Società Italiana di Ematologia

Convegno Interregionale SIE
Delegazione Triveneto

NUOVE TERAPIE NEI LINFOMI B AGGRESSIVI E NEL MIELOMA MULTIPLO

Terapia di salvataggio dei pazienti non eleggibili a CAR-T o bispecifici

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CRO Aviano (PN) - 9 ottobre 2024

Convegno Regionale SIE

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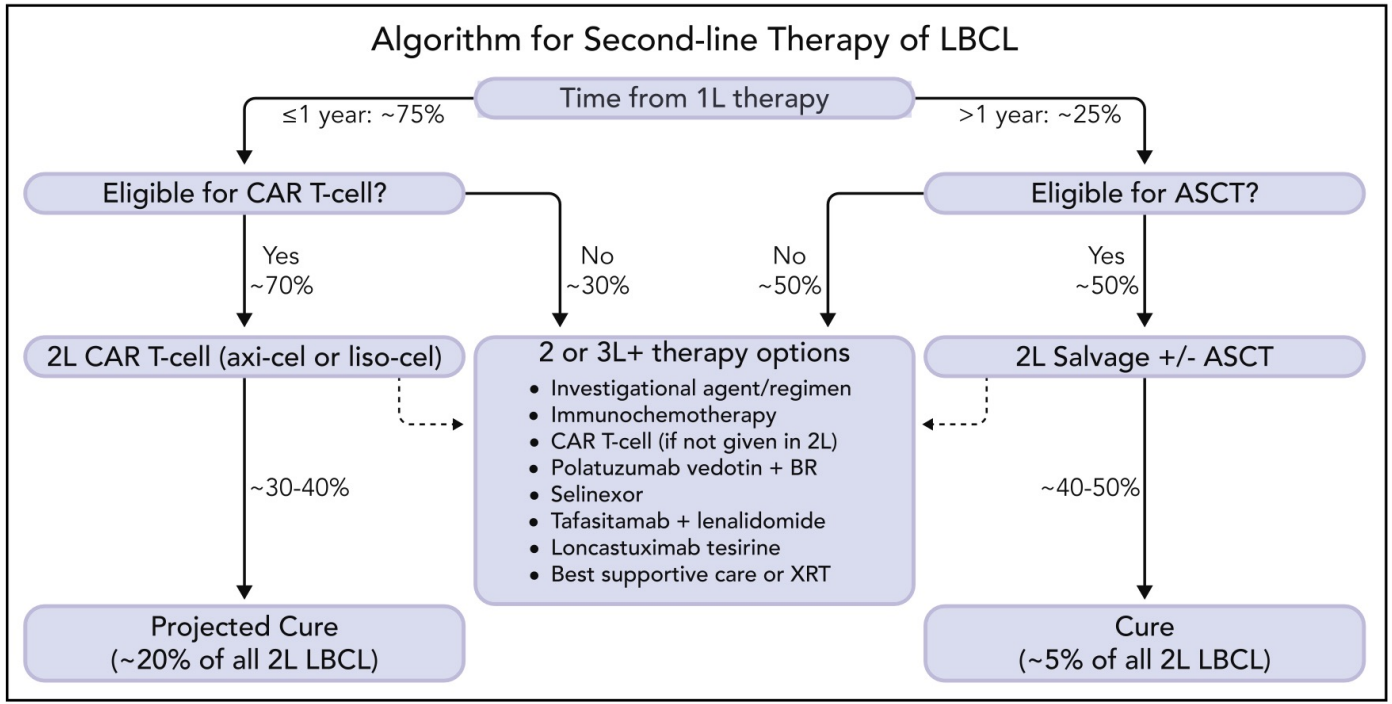
Takeda							
Janssen							
Bejgene							+
Incyte						+	+

Current algorythm for R/R LBCL



Westin and Sehn, Blood, 2022

Therapeutic options for R/R DLBCL/LBCL available in Italy (late 2024)

2L+	• SALVAGE IMMUNO-CHEMO (HDT-ASCT, R-BENDA, R2, R-GEMOX, PIXANTRONE) • CAR-T • R-TAFASITAMAB-LENALIDOMIDE • R-POLA-BENDA
3L+	• BiSpAb: GLOFITAMAB, EPCORITAMAB • LONCASTUXIMAB TESIRINE

In red = new options

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Exclusion criteria for T-cell engaging therapies: Bispecific and CAR-T (AIFA)

	Age	Istotype	Life Expectancy	ECOG	CD19 or CD20 status	Hb	WBC	PLT	AST/ALT Bilirubin Liver function	Renal eGFR	CNS disease	Heart/Lung f(x)
CAR-T	>75	Richter	<12 weeks	≥2	CD19-	<80g/L	ANC <1000/mm3	<75000/mm3	>2.5 fold >1.5 mg/dL		+	LVEF<50% IMA Heart disease within 12 months
Axi Cel							ALC <100/mm3			<60 ml/min		
Tisa Cel							ALC <300/mm3			<30 ml/min		
Liso Cel							ALC <300/mm3			<30 ml/min		
Bispecific Abs	<18											
Glofitamab Epcoritamab	-	Other than DLBCL, NOS	-	≥1 (Glofi) ≥2 (Epco)	CD20-	-	-	-	Liver insufficiency moderate/severe	<30 ml/min	-	NYHA III-IV, angina instabile, angioplastica coronarica IMA entro i sei mesi precedenti, aritmia atriale o ventricolare non controllata, o altra grave malattia cardiovascolare o polmonare cronica

De-escalation of Therapy Intensity in the allocation of R/R (>1 LOT) DLBCL Patients based on age, fitness and comorbidity

- ASCT
- CAR-T
- Allo-SCT

- Young < 75 years (CAR-T) or < 70 years (ASCT)
- Fit
- No/very mild comorbidities

- Bispecific Antibodies (3L+)
- Tafa-Lenalidomide (2L+)
- R-POLA-B (2L+)
- Loncastuximab Tesirine (3L+)
- Immuno-chemotherapy standard intensity

- Older (> 70 or 75 years)
- Unfit
- Mild/moderate comorbidities
- No adequate support (care giver) or compliance

- Immunochemotherapy low/moderate intensity
- Tafa-Lenalidomide (2L+)
- Loncastuximab Tesirine (3L+)

- Older (> 80 years)
- Frail
- Severe comorbidities

Salvage Chemotherapy

Reference	Therapy	Study type	N patients	ORR (CR)	PFS	OS
Cazelles et al, Leuk & Lymph, 2021	**R-GemOx**	Retrospettivo	196	38% (33%)	mPFS 5 mesi (mPFS se CR 22 mesi)	mOS 10 mesi (mOS se CR 40 mesi)
Mounier et a. Haematologica 2013l	**R-GemOx**	Fase II	48	46% (38%)	PFS a 5 anni 13%	OS a 5 anni 14%
Vacirca et al, Ann Hematol, 2014	**R-Bendamustina**	Prospettico	61	45.8% (15.3%)	mPFS 3,6 mesi	mOS NR (per alto tasso di uscita)
Pettengel et al, Br J Haemat, 2016	**Pixantrone**	Fase 3	97	30% (20%)	mPFS 3,5 mesi	mOS 7,5 mesi (considerando solo terza e quarta linea)
Wang et al, Leukemia, 2013	**Lenalidomide**	Fase 2	45	33% (13%)	mPFS 3,7 mesi	mOS 10,7 mesi

Factors affecting outcome upon immuno-chemotherapy

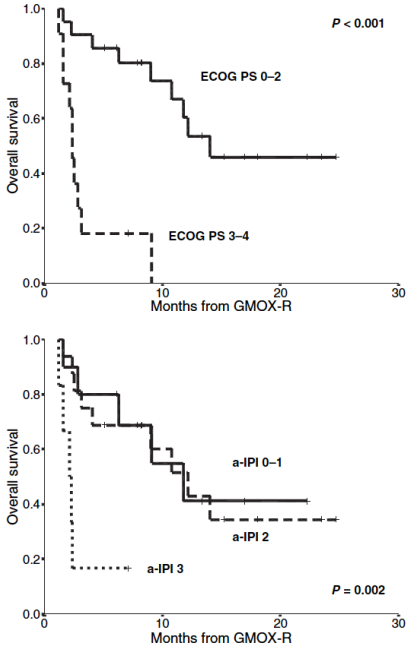


Figure 2 Prognostic factor influencing overall survival.

Lopez et al 2007

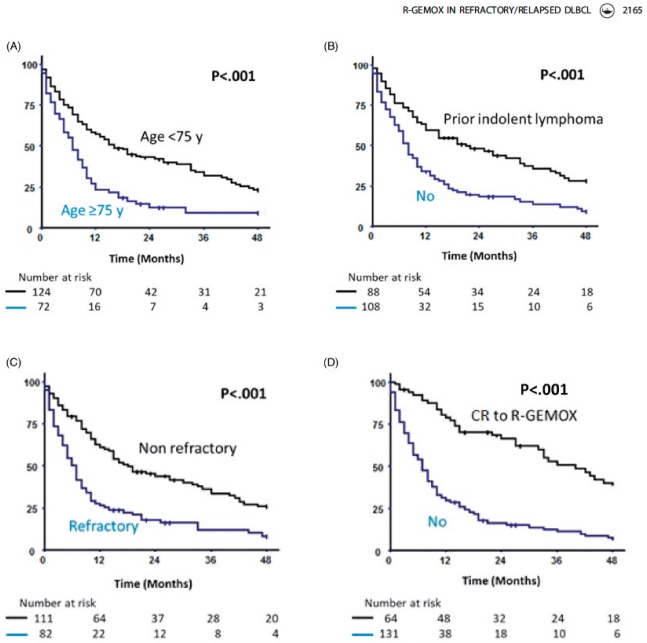


Figure 3. Overall survival according to select patient characteristics. (A) Age, <75 years; median: 16 months; mean: 75 years; median: 7 months. (B) Prior history of indolent disease, Yes; median: 21 months, No; median: 8 months. (C) Refractory to previous therapy, No; median: 7 months, Yes; median: 18 months. (D) Response to R-GemOx, Complete response; median: 40 months, Less than complete response; median: 7 months.

Cazelles et al 2021

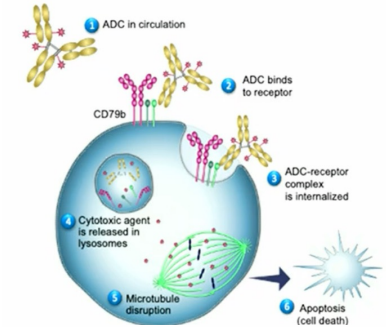
Salvage Chemotherapy + anti CD79b ADC

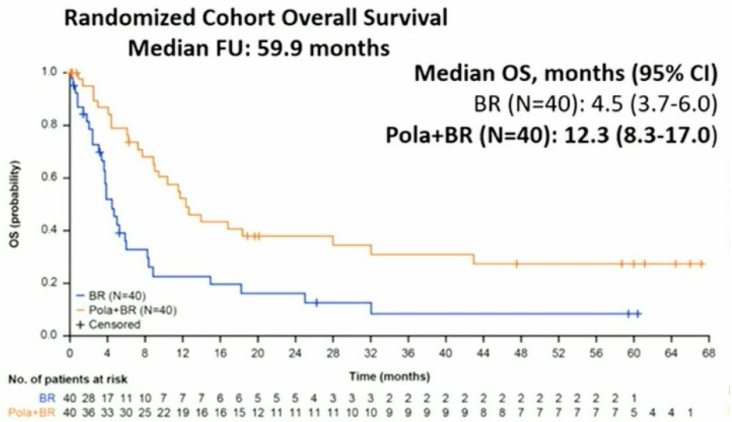
Polatuzumab Rituximab Bendamustine

ADC anti-CD79b + drug payload monometil auristatine E

Activity also as **single agent → ORR 56%, CR 16%**
(Palanca-Wessel et al, Lancet Onc., 2015)
or in association to R → **ROMULUS ORR 54%, CR 21%**
(Morschhauser et al, Lancet Haem., 2019)

Phase II study **GO29365** R-Pola-Benda vs R-Benda:
ORR (CR): 45% (40%) vs 17.5% (17.5%)
mPFS: 9.7 vs 3.7 months
mOS: 12.3 vs 4.5 months





FDA and EMA approved from II line of therapy in DLBCL not transplant eligible.

Sehn et al, Blood, 2022

Polatuzumab Rituximab Bendamustine

Dati di **real-life** americani ed europei – derivanti da coorti di pazienti fortemente pretrattati, talora anche già sottoposti a CAR-T - confermano le percentuali di risposta e le curve di sopravvivenza degli studi clinici:

ORR (CR): 31-61% (10-40%)
mPFS: 2 mesi - NR
mOS: 5.3 mesi - NR

Tuttavia il nostro ente regolatore ci impone delle limitazioni:
→ **Non prescrivibile** in linfomi indolenti **trasformati** o **LF G3b**
→ Possibile somministrazione post CAR-T, ma **dopo minimo 100 giorni**
→ Non prescrivibile **post allo-SCT**

Tossicità any grade: prevalentemente **ematologica e infettiva**.
Tossicità G3-4: neutropenia e neuropatia periferica.

Smith et al, Clin Lymphoma Myeloma Leukemia, 2021; Segman et al, Leuk Lym, 2021; Liebers et al, Blood Adv, 2021; Northend et al, Blood Adv, 2022; Vodicka et al, EJH, 2022; Dimou et al, Hemat Oncol, 2021

Anti-CD19 naked mAb

Tafasitamab Lenalidomide

Anticorpo anti-CD19 **ingegnerizzato** → aumento dell'affinità per FcγRII-IIIa mediamente x40 → **aumento di ADCC e ADCP**

Limitata - seppure presente- attività **come single-agent (ORR 25.7%, CR 5.7%)**

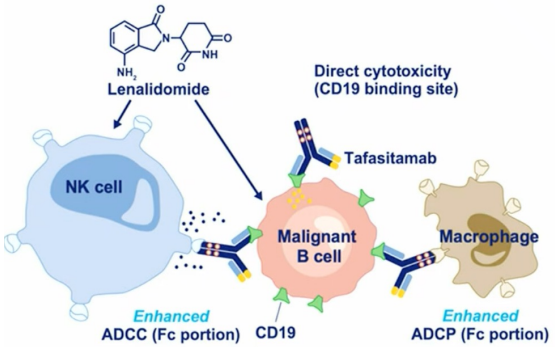
Studio di fase II **L-MIND** – inclusi DLBCL R/R non eleggibili ad ASCT **(50% aveva ricevuto 1 linea e 43% 2 linee di CT)**, **primary refractory sono stati esclusi**

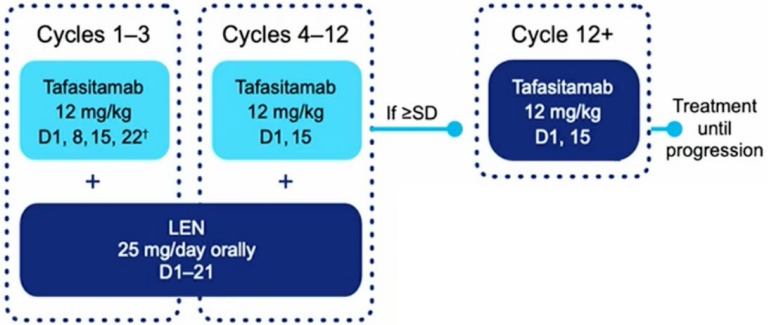
Somministrazione: ev, durata indefinita fino a progressione o intolleranza

Outcome: **ORR 47%, CR 32%** dopo 2 linee di CT

ORR 67%, CR 47% dopo 1 linea di CT

mDOR NR, **mPFS 11.6 mesi, mOS 33.5 mesi**





FDA and EMA approved from II line of therapy in DLBCL not transplant eligible.

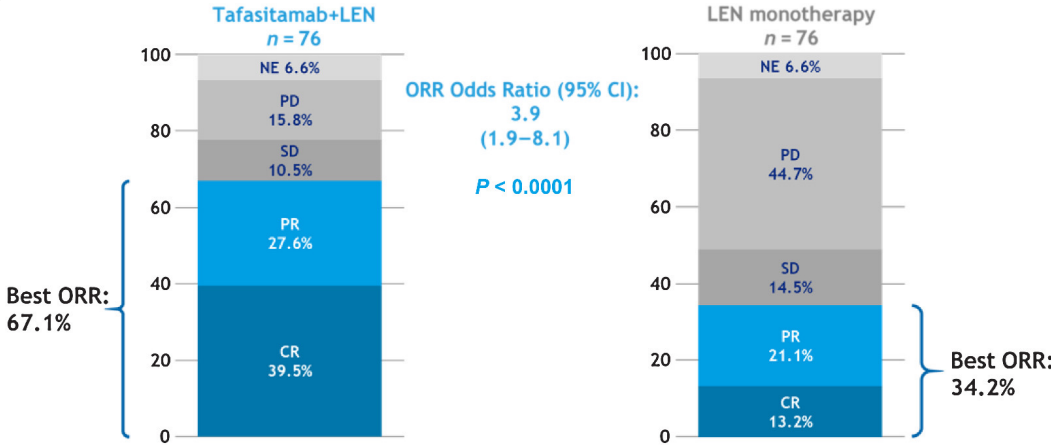
Duell et al, Hemasphere, 2023

REMIND: confronto indiretto (propensity score) tra L-MIND e coorte real-life di pazienti trattati con Lenalidomide (monoterapia)

REMIND2: confronto con BR, R-GemOx, Pola-B-R, R-Lena, CAR-T →

Tafa-Len **appare superiore in termini di mOS e mPFS a tutti questi regimi, con l'eccezione dei CAR-T**

(Nowakowski et al, Clin Canc Res, 2022)
(Nowakowski et al, Ann Hematol, 2023)



DATI DI REAL LIFE (US):

Series	N	Prior Therapies Median (Range)	IPI 3-5	Prior ASCT	Prior CART	mFU (months)	ORR (CR)	mPFS (months)
L-MIND	80	2 (1-4)	51%	11%	0%	65.6	56.2% (40%)	**11.6**
Real-World	82	2 (0-11)	**79%**	15%	**21%**	NR	27% (17%)	**2.8**

Zinzani et al, Clin Cancer Res, 2021
Qualls et al, Blood, 2022

Dati real-life Triveneto (fino a Nov 2023)

Convegno Regionale SIE

Features of the Patients Population of the NORTHEAST ITALY: Comparison with that of L-MIND Study

		All patients NORDEST n(%)	All patients L-MIND STUDY n(%)	*1 pLoT NORDEST* n(%)	1 pLoT L-MIND STUDY n(%)	*≥2 pLoT NORDEST* n(%)	≥2 pLoT L_MIND STUDY n(%)
N		**35**	80	**14 (40)**	40 (50)	**21 (60.0)**	40 (50)
Median age, years (range)		**75.0 (29.0–89.0)**	72.0 (41.0–86.0)	**79.5 (70.0–84.0)**	72.0 (53.0–86.0)	**72.5 (29.0–89.0)**	70.5 (41.0–82.0)
Age >70 years, n (%)		**29 (82.8)**	45 (56.2)	**12 (85.7)**	25 (62.5)	**12 (57.1)**	20 (50.0)
Sex, n (%)	Female Male	**14 (40.0)** **21 (60.0)**	37 (46.2) 43 (53.8)	**5 (35.7)** **9 (64.2)**	19 (47.5) 21 (52.5)	**9 (42.8)** **12 (57.1)**	18 (45.0) 22 (55.0)
Ann Arbor stage, n (%)	I–II III–IV	**10 (28.6)** **25 (71.4)**	20 (25) 60 (75)	**2 (14.2)** **12 (85.7)**	11 (27.5) 29 (72.5)	**8 (38.0)** **13 (61.9)**	9 (22.5) 31 (77.5)
IPI score, n (%)	0–2 3–5	**10 (28.5)** **25 (71.4)**	40 (50) 40 (50)	**1 (7.2)** **13 (92.8)**	25 (62.5) 15 (37.5)	**9 (42.8)** **12 (57.1)**	15 (37.5) 25 (62.5)
Primary refractory*, n (%)	Yes No	**13 (37.1)** **22 (62.8)**	15 (18.8) 65 (81.2)	**6 (42.8)** **8 (57.2)**	6 (15.0) 34 (85.0)	**7 (33.3)** **14 (66.7)**	9 (22.5) 31 (77.5)
Refractory to previous therapy line, n (%)	Yes No	**16 (45.7)** **19 (54.3)**	35 (43.8) 45 (56.2)	**3 (21.4)** **11 (78.6)**	6 (15.0) 34 (85.0)	**13 (61.9)** **8 (38.1)**	29 (72.5) 11 (27.5)
Prior ASCT, n (%)	Yes No	**2 (5.7)** **33 (94.3)**	9 (11.2) 71 (88.8)	**1 (7.1)** **13 (92.8)**	2 (5.0) 38 (95.0)	**1 (5.0)** **20 (95.0)**	7 (17.5) 33 (82.5)

Number of previous lines of therapy (median) = 3 (range 1-7)

*progression during or within 6 months after completing their first line of therapy

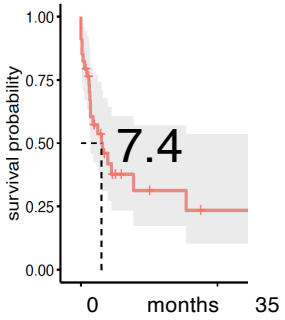
Bulky disease (>=10 cm) = 11/35 (**31.4% vs 19%**)
DHL/THL = 2/35 (**5.7%**)
Previous CAR-T = 0/35 (0%)

Piazza F, Scapinello G, Danesin N et al. unpublished

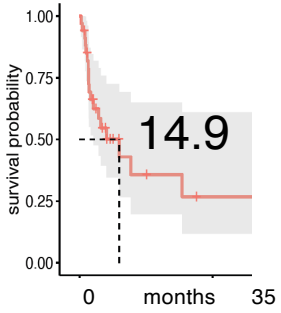
Efficacy

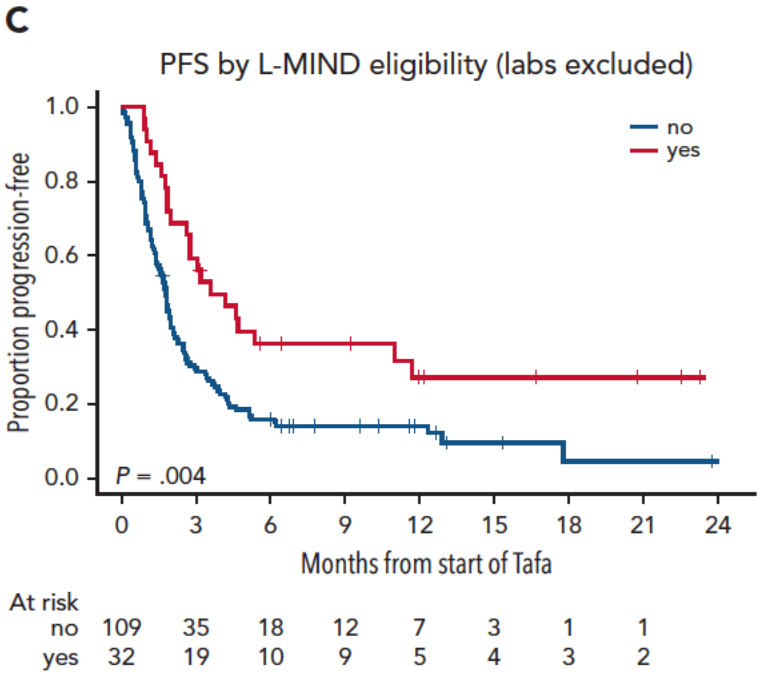
Patients	ORR (%)	CR (%)	PR (%)
TOTAL (n=35)	19/35 **(54.2%)**	9/35 **(25.7%)**	10/35 **(28.6%)**
• 1pLoT (n=13)	7/14 **(53.8%)**	3/14 **(23.0%)**	5/14 **(38.4)**
• ≥2 pLoT (n=22)	12/21 **(54.5%)**	7/21 **(31.8%)**	5/21 **(22.7%)**

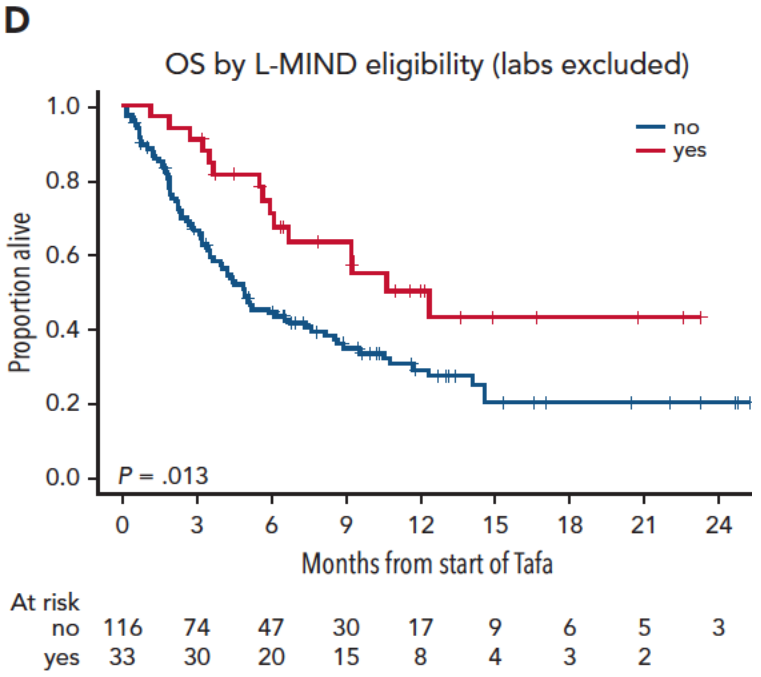
median PFS = 7.4 months (IC 95% 3.4 - NA)



median OS = 14.9 months (IC 95% 5.2 - NA)







Qualls et al, Blood, 2022

905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

Tafasitamab for the Treatment of Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) in the US Real-World Setting

Kimberly Saverno, PhD[1], Kristin M. Zimmerman Savill[2], Bruce Feinberg[2], John Galvin[1], Prathamesh Pathak[2], Sarah Gordon[2], Theresa Amoloja[1], Mae Llorente[1], Narendranath Epperla, MDMS[3], Loretta J. Nastoupil, MD[4]

[1]Incyte Corporation, Wilmington, DE
[2]Cardinal Health, Dublin, OH
[3]The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH
[4]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

	All Patients (N=181)	Tafasitamab Received in 2L (n=130)	Tafasitamab Received in 3L (n=43)
Disease response			
Disease response available, n (%)	168 (92.8)	123 (94.6)	39 (90.7)
rwORR (95% CI), %	75.6 (69.1-82.1)	79.7 (72.6-86.8)	64.1 (49.0-79.2)
rwCRR (95% CI), %	18.5 (12.6-24.3)	21.1 (13.9-28.4)	10.3 (0.7-19.8)

«Findings from this real-world analysis support the clinical beneit of tafa when used in early lines of treatment for R/R DLBCL, as demonstrated in L-MIND.»

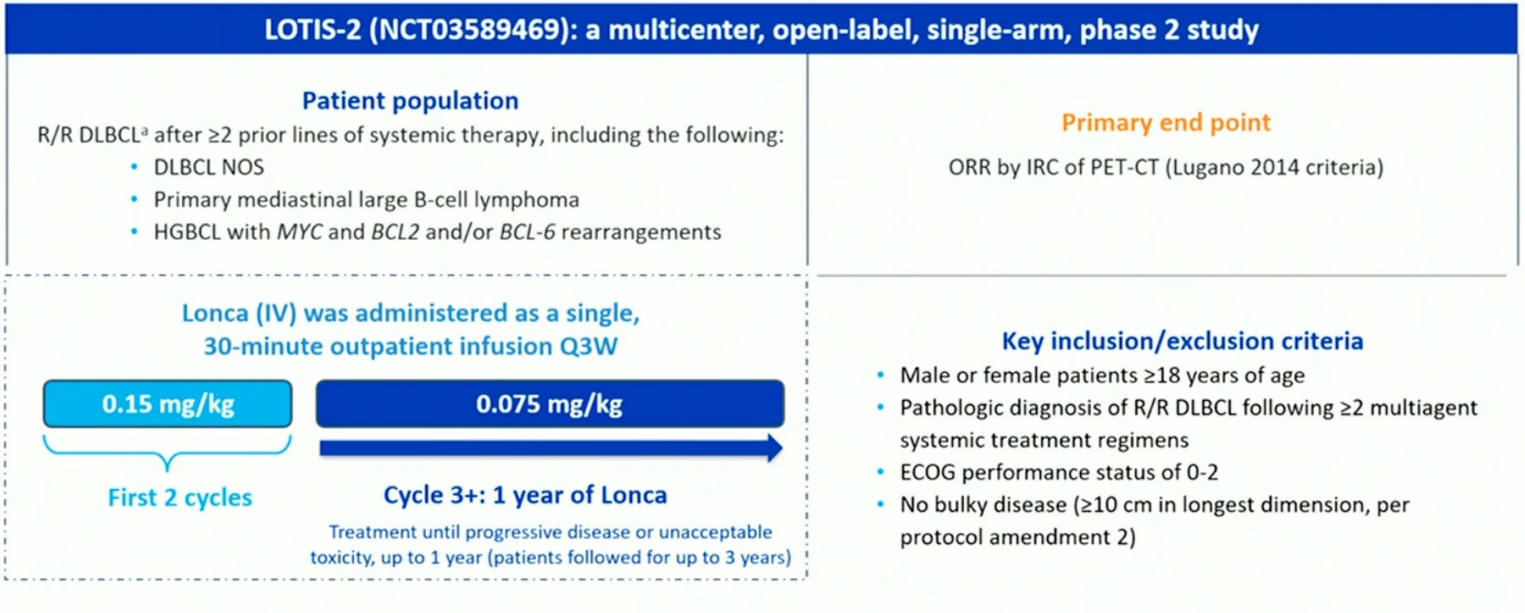
Saverno K et al. ASH 2023

Anti-CD19 ADC

Loncastuximab tesirine

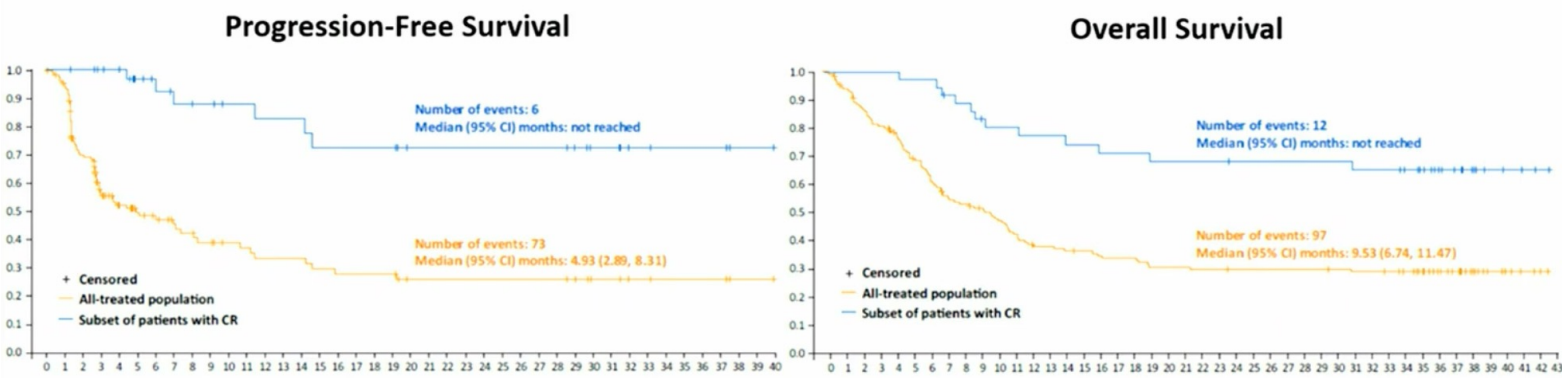
Antibody drug conjugate anti-CD19 + drug payload pirrolobenzodiazepine

Approved after 2 or more lines in **DLBCL AND HGBCL (including MYC and BCL2 or BCL6 translocated)**



Caimi et al, 17th ICML, 2023

«68 (47%) of 145 patients received subsequent therapy after loncastuximab tesirine treatment, including nine **(6%)** patients who had subsequent **HSCT, autologous** (five [**3%**]) **or allogeneic HSCT** (four [**3%**]) as consolidation therapy. 15 (**10%**) of 145 patients received subsequent **CD19-directed CAR T-cell therapy**. Investigator-assessed overall response rate to CAR T-cell therapy after loncastuximab tesirine was 47% (seven of 15 patients), of whom six (40%) had complete response»



Caimi et al, 17° ICML, 2023

Table 2. Summary of efficacy.

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

Caimi P et al Haematologica 2024

Therapy	Study type	N patients	Median age	Primary Refractory (%)	ORR (CR) (%)	DOR median (months)	PFS median (months)	OS median (months)	Tossicità
Rituximab Polatuzumab Bendamustine	Phase 1b/2 randomized -single arm	6+80+106	70	64	62% (52%)	9.5	6.6	12.3	Neutropenia Peripheral Neuropathy
Tafasitamab Lenalidomide	Phase 2 single arm	81	72	19	60% -57.5% (43%-41.3%)	n.r.	24	n.r	Diarrhea Rash Neutropenia
Loncastuximab Tesirine	Phase 2 single arm	145	66	20	48.3% (24.8%)	13.4	4.9	9.5	Neutropenia Peripheral edema Rash

Sehn L et al.
JCO 2020 Blood 2022

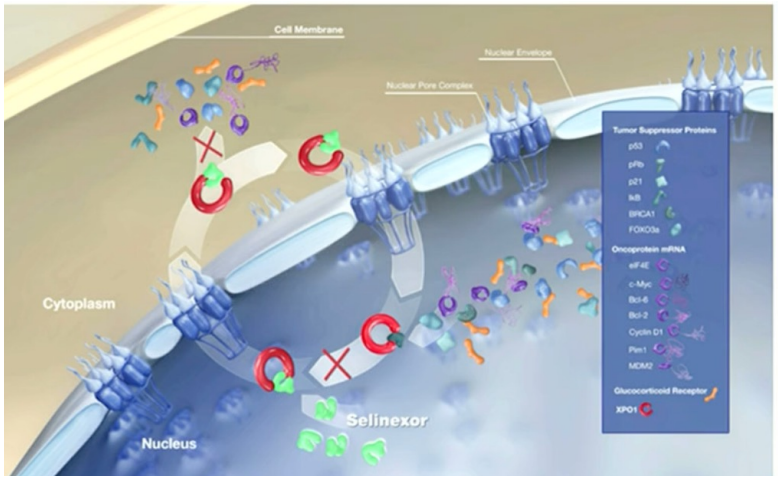
Duell J et al Lancet Hematol 2020
Duell J et al. Haematologica 2024
Caimi PF et al. Lancet Oncol 2021
Caimi PF et al.Haematologica 2024

	CAR-T	Glofitamab	Epcoritamab
ECOG PS >1	blocca	blocca	Blocca se >2
Heart **insufficiency (NYHA 3-4)**	blocca	blocca	blocca
Renal **insufficiency**	blocca	blocca	blocca
Liver **insufficiency (Child-Pugh B-C)**	blocca	blocca	blocca
Bulky **disease (≥10 cm)**			
Neuropatia > G1			
Previous **thromboembolism**			
αCD19 therapies	blocca		
Loss of CD19 after **αCD19 therapies**	blocca		
tFL/**tiNHL/FLG3B**		Blocca ?	Blocca ?
HGBCL DHL/THL		blocca	blocca

Not approved therapies (Italy)

Exportin 1 inhibitor - Selinexor

XPO1 inhibitor → blocks exportin 1 (nuclear membrane transporter) causing increase levels of nuclear tumor suppressor and subsequent apoptosis



- Phase 1 (NHL-B): ORR 32% e CR 10%
- **SADAL trial** (KCP-330-009; NCT02227251), a multicenter, single-arm, phase II open-label trial in patients with DLBCL after 2 to 5 systemic regimens.
- Patients received selinexor 60 mg orally on days 1 and 3 of each week until PD or intolerance

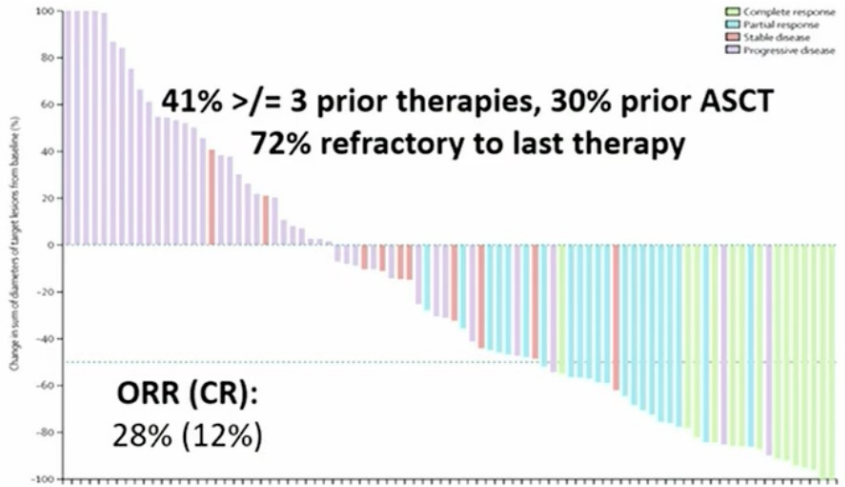
Approvato FDA a partire dalla III linea per DLBCL, NOS

Kalakonda et al, Hemat Oncol, 2020

Kalakonda et al, Lancet Hemat, 2020

Selinexor - efficacy

- In 134 patients, the **ORR was 29%** (95% CI: 22, 38), with **complete response in 13%.**
- medianOS 9 months
- Of the 39 patients who achieved a partial or complete response, 38% had response durations of at least 6 months and 15% had response durations of at least 12 months.
- **Median OS in CR/PR 29.7 months**



Kalakonda et al, Hemat Oncol, 2020
Kalakonda et al, Lancet Hemat, 2020

Selinexor - safety

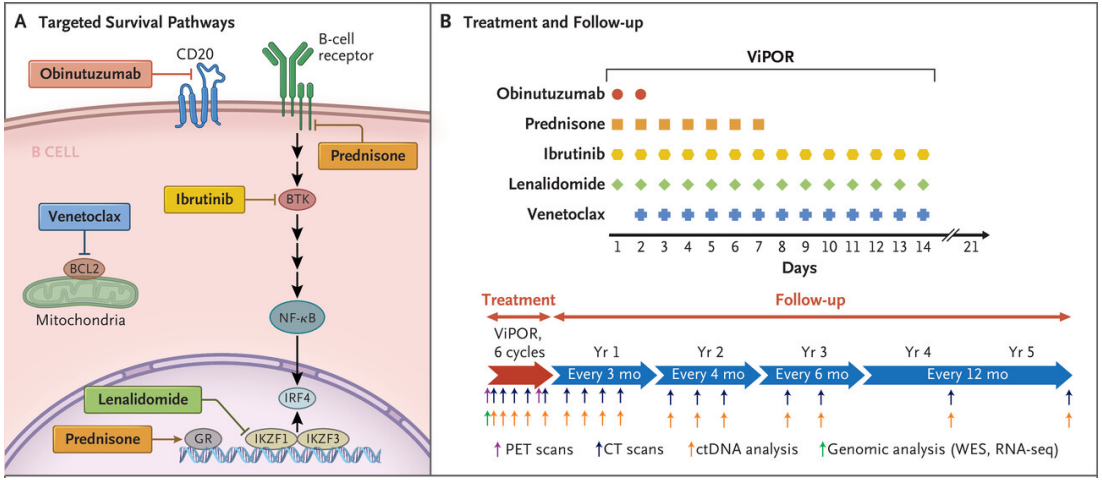
- Incidence ≥20%: **fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia**.
- Grade 3-4 laboratory abnormalities in ≥15%:**thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia**.
- Serious adverse reactions in 46% of patients, most often from **infections**.
- **Thrombocytopenia** was the leading cause of dose modifications.
- **Gastrointestinal toxicity** developed **in 80%** of patients and any grade
- **Hyponatremia** developed in **61%**.
- **Central neurological adverse reactions** occurred in **25%** of patients, including dizziness and mental status changes.

What's going on?

- No bispecifics
- No CAR-T

ViPOR Study

Features
Phase 1b/2 R/R NHL
DLBCL 83%
ECOG score ≥2 14%
IPI≥3 68%
Primary Refractory 60%
Preious ASCT 10%
Previous CAR-T 40%



Melani C et al. NEJM 2024

Efficacy

ORR 54%

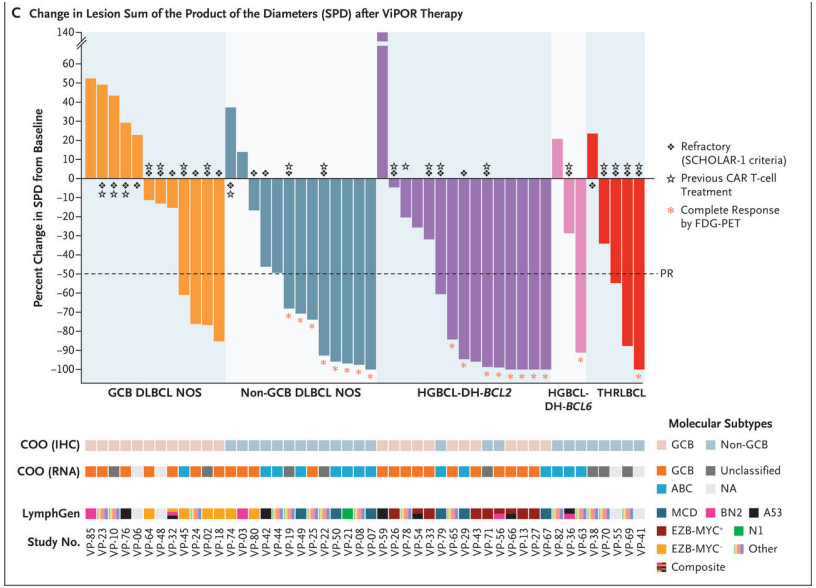
CRR 38%

Better non-GCB (CRR 62%) and HGBCL-DHL (CRR 53%)

Table 2. Response and Survival.

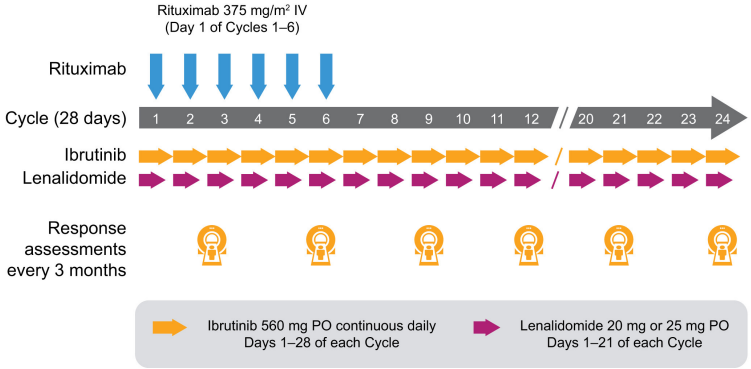
Variable	Overall Response	Complete Response	Progression-free Survival at 2 yr	Overall Survival at 2 yr
	no./total no. (%)		*% (95% CI)*	
All DLBCL	26/48 (54)	18/48 (38)	34 (21–47)	36 (23–49)
Histologic type				
Non-GCB DLBCL NOS	8/13 (62)	8/13 (62)	39 (14–63)	39 (14–63)
HGBCL-DH-*BCL6*	1/3 (33)	1/3 (33)	33 (1–77)	33 (1–77)
THRLBCL	3/5 (60)	1/5 (20)	40 (5–75)	40 (5–75)
GCB DLBCL NOS	4/12 (33)	0/12 (0)	8 (1–31)	17 (3–41)
HGBCL-DH-*BCL2*	10/15 (67)	8/15 (53)	47 (23–68)	47 (23–68)
Line of therapy				
Second-line therapy	12/15 (80)	11/15 (73)	60 (32–80)	60 (32–80)
Third-line therapy or later	14/33 (42)	7/33 (21)	23 (11–38)	25 (13–41)
Transformed lymphoma	7/15 (47)	5/15 (33)	29 (11–51)	28 (10–51)
Previous CAR T-cell therapy	9/20 (45)	4/20 (20)	30 (12–50)	30 (12–50)
Refractory disease*	12/27 (44)	5/27 (19)	21 (8–37)	24 (11–41)

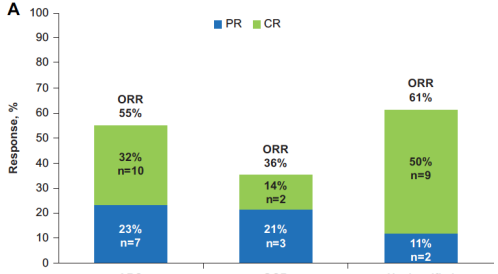
* Refractory disease was determined according to criteria from the SCHOLAR-1 study.[9]

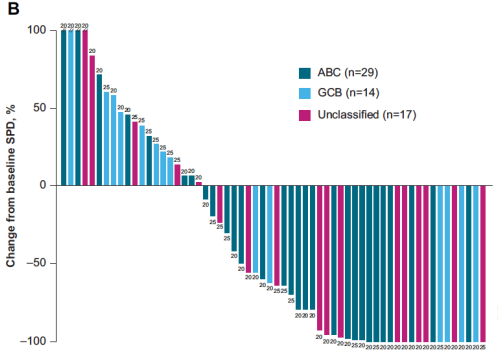


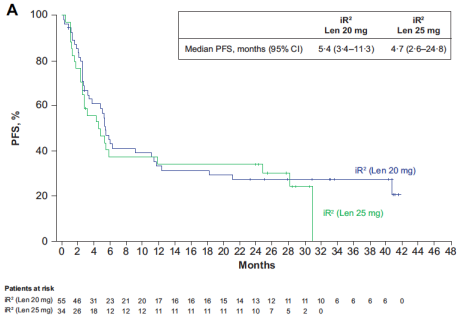
The iR^2 regimen (ibrutinib plus lenalidomide and rituximab) for relapsed/refractory DLBCL: a multicentre, non-randomised, open-label phase 2 study

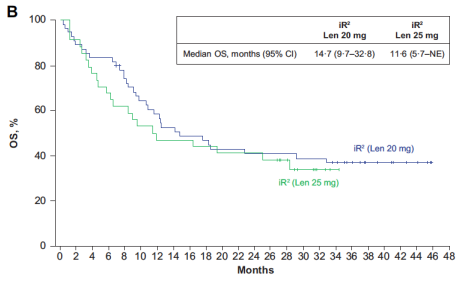
Radhakrishnan Ramchandren,[a,*] Peter Johnson,[b] Nilanjan Ghosh,[c] Jia Ruan,[d] Kirit M. Ardeshna,[e] Roderick Johnson,[f] Gregor Verhoef,[g] David Cunningham,[h] Sven de Vos,[i] Shireen Kassam,[j] Luis Fayad,[k] John Radford,[l] Sarah Bailly,[m] Fritz Offner,[n] David Morgan,[o] Javier Munoz,[p,s] Jerry Ping,[q] Edith Szafer-Glusman,[q] Karl Eckert,[q] Jutta K. Neuenburg,[q] and Andre Goy[r]











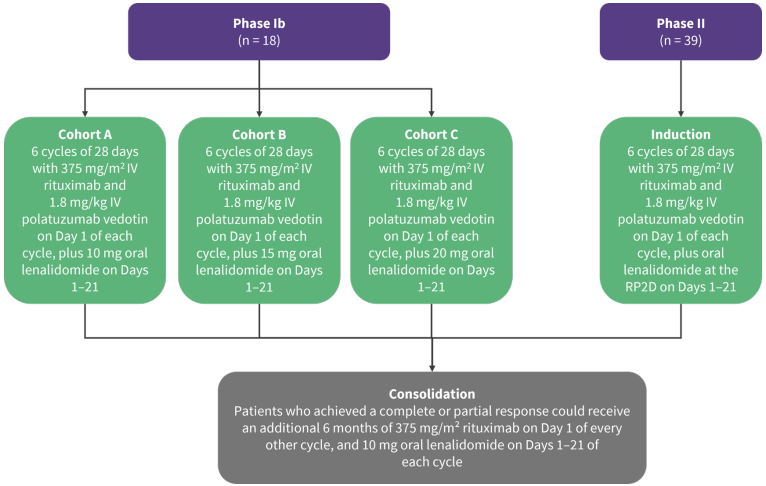
Polatuzumab vedotin plus rituximab and lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma: a cohort of a multicentre, single-arm, phase 1b/2 study

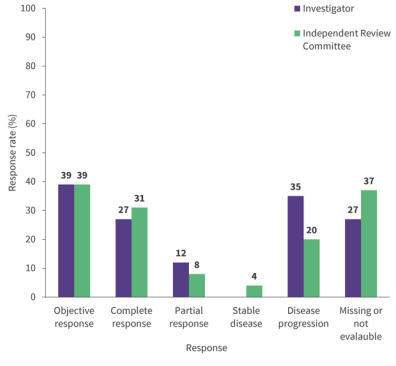
Pau Abrisqueta, Eva González-Barca, Carlos Panizo, José María Arguiñano Pérez, Fiona Miall, Mariana Bastos-Oreiro, Ana Triguero, Lalita Banerjee, Andrew McMillan, Erlene Seymour, Jamie Hirata, Jayson de Guzman, Sunil Sharma, Hyun Yong Jin, Lisa Musick, Catherine Diefenbach

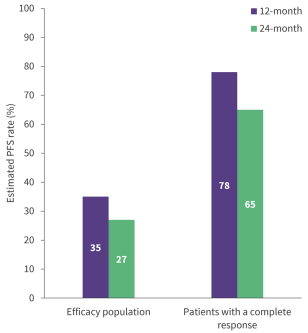
- Relapsed or refractory diffuse large B-cell lymphoma
- Ineligible for ASCT
- ECOG≤2
- ≥2L

Dose-escalation phase (1b) used escalating doses of lenalidomide to find the recommended phase 2 dose
(10, 15, 20 mg)
Rituximab D1
Polatuzumab D1
28 days cycle x 6 cycles

ORR **39%**
CR **27-31%**
ePFS 12 mo 35% (78% if CR)



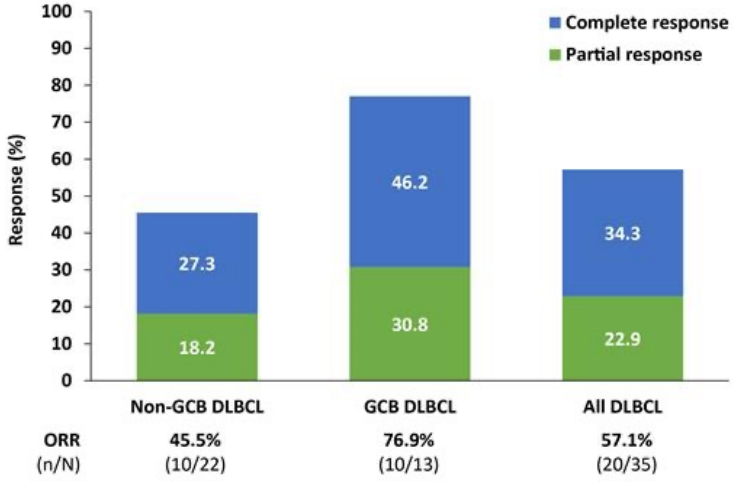




Abrisqueta P et al. Lancet hematol 2024

- Depaus J, Wagner-Johnston ND, Zinzani PL, et al. Interim results of **loncastuximab tesirine combined with ibrutinib** in diffuse large B-cell lymphoma or mantle cell lymphoma **(LOTIS-3)**. 62nd American Society of Hematology Annual Meeting and Exposition; San Diego, CA, USA; Dec 5–8, 2020 (abstr 2099)

Figure 1. ORR in the overall DLBCL cohort and by cell of origin (planned interim analysis set)

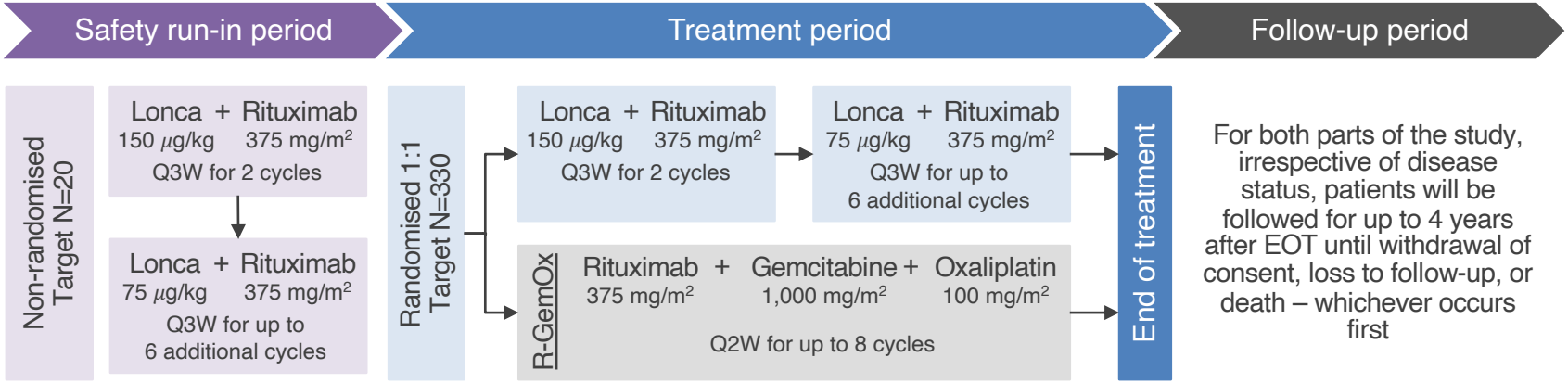


DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell like; ORR, overall response rate

LOTIS-5 trial design:

Phase 3 trial of Lonca in combination with rituximab versus immunochemotherapy in R/R diffuse large B cell lymphoma (DLBCL)[1-3]

- Pathologic diagnosis of R/R DLBCL (including DLBCL transformed from indolent lymphoma), or HGBCL, with MYC and BCL2 and/or BCL6 rearrangements
- R/R disease following ≥1 multi-agent systemic treatment regimen
- Not a candidate for SCT based on performance status, advanced age, and/or significant medical comorbidities (as considered by the investigator)



Primary Endpoints: Progression-free survival* by independent central review (up to 4 years)

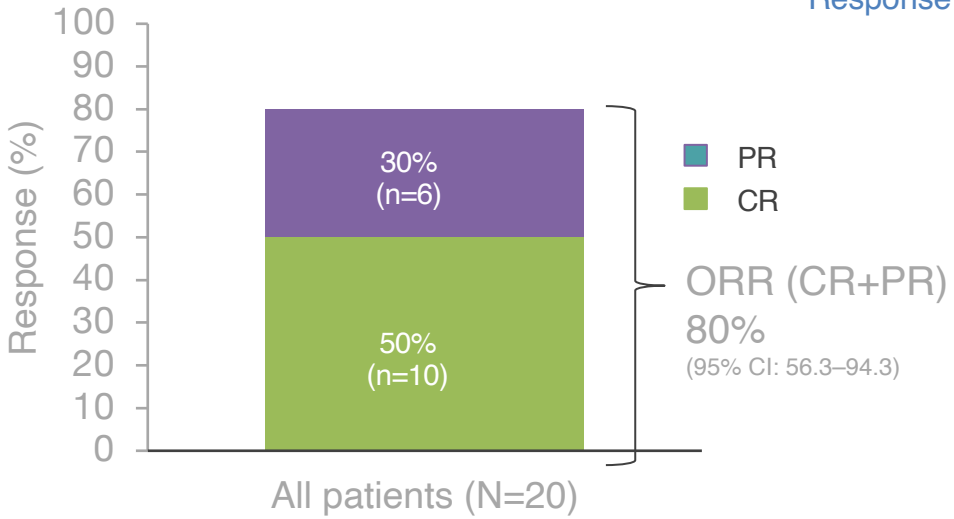
Secondary Endpoints: Overall survival, overall response rate, complete response rate, and duration of response (up to 4 years)

EOT, end of treatment; Lonca, loncastuximab tesirine; Q2W, every 2 weeks; Q3W, every 3 weeks; R-GemOx, rituximab, gemcitabine, and oxaliplatin.

1. Hamadani et al. ICML 2021 2. Kingsley et al. SOHO 2022 3. Clinicaltrials.gov NCT04384484.

Non-randomized safety run-in (n=20) results of LOTIS-5

Response rates[1]



By central review:

ORR was 80% (16/20) (95% CI: 56.3–94.3)

CR rate was 50% (95% CI: 27.2–72.8)
PR rate was 30% (95% CI: 11.9–54.3)

Data cut-off: April 10, 2023.
CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response.
1. Kwiatek et al. SOHO 2023.

NP-32914

ECHELON-3: Study Design

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

Stratified by CD30 status (≥1% vs <1%), cell of origin (GCB vs non-GCB), prior CAR T-cell therapy (yes vs no), prior SCT (yes vs no)

Patients with R/R DLBCL* after ≥2 lines of systematic therapy (no prior BV or lenalidomide), ineligible for/PD after HSCT or CAR T-cell tx, ECOG PS ≤2, FDG-avid measurable disease, and no active cerebral/meningeal disease or grade ≥2 peripheral neuropathy (N = 230)

→ BV 1.2 mg/kg Q3W + rituximab 375 mg/m^2 IV Q3W + lenalidomide 20 mg PO QD (n = 112)

→ Placebo + rituximab 375 mg/m^2 IV Q3W + lenalidomide 20 mg PO QD (n = 118)

- Primary endpoint: OS in ITT population
- Key secondary endpoints: PFS and ORR by investigator in ITT population, CR and DoR by investigator, OS in patients with CD30+ disease, safety/tolerability

Kim. ASCO 2024. Abstract LBA7005. NCT04404283.

ECHELON-3: Baseline Characteristics

Characteristic	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
Median age, yr (range)	74 (29-87)	70 (21-89)
▪ ≥65 yr, n (%)	79 (71)	76 (64)
▪ ≥80 yr, n (%)	23 (21)	15 (13)
Male, n (%)	60 (54)	70 (59)
ECOG PS 2, n (%)	12 (11)	13 (11)
Race, n (%)		
▪ White	65 (58)	56 (47)
▪ Asian	28 (25)	32 (27)
▪ Other/unknown	19 (17)	30 (25)

Prior Therapies	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
Median no. of prior lines, (range)	3 (2-8)	3 (2-7)
Prior therapy, n (%)		
▪ Anthracycline	110 (98)	115 (97)
▪ Anti-CD20 Ab	110 (98)	114 (97)
▪ CAR T-cell	32 (29)	35 (30)
▪ Bispecific Ab	14 (13)	20 (17)
▪ HSCT	10 (9)	18 (15)

ECHELON-3: OS and PFS in ITT Population

OS	BV + Len + R (n = 112)	Placebo + Len + R **(n = 118)**
Median OS, mo	**13.8**	8.5
HR (95% CI)	0.629 (0.445-0.891)	
P	.0085	
Median follow-up, mo	15.5	18.9
PFS	n = 112	n = 118
Median PFS, mo	**4.2**	2.6
HR (95% CI)	0.527 (0.380-0.729)	
P	<.0001	
Median follow-up, mo	11.1	8.8

- OS prespecified efficacy boundary was crossed at interim analysis
- Median duration of treatment: 3.6 mo (BV) vs 2.0 mo (placebo)

ECHELON-3: Response

All patients	BV + Len + R **(n = 112)**	Placebo + Len + R **(n = 118)**	P
ORR, % ▪ CR	64.3 **40.2**	41.5 18.6	.0006
With CD30-negative disease (<1%)	n = 76	n = 80	P
ORR, % ▪ CR	60.5 **40.8**	37.5 15.0	.0063
With CD30-positive disease (≥1%)	n = 36	n = 38	P
ORR, % ▪ CR	72.2 **38.9**	50.0 26.3	.0602

» Median DoR:
  – All patients: 8.3 mo (BV) vs 3.0 mo (placebo)
  – In patients who achieved a CR: 18.9 mo (BV) vs not reached (placebo)

» Median time to CR onset: 1.58 mo (BV) vs 1.61 mo (placebo)

Kim. ASCO 2024. Abstract LBA7005.

Conclusions

What we've learned so far:

» Non eligibility criteria to CAR-T and bispecific are mostly based on RCT: other criteria?

» Determinants of eligibility shared by different therapeutic options

» RWD will help delineate better the profile of patients suitable/unsuitable for CAR-T/BSA

» Some distinct features may permit to identify subgroups of non TCE therapies-eligible R/R LBCL patients for specific alternative treatments (R-POLA BENDA; TAFA-LENA; LONCASTUXIMAB; OTHER)

Caveats:

» Lack of phase III randomized controlled trials in the R/R setting

» Trials ongoing still may risk to not recapitulate the RW scenario (selection bias)