FONDAZIONE ITALIANA LINFOMI

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

Il ruolo della immunoterapia (Ab monoclonali, Ab drug-conjugated e bispecifici) nella terapia dei Linfomi a grandi cellule recidivati/refrattari non eleggibili a trapianto o CAR-T

Federica Cavallo, MD, PhD

Divisione di Ematologia, AOU Cittá della Salute e della Scienza, Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università di Torino

Disclosures of Federica Cavallo

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

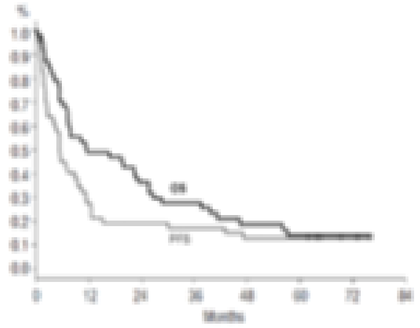
Quali sono i pazienti non eleggibili a ASCT e/o a CAR-T?

- PERFORMANCE STATUS
  - >1
- COMORBIDITA'
  - BCC < 60ml/min
  - FEV < 50%
  - Inadeguata funz. polmonare
  - Inadeguata funz.epatica
  - Inadeguata riserva midollare
- ETA'
  - >70 ASCT
  - >75 CAR T

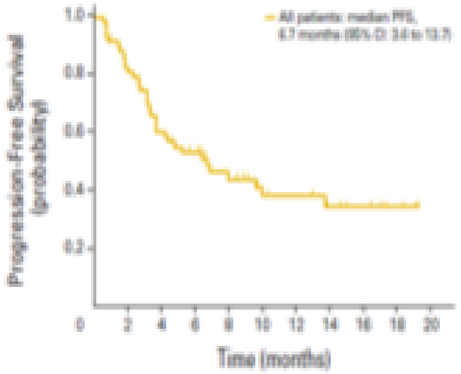
Unsatisfactory outcome among patients non-eligible to ASCT

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	32	65	78	50	Median 9 mo	Corazzelli G, Cancer Oncol 2009
R-Bendamustine	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

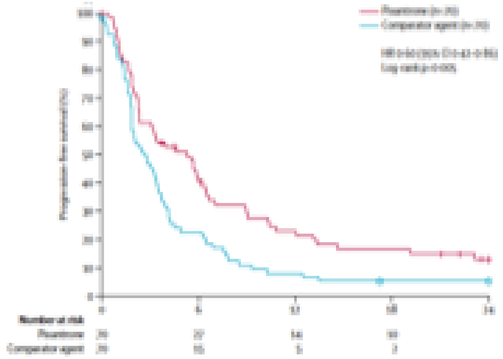
R-GemOx



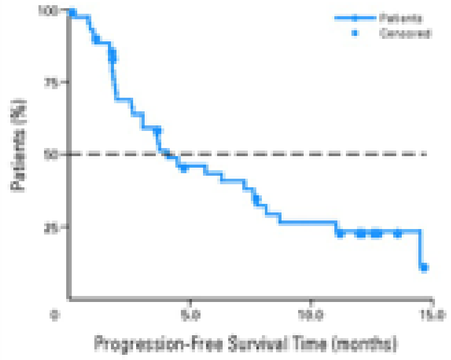
R-bendamustine



Pixantrone



Lenalidomide

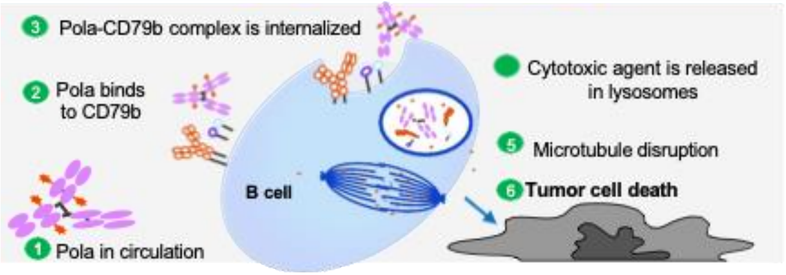


Immunoterapia: anticorpi monoclonali e ADC

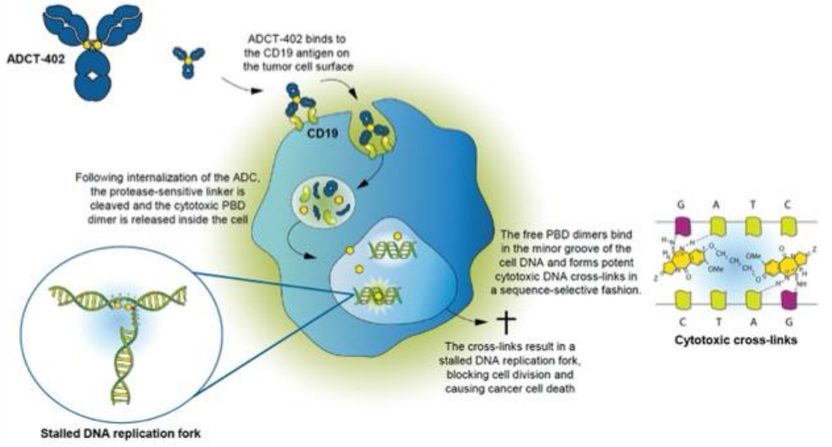
Tafasitamab (Fc-enhanced, anti-CD19 mAb)

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

Polatuzumab vedotin
CD79b targeting antibody-drug conjugate[2]



Loncastuximab Tesirine (ADCT-402)



Immunoterapia: anticorpi monoclonali e ADC studi registrativi

	Pola-BR	Loncastuximab Tesirine	Tafasitamab/Lenalidomide
MOA	Anti-CD79b ADC	Anti-CD19 ADC	Anti-CD19 mAb/Immunomodulator
STUDY	NCT02257567[1]	LOTIS-2[2]	L-MIND[3]
Median previous lines	2	3	2
Median age	67 (33-86)	66 (23-94)	72 (62-76)
ORR	45%	48.3%	60%
CR rate	40%	24%	42,5%
PFS	9.2 m	4.9 m	11.6 m
OS	12.4 m	9.5 m	33.5 m

1. Sehn LH et al JCO 2018

2. Caimi F.L et al Lancet Oncology 2021

3.Salles G et al. Lancet Oncology 2020

Attuale algoritmo terapeutico R/R DLBCL

Second line therapy

Primary refractory/early relapse (≤ 12 mo) CAR-T eligible patients	Late relapse (> 12 mo) HDTC/ASCT eligible patients	CAR-T and HDTC/ASCT ineligible patients
CAR-T therapy (Axi-cel or Liso-cel)	Platinum based salvage CIT followed by ASCT	Pola-BR/Tafa-lena

Third line therapy

Previous CAR-T therapy	CAR-T naive	CAR-T inelegible
	CAR-T therapy (Axi-cel or Liso-cel)	
BsAb (Glofitamab or Epcoritamab)		
Loncastuximab		

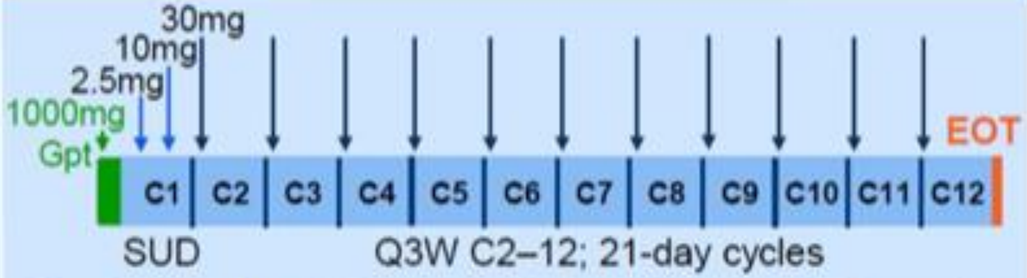
Quali fattori influenzano la scelta sulla terapia di II linea?

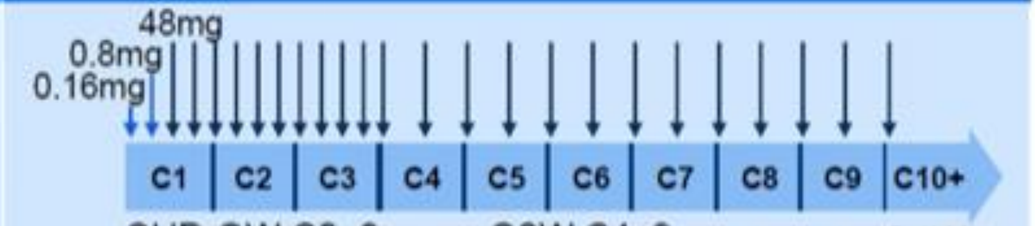
ATTESA DI RISPOSTA
- Non significative differenze tra Tafa-Lena e Pola-BR

TIPO DI RECIDIVA
- Malattia refrattaria
- Malattia recidivata

CAREGIVER
- ASSENTE
- PRESENTE

Immunoterapia: anticorpi bispecifici

Glofitamab	Formulation	Dosing schedule[7]
 Full-length, humanized IgG1 CD20xCD3, **2:1 binding**[1]	IV[6,7]	 **Fixed duration:** 14 doses (including Gpt) over ~8.3 months

Epcoritamab	Formulation	Dosing schedule[12]
 Full-length, human IgG1 CD20xCD3, 1:1 binding[8]	SC[11,12]	 **Treatment until progression or unacceptable toxicity**

Glofitamab baseline characteristics

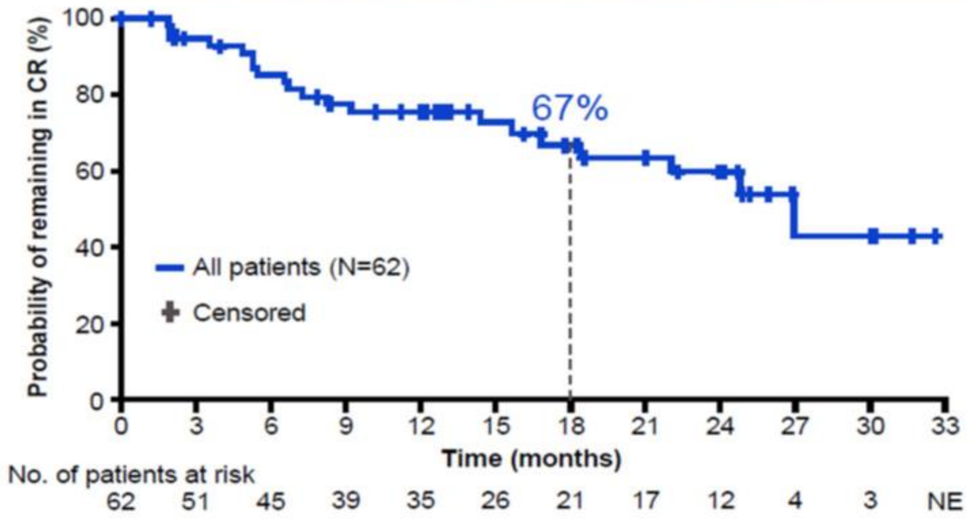
n (%)*		All patients (N=154)†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I/II	35 (22.7)
	III/IV	116 (75.3)
NHL subtype	DLBCL	110 (71.4)
	trFL	28 (18.2)
	HGBCL	10 (6.5)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	19 (12.3)

n (%)*	All patients (N=154)†
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	61 (39.6)
≥3 prior lines	93 (60.4)
Prior CAR-T	51 (33.1)
Refractory to prior CAR-T§	46 (29.9)
Prior ASCT	29 (18.8)
Refractory to any prior therapy	138 (89.6)
Refractory to last prior therapy	131 (85.1)
Refractory to first line of prior therapy	90 (58.4)
Refractory to any prior anti-CD20	128 (83.1)

Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Glofitamab: efficacy and safety

An estimated 67% of patients with a CR at any time remained in remission at 18 months[1,2]



Median DoCR: 26.9 months
Median OS: 11.5 months
Median PFS: 4.9 months

Efficacy outcomes (N=155)[2–4]

CR rate	ORR	Median time to CR
40%	52%	42 days

Safety (N=154)[2–4]

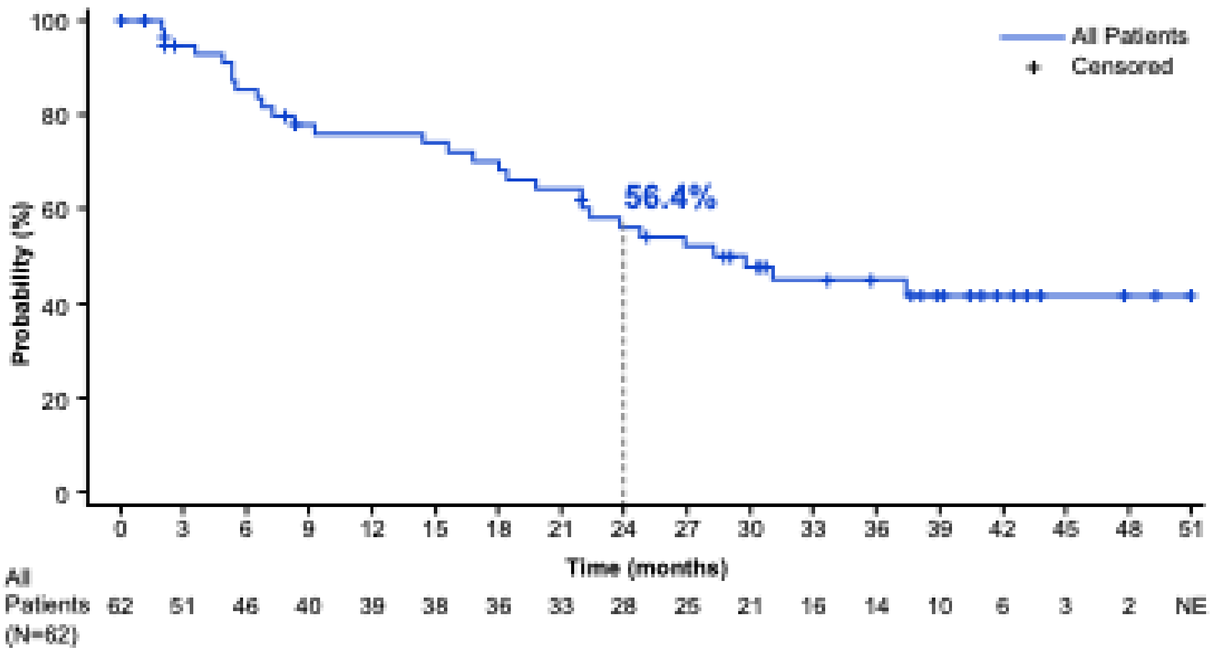
CRS	Most common Grade ≥3 AE	Treatment discontinuation
60% Grade 1/2 4% Grade 3/4	27% neutropenia	9% due to AEs

1. Dickinson M, et al. Presented at ICML 2023. Oral 095; 2. Falchi L, et al. Presented at ASCO 2023. Poster P7550; 2. 3. Hutchings M, et al. Presented at ASH 2023. Oral; 4. Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Complete responses remained durable following fixed-duration glofitamab treatment

	(N=155)*
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median DoCR, months (95% CI)	29.8 (22.0–NE)
24-month DoCR, % (95% CI)	56.4 (42.9–69.8)
Ongoing CRs, n/N (%)	33/62 (53.2)
Median CR follow-up, months (range)	37.7 (0–51)

DoCR by IRC

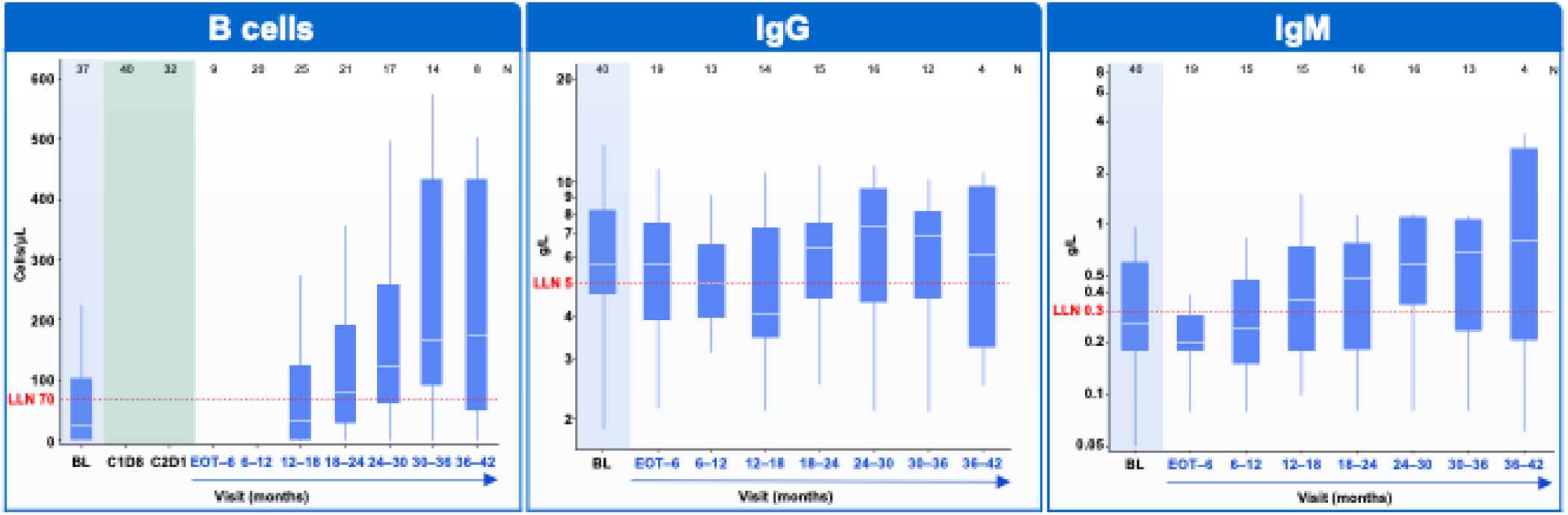


- Median time on study: 41.0 months (range: 0–52)

An estimated 56.4% of patients with a CR at any time remained in remission at 24 months

Dickinson M et al; Oral Presentation ASH 2024 (abstract #865).

Immune recovery after fixed-duration glofitamab monotherapy



- Between 18–24 months* after EOT, 52% (11/21) of patients showed B cells above LLN, 67% (10/15) of patients showed IgG above LLN and 62% (10/16) patients showed IgM above LLN

B-cell recovery was observed starting from 12–18 months after EOT in patients completing treatment and in ongoing remission*

Dickinson M et al; Oral Presentation ASH 2024 (abstract #865).

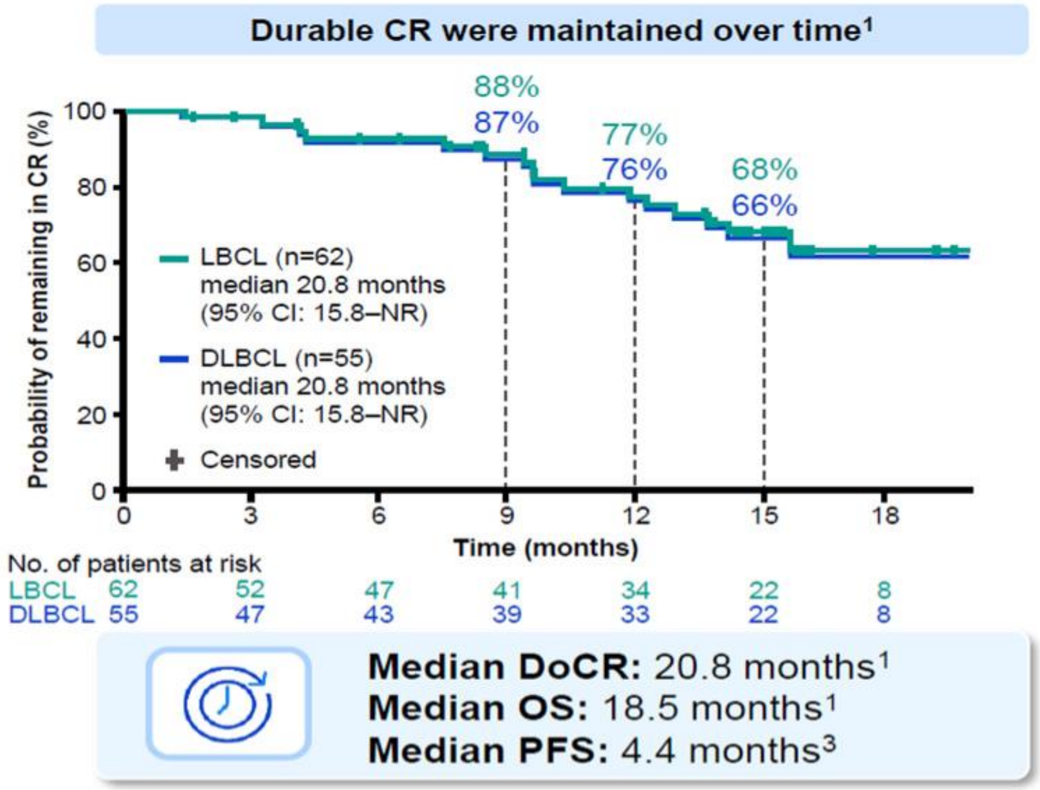
Epcoritamab: baseline characteristics

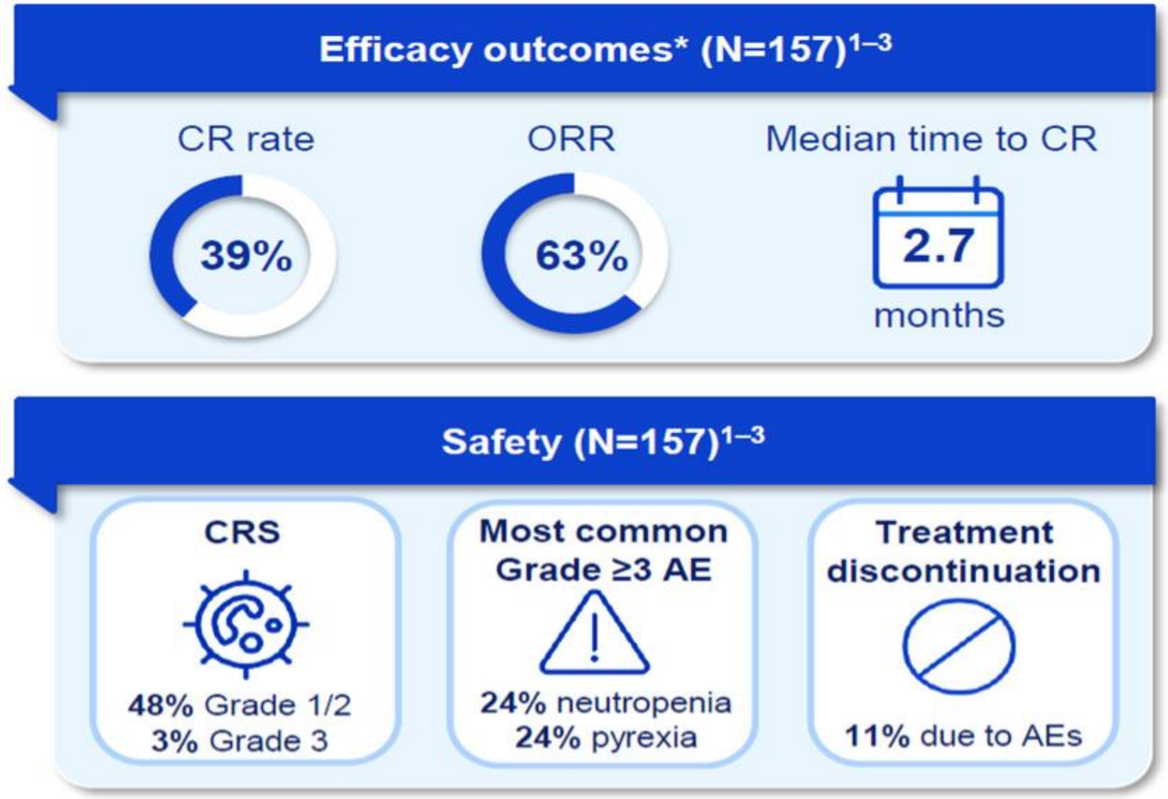
Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics[a]	**LBCL, N=157**
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown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

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

Thieblemont et al. J Clin Oncol. 2023; 41:2238-2247

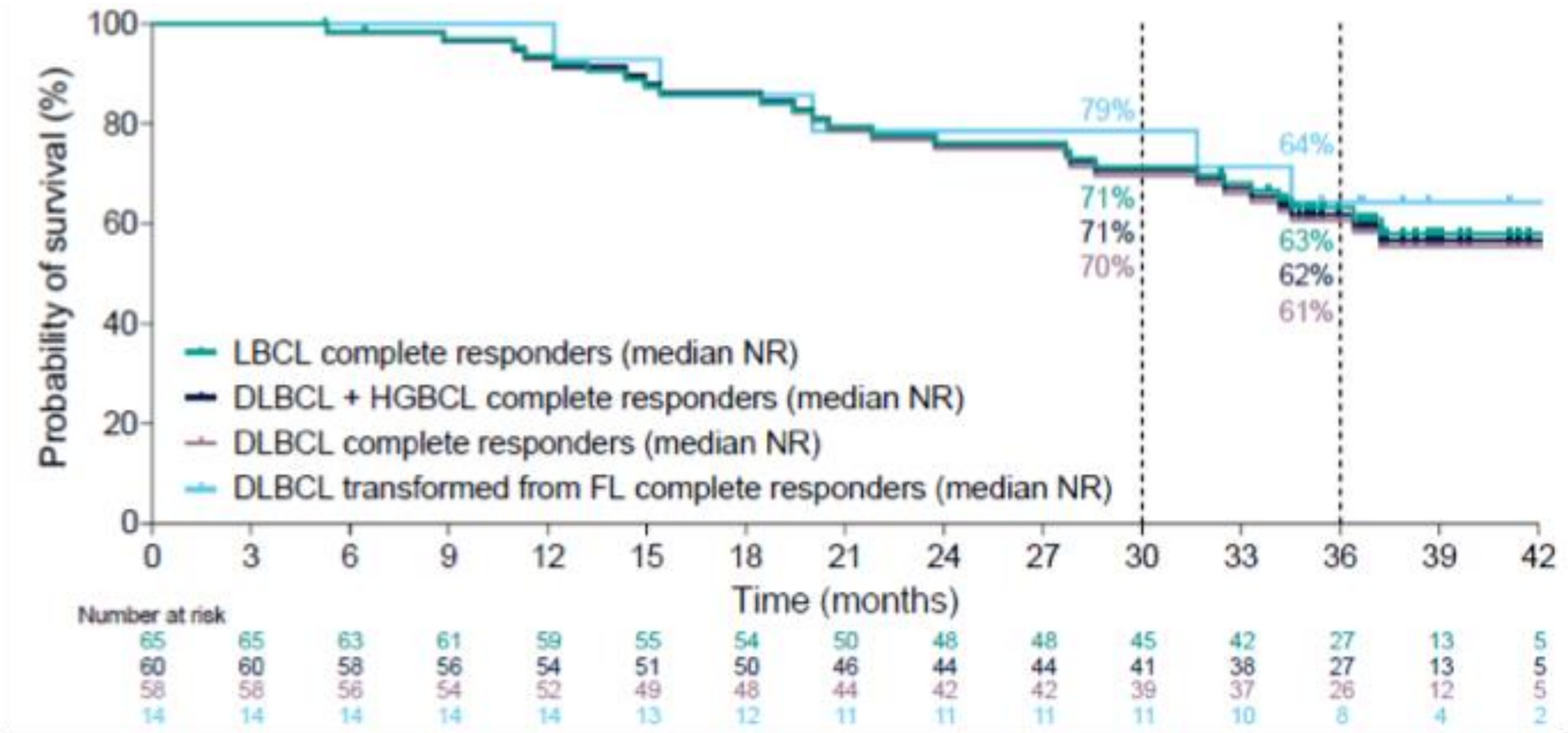
Epcoritamab: efficacy and safety





1. ThiebelmontC, et al. Presented at ICML 2023. Abstract 334; 2. JurczakW, et al. Presented at EHA 2023. Abstract P1118; 2. 3. ThiebelmontC, et al. J Clin Oncol 2023;41:2238–24.

Long term PFS and OS Benefits with CR

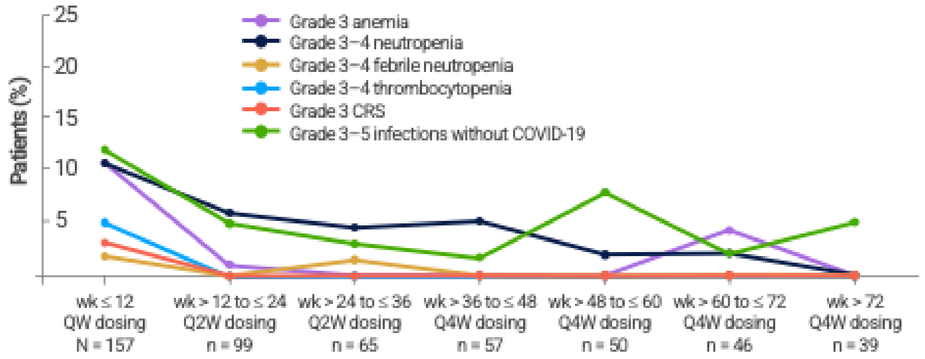


6 out of 10 patients in CR were still alive at 36 months

- **Among complete responders** (n=65), **median PFS** was **37.3 mo** (95% CI, 26-NR)

Vose JM et al. ASH 2024; Dec 2024; P4480, San Diego, Virtual

Infection rates with epcoritamab remained consistent over time in the NHL-1 expansion LBCL cohort (N = 157)[1–4]



Infections (Grade 3–4 in ≥ 2% patients)	Any grade No. (%)	Grade ≥ 3 No. (%)
COVID-19	30 (19.1)	13 (8.3)
Pneumonia	13 (8.3)	5 (3.2)
Sepsis	5 (3.2)	5 (3.2)
COVID-19 pneumonia	9 (5.7)	4 (2.5)

29% Had Grade ≥ 3 serious infections

10% Discontinued treatment due to infections

11% Had fatal TEAEs

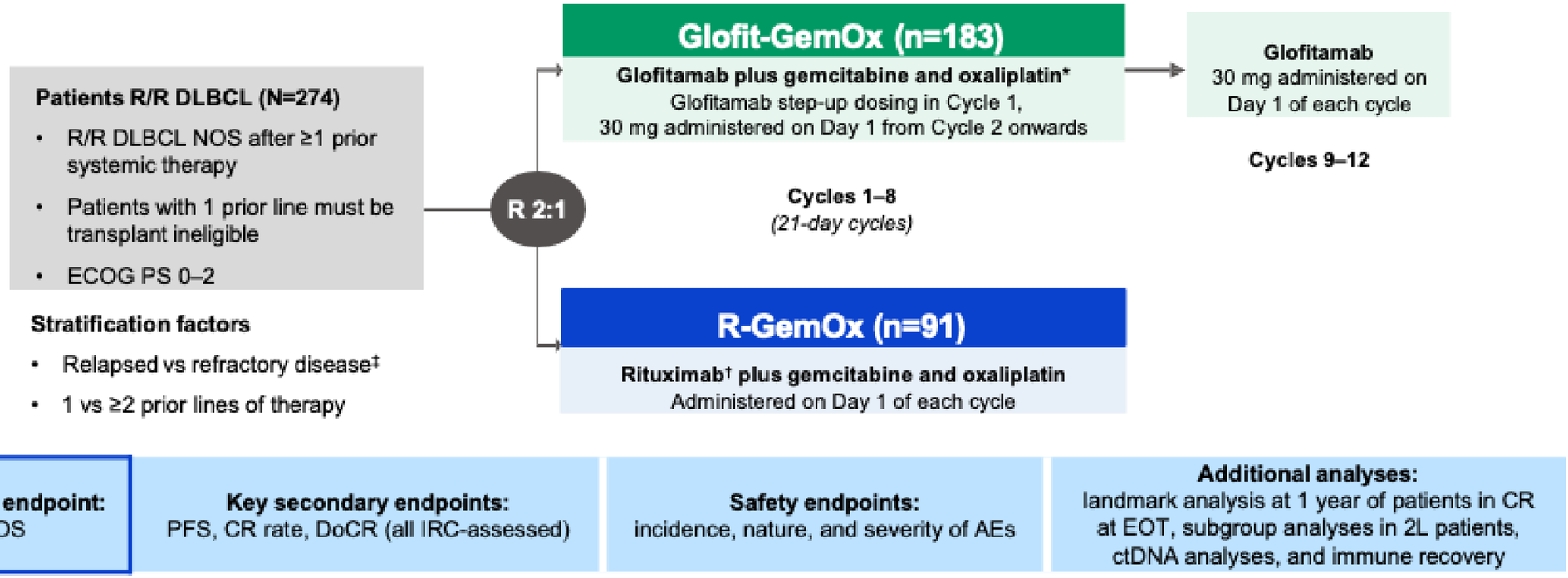
12 Had Grade 5 infections[a]

2 of 3 Treatment-related Grade 5 AEs were infections[b]

6% Had ICANS[c]

1. Thieblemont C, et al. *Leukemia* 2024 Sep 25:1-0.
2. Thieblemont C, et al. EHA, 2024;.
3. Thieblemont C, et al. ASCO 2024
4. Thieblemont C, et al. *J Clin Oncol* 2023;41:2238–47.

STARGLO: a randomized, global, Phase III trial



*Gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m². In C1, Gpt administered on D1, GemOx on D2, followed by Glofit 2.5 mg on D8 and Glofit 10 mg on D15; in C2–8, Glofit 30 mg and GemOx are administered on D1. †Rituximab 375 mg/m². ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after completion of the last line of therapy.
2L, second-line; AEs, adverse events; C, cycle; ctDNA, circulating tumor DNA; D, day; DoCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; Gpt, obinutuzumab pre-treatment; IRC, independent review committee; R 2:1, patients randomized in a 2:1 ratio.

NCT04408638. Available at: https:www.clinicaltrials.gov.
Abramson JS; et al ICML 2025 oral presentation (abstract #076)

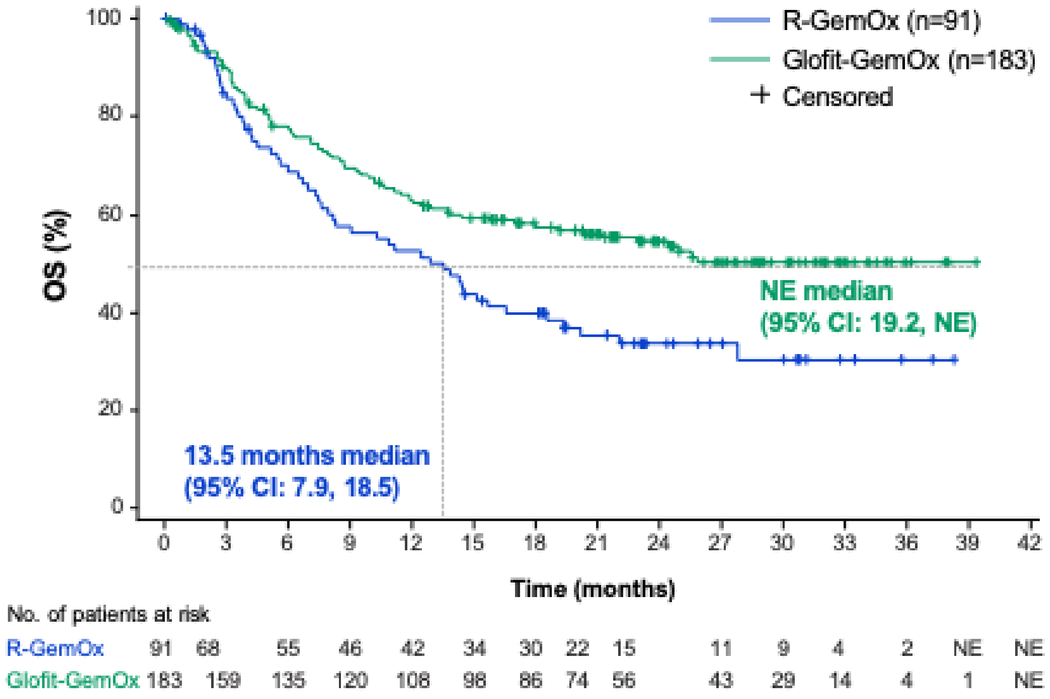
Baseline demographics and characteristics

n (%), unless otherwise stated	R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years; median (range)	69.0 (20–84)	68.0 (22–88)
≥65 years	57 (62.6)	116 (63.4)
Sex, male	53 (58.2)	105 (57.4)
Race		
Asian	51 (56.0)	86 (47.0)
White	33 (36.3)	82 (44.8)
Black or African American	1 (1.1)	2 (1.1)
Unknown	6 (6.6)	13 (7.1)
Number of prior lines of therapy; 1 / ≥2	57 (62.6) / 34 (37.4)	115 (62.8) / 68 (37.2)
R/R status to last therapy; relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Primary refractory*	47 (51.6)	106 (57.9)
ECOG PS	(n=88)	(n=180)
0–1 / 2	80 (90.9) / 8 (9.1)	160 (88.9) / 20 (11.1)
Ann Arbor staging	(n=90)	(n=183)
III–IV	70 (77.8)	122 (66.7)
Bulky disease	(n=90)	(n=183)
≥10 cm	14 (15.6)	23 (12.6)
Prior CAR T-cell therapy	8 (8.8)	14 (7.7)

Abramson JS; et al ICML 2025 oral presentation (abstract #076)

Sustained OS benefit with Glofit-GemOx

Overall survival with ~2 years of follow up



Outcome	R-GemOx (n=91)	Glofit-GemOx (n=183)
2-year follow up analysis (median follow up: 24.7 months)		
OS, median (95% CI); months	13.5 (7.9, 18.5)	NE (19.2, NE)
HR (95% CI)	**0.60** (0.42, 0.85)	
p-value*	0.003	
24-month OS, % (95% CI)	**33.6** (22.9, 44.2)	**54.4** (46.8, 62.0)

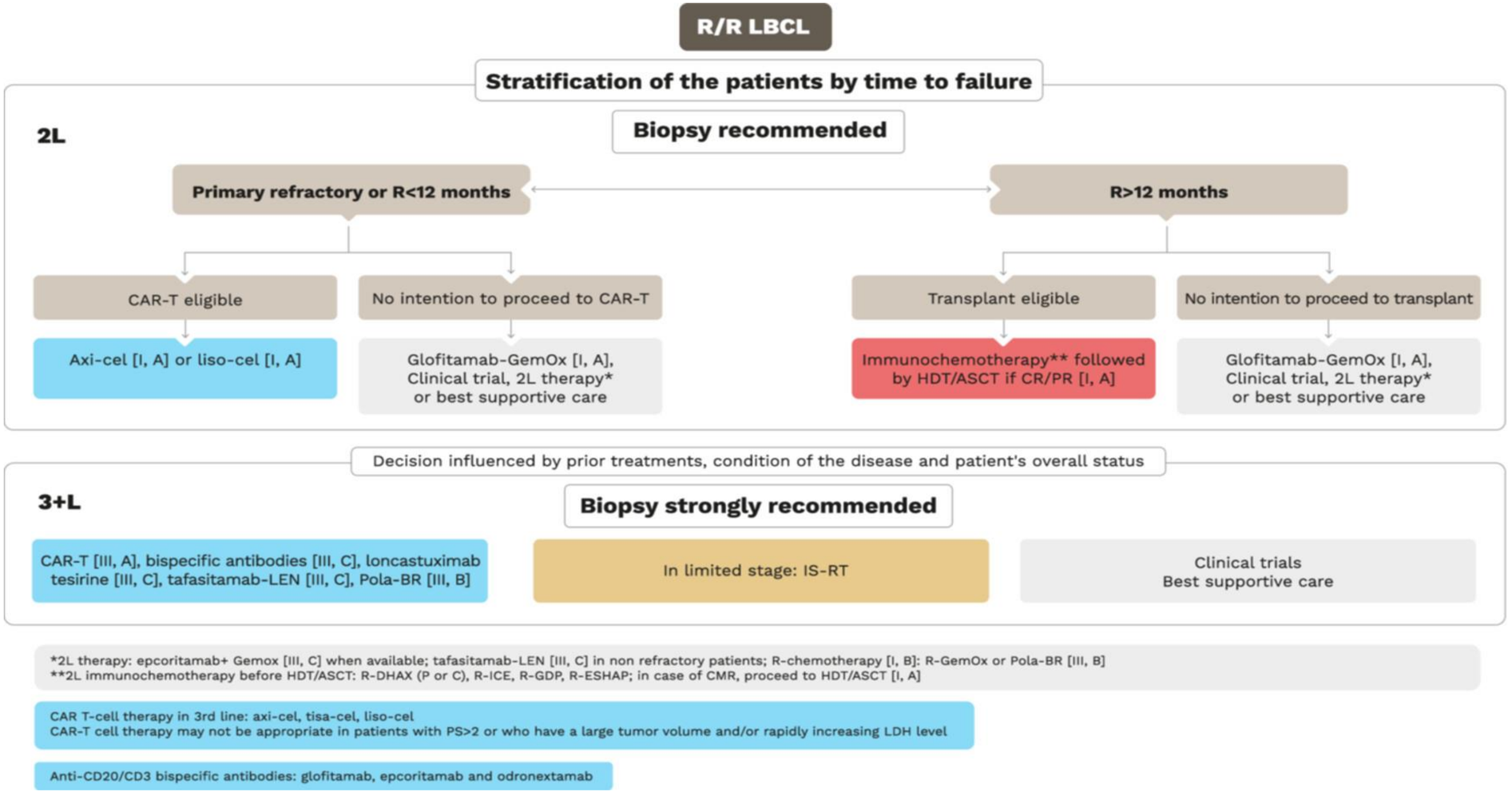
- 26.9% of Glofit-GemOx-treated patients and 57.1% of R-GemOx-treated patients had received ≥1 NALT

Clinically meaningful OS benefit for Glofit-GemOx versus R-GemOx remains after 2 years of follow up

CCOD: June 17, 2024. *p-value is descriptive.
CI, confidence interval; HR, hazard ratio; NALT, new anti-lymphoma treatment; NE, not evaluable.

Abramson JS; et al ICML 2025 oral presentation (abstract #076)

Algoritmo terapeutico R/R DLBCL: futuro prossimo



Thieblemont C. et al. HemaSphere, Volume: 9, Issue: 9, First published: 23 September 2025, DOI: (10.1002/hem3.70207)

Glofitamab

- polatuzumab
- atezolizumab
- englumafusp alpha

Epcoritamab

- lenalidomide
- golcadomide
- ibrutinib+lenalidomide
- GEMOX

Loncastuximab

- IBRUTINIB
- Rituximab
- Polatuzumab or Glofitamab or Mosunetuzumab

Polatuzumab

- Mosunetuzumab
- R-Gemox

CONCLUSIONI

- **Immunoterapia sta migliorando outcome R/R DLBCL non eleggibili a ASCT/CAR-T**
- **Importante adeguata selezione dei pazienti**
- **Attento monitoraggio per gestione AE**

Studio di coorte osservazionale prospettico per valutare nei pazienti con linfoma non-Hodgkin a cellule B l'impatto clinico dei nuovi anticorpi monoclonali (MAB) nella pratica clinica italiana

FIL_MAB

PRINCIPAL INVESTIGATOR: Marco Ladetto, Alessandria

SPONSOR **Fondazione Italiana Linfomi - FIL ETS**

- **Cohort 1** (Polatuzumab vedotin - Bendamustina e Rituximab) - DLBCL R/R
- **Cohort 2** (Polatuzumab vedotin - R-CHP) - DLBCL
- **Cohort 3** (Tafasitamab - Lenalidomide) - DLBCL R/R
- **Cohort 4** (Mosunetuzumab) - FL R/R
- **Cohort 5** (Loncastuximab tesirine) - DLBCL R/R
- **Cohort 6** (Glofitamab) - DLBCL R/R
- **Cohort 7** (Epcoritamab) - DLBCL R/R **NEW!!!!**

Grazie per l'attenzione!

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Daniela Drandi
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