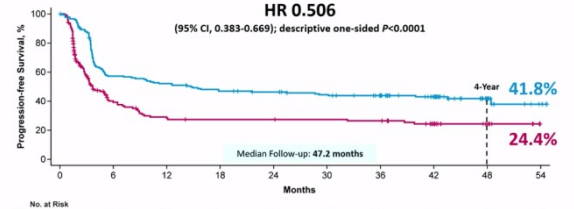
PFS By Investigator Confirmed Benefit of Axi-Cel Over SOC



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; PFS, progression-free survival; SOC, standard of care.

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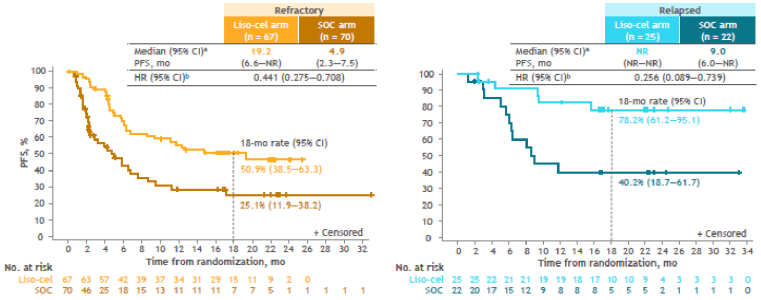
TRANSFORM: Liso vs. SOC in first relapse

Patient demographics and baseline disease characteristics by prior response status (ITT set)

	Refractory		Relapsed	
	Liso-cel arm (n = 67)	SOC arm (n = 70)	Liso-cel arm (n = 25)	SOC arm (n = 22)
Male, n (%)	34 (51)	47 (67)	10 (40)	14 (64)
Age, median (range), y	61 (21–74)	56 (26–75)	56 (20–71)	65 (28–72)
LBCL types,[a] n (%)				
DLBCL NOS	39 (58)	34 (49)	14 (56)	16 (73)
HGBCL with rearrangements in *MYC* and *BCL2*, *BCL6*, or both[b]	18 (27)	19 (27)	4 (16)	2 (9)
PMBCL	5 (7)	7 (10)	3 (12)	2 (9)
DLBCL transformed from any indolent lymphoma	4 (6)	7 (10)	3 (12)	1 (5)
THRBCL	1 (1)	3 (4)	0	1 (5)
FL3B	0	0	1 (4)	0
LBCL subtype based on cell of origin, n (%)				
GCB	36 (54)	32 (46)	9 (36)	8 (36)
ABC, non-GCB	12 (18)	23 (33)	9 (36)	6 (27)
ECOG PS, n (%)				
0	32 (48)	40 (57)	16 (64)	17 (77)
1	35 (52)	30 (43)	9 (36)	5 (23)
sAAIPI, n (%)				
0 or 1	42 (63)	40 (57)	14 (56)	15 (68)
2 or 3	25 (37)	30 (43)	11 (44)	7 (32)
LDH ≥ 500 U/L	7 (10)	9 (13)	3 (12)	2 (9)
SPD > 50 cm²	6 (9)	9 (13)	4 (16)	1 (5)

PFS per IRC by prior response status (ITT set)



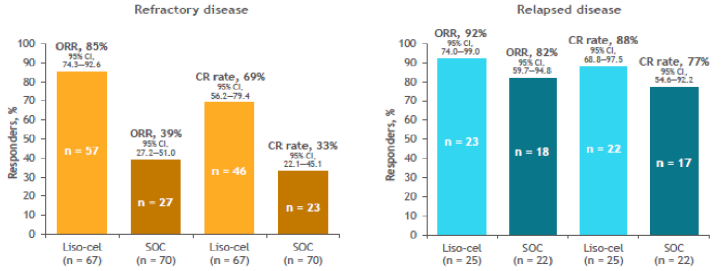
- PFS in the overall study population: NR (95% CI, 12.6–NR) versus 6.2 months (95% CI, 4.3–8.6); HR, 0.400; 95% CI, 0.261–0.615; $P < 0.0001$[1]

Most common TEAEs by prior response status (safety set)

	Refractory		Relapsed	
	Liso-cel arm (n = 67)	SOC arm (n = 69)	Liso-cel arm (n = 25)	SOC arm (n = 22)
Any-grade TEAE, n (%)	67 (100)	68 (99)	25 (100)	22 (100)
TEAEs ≥ 30% in any liso-cel subgroup arm, n (%)				
Neutropenia	56 (84)	39 (57)	20 (80)	11 (50)
Anemia	48 (72)	46 (67)	14 (56)	16 (73)
Thrombocytopenia	40 (60)	52 (75)	15 (60)	14 (64)
CRS	33 (49)	0	12 (48)	0
Nausea	32 (48)	40 (58)	17 (68)	13 (59)
Fatigue	26 (39)	26 (38)	11 (44)	11 (50)
Headache	24 (36)	15 (22)	16 (64)	6 (27)
Pyrexia	21 (31)	18 (26)	7 (28)	5 (23)
Constipation	20 (30)	19 (28)	10 (40)	5 (23)
Dizziness	14 (21)	8 (12)	8 (32)	5 (23)

- Incidences of grade 3–4 TEAEs were mostly similar between liso-cel–treated patients with refractory or relapsed disease, except anemia (57% vs 40%, respectively)
- Results were consistent with the overall TRANSFORM population

Response rates per IRC by prior response status (ITT set)



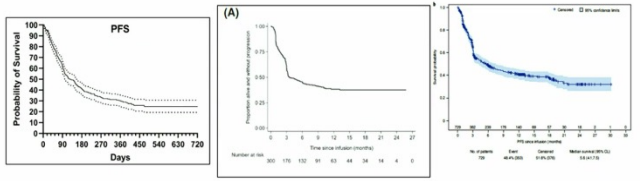
- CR rates favored liso-cel over SOC in both subgroups, consistent with the overall study population (liso-cel, 74% [95% CI, 63.7–82.5] vs SOC, 43% [95% CI, 33.2–54.2]; $P < 0.0001$),[1] though differences between treatment arms were larger in patients with refractory disease

CART per DLBCL RR in III linea

Anti-CD19 CAR-T Cell Therapies in R/R 3rd line LBCL (2)

	KTE-C19 Axi-cel	CTL019 Tisagenlecleucel	JCAR017 Liso-cel
Vector	Gammaretroviral	Lentiviral	Lentiviral
Costimulatory domain	CD28	4-1BB	4-1BB
Disease state	DLBCL, TFL, PMBCL	DLBCL, TFL	DLBCL, PMBCL, T-iNHL, FL3B
ORR	84%	54%	73%
CR Rate	58%	40%	53%
Median follow-up (months)	27	32	12
Median PFS (months)	5.9	2.9	6.8
Median DOR (months)	NR	NR	NR
Median OS (months)	26	11.1	21
	FDA 11/2017 EMA 06/2018	*FDA 05/2018 EMA 08/2018*	*FDA 02/2021 EMA 08/2018*

CAR T-cell in LBCL: Europe Real World Outcomes

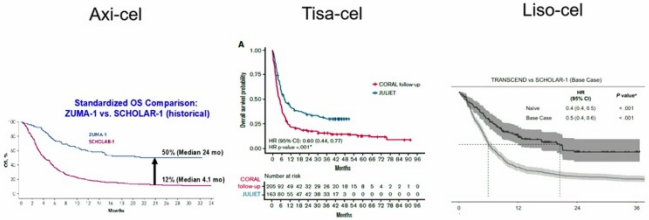


	Germany	UK	France
Nb pts	344	300	729
ORR	65%	48%	74% *
CR rate	37%	40%	52% *
PFS (median)	na	3.0 months	5.6 months

* Subset of pts

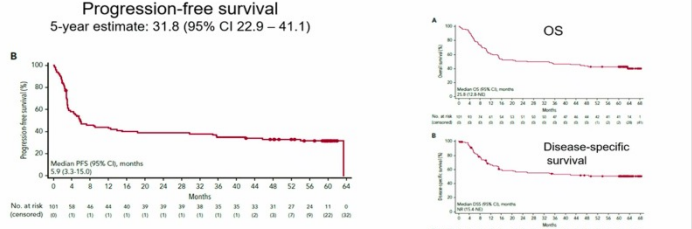
Bethge WA et al, Blood 2022 | Kuhnl A et al, BJH 2022. | Bachy E et al., Nat Med 2022

CD19 CART in ≥3rd line LBCL: comparison with "SoC"



Neelapu S et al. *Blood Adv* 2021 | Maziarz RT et al. *Blood Adv* 2022 | Salles G et al., Adv Therapy 2021

ZUMA-1: 5-year follow-up

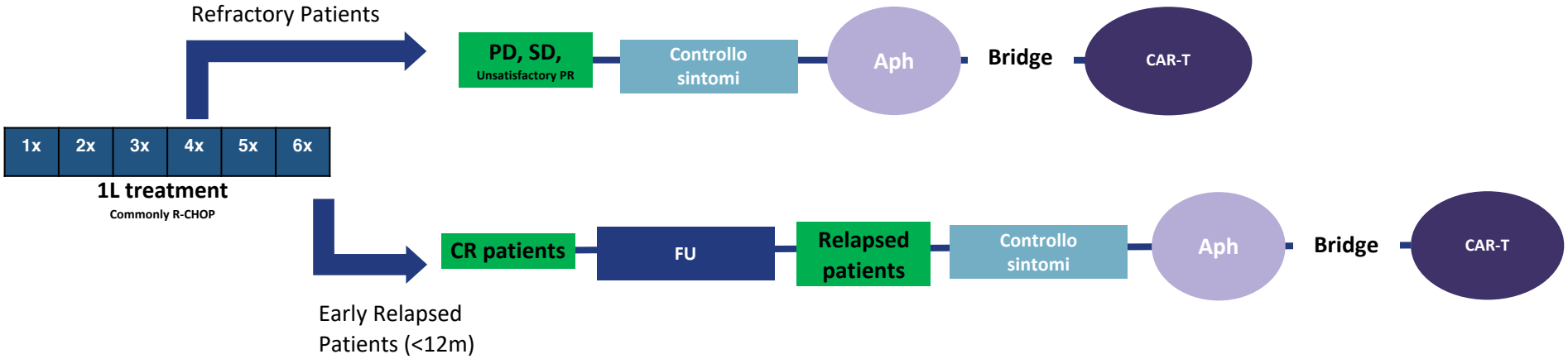


Neelapu SS et al, Blood 2023

BLOCCHI AIFA A PRESCRIVIBILITA' CAR-T

- Sdr. di Richter e PCNSL (solo Axi)
- ECOG >2
- a/cGVHD
- ASCT < 12 m
- Precedente terapia anti-CD19
- Assente espressione di CD19 dopo terapia anti-CD19
- Localizzazione attiva CNS
- Epilessia nei 3 mesi precedenti
- Uso concomitante di anticorpi monoclonali anti-EGFR (solo Liso)
- trombosi nei 6 mesi precedenti
- neutrofili < 1.000/mcl, linfociti < 100/mcl, piastrine < 75.000/mcl, emoglobina < 8 g/dl
- patologia autoimmune con danno d'organo terminale o trattata con terapia sistemica immunosoppressiva o disease modifying nei due anni precedenti
- Cr Cl < 60 ml/min (Cr Cl >30 ml/min solo Liso)
- AST e ALT >2,5 volte il limite superiore normale per età, bilirubina > 1,5 mg/dl o > 3 nei pazienti affetti da sindrome di Gilbert
- frazione di eiezione < 50%, (frazione di eiezione < 45% solo Tisa)
- dispnea > 1, sO_2 < 92% in aria ambiente, versamento pericardico.

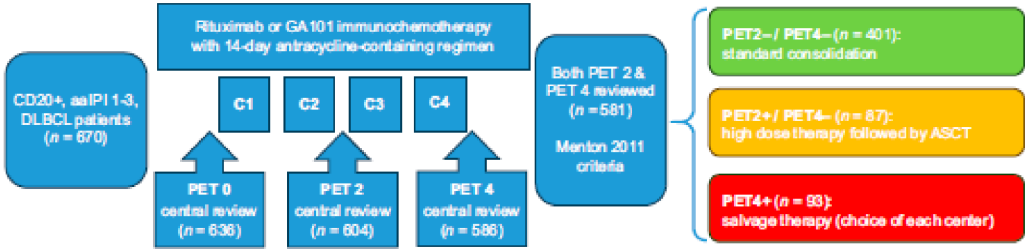
Patient monitoring key moments for 2L CAR-T usage



MA:
1)QUALE E' IL SIGNIFICATO DECISIONALE DELLA INTERIM PET nel DLBCL?
2)E' OMOGENEO PER LE DIVERSE ENTITA'? (es. PMDLBCL)
3)ΔSUV??

Validation of the ΔSUV_{max} for Interim PET Interpretation in Diffuse Large B-Cell Lymphoma on the Basis of the GAINED Clinical Trial

Emmanuel Itti



CONCLUSION

Assessment of interim metabolic response by −Menton 2011 criteria is quite reproducible and translatable to routine practice. However, we recommend the use of the ΔSUV_{max} alone for interim PET evaluation in DLBCL as many patients with PET-negative scan results and interim SUV_{max} of greater than 5.0 are considered to have PET-positive scan results when Menton 2011 is used. These special cases demonstrate similar or better outcome when using the ΔSUV_{max} alone and better agreement between local and central readers. The only situation where ΔSUV_{max} should be interpreted with caution is when baseline SUV_{max} is less than 10.0.

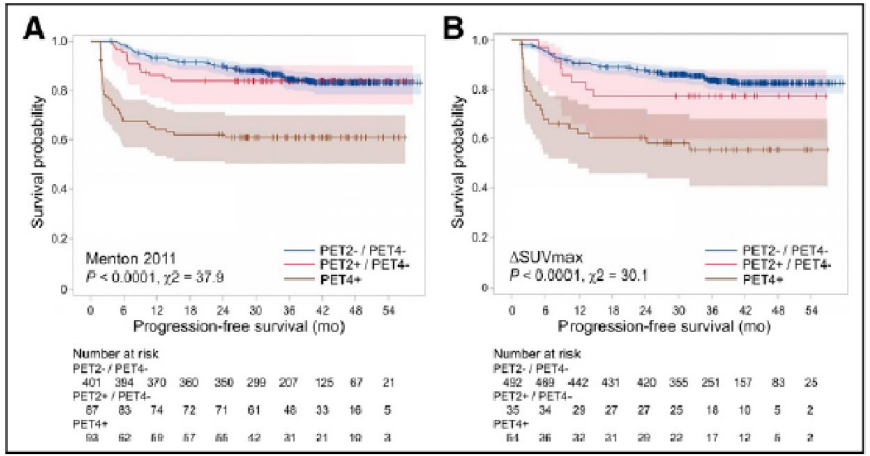


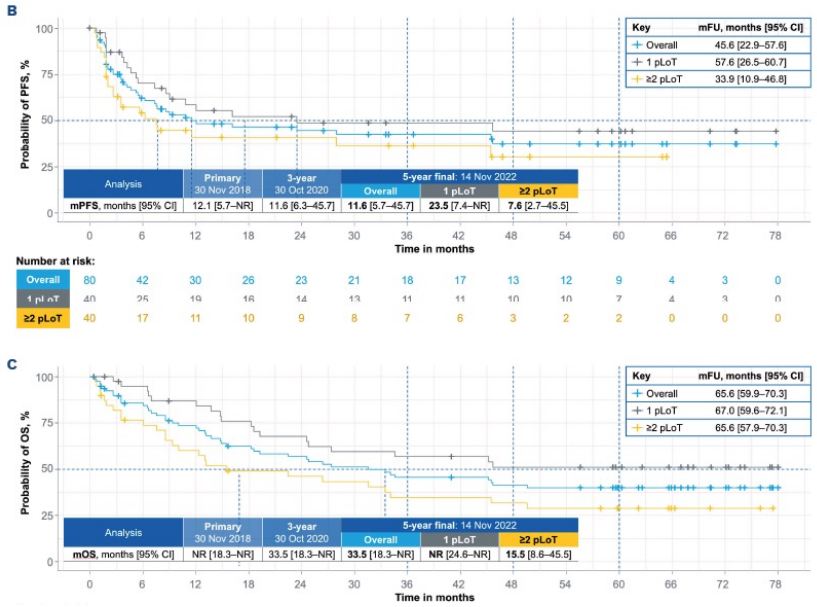
FIGURE 2. Kaplan–Meier estimates of progression-free survival according to metabolic response at PET2 and PET4 using Menton 2011 criteria (per protocol) (A) and ΔSUV_{max} alone (post hoc analysis) (B).

J Nucl Med 2023; 64:1706–1711

Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: final 5-year efficacy and safety findings in the phase II L-MIND study

Johannes Duell, Haematologica | 109 February 2024

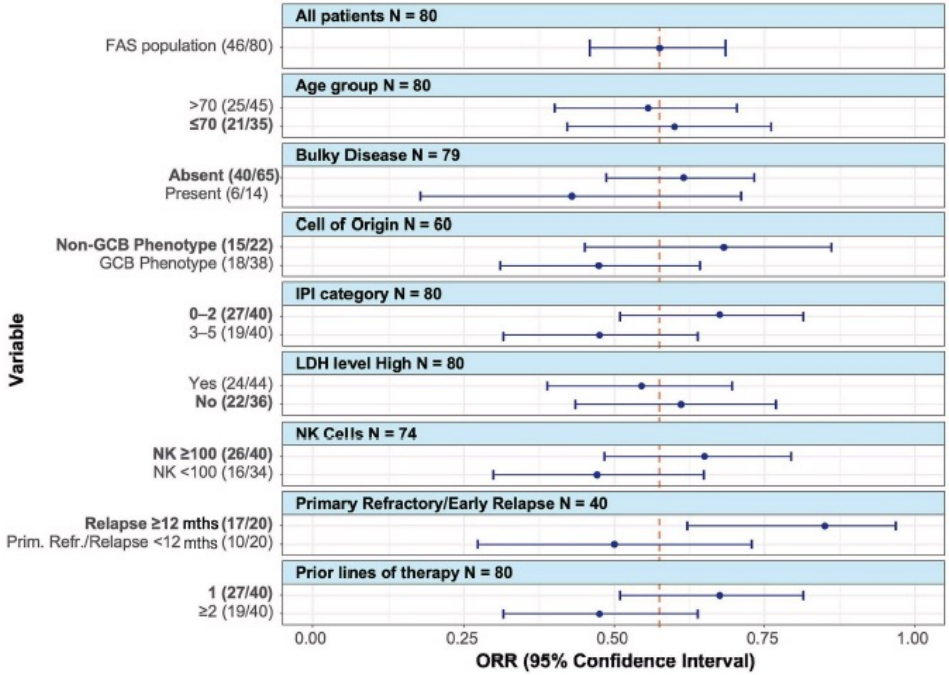
Tx: tafa 12 mg/kg IV/lena 25 mg d1-21 for up to 12 cycles (28d) -> tafasitamab monotherapy (once every 2 weeks) in patients with SD or better, until progressive disease.



Characteristics	Primary analysis	3-year follow-up	Final 5-year data	5-year data for patients with 1 prior line of therapy, N=40	5-year data for patients with ≥2 prior lines of therapy, N=40
Data cut-off date	Nov 30, 2018	Oct 30, 2020	Nov 14, 2022	Nov 14, 2022	Nov 14, 2022
Best ORR, N (%) [95% CI]	48 (60.0) [48.4-70.9]	46 (57.5) [45.9-68.5]	46 (57.5) [45.9-68.5]	27 (67.5) [50.9-81.4]	19 (47.5) [31.5-63.9]
CR rate, N (%) [95% CI]	34 (42.5) [32.0-54.0]	32 (40.0) [29.2-51.6]	33 (41.3) [30.4-52.8]	21 (52.5) [36.1-68.5]	12 (30.0) [16.6-46.5]
PR rate, N (%) [95% CI]	14 (17.5) [10.0-28.0]	14 (17.5) [9.9-27.6]	13 (16.3) [8.9-26.2]	6 (15.0) [5.7-29.8]	7 (17.5) [7.3-32.8]
Median DoR in months [95% CI]	21.7 [21.7-NR]	43.9 [26.1-NR]	NR [33.8-NR]	NR [9.1-NR]	NR [26.1-NR]
Median PFS in months [95% CI]	12.1 [5.7-NR]	11.6 [6.3-45.7]	11.6 [5.7-45.7]	23.5 [7.4-NR]	7.6 [2.7-45.5]
Median OS in months [95% CI]	NR [18.3-NR]	33.5 [18.3-NR]	33.5 [18.3-NR]	NR [24.6-NR]	15.5 [8.6-45.5]

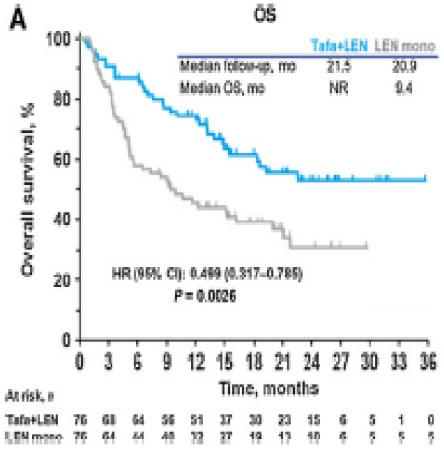
Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: final 5-year efficacy and safety findings in the phase II L-MIND study

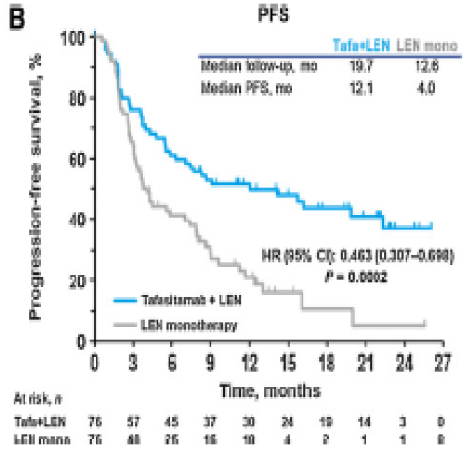
Johannes Duell,

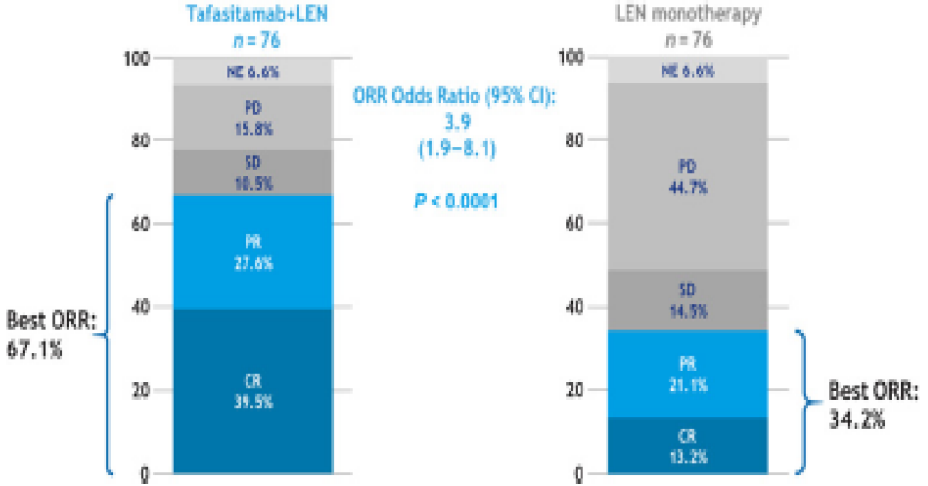


Haematologica | 109 February 2024

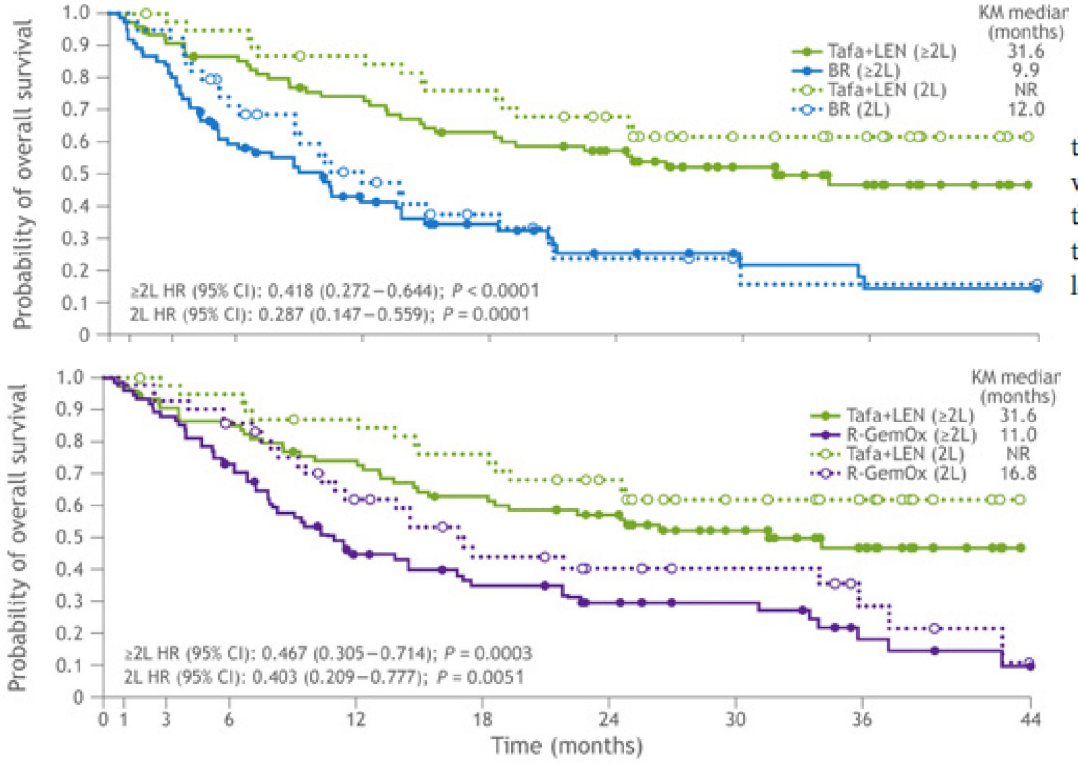
RE-MIND: Comparing Tafasitamab - Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma. Zinzani PL. Clin Cancer Res 2021;27:6124–34







Improved Efficacy of Tafasitamab plus Lenalidomide versus Systemic Therapies for Relapsed/Refractory DLBCL: RE-MIND2, an Observational Retrospective Matched Cohort Study. Nowakowski GS. Clin Cancer Res 2022;28:4003–17



In conclusion, a significant clinical advantage in OS was observed in the cohort treated with tafasitamab plus lenalidomide in a clinical trial versus matched observational cohorts treated with pooled systemic therapies, BR, and R-GemOx. In the context of current treatments, these data further highlight the clinical value of the tafasitamab plus lenalidomide combination in patients with R/R DLBCL.

RE-MIND2: comparative effectiveness of tafasitamab plus lenalidomide versus polatuzumab vedotin/bendamustine/ rituximab (pola-BR), CAR-T therapies, and lenalidomide/rituximab (R2) based on real-world data in patients with relapsed/refractory diffuse large B-cell lymphoma

Grzegorz S. Nowakowski[1] · Dok Hyun Yoon[2] · Patrizia Mondello[3] · Erel Joffe[3] · Anthea Peters[4] · Isabelle Fleury[5]

Annals of Hematology (2023) 102:1773–1787

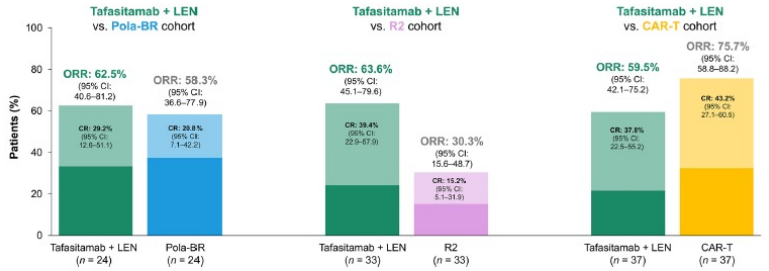
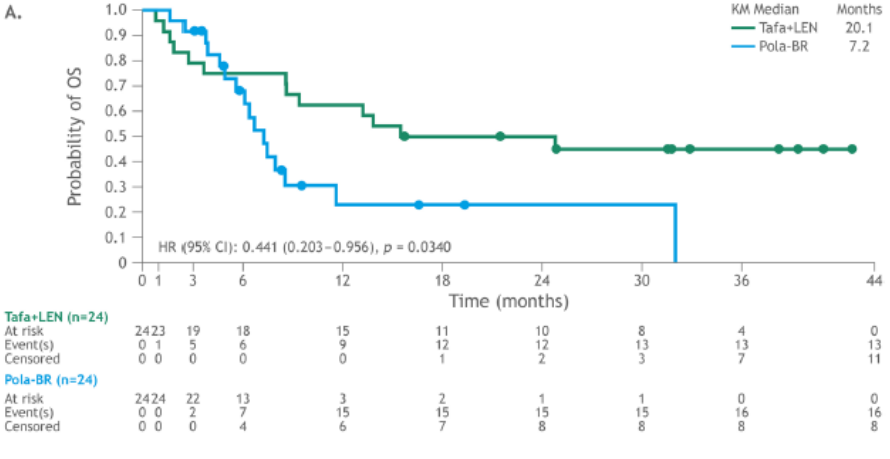
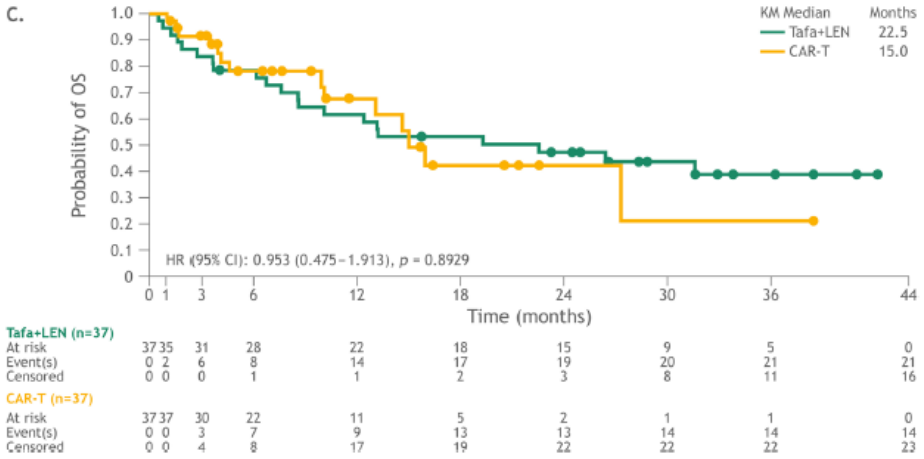


Fig. 3. ORR and CR rate for tafasitamab plus lenalidomide versus pola-BR, R2, and CAR-T therapies. Abbreviations: *CAR-T*, CD19 chimeric antigen receptor T-cell therapy; *CI*, confidence interval; *CR*, complete response; *LEN*, lenalidomide; *ORR*, overall response rate; *pola-BR*, polatuzumab vedotin + bendamustine + rituximab; *R2*, rituximab + lenalidomide



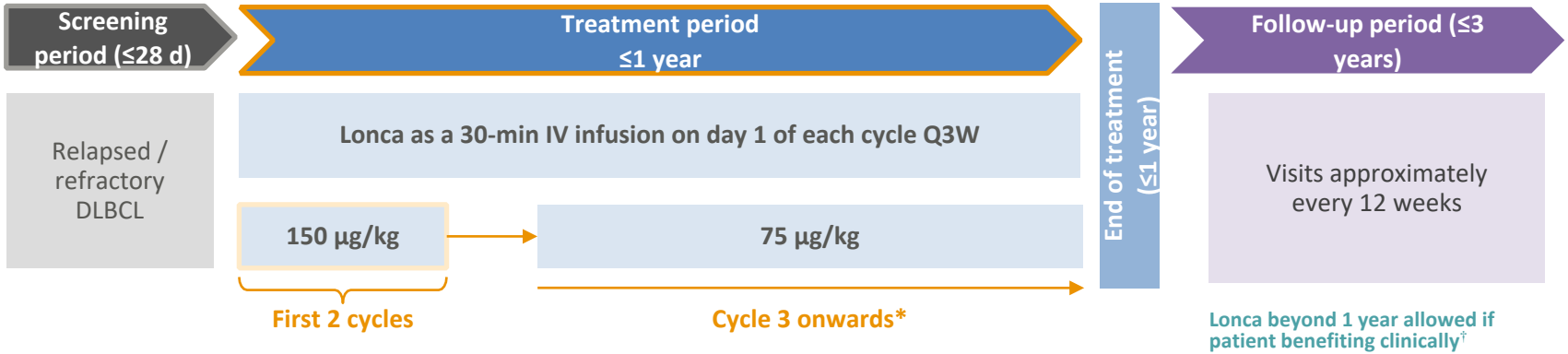


Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study

Paolo F. Caimi, Haematologica | 109 April 2024

145 patients were enrolled in US, UK, Italy, Switzerland

Enrolment period: August 2018 – Sept 2019



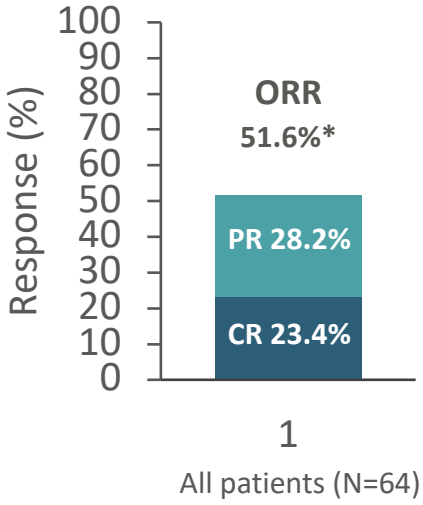
- **Patients received oral dexamethasone premedication per protocol**
- **Disease assessment by central independent review using PET-CT at baseline, W6, W12, then Q9W until EOT**
  During the follow-up period, patients who discontinued Lonca for reasons other than PD or initiation of other anti-cancer therapy except SCT had imaging performed every 12 weeks until 1 year from EOT, then every 6 months, until progression up to 3 years from EOT
- **Data cut-offs:**
  - **Primary analysis:** April 6, 2020[3], median follow-up of 7.3 months[4]
  - **Follow-up analysis:** March 1, 2021, median follow-up of 7.8 months[5]
  - **Final analysis:** September 15, 2022, median follow-up of 7.8 months[4]

* Patients continued on treatment for up to one year **or** until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision. † If agreed with the sponsor. d, days; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; IV, intravenous; Lonca, loncastuximab tesirine; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; Q3W, every 3 weeks; Q9W, every 9 weeks; SCT, stem cell transplantation; W, week.

1. ClinicalTrials.gov NCT03589469 **2.** LOTIS-2 study protocol 2019 **3.** Caimi et al. *Lancet Oncol* 2021 **4.** Caimi et al. *Haematologica* 2023 **5.** Zinzani et al. ICML 2021.

Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study

Paolo F. Caimi, Haematologica | 109 April 2024



	All-treated N=145	Best response of CR N=36	Patients with CR who were event-free ≥1 year N=16	Patients with CR who were event-free ≥2 years N=11
Sex, N (%)				
Female	60 (41.4)	22 (61.1)	13 (81.3)	9 (81.8)
Age in years, N (%)				
Median (range)	66.0 (23-94)	67.5 (45-94)	71.0 (53-84)	70.0 (53-82)
<65	65 (44.8)	13 (36.1)	3 (18.8)	3 (27.3)
≥65 to <75	59 (40.7)	15 (41.7)	7 (43.8)	5 (45.5)
≥75	21 (14.5)	8 (22.2)	6 (37.5)	3 (27.3)
Race, N (%)				
White	130 (89.7)	34 (94.4)	15 (93.8)	11 (100)
Black or African American	5 (3.4)	1 (2.8)	0	0
Asian	3 (2.1)	0	0	0
Other	7 (4.8)	1 (2.8)	1 (6.3)	0
ECOG score, N (%)				
0	58 (40.0)	19 (52.8)	9 (56.3)	7 (63.6)
1	78 (53.8)	14 (38.9)	6 (37.5)	3 (27.3)
2	9 (6.2)	3 (8.3)	1 (6.3)	1 (9.1)
Histology,[a] N (%)				
DLBCL, NOS	128 (88.3)	31 (86.1)	11 (68.8)	8 (72.7)
HGBCL[b]	10 (6.9)	5 (13.9)	5 (31.3)	3 (27.3)
Primary mediastinal DLBCL	7 (4.8)	0	0	0
Transformed DLBCL, N (%)	30 (20.7)	7 (19.4)	4 (25.0)	2 (18.2)
Double/triple hit, N (%)				
Double hit	12 (8.3)	5 (13.9)	5 (31.3)	3 (27.3)
Triple hit	3 (2.1)	0	0	0
Stage, N (%)				
I-II	33 (22.8)	9 (25.0)	3 (18.8)	2 (18.2)
III-IV	112 (77.2)	27 (75.0)	13 (81.3)	9 (81.8)
Prior systemic therapies, N (%)				
Median (range)	3.0 (2-7)	3.0 (2-7)	2.0 (2-7)	2.0 (2-7)
2 prior lines	63 (43.4)	15 (41.7)	10 (62.5)	8 (72.7)
3 prior lines	34 (23.4)	5 (13.9)	2 (12.5)	1 (9.1)
>3 prior lines	48 (33.1)	16 (44.4)	4 (25.0)	2 (18.2)
Refractory, N (%)				
Primary refractory	29 (20.0)	5 (13.9)	2 (12.5)	0
Refractory to last therapy	89 (61.4)	11 (30.6)	5 (31.3)	4 (36.4)
Prior SCT, N (%)	24 (16.6)	8 (22.2)	1 (6.3)	1 (9.1)
Prior CAR T therapy, N (%)	14 (9.7)	3 (8.3)	2 (12.5)	0

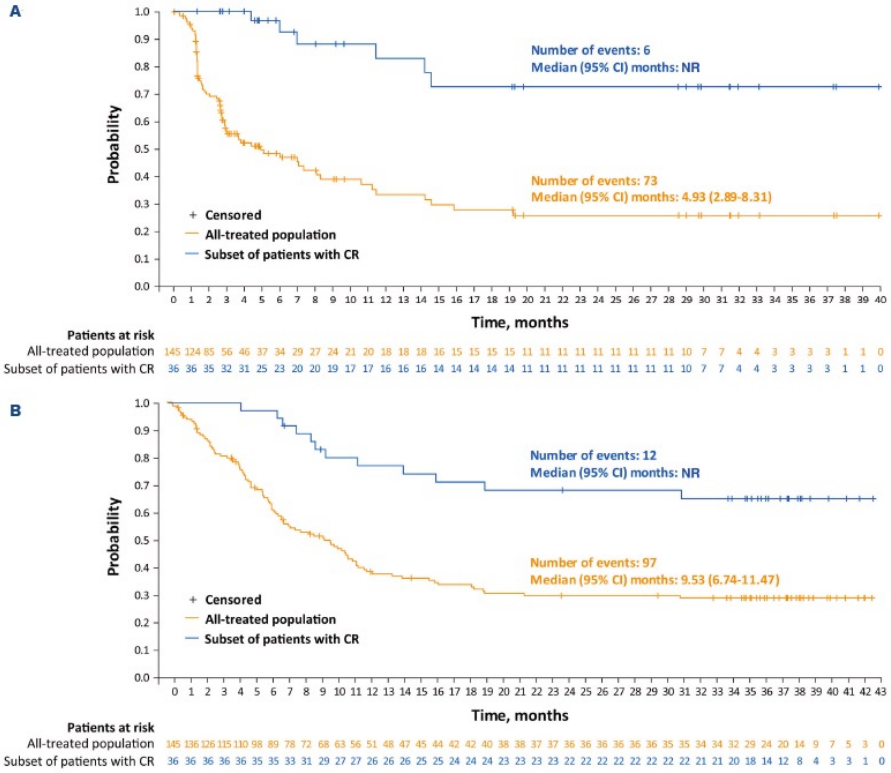
Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study

Paolo F. Caimi, Haematologica | 109 April 2024

	All-treated population N=145 (95% CI)	Best response of CR N=36 (95% CI)
Median DOR in months	13.4 (6.9-NR)	NR
Probability % of maintaining response at 12 months	54.7 (37.9-68.8)	82.8 (59.9-93.3)
Probability % of maintaining response at 24 months	44.6 (27.9-60.0)	72.4 (48.1-86.8)
Median DOR in months	4.9 (2.9-8.3)	NR
Probability % of maintaining PFS at 12 months	33.5 (23.3-44.0)	82.9 (60.0-93.3)
Probability % of maintaining PFS at 24 months	25.9 (16.2-36.7)	72.5 (48.2-86.8)
Median DOR in months	9.5 (6.7-11.5)	NR
Probability % of maintaining OS at 12 months	39.0 (30.7-47.1)	77.1 (59.4-87.9)
Probability % of maintaining OS at 24 months	29.5 (22.0-37.4)	68.2 (50.0-81.0)
Median DOR in months	-	NR
Probability % of maintaining RFS at 12 months	-	83.2 (60.5-93.5)
Probability % of maintaining RFS at 24 months	-	72.8 (48.5-87.0)

CI: confidence interval; CR: complete response; DOR: duration of response; NR: not reached; OS: overall survival; PFS: progression-free survival; RFS: relapse-free survival.

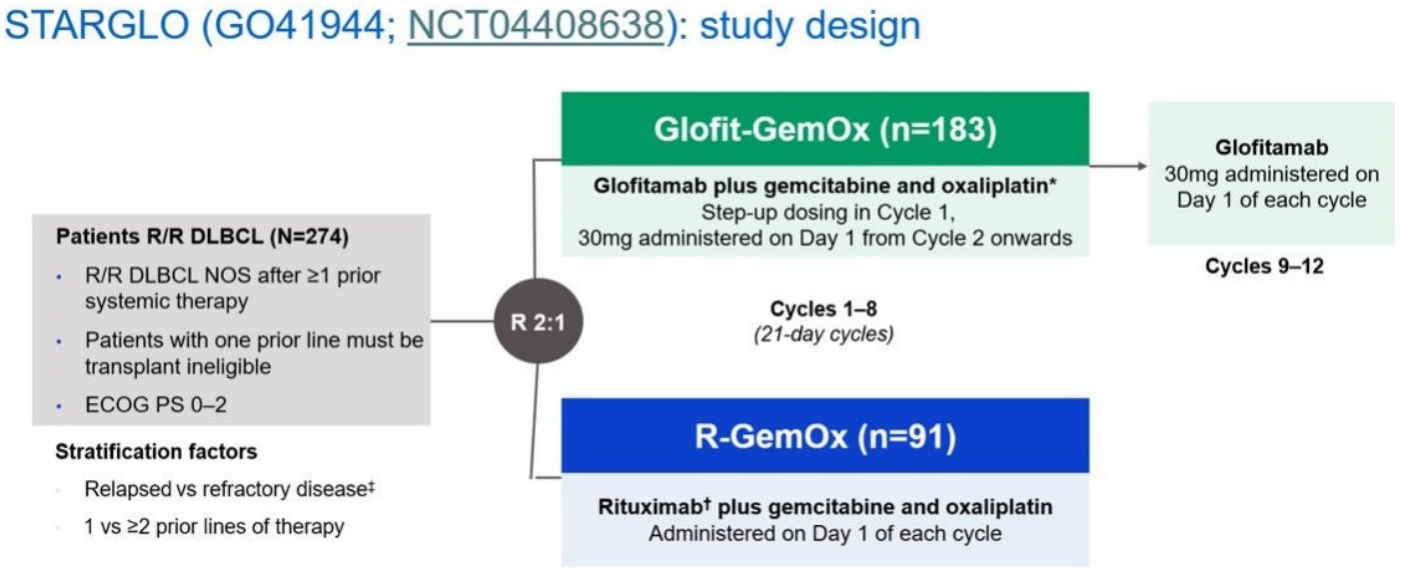
In conclusion, among heavily pretreated patients with R/R DLBCL in the pivotal LOTIS-2 study, Lonca continued to demonstrate durable responses with a manageable safety and tolerability profile in this long-term follow-up analysis. Further, a subset of 11 patients with CR remained event-free for ≥2 years with no evidence of disease, no new anticancer treatment, and a median treatment-free duration of 27.7 months post-Lonca treatment.



GLOFITAMAB PLUS GEMCITABINE AND OXALIPLATIN (GLOFIT-GEMOX) FOR RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS OF A GLOBAL RANDOMIZED PHASE III TRIAL (STARGLO), EHA 2024; Abramson JS et al. oral presentation (abstract LB3438).

Random 2:1; 8 Glofit-GemOx + 4 Glofit vs. 8 R-GemOx (8 cycles). 274 pts DLBCL (Glofit-GemOx: 183; R-GemOx: 91);

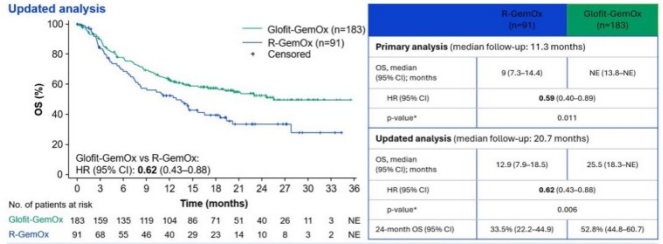
62.8% > 1L and 102 >2L, 55.8% primary refractory disease.



Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438)

GLOFITAMAB PLUS GEMCITABINE AND OXALIPLATIN (GLOFIT-GEMOX) FOR RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS OF A GLOBAL RANDOMIZED PHASE III TRIAL (STARGLO), EHA 2024; Abramson JS et al. oral presentation (abstract LB3438).

STARGLO: Overal Survival

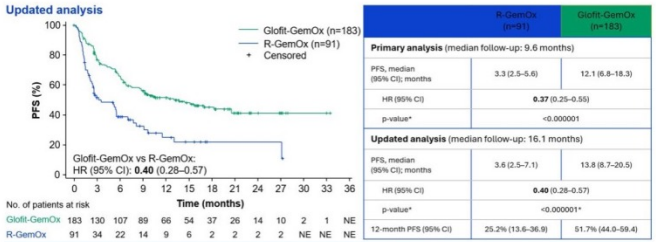


	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

- Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** versus R-GemOx

Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438)

STARGLO: Progression Free Survival



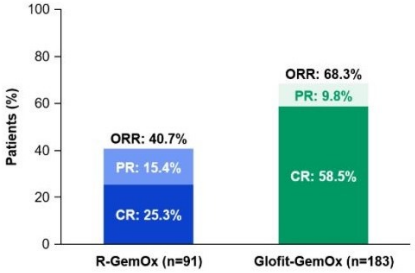
	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 9.6 months)		
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)
HR (95% CI)	**0.37** (0.25–0.55)	
p-value*	<0.000001	
Updated analysis (median follow-up: 16.1 months)		
PFS, median (95% CI); months	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.40** (0.28–0.57)	
p-value*	<0.000001*	
12-month PFS (95% CI)	25.2% (13.6–36.9)	51.7% (44.0–59.4)

- Statistically significant and clinically meaningful **PFS benefit for Glofit-GemOx** versus R-GemOx

Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438)

STARGLO: response rates

Response rates at the updated analysis



33.2% difference in CR rate between treatment arms (95% CI: 19.7–44.5)

CR rate significantly better with Glofit-GemOx vs R-GemOx (descriptive p-value **<0.0001***)

- CR rate was statistically significant at primary analysis, with increased difference between treatment arms at the updated analysis

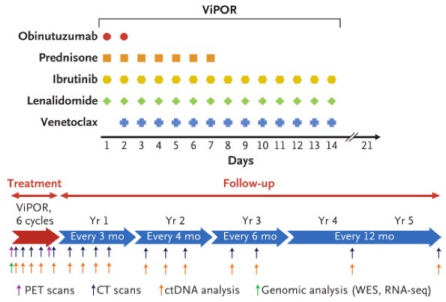
Abramson JS, et al. EHA 2024; Oral presentation (abstract#LB3438)

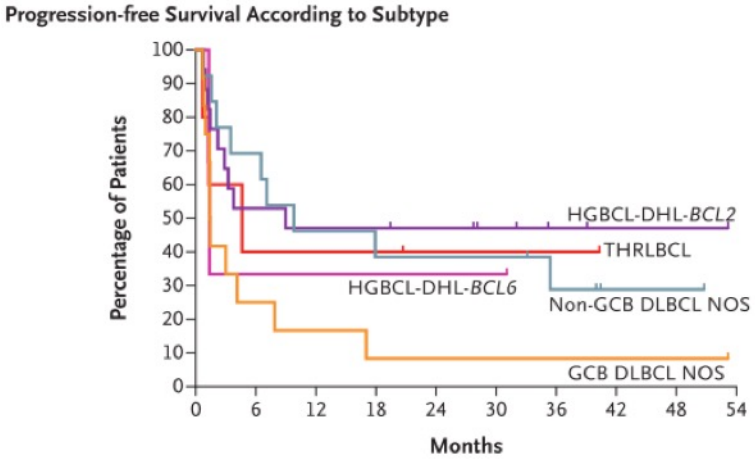
AE rates were higher with Glofit-GemOx versus R-GemOx, including Grade (Gr) 3–4 AEs (69.4 vs 36.4%). CRS: Gr 1: 31.4%, Gr 2: 10.5%, and Gr 3: 2.3%. ICANS 2.3%.

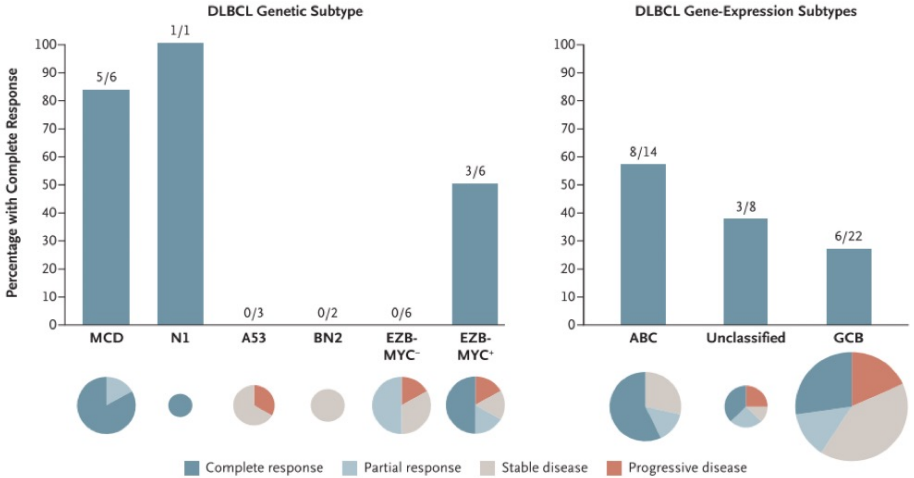
Glofit-GemOx demonstrated statistically significant and clinically meaningful benefit in OS, PFS, and CR rate over R-GemOx in ASCT-ineligible pts with R/R DLBCL.

Combination Targeted Therapy in Relapsed Diffuse Large B-Cell Lymphoma

C. Melani, R. Lakhotia, S. Pittaluga, J.D. Phelan, D.W. Huang, G. Wright, J. Simard, J. Muppidi, C.J. Thomas,







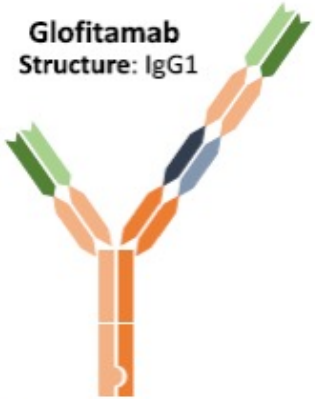
CONCLUSIONS

Treatment with ViPOR was associated with durable remissions in patients with specific molecular DLBCL subtypes and was associated with mainly reversible adverse events. (Funded by the Intramural Research Program of the National Cancer Institute and the National Center for Advancing Translational Sciences of the National Institutes of Health and others; ClinicalTrials.gov number, NCT03223610.)

N Engl J Med 2024;390:2143-55.

GLI ANTICORPI BISPECIFICI

Glofitamab
Structure: IgG1



- CD3 binding domain
- 2 x CD20 binding domains
- Knob-into-hole technology: Complementary FC mutations

Epcoritamab
Structure: IgG1

- CD3 binding domain
- CD20 binding domain
- Fc silencing by single matched point mutations in Fc region

Odronextamab
Structure: IgG4

- CD3 binding domain
- CD20 binding domain
- Dipeptide substitution in FC region with unique common light chain: purified by selective protein A chromatography

GLOFITAMAB

Single-arm pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies[1]

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

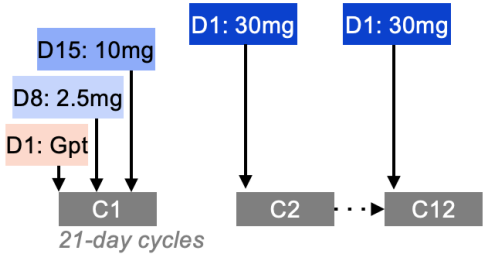
Glofitamab IV administration

Fixed-duration treatment

- Max. 12 cycles

CRS mitigation:

- Obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

Primary: CR (best response) rate by IRC*

Key secondary: ORR rate,† DoR, DoCR,† PFS, and OS

*By PET-CT (Lugano criteria).[1] †By IRC and investigator. BCL, B-cell lymphoma; CRS, cytokine release syndrome; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ECOG, European Cooperative Oncology Group performance status; FL, follicular lymphoma; Gpt, obinutuzumab pretreatment; HGBCL, high-grade BCL; IRC, Independent Review Committee; NOS, not otherwise specified; PET, positron emission tomography; PMBCL, primary mediastinal BCL.

Response rates

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[2†‡]	Prior CAR-T (N=52)†
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DOCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DOCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1(7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

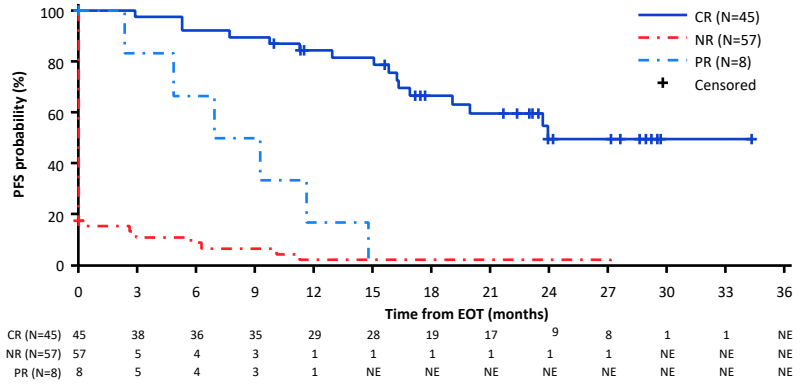
	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)†	**4.9 (3.4–8.1)**
6-month event-free rate, % (95% CI)	45.5 (37.2–53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5–45.8)
Median OS, months (95% CI)†	**11.5 (7.9–15.7)**
12-month OS rate, % (95% CI)	49.8 (41.1–58.5)

The IRC-assessed ORR/CR rate was 52/40%. After a median follow-up of 37.7 months in patients with a CR, mDOR CR was 29.8 months. In patients with a CR at EOT, the PFS and OS rates 2 years after EOT were 57% and 77%, respectively.

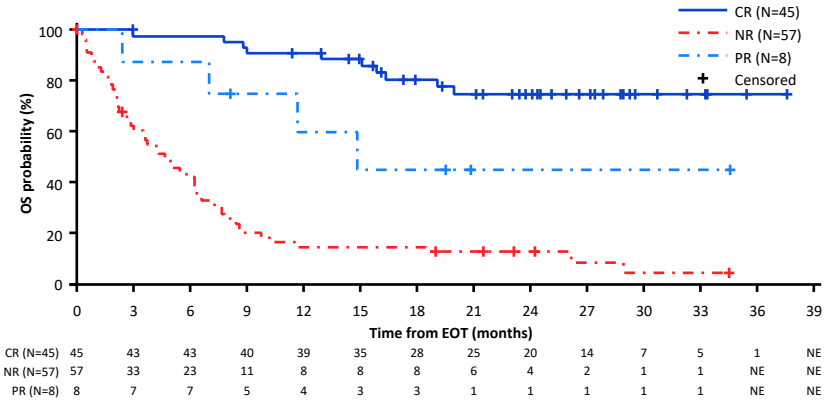
Hutchings M, et al. ASH 2023; oral presentation (abstract #433); ASH 2024; oral presentation (abstract #865) .

Landmark analysis by response at Cycle EOT: Extended follow-up

PFS



OS



Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	**24.0 (19.1–NE)**
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)

Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	**NE (NE)**
18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

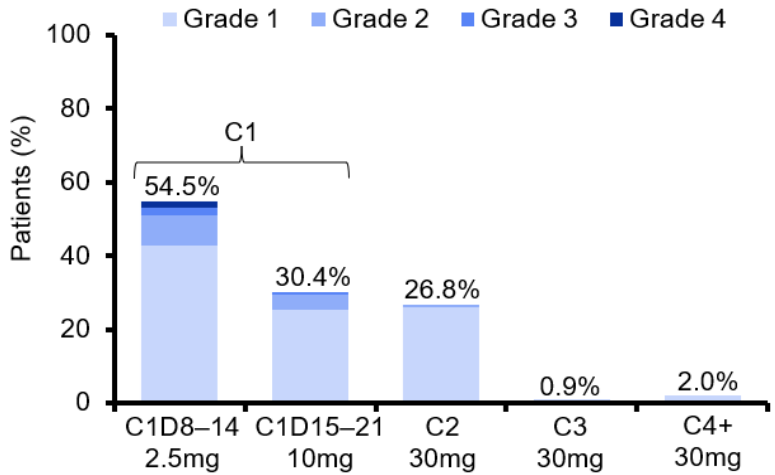
Clinical cut-off date: September 4, 2023. Median time on study: 32.1 months (range: 0–43). *KM estimates. C, cycle; CI, confidence interval; CR, complete response; EOT, end-of-treatment; NE, not estimable; NR, no response; PFS, progression-free survival; PR, partial response; OS, overall survival; RP2D, recommended Phase II dose.

Hutchings M, et al. ASH 2023; oral presentation (abstract #433).

Cytokine release syndrome

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	**13.6 (6.2–51.8)**
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	**31/97 (32.0)**

CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

*CRS reported by ASTCT grade derived based on reported data and INV graded CRS according to Lee 2014 criteria.[3,4] ASTCT, American Society for Transplantation and Cellular Therapy criteria; C, cycle; CAR-T, chimeric antigen receptor T-cell therapy; CCOD, clinical cut-off date; CRS, cytokine release syndrome; D, day; INV, investigator; RP2D, recommended Phase II dose.

1. Dickinson M, et al. ASCO 2022 oral presentation (abstract #7500);
2. Dickinson M, et al. NEJM 2022;387:2220–31;
3. Lee, at al. Blood 2014;124:188–95;
4. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from the pivotal EPCORE NHL-1 trial

Catherine Thieblemont[1✉], Yasmin H. Karimi[2], Herve Ghesquieres[3], Chan Y. Cheah[4], Michael Roost Clausen[5], David Cunningham[6]

Characteristic	LBCL (*N* = 157)	Characteristic	LBCL (*N* = 157)
Age, years, median (range)	64.0 (20–83)	Age, years, median (range)	64.0 (20–83)
Age group, years, No. (%)		Age group, years, No. (%)	
<65	80 (51.0)	<65	80 (51.0)
65 to <75	48 (30.6)	65 to <75	48 (30.6)
≥75	29 (18.5)	≥75	29 (18.5)
Male sex, No. (%)	94 (59.9)	Male sex, No. (%)	94 (59.9)
Race, No. (%)		Race, No. (%)	
White	78 (49.7)	White	78 (49.7)
Asian	30 (19.1)	Asian	30 (19.1)
Black or African American	0	Black or African American	0
Other	6 (3.8)	Other	6 (3.8)
Not reported	43 (27.4)	Not reported	43 (27.4)
ECOG performance status,[a] No. (%)		ECOG performance status,[a] No. (%)	
0	74 (47.1)	0	74 (47.1)
1	78 (49.7)	1	78 (49.7)
2	5 (3.2)	2	5 (3.2)

Leukemia; https://doi.org/10.1038/s41375-024-02410-8

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Malignancy type, No. (%)	
DLBCL[b]	139 (88.5)
De novo	97 (61.8)
Transformed[c]	40 (25.5)
Unknown	2 (1.3)
High-grade B-cell lymphoma[b]	9 (5.7)
Primary mediastinal large B-cell lymphoma	4 (2.5)
Follicular lymphoma grade 3B	5 (3.2)
Central laboratory FISH analysis: double-hit/triple-hit lymphoma (*MYC* and *BCL2* and/or *BCL6* rearrangement), No. (%)	13 (8.3)
DLBCL cell of origin per local laboratory, No. (%)	
Germinal center B cell	65 (41.4)
Activated B cell/non-germinal center B cell	56 (35.7)
Unknown	18 (11.5)

Ann Arbor stage, No. (%)	
I/II	39 (24.8)
III	22 (14.0)
IV	96 (61.1)
IPI, No. (%)	
0–2	55 (35.0)
≥3	83 (52.9)
Unknown	1 (0.6)
Not applicable	18 (11.5)
Time from initial diagnosis to first dose of epcoritamab, years, median (range)[d]	1.6 (0.0–28.4)
Time from end of last therapy to first dose of epcoritamab, months, median (range)	2.4 (0–153)
Prior lines of antilymphoma therapy, median (range)	3.0 (2–11)
Prior lines of antilymphoma therapy, No. (%)	
2	47 (29.9)
3	48 (30.6)
≥4	62 (39.5)
Primary refractory disease,[e] No. (%)	95 (60.5)

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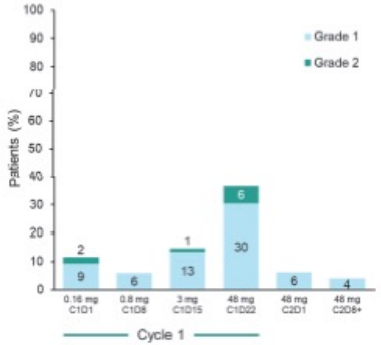
Characteristic	LBCL (*N* = 157)
Refractory to last systemic therapy,[e] No. (%)	130 (82.8)
Refractory to ≥2 consecutive lines of therapy,[e] No. (%)	118 (75.2)
Prior autologous stem cell transplant, No. (%)	31 (19.7)
Relapsed within 12 months after prior autologous stem cell transplant, No. (%)	18 (11.5)
Prior CAR T-cell therapy, No. (%)	61 (38.9)
Progressed within 6 months of CAR T-cell therapy, No. (%)	46 (29.3)



Dose escalation*

Expansion part

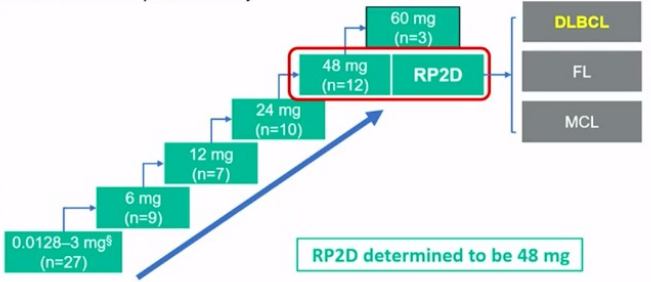
Flat-dose epcoritamab administered in 28-day cycles until disease progression or unacceptable toxicity

Objectives

Primary
- Maximum tolerated dose (MTD)
- Recommended Phase II dose (RP2D)

Secondary
- Safety/tolerability
- Anti-tumor activity

Inclusion criteria†
- Adults with R/R CD20+ B-NHL
- Prior treatment with anti-CD20 mAbs
- ECOG PS 0–2
- Measurable disease by CT, MRI, or PET/CT scan‡
- Adequate renal, liver, and hematologic function



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Overall response, No. (%) [95% CI][a]	99 (63.1) [55.0–70.6]
CR	63 (40.1) [32.4–48.2]
PR	36 (22.9) [16.6–30.3]
SD, No. (%)	5 (3.2)
PD, No. (%)	37 (23.6)
Nonevaluable,[b] No. (%)	16 (10.2)
DOR,[c] months, median (range) [95% CI]	17.3 (0.0+ to 27.8+) [9.7–26.5]
DOR in complete responders,[c] % (95% CI)	
Estimated pts remaining in response at 12 mo	85.7 (73.4–92.6)
Estimated pts remaining in response at 24 mo	64.4 (47.1–77.2)
Duration of CR,[c] % (95% CI)	
Estimated pts with CR remaining in CR at 12 mo	79.2 (65.5–87.9)
Estimated pts with CR remaining in CR at 24 mo	64.2 (47.5–76.8)

Time to response, months, median (range)	1.4 (1.0–8.4)
Time to CR, months, median (range)	2.6 (1.2–23.2)
PFS,[c] months, median (range) [95% CI]	4.4 (0.0+ to 29.0+) [3.0–8.8]
PFS in the overall population,[c] % (95% CI)	
Estimated PFS rate at 12 mo	39.9 (31.8–47.8)
Estimated PFS rate at 24 mo	27.8 (20.0–36.2)
PFS in complete responders,[c] % (95% CI)	
Estimated PFS rate at 12 mo	87.6 (75.6–93.9)
Estimated PFS rate at 24 mo	65.1 (48.4–77.6)
PFS in MRD-negative patients,[c] % (95% CI)	
Estimated PFS rate at 12 mo	84.3 (71.0–91.8)
Estimated PFS rate at 24 mo	61.6 (43.6–75.3)

OS,[c] months, median (range) [95% CI]	18.5 (0.3 to 32.7+) [11.7–27.7]
OS in the overall population,[c] % (95% CI)	
Estimated OS rate at 12 mo	58.0 (49.7–65.4)
Estimated OS rate at 24 mo	44.6 (36.4–52.4)
OS in complete responders,[c] % (95% CI)	
Estimated OS rate at 12 mo	95.1 (85.5–98.4)
Estimated OS rate at 24 mo	78.2 (65.4–86.7)
OS in MRD-negative patients,[c] % (95% CI)	
Estimated OS rate at 12 mo	94.4 (83.8–98.2)
Estimated OS rate at 24 mo	77.7 (64.1–86.7)

The ORR/CR rate per INR were 59% and 41%; mFU was 37.1 mo, mDOR was 20.8 mo, mDOCR was 36.1 mo. mPFS was 4.2 mo; among complete responders, it was 37.3 mo. mOS was 18.5 mo; among complete responders, it was NR. At 36 mo PFS of complete responders 63% of complete responders remained alive (estimated).
Vose; poster presentation ASH 2024 (abstract # 4480)

Leukemia; https://doi.org/10.1038/s41375-024-02410-8

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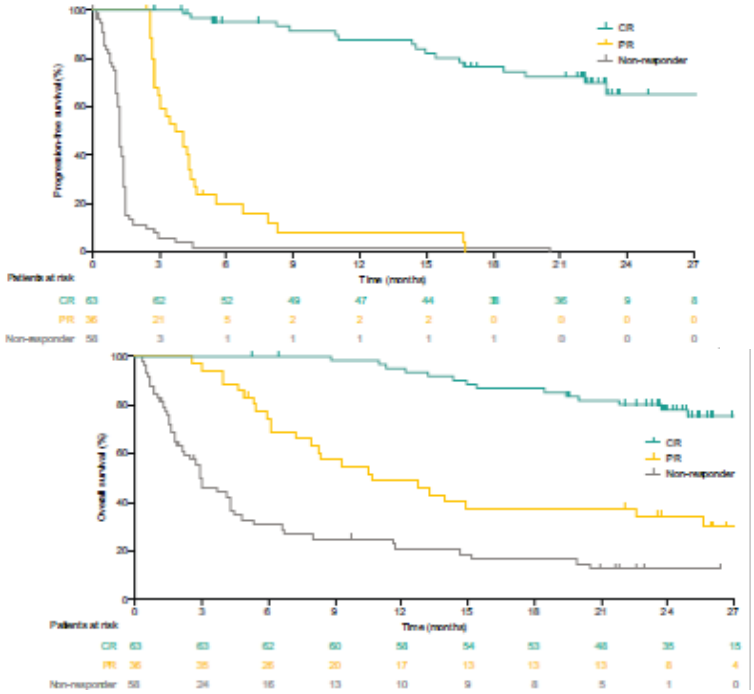
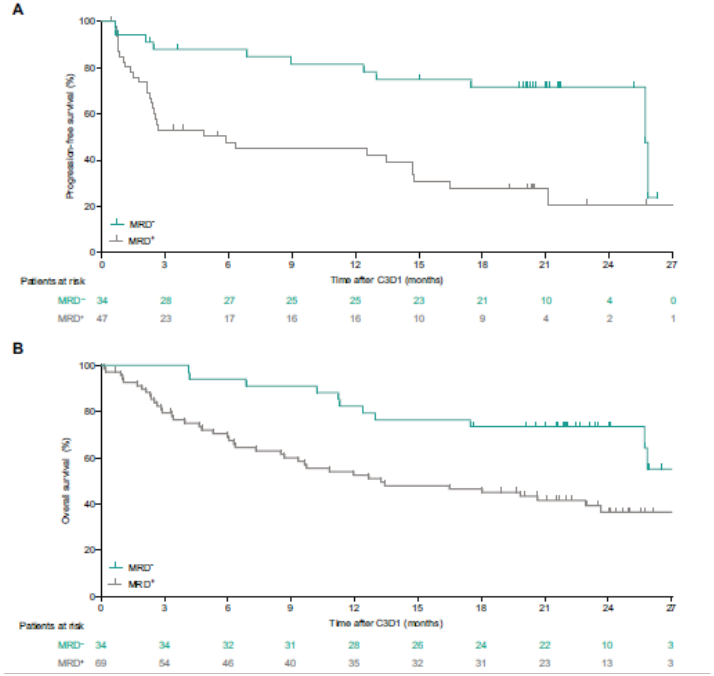




Leukemia; https://doi.org/10.1038/s41375-024-02410-8

Dual target dilemma: navigating epcoritamab vs. glofitamab in relapsed refractory diffuse large B-cell lymphoma

James A. Davis, Katelynn Granger, Alex Sakowski, Sara Goodwin, Amanda Herbst, Deidra Smith, Lindsey Hendrickson & Victoria R. Nachar

EXPERT REVIEW OF HEMATOLOGY
2023, VOL. 16, NO. 12, 915–918

	Epcoritamab	Glofitamab
Mechanism of action	CD20/CD3 BsAb	CD20/CD3 BsAb
FDA approval	After failure of two or more lines of systemic therapy	After failure of two or more lines of systemic therapy
REMS requirement	No	No
Boxed warning	CRS and ICANS	CRS
Recommended admission duration during dose step-up	24-hour hospitalization after cycle 1 on day 15 (first 48 mg dose)	24-hour hospitalization during and after step-up dose 1 (cycle 1, day 8)
Cycle length and dosing schedule	Cycle length: 28 days Cycle 1: SQ dose step-up: Day 1: 0.16 mg Day 8: 0.8 mg Days 15, 22: 48 mg Cycles 2–3: 48 mg SQ days 1, 8, 15, 22 Cycles 4–9: 48 mg SQ days 1, 15 Cycles 10+: 48 mg SQ day 1	Cycle length: 21 days Cycle 1: IV dose step-up Day 1: obinutuzumab 1000 mg Day 8: 2.5 mg over 4 hours Day 15: 10 mg over 4 hours Cycle 2: 30 mg over 4 hours Cycles 3–12: 30 mg over 2 hours
Treatment duration	Until disease progression or toxicity	Until disease progression, toxicity, or up to 12 cycles
Required pre-medications	Antipyretic and antihistamine are recommended during cycle 1. Dexamethasone 15 mg oral/IV or prednisone 100 mg is recommended during cycle 1 and for 3 days following dose for subsequent cycles if prior grade 2/3 CRS until CRS grade <2	Antipyretic and antihistamine are recommended for all cycles. Dexamethasone 20 mg IV is recommended for cycles 1–3 and subsequently if prior CRS.
Renal dose adjustment	No	No
Hepatic dose adjustment	No	No
Infection prophylaxis	PJP and consider herpes zoster	Consider PJP, herpes zoster, and CMV

Table 1. Comparison of available anti-CD20 bispecific antibodies for DLBCL.

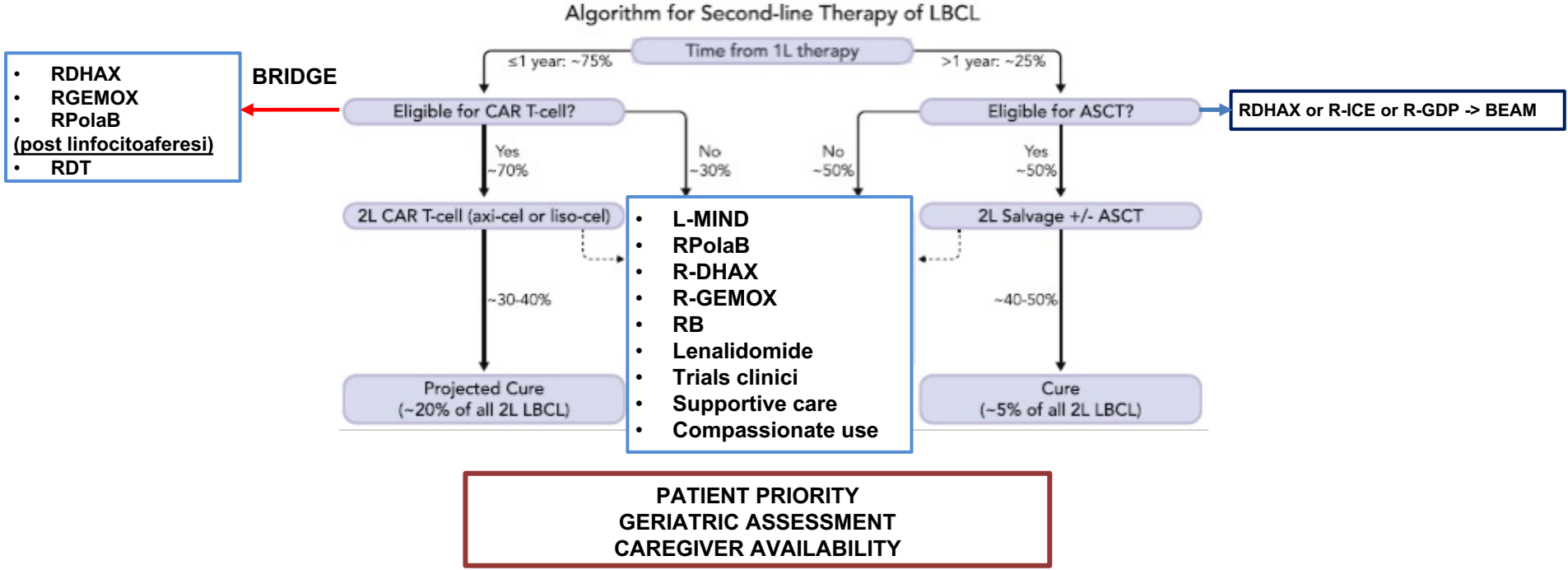
	Epcoritamab ($n = 157$)	Glofitamab ($n = 154$)
Baseline characteristics		
Median age (range)	64 years (20–83)	66 years (21–90)
Median prior lines (range)	3 (2–11)	3 (2–7)
Non-Hodgkin lymphoma subtype, %		
DLBCL, not otherwise specified	74	71
Transformed	28.8	18
High-grade BCL	5.7	7
Primary mediastinal BCL	2.5	4
ECOG PS ≥ 2, %	3.2	0
Ann Arbor stage, %		
I/II	24.8	22
III	13.4	20
IV	61.8	55
Missing data	0	2
International Prognostic Index, %		
0–2	35	Not reported
≥3	52.2	
Double/Triple hit per FISH analysis, %	13.1	Not reported
Prior ASCT, %	19.7	18
Prior CAR T-cell therapy, %	39	33
Primary refractory disease, %	61	58
Adverse events		
CRS, all (grade ≥3)	50% (2.5%)	63% (4%)
Median onset of CRS, duration	20 hours, 48 hours	13 hours, 30 hours
ICANS, all (grade ≥3)	6% (0.6%)	8% (3%)
Infections, all (grades 3–4)	45% (15%)	38% (15%)
Neutropenia, all (grade ≥3)	21.7% (14.6%)	38% (27%)
Thrombocytopenia, all (grade ≥3)	13.4% (5.7%)	25% (8%)
Tumor lysis syndrome, all (grade ≥3)	1.3% (1.3%)	Not reported (1.9%)
Grade 5 adverse event	5.7%	5%
Efficacy		
ORR	63%	52%
CR	39%	39%
MRD negativity rate	45.8%	Not reported
Median PFS	4.4 months (95% CI, 3–7.9)	4.9 months (95% CI, 3.4–8.1)
Median OS	NR (95% CI, 11.3–NR)	11.5 months (95% CI, 7.9–15.7)
Median time to best response (range)	2.7 months (1.2–11.1)	1.4 months (95% CI, 1.4–1.44)
Median duration of response (range)	12 months (0–15.5)	18.4 months (95% CI, 13.7–NR)

Long-Term Efficacy and Safety of Odronextamab in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Pooled Analysis from the ELM-1 and ELM-2 Studies

Allan JN ; poster presentation ASH 2024 (abstract # 3118)

- Odronextamab IV/21. Rump-up con profilassi steroidea in corso del C1 seguito da 160 mg on G1, 8, e 15 del C2. Mantenimento: 320 mg/2 sett fino a progressione/tossicità. Pazienti in CR oltre 9 m passano a mantenimento ogni 4 sett.
- 187 pts; età media 65 aa.. (24–88); in media 3 linee precedenti, 32,1% post-CART. mFU: 23 m.
- ORR/CR per ICR: 50% e 31,6%, mDOR 10.5 mo, mDoCR: 36,6 mo, probabilità di mantenere CR a 36 m 51.0%
- CRS (52,9%), anemia (35,8%), iperpiressia (39,6%). ICANS solo 1 pt (Gr 2), infezioni >G3 24,6%.

CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Westin J and Sehn LH. Blood 2022;139(18):2737-46



LE OPZIONI PER APPROVAZIONE AIFA

Tx	I LINEA	II LINEA		III LINEA	
		<65-70	>70-75	<65-70	>70-75
Pola	✓R-Pola-CHP DLBCL IPI 3-5	✓ R-Pola Bendamustina DLBCL R/R e non idonei a ASCT tranne PRECEDENTE CAR T entro 100 gg e risposta a precedente Benda > 12 m,			
ASCT	✗	✓	✗	✓	✗
Axicel	✗	✓ DLBCL e HG NHL refrattario entro 12 m o R/R >2L			
Lisocel	✗	✗	✗	✓ DLBCL e HG NHL in R/R >2L, PMDLBCL	
Tisacel	✗	✗	✗	✓ DLBCL incluso HG NHL in recidiva o refrattario >2L	
Tafasitamab	✗	✓ DLBCL R/R e non idonei a ASCT tranne HG, PMDLBCL, > 3 linea, PRECEDENTE CAR T o altri trattamenti anti-CD19, localizzazione SNC, diatesi trombofilica			
Loncastuximab	✗	✗	✗	✓ DLBCL NOS, HG e trasformati tranne CD19 non espresso dopo terapia anti-CD19, GVHD, Bulky localizzazione SNC, neuropatia > G1	
Glofitamab	✗	✗	✗	✓ DLBCL NOS dopo la II linea tranne <100 gg da ASCT, precedente terapia con bispecifico, precedente AlloSCT, coinvolgimento SNC HLH o leucoencefalopatia multifocale progressiva (solo Glofitamab), Malattia autoimmune che richiede immunosoppressione permanente (solo Epcoritamab), ClCr <30 ml/min, Child-Pugh B e C	
Epcoritamab	✗	✗	✗		

CONCLUSIONI e UNMET NEED

- Implementare la diagnostica molecolare in particolare per HG-NHL.
- Il piano di cura nelle varie fasi e nel «lungo» termine deve comprendere le valutazioni di concomitanti rimborsabilità AIFA anche in funzione dell'andamento clinico (es. PET dopo il IV ciclo e/o entro i 12 mesi).
- compatibilmente con età, comorbidità, logistica, disponibilità del caregiver, patient priority.
- seguire l'evoluzione dei processi registrativi per le singole opzioni e/o associazioni terapeutiche.
- quali opzioni per DLBCL RR over 75 aa. e/o unfit to ASCT/CART dopo la 1L?
- disponibilità trials attivi con arruolamento aperto, usi compassionevoli.
- **RUOLO dei CENTRI HUB della REV anche come attività di COUNSELING ???**