Target Therapy : anticorpi bispecifici nel DLBCL recidivato

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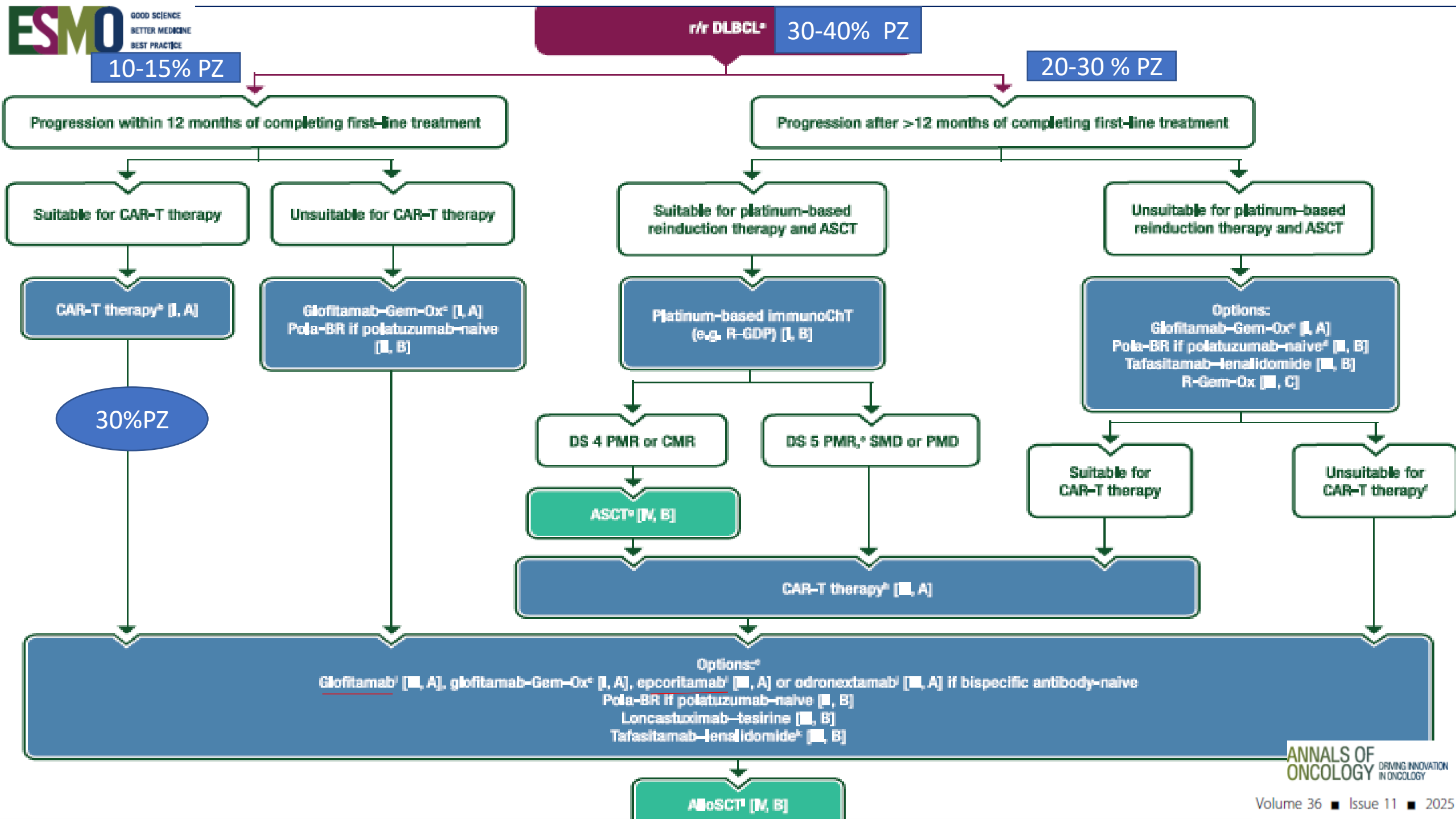
Disclosures of Catello Califano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead							X
Astra Zeneca							x
Jonshon							X



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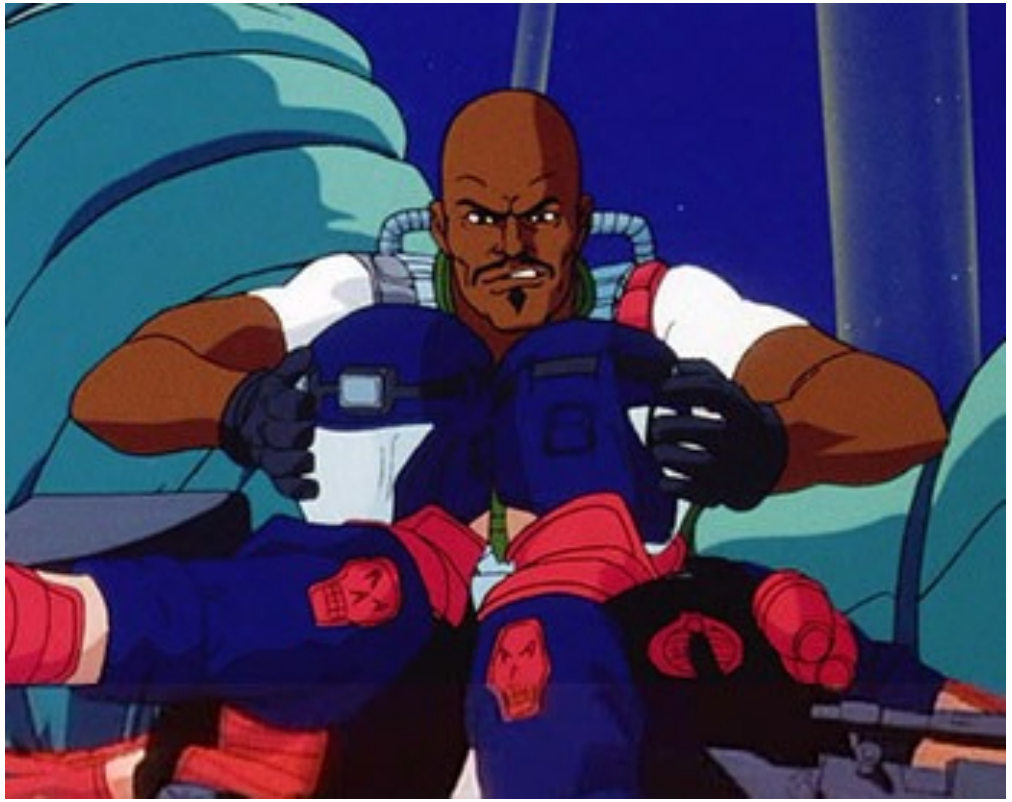
Cosa sono gli anticorpi bispecifici?

Sono anticorpi ingegnerizzati per legare **due bersagli diversi contemporaneamente**:

•da un lato una proteina sulla cellula tumorale (di solito **CD20** nei linfomi B)

•dall'altro un recettore sui linfociti T (**CD3**)

👉 In questo modo "mettono in contatto" diretto le cellule immunitarie con quelle tumorali, attivando una risposta citotossica mirata.



Bispecific Antibody Engineering Platforms

BiTEs (Bispecific T-cell Engagers)

- Small, flexible proteins made of **two single-chain variable fragments (scFvs)**.
- One arm binds **CD3 on T cells**, the other binds a **tumor antigen**.
- No Fc region → **short half-life**, requires continuous infusion.
- Famous example: **blinatumomab**.

👉 Key idea: physically "link" a T cell to a cancer cell → triggers killing.

TandAbs (Tandem Diabodies)

- Larger than BiTEs; composed of **four variable domains**.
- Typically **bivalent for each target** (2 binding sites per antigen).
- Increased **avidity** and longer half-life than BiTEs.

👉 Key strength: stronger binding and potentially better tumor targeting.

👉

DART (Dual-Affinity Re-Targeting)

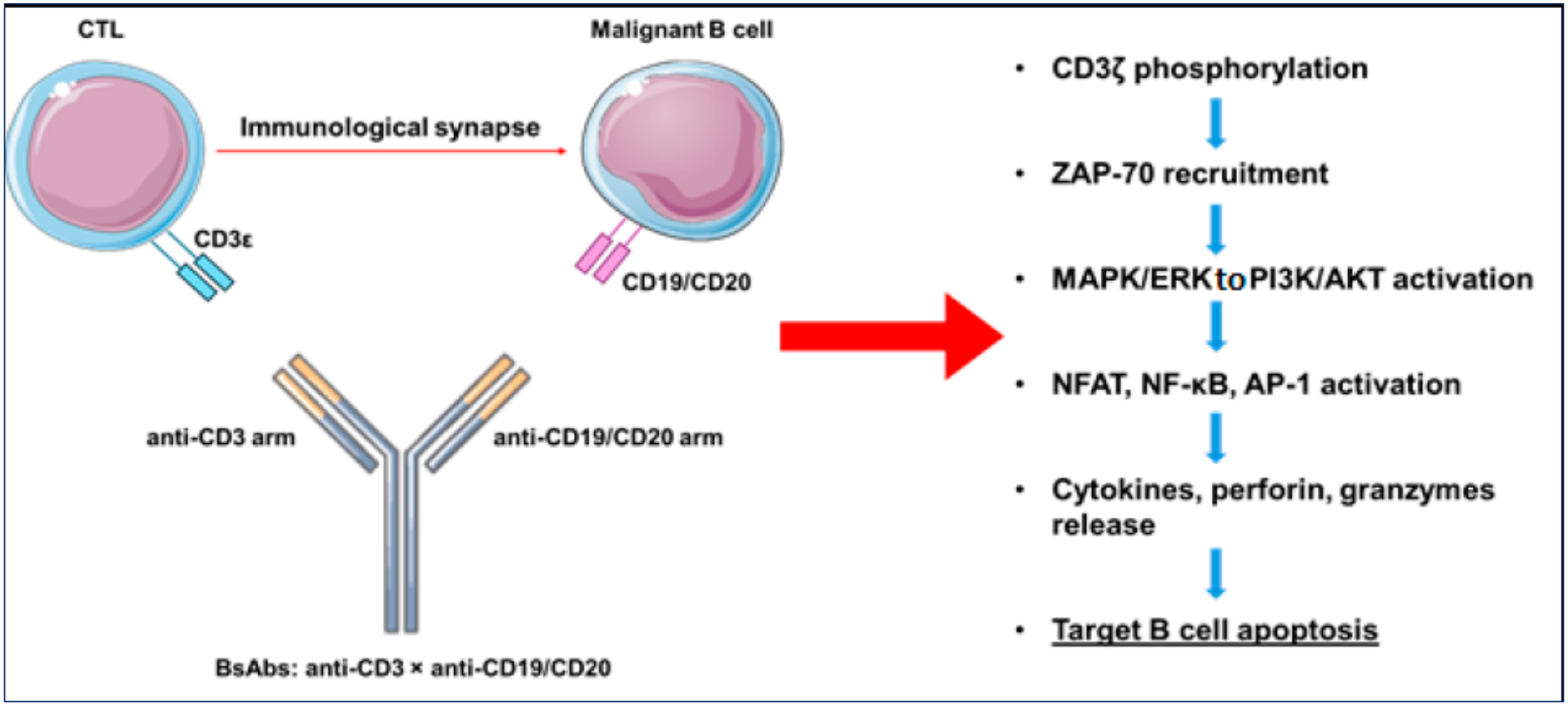
- Structurally more **stable than BiTEs** due to engineered disulfide bonds.
- Better **binding geometry and reduced mispairing**.
- Can include Fc domains for longer half-life (depending on design).

👉 Key advantage: improved **stability and potency** vs BiTEs.

IgG-like Bispecific Antibodies (with engineered Fc)

- Resemble natural antibodies (full-length IgG structure).
- Engineered Fc region allows:
  - **Long half-life** (via FcRn recycling)
  - Potential **effector functions** (ADCC, CDC)
  - Easier **manufacturing and dosing**

Mechanism of action of BsAbs.



Concurrently, pro-inflammatory cytokines, including IFN-., TNF-a, and IL-2, are secreted, enhancing the anti-tumor response and facilitating the recruitment of additional immune cells into the tumor microenvironment

Cancers **2025**, *17*, 2479

. Mechanisms of resistance to BsAb within the lymphoma microenvironment.

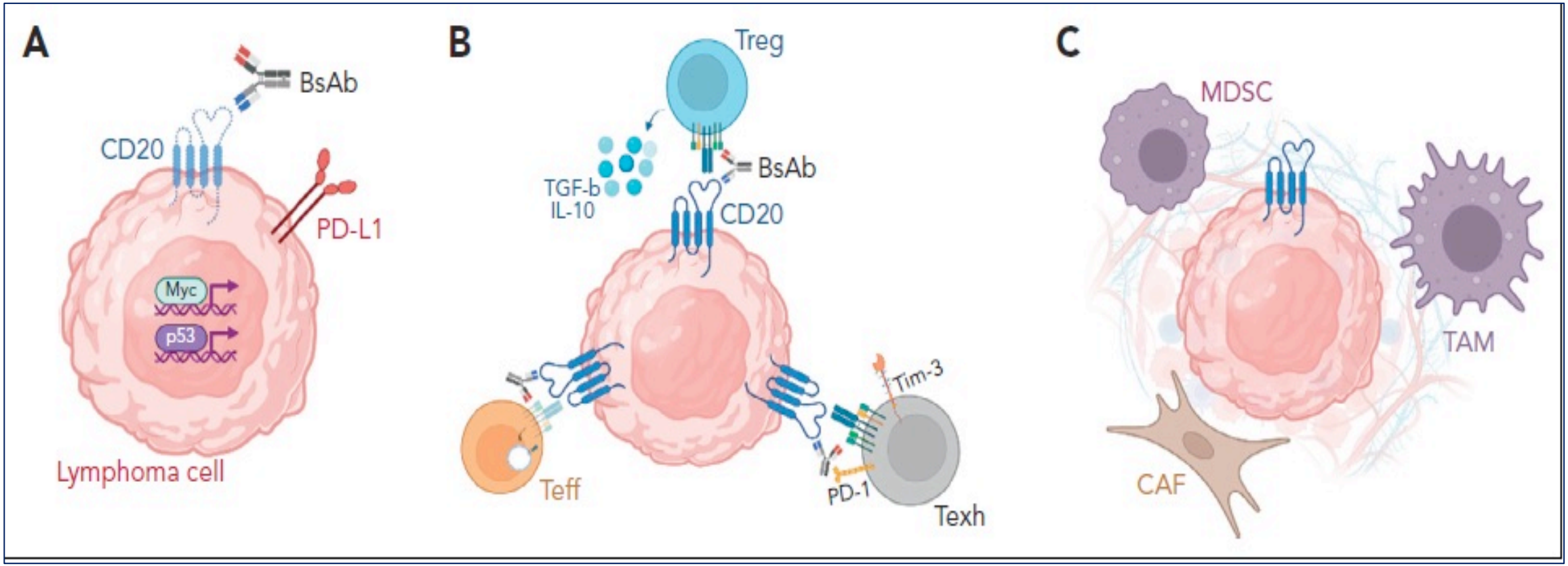
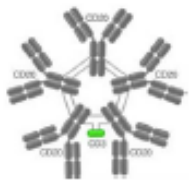


Figure 1. Mechanisms of resistance to BsAb within the lymphoma microenvironment. Potential mechanisms of resistance to BsAb therapy include (A) tumor cell–intrinsic mechanisms, such as antigen loss and activation of immune-evasive gene expression programs, (B) T-cell intrinsic mechanisms, including activation of regulatory T-cells, downregulation of the T-cell receptor, and development of T-cell exhaustion, and (C) T-cell extrinsic mechanisms, including recruitment of immunosuppressive myeloid and/or stromal cells. CAF, cancer-associated fibroblast; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TAM, tumor-associated macrophage; Teff, effector T cell; Texh, exhausted T cell; TGF-b, transforming growth factor beta; Tim-3, T-cell immunoglobulin mucin-3; Treg, regulatory T cell.

Comparative characteristics of CD20XCD3 BsAb

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRII binding)
Plamotamab[90]		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

New bispecific antibodies in diffuse large B-cell lymphoma

Agent	Route of administration	Half-life in days, median	Dosing schedule	Cycle length in days	Step-up doses as percentage of target dose, %	Duration of therapy	CRS mitigation: anti-CD20 pre-treatment	CRS mitigation: corticosteroid	Hospitalization recommendations	Visits in first 6 months
Glofitamab	IV	10	*Step-up:* D-7 GPT D1 2.5 mg D8 10 mg *Target*: 30 mg Q3W	21	8.3 33	Fixed: up to 12 cycles	Obinutuzumab 1,000 mg IV D-7	Dexamethasone 20 mg PO/IV for first 3 doses*	First dose	~12
Mosunetuzumab	IV	6-11	*Step-up*: D1 1 mg D8 2 mg D15 60 mg *Target*: D15 60 mg Q3W	21	1.6 3.3	Fixed: up to 17 cycles (8 if CR achieved, 17 if partial response or stable disease)	Nil	Dexamethasone 20 mg PO/IV or methylprednisolone 80 mg for first 4 doses	Nil mandated	~12
Epcoritamab	SC	8.8	*Step-up*: D1 0.16 mg D8 0.80 mg *Target*: 48 mg QW for C1-C3 then Q2W for C4-9, then Q4W C10+	28	0.33 1.7	Indefinite - to progression or intolerance	Nil	Dexamethasone 15 mg or equivalent for 4 days with each of the first 4 doses	First target dose	~18
Odronextamab	IV	14	*Step-up*: D1 0.7 mg D8 4 mg D15 20 mg *Target*: 160 mg QW for C2-4 320 mg Q2W C5+, then Q4W C9+ (if CR)	21	0.4 2.5 12.5	Indefinite - to progression or intolerance	Nil	Dexamethasone 20 mg 1 day prior, on days of dosing, and 1 day after dosing during step-up and first target dose	First 3 doses	~21

AGENZIA ITALIANA DEL FARMACO

DETERMINA 19 settembre 2024

Riclassificazione del medicinale per uso umano «Tepkinly», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 497/2024). (24A05021)

(GU n.225 del 25-9-2024)

«Tepkinly», in monoterapia, e' indicato per il trattamento di pazienti adulti affetti da linfoma diffuso a grandi cellule B (DLBCL) recidivato o refrattario, dopo due o piu' linee di terapia sistemica.

«4 mg / 0,8 ml - Concentrato per soluzione iniettabile - uso sottocutaneo - flaconcino (vetro) 0,8 ml» 1 flaconcino - A.I.C. n.

classe di rimborsabilita': H;
prezzo ex factory (IVA esclusa): euro 563,33;
prezzo al pubblico (IVA inclusa): euro 929,72;

«48 mg - soluzione iniettabile - uso sottocutaneo - flaconcino (vetro) 0,8 ml (60 mg / ml)» 1 flaconcino - A.I.C. n. 050855028/E (in

prezzo ex factory (IVA esclusa): euro 6.760,00;
prezzo al pubblico (IVA inclusa): euro 11.156,70.

AGENZIA ITALIANA DEL FARMACO

DETERMINA 1 marzo 2024

Regime di rimborsabilita' e prezzo del medicinale per uso umano «Columvi». (Determina n. 7/2024). (24A01336)

(GU n.63 del 15-3-2024)

«Columvi» in monoterapia e' indicato per il trattamento di pazienti adulti con linfoma diffuso a grandi cellule B (DLBCL) recidivante o refrattario dopo due o piu' linee di terapia sistemica.

Il medicinale «Columvi» (glofitamab) e' classificato come segue ai fini della rimborsabilita'.

Confezioni:

«2,5 mg concentrato per soluzione per infusione» - 1 flaconcino da 2,5 ml - A.I.C. n. 050753019/E (in base 10);

classe di rimborsabilita': H;

prezzo ex-factory (IVA esclusa): euro 1.000,00;

prezzo al pubblico (IVA inclusa): euro 1.650,40;

«10 mg concentrato per soluzione per infusione» - 1 flaconcino da 10 ml - A.I.C. n. 050753021/E (in base 10);

classe di rimborsabilita': H;

prezzo ex-factory (IVA esclusa): euro 4.000,00;

prezzo al pubblico (IVA inclusa): euro 6.601,60.

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

EPCORE NHL-1

June 19, 2020, January 31, 2022,

54 global sites

median follow-up of 10.7 months,

Characteristic	Patients (N = 157)
Age, years, median (range)	64 (20-83)
Age group, years, No. (%)	
< 65	80 (51.0)
65 to < 75	48 (30.6)
≥ 75	29 (18.5)
Male sex, No. (%)	94 (59.9)
Malignancy type	
DLBCL, No. (%)	139 (88.5)
De novo, No./n (%)	97/139 (69.8)
Transformed, No./n (%)	40/139 (28.8)
Unknown, No./n (%)	2/139 (1.4)
High-grade B-cell lymphoma, not otherwise specified, No. (%)	9 (5.7)
Primary mediastinal LBCL, No. (%)	4 (2.5)
Follicular lymphoma grade 3B, No. (%)	5 (3.2)
Central laboratory FISH analysis: Double-hit/ triple-hit lymphoma (*MYC* and *BCL2* and/or *BCL6* rearrangement), No./n (%)	13/99 (13.1)
ECOG performance status,[a] No. (%)	
0	74 (47.1)
1	78 (49.7)
2	5 (3.2)
Ann Arbor stage, No. (%)	
I/II	39 (24.8)
III	21 (13.4)
IV	97 (61.8)
International Prognostic Index, No. (%)	
0-2	55 (35.0)
≥ 3	82 (52.2)
Unknown	2 (1.3)
Not applicable	18 (11.5)

106 patients (67,5%) discontinued study treatment

83 (52.9%) disease progression

11 (7.0%) AEs,

7,6%

7 (4.5%) allogeneic transplantation

5 (3,1%) CAR T-

Characteristic	Patients (N = 157)
Time from end of last therapy to first dose, months, median (range)	2.4 (0.0-153.0)
Median prior lines of antilymphoma therapy, No. (range)	3 (2-11)
Prior lines of antilymphoma therapy, No. (%)	
2	46 (29.3)
3	50 (31.8)
≥ 4	61 (38.9)
Primary refractory disease,[c] No. (%)	96 (61.1)
Refractory to last systemic therapy,[c] No. (%)	130 (82.8)
Refractory to ≥ 2 consecutive lines of therapy,[c] No. (%)	119 (75.8)
Prior autologous stem-cell transplant, No. (%)	31 (19.7)
Relapsed within 12 months after prior autologous stem-cell transplant, No./n (%)	18/31 (58.1)
Prior CAR T-cell therapy, No. (%)	61 (38.9)
Progressed within 6 months of CAR T-cell therapy, No./n (%)	46/61 (75.4)
Prior anthracycline therapy, No. (%)	154 (98.1)
First line	139 (88.5)
Second line	16 (10.2)

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

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

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End Point	Patients (N = 157)
Best overall response per IRC, No. (%)	
Overall response of CR or PR, No. (%) [95% CI]	99 (63.1) [55.0 to 70.6]
CR	61 (38.9) [31.2 to 46.9]
PR	38 (24.2)
SD	5 (3.2)
PD	37 (23.6)
Nonevaluable[a]	16 (10.2)
DOR, months, median[b] (range) [95% CI]	12.0 (0.0+ to 15.5+) [6.6 to not reached]
DOR among complete responders, months, median[b] (range) [95% CI]	Not reached (1.4+ to 15.5+) [12.0 to not reached]
Duration of CR, months, median[b] (range) [95% CI]	12.0 (0.0 to 14.9+) [9.7 to not reached]
PFS, months, median[b] (range) [95% CI]	4.4 (0.0+ to 16.9+) [3.0 to 7.9]
OS, months, median[b] (range) [95% CI]	Not reached (0.3 to 17.9+) [11.3 to not reached]
Time to response, months, median (range) [No.]	1.4 (1.0-8.4) [99]
Time to CR, months, median (range) [No.]	2.7 (1.2-11.1) [61]

primary refractory disease	(n = 96)	ORR was 55.2%	CR rate was 30.2%
prior CAR T	(n = 61)	ORR was 54.1%	CR rate was 34.4%
not prior CAR T	(n = 96)	ORR was 68.8%	CR rate was 41.7%

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Safety

Patient	Any Grade (N = 157), No. (%)	Grade ≥ 3 (N = 157), No. (%)
Any AE	156 (99.4)	96 (61.1)
Any treatment-related AE	130 (82.8)	42 (26.8)
SAE	89 (56.7)	—
Serious treatment-related AE	55 (35.0)	—
Treatment-emergent AE leading to treatment discontinuation	12 (7.6)	11 (7.0)
AEs of special interest		
CRS[c]	78 (49.7)	4 (2.5)
ICANS[d]	10 (6.4)	1 (0.6)
Clinical tumor lysis syndrome	2 (1.3)	2 (1.3)

CRS resolved (98.7%)

median time to resolution 2 days (48 hours)

tocilizumab 22 (28.2%)

Patient	Any Grade (N = 157), No. (%)	Grade ≥ 3 (N = 157), No. (%)
Pyrexia[b]	37 (23.6)	0
Fatigue	36 (22.9)	3 (1.9)
Neutropenia	34 (21.7)	23 (14.6)
Diarrhea	32 (20.4)	0
Nausea	31 (19.7)	2 (1.3)
Injection site reaction	31 (19.7)	0
Anemia	28 (17.8)	16 (10.2)
Abdominal pain	22 (14.0)	3 (1.9)
Thrombocytopenia	21 (13.4)	9 (5.7)
Headache	21 (13.4)	1 (0.6)
Constipation	20 (12.7)	0
Decreased appetite	19 (12.1)	1 (0.6)
Vomiting	19 (12.1)	1 (0.6)
Peripheral edema	17 (10.8)	0
Back pain	16 (10.2)	1 (0.6)

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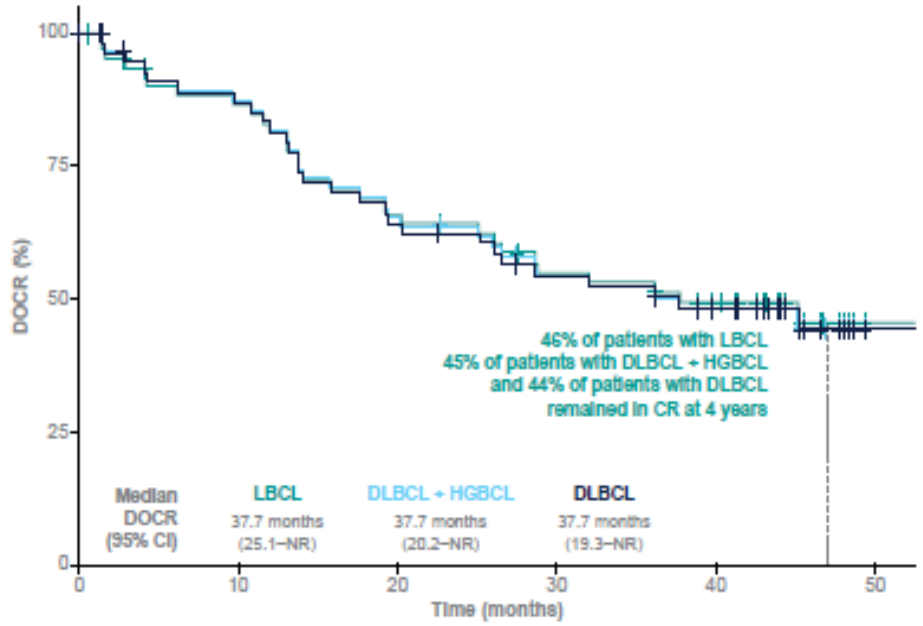
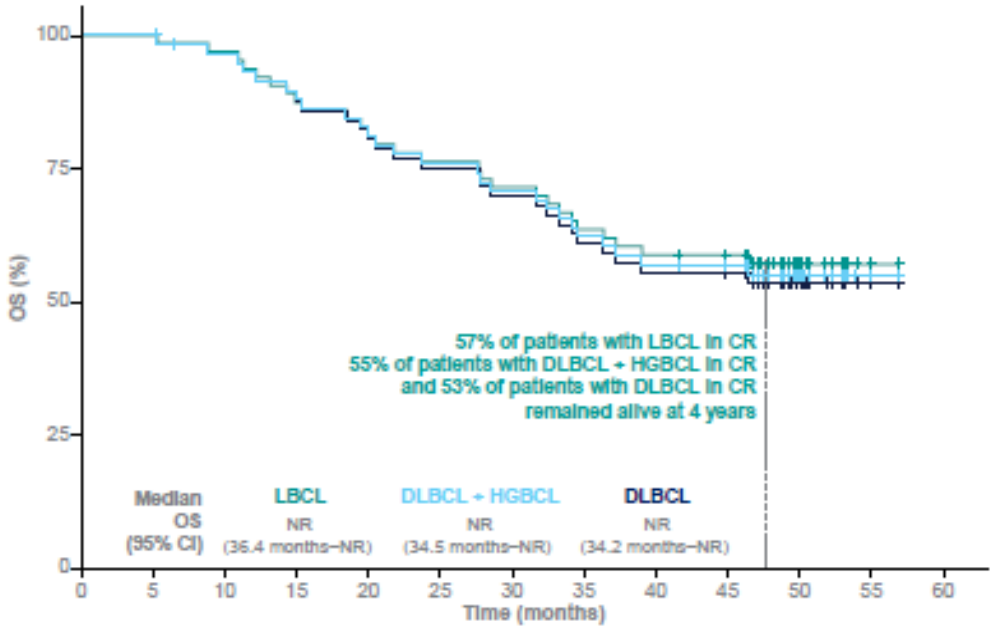
blood® 3 NOVEMBER 2025 | VOLUME 146, NUMBER Supplement 1

Sustained remissions beyond 4 years with epcoritamab monotherapy: Long term follow-up results from the pivotal EPCORE NHL-1 trial in patients with relapsed or refractory large B-cell lymphoma

Durable CRs > 4 Years



Sustained OS > 4 Years in Complete Responders



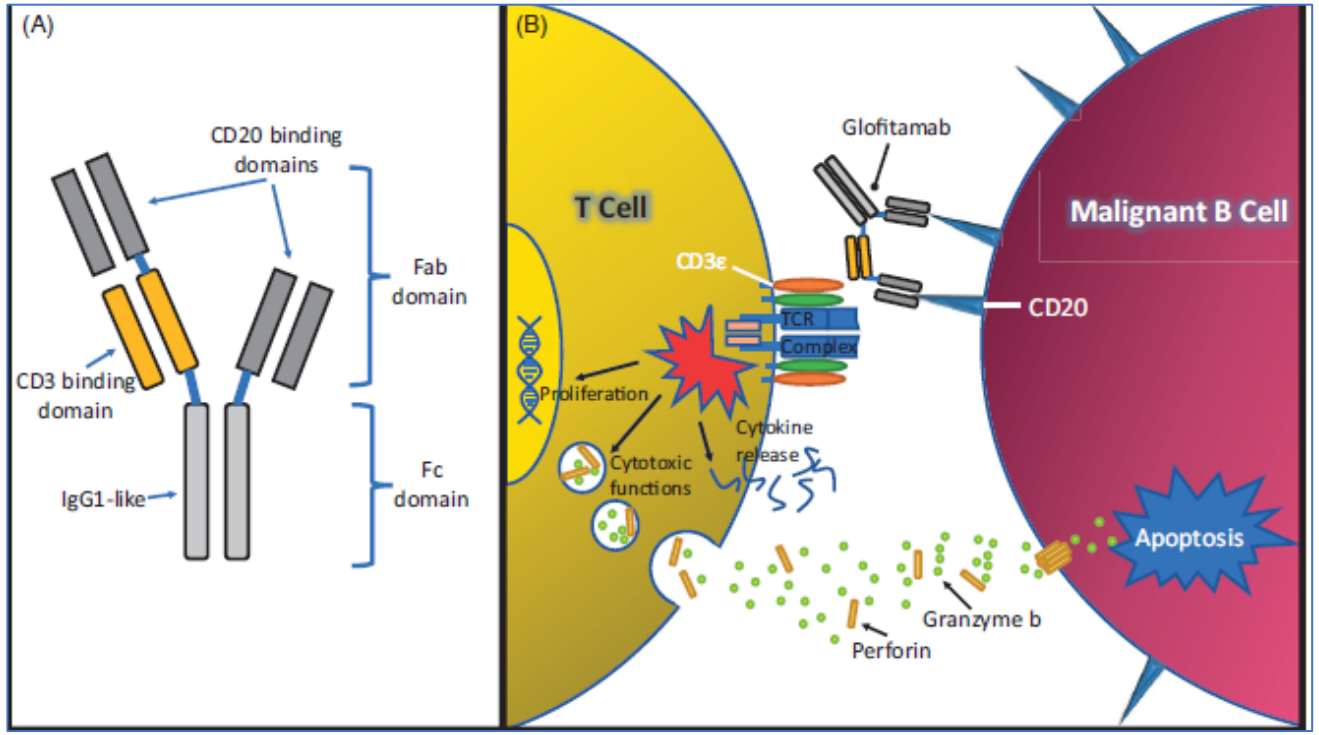
- Median treatment duration in patients with a CR was 19.8 months (range, 2.6–54.8)
- Median DOCR was 37.7 months (95% CI, 25.1 to NR)
- At data cutoff, 42% (27/65) of all CRs were ongoing
  - The longest ongoing CR at data cutoff was 54.5 months

Conclusions

37.7 months median DOCR	No patients progressed from years 3–4	42% of CRs were ongoing at data cutoff	57% of patients with CR remained alive at 4 years

- With > 4 years of follow-up, epcoritamab monotherapy continues to show deep, durable remissions and long-term disease-free survival in patients with R/R LBCL

Glofitamab CD20-TCB bispecific antibody



Glofitamab is administered in 21-day cycles

Seven days prior pretreatment with obinutuzumab

Glofitamab therapy is to be initiated using a step-up dosing schedule commencing with glofitamab 2.5 mg 7 days after obinutuzumab pretreatment (i.e. on day 8) followed by glofitamab 10 mg on day 15. The recommended glofitamab dose after step-up is 30 mg, administered on day 1 of cycle 2 and of each subsequent cycle, with treatment to continue for a maximum of 12 cycles or until disease progression or unmanageable toxicity.

CD20×CD3 bispecific monoclonal antibodies

2:1 tumor–T-cell binding

bivalency for CD20 (B cells) and monovalency for CD3 (T cells)

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

January 2020 September 2021,

Demographic and Clinical Characteristics at Baseline of All 154 Patients Treated at the Phase 2 Dose

Characteristic	Value
Median age (range) — yr	66 (21–90)
Male sex — no. (%)	100 (65)
Non-Hodgkin's lymphoma subtype — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	110 (71)
Transformed follicular lymphoma	27 (18)
High-grade B-cell lymphoma	11 (7)
Primary mediastinal B-cell lymphoma	6 (4)
Bulky disease at study entry	
>6 cm	64 (42)
>10 cm	18 (12)
ECOG performance-status score — no. (%)†	
0	69 (45)
1	84 (55)
Ann Arbor stage at time of study entry — no. (%)	
I	10 (6)
II	25 (16)
III	31 (20)
IV	85 (55)
Previous lines of therapy	
Median no. of lines (range)	3 (2–7)
Only 2 previous lines — no. (%)	62 (40)
≥3 previous lines — no. (%)	92 (60)
Previous therapy for lymphoma — no. (%)	
Anti-CD20 antibody	154 (100)
Anthracycline	149 (97)
CAR T-cell therapy	51 (33)
Autologous stem-cell transplantation — no. (%)	28 (18)
Relapsed or refractory status — no. (%)‡	
Refractory to any previous therapy	139 (90)
Refractory to last previous therapy	132 (86)
Primary refractory	90 (58)
Refractory to any previous anti-CD20 therapy	128 (83)
Refractory to previous CAR T-cell therapy	46 (30)

Table 2. Efficacy According to Independent Review Committee and Investigator Assessment (Intention-to-Treat Population).*

Outcome	Assessment According to Independent Review Committee (N=155)	Assessment According to Investigator (N=155)
Complete response		
No. of patients with response	61	58
Percentage of patients (95% CI)	39 (32–48)	37 (30–46)
Objective response		
No. of patients with response	80	89
Percentage of patients (95% CI)	52 (43–60)	57 (49–65)
Duration of complete response†		
Median (95% CI) — mo	NR (16.8–NR)	19.8 (18.2–NR)
Complete response at 12 mo (95% CI) — %	78 (64–91)	72 (59–86)
Duration of objective response‡		
Median (95% CI) — mo	18.4 (13.7–NR)	10.4 (6.8–NR)
Objective response at 12 mo (95% CI) — %	64 (51–76)	49 (37–61)
Median time to first complete response (range) — days†	42 (31–308)	43 (31–274)
Progression-free survival		
Median (95% CI) — mo	4.9 (3.4–8.1)	3.8 (3.3–5.4)
Alive without progression at 12 mo (95% CI) — %	37 (29–46)	30 (22–38)
Overall survival		
Median (95% CI) — mo	—	11.5 (7.9–15.7)
Alive at 12 mo (95% CI) — %	—	50 (41–58)

Table 3. Adverse Events in All the Patients Treated at the Phase 2 Dose (Safety Population).*

Event	Patients (N = 154)
	no. (%)
Any adverse event	152 (99)
Most common adverse events	
Cytokine release syndrome, per ASTCT	97 (63)
Cytokine release syndrome, per Lee et al.[28]	101 (66)
Neutropenia	58 (38)
Anemia	47 (31)
Thrombocytopenia†	38 (25)
Any glofitamab-related adverse event	140 (91)
Any grade 3 or 4 adverse event	87 (56)
Adverse events of special interest	
Cytokine release syndrome, grade ≥2 per ASTCT	24 (16)
Event grade consistent with ICANS, any grade§	12 (8)
Infection, any grade	59 (38)
Febrile neutropenia, grade ≥3	4 (3)

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

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

	Epcoritamab ($n = 157$)	Glofitamab ($n = 154$)
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)
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%

Table 2. Details of treatment regimens.

	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

EDITORIAL

Check for updates

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

James A. Davis [a], Katelynn Granger[a], Alex Sakowski[a], Sara Goodwin[a], Amanda Herbst[a], Deidra Smith[a], Lindsey Hendrickson[a] and Victoria R. Nachar[b]

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3. Where we stand

The introduction of two commercially approved BsAb therapy products is a breakthrough in the treatment landscape of R/R DLBCL. Both products offer notable effectiveness coupled with tolerable safety profiles. In the absence of a head-to-head comparison, selection of BsAb should be tailored to each patient after a thorough review of the safety and efficacy and perhaps more importantly, patient preference for time limited or indefinite therapy.

Patient preferences for attributes of bispecific antibodies for relapse/refractory diffuse large B-cell lymphoma in the US

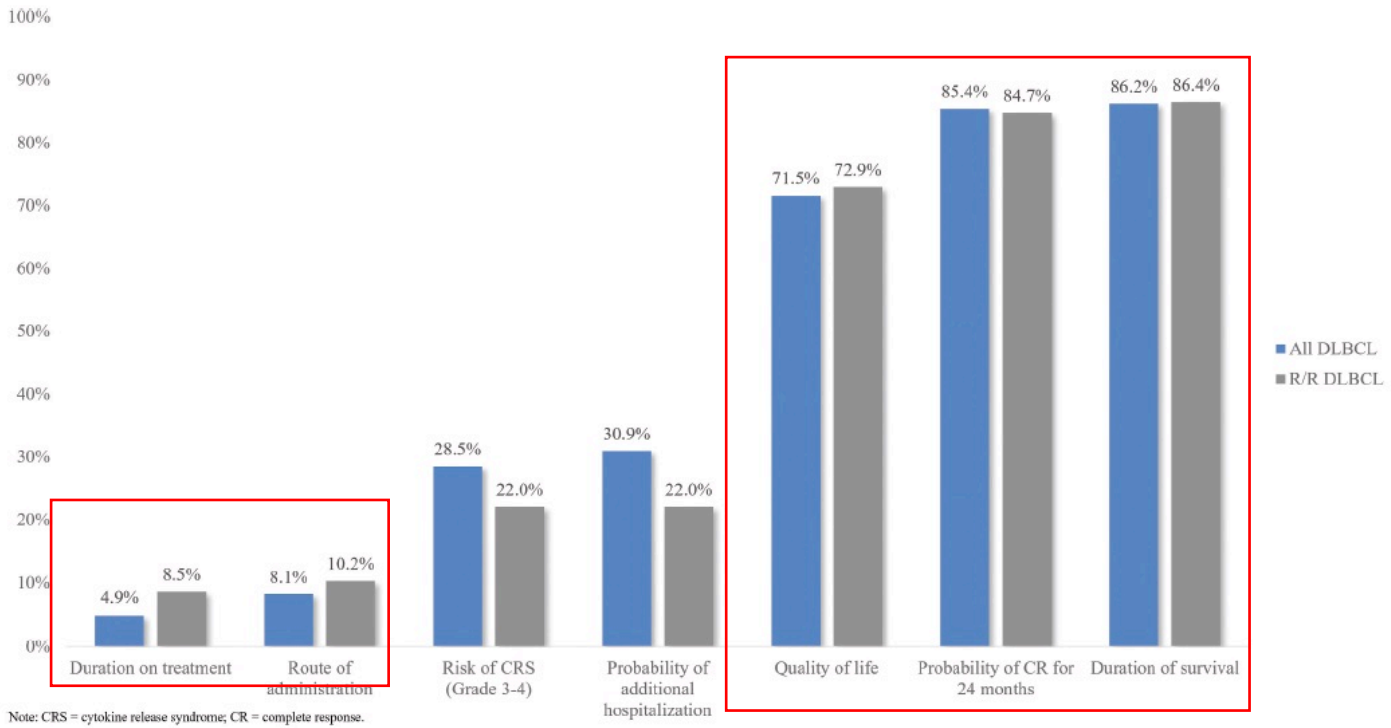


Figure 4. Respondents stating treatment attribute has "great deal" of importance among DLBCL and R/R DLBCL patients.

Conclusion: Efficacy and safety were the most important factors, along with QoL. Patients favored FTD but were willing to tradeoff for TTP with increased efficacy or safety. These findings may guide physician/patient discussions in therapy selection.

Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial

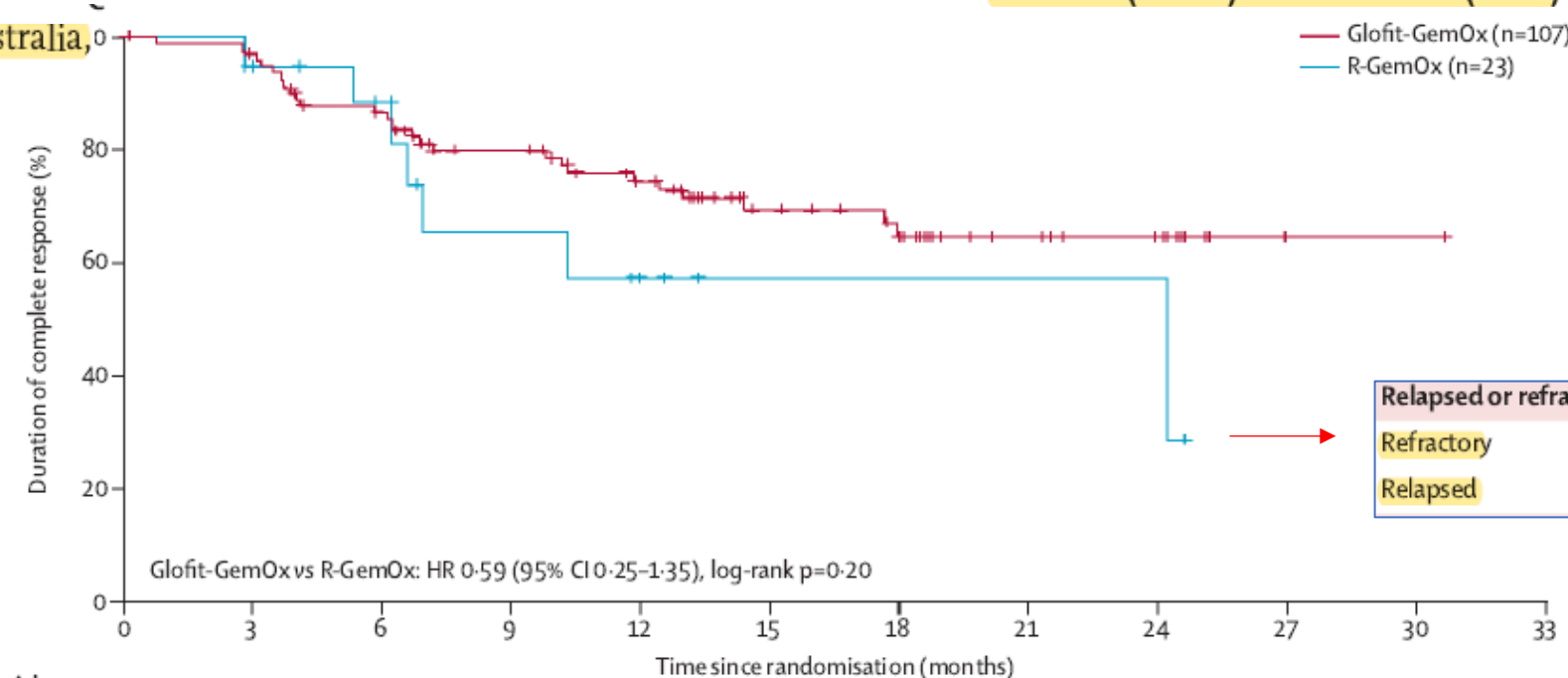
www.thelancet.com Vol 404 November 16, 2024

62 sites in 13 countries in Asia and Australia, Europe, and North America

From Feb 23, 2021, to March 14, 2023, 274 patients were enrolled

GemOx (n=183) or R-GemOx (n=91)

ASCT-ineligible



Relapsed or refractory to any previous therapy**		
Refractory	58 (64%)	125 (68%)
Relapsed	33 (36%)	58 (32%)

Number at risk number censored)												
Glofit-GemOx	107 (0)	95 (9)	79 (15)	63 (25)	51 (33)	33 (48)	25 (54)	14 (65)	10 (69)	1 (78)	1 (78)	0 (0)
R-GemOx	23 (0)	16 (6)	13 (8)	8 (10)	4 (13)	2 (15)	2 (15)	2 (15)	2 (15)	0 (0)	0 (0)	0 (0)

IRC-assessed best overall response‡, %	..	..
Objective response	40·7 (30·5–51·5)	68·3 (61·0–75·0)
Complete response	25·3 (16·8–35·5)	58·5 (51·0–65·7)

IRC-assessed duration of complete response	n=23	n=107
HR	..	0·59 (0·25–1·35)§
Median, months	24·2 (6·9–NE)	NE (NE–NE)

Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial

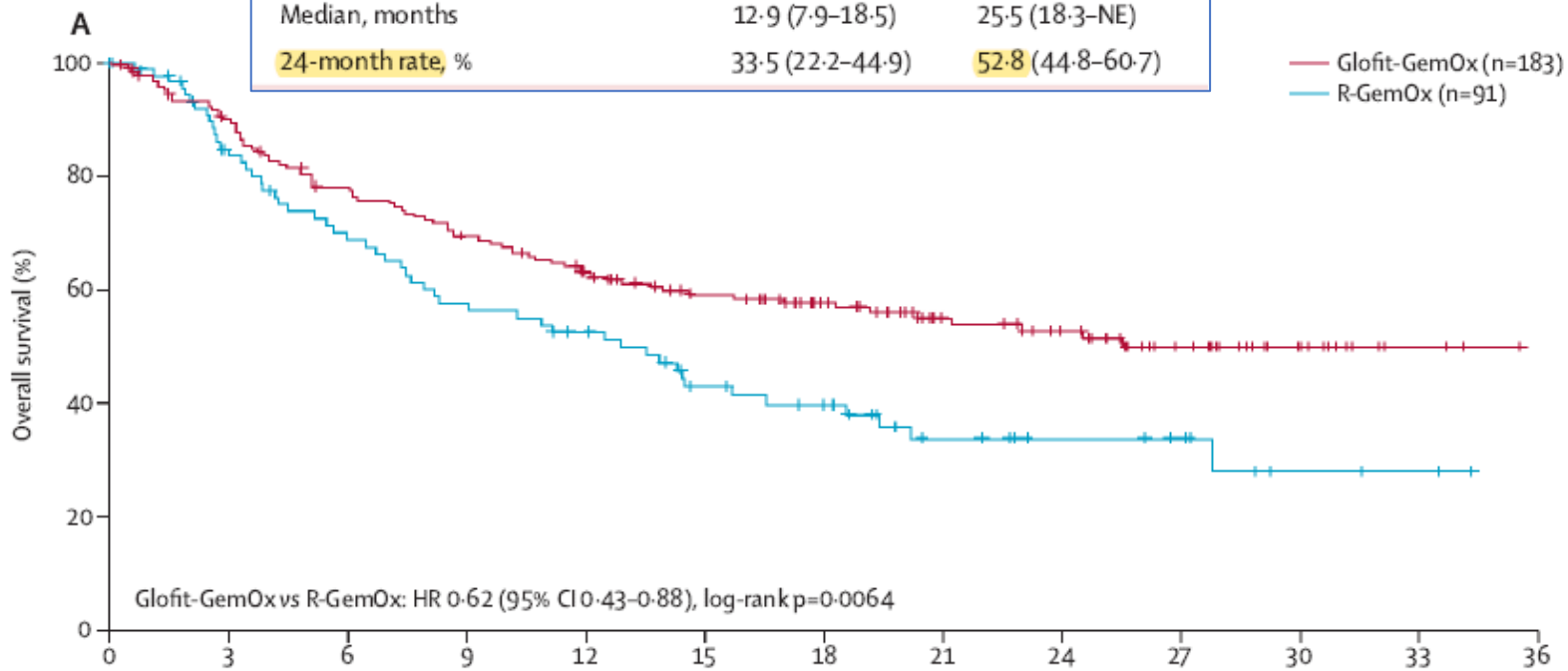
62 sites in 13 countries in Asia and Australia, Europe, and North America

From Feb 23, 2021, to March 14, 2023, 274 patients were enrolled

GemOx (n=183) or R-GemOx (n=91)

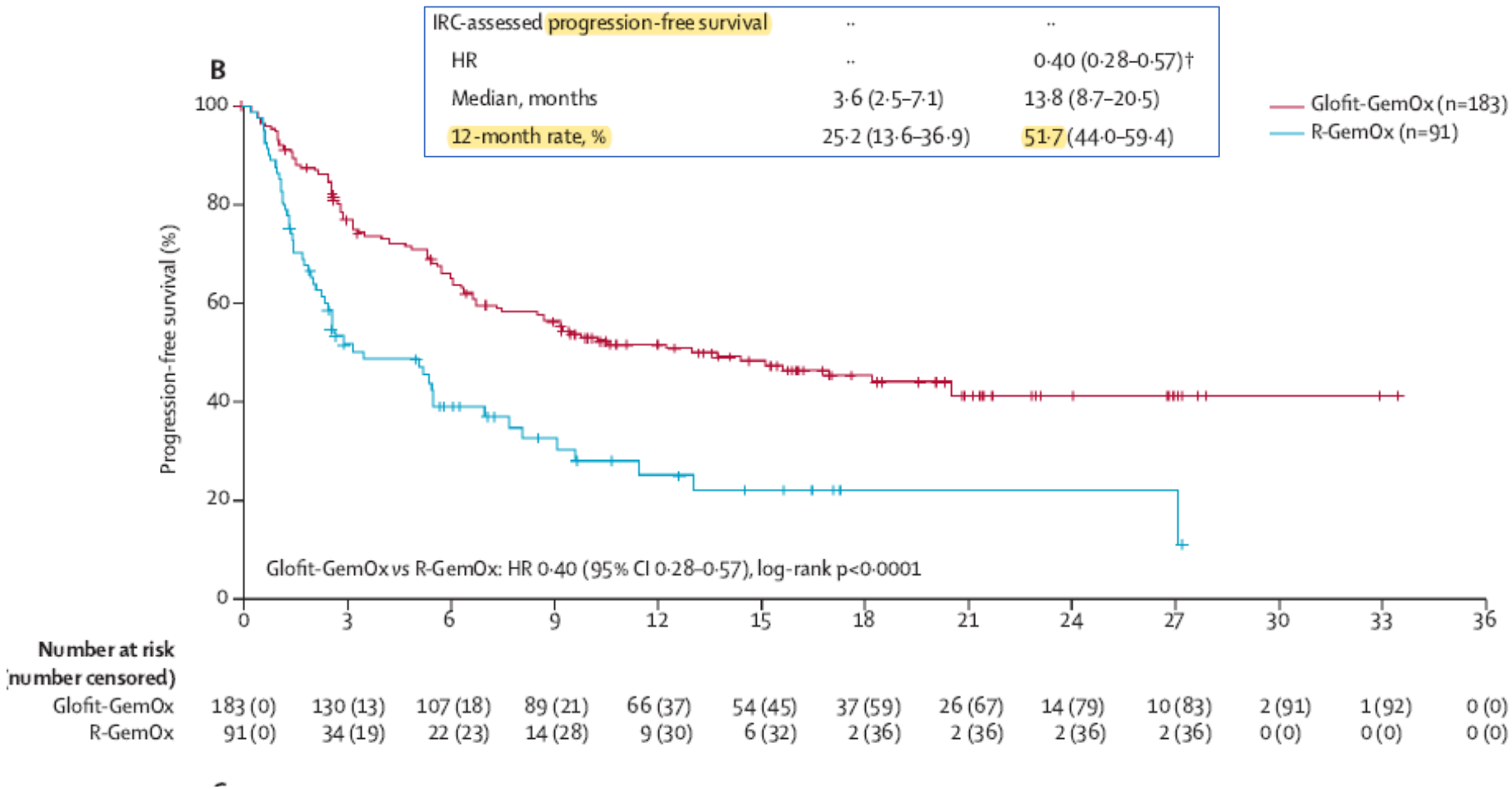
ASCT-ineligible

Investigator-assessed overall survival	..	..
HR	..	0·62 (0·43–0·88)†
Median, months	12·9 (7·9–18·5)	25·5 (18·3–NE)
24-month rate, %	33·5 (22·2–44·9)	52·8 (44·8–60·7)



Number at risk (number censored)													
Glofit-GemOx	183 (0)	159 (6)	135 (9)	119 (10)	104 (14)	86 (26)	71 (39)	51 (56)	40 (65)	26 (77)	11 (92)	3 (100)	0 (0)
R-GemOx	91 (0)	68 (9)	55 (10)	46 (10)	40 (12)	29 (16)	23 (20)	14 (26)	10 (30)	8 (32)	3 (36)	2 (37)	0 (0)

Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial



Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial

	R-GemOx (n=88)	Glofit-GemOx (n=180)
CRS†	NA	76 (44%)†
Grade 1	NA	54 (31%)†
Grade 2	NA	18 (11%)†
Grade 3	NA	4 (2%)†
Neurological adverse event (grade ≥2)	11 (13%)	55 (31%)
Serious infections	11 (13%)	46 (26%)

Glofit-GemOx demonstrated superior survival outcomes vs R-GemOx in both 2L and 3L+ settings

Outcome (95% CI)	R-GemOx 2L (n=57)	Glofit-GemOx 2L (n=115)	R-GemOx 3L+ (n=34)	Glofit-GemOx 3L+ (n=68)
Median OS, mo	14.4 (10.3–26.8)	NR (22.8–NE)	6.7 (4.2–14.3)	17.0 (10.7–25.8)
36-month OS, %	30.8 (17.7–44.0)	54.6 (45.2–64.0)	21.8 (6.7–36.9)	33.2 (21.2–45.3)
Median PFS, mo	5.5 (2.6–9.7)	20.4 (9.2–NE)	1.9 (1.4–3.6)	9.2 (5.4–18.3)
CR rate, %	28.1 (17.0–41.5)	63.5 (54.0–72.3)	20.6 (8.7–37.9)	50.0 (37.6–62.4)

mo, months; NE, not estimable; NR, not reached.

Abdulhaq H et al. ASH 2025 poster presentation, *Blood* (2025) 146 (Supplement 1): 3743.

Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial

blood* 10 APRIL 2025 | VOLUME 145, NUMBER 15

From 25 January 2021 to 15 December 2023,

103 patients ASCT-ineligible R/R DLBCL

Region, n (%)	
Europe	74 (71.8)
North America	28 (27.2)
Australia	1 (1.0)

	IRC assessment N = 103
ORR, n (%)	88 (85.4)
CR	63 (61.2)
PR	25 (24.3)
Stable disease, n (%)	3 (2.9)
Progressive disease, n (%)	8 (7.8)
Not evaluable, n (%)	4 (3.9)
Time to response, median (range), mo	1.5 (0.9-3.0)
Time to CR, median (range), mo	2.6 (1.3-22.1)

Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial

	Overall N = 103	Patients with CR by IRC, n = 63	Patients with 1 pLOT, n = 39	Patients with ≥2 pLOT, n = 64
Patients remaining in response at 12 mo,* %	47.6 (32.8-61.1)	63.5 (43.5-78.1)	58.9 (29.5-79.5)	40.4 (23.9-56.3)
Patients remaining in CR at 12 mo,* %	62.6 (42.3-77.5)	62.6 (42.3-77.5)	61.7 (24.5-84.7)	62.1 (39.9-78.1)
PFS at 12 mo,* %	44.0 (31.7-55.5)	68.5 (50.0-81.3)	63.2 (40.1-79.4)	32.8 (19.0-47.2)
OS at 12 mo,* %	56.6 (45.5-66.3)	84.4 (70.8-92.0)	69.1 (49.3-82.4)	49.6 (36.0-61.8)

Overall, N = 103	Any grade, n (%)	Grade ≥3, n (%)
AEs of special interest		
CRS¶	54 (52.4)	1 (1.0)
ICANS	3 (2.9)	1 (1.0)
Clinical tumor lysis syndrome	0	0

Disease setting	Trial ID/Name	Phase	Treatment	Patient population	N of patients	ORR/CRR, %	PFS/OS/DOR	CRS rates, %					Follow up in months median
								Total	G1	G2	G3	G4	
Second line and beyond	NCT04663347[91] EPCORE NHL-2	I/II	Epcor + R-DHAX/C*	Transplant eligible 2L+	29	76/69	2-year PFS 60% 2-year OS 86%	45	38	7	0	0	27.5
	NCT04663347[59,92] EPCORE NHL-2 (Arm 5)	I/II	Epcor + GemOx	Transplant ineligible 2L+	103	85/61	15-month DOCR 56%	52	28	23	1	0	13.2
	NCT05283720 EPCORE NHL-5	II	Epcor + Lenalidomide Olamide	Transplant eligible and ineligible 2L+	26	75/58	NR	73	65		8	0	NR
	NCT03533283[37] STARGLO	III	Glofit + GemOx *vs.* R-GemOx	Transplant ineligible 2L+	183	68/59	1-year PFS 52% 2-year OS 53%	44	31	11	2	0	20.7
	NCT05364424[93]	I	Glofit + R-ICE†	Transplant or CAR-T eligible 2L	41	78/69	NR	49	29	20	0	0	NR
	NCT04077723[64]	I/II	Glofit + Englumafusp alpha (CD19x4-1BB)	Transplant ineligible 2L+	83	67/57	1-year PFS 46%	55	49	13	1	0	16.2
	NCT05219513[28]	I	Glofit + RO7443904 (CD19xCD28)	Transplant ineligible 2L+	33	64/39	NR	59	36	19	0	4	NR
	NCT03533283[57,94]	I/II	Glofit + Pola	Transplant ineligible 2L+	129	80/62	Median PFS 12 months Median OS 39.2 months	43	27	15	1	0	23.5
	NCT03671018[56]	I/II	Mosun + Pola 2L+	Transplant ineligible 2L+	117	62/50	1-year PFS 46% 1-year OS 66%	17	10	4	3	0	23.9
	NCT05335018[95]	II	Glofitamab + Poseltinib + Lenalidomide	Transplant ineligible Primary refractory or 3L+	28	89/43	6-month PFS 55% 6-month OS 81%	19	14		5		3.6
	NCT03533283[67]	I/II	Glofit + Atezolizumab	Transplant ineligible	31	29/10	NR	42	24	18	0	0	NR

627 **Glofitamab in Combination with Rituximab Plus Ifosfamide, Carboplatin, and Etoposide Shows Favorable Efficacy and Manageable Safety in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma, Eligible for Stem Cell Transplant or Chimeric Antigen Receptor T-Cell Therapy: Results from a Phase Ib Study**

Results: As of May 31, 2024, 41 pts provided informed consent and received study treatment. At baseline, median age was 66 years (range: 41-78) and 71.1% of pts were male. Most pts were White (65.9%; Asian: 7.3%; Black/African American: 7.3%; Native Hawaiian: 2.4%; unknown: 12.2%; and 4.9% not reported). Histological subtypes were confirmed as DLBCL NOS (70.7%), HGBCL with *MYC* and *BCL-2/6* rearrangements (12.2%), HGBCL NOS (4.9%), and DLBCL activated B cell (2.4%); 9.8% were unknown. Extranodal disease was reported in 39.0% of pts. Median duration of glofitamab treatment was 28.0 days (range: 1-65). At the time of this interim analysis, the best ORR (CMR or PMR) was 78.1% (95% confidence interval [CI]: 60.0—90.7) and the CMR rate was 68.8% (95% CI: 50.0—83.9) in the interim efficacy-evaluable population (n=32). In the safety-evaluable population (n=41), the most common adverse event (AE) was cytokine release syndrome (CRS; 48.8%; Grade [Gr] 1, 29.3%; Gr 2, 19.5%); no Gr ≥3 CRS events were reported and all events resolved. No immune effector cell-associated neurotoxicity syndrome events were reported. Infections occurred in 19.5% of pts (Gr 1, 4.9%; Gr 2, 7.3%; Gr 3, 7.3%). Gr 3/4 AEs occurred in 61.0% of pts; platelet count decreased/thrombocytopenia was the most common (26.8%). Serious AEs were reported in 41.5% of pts. No Gr 5 AEs were reported. In total, one pt discontinued glofitamab treatment due to AEs. This pt had transformed Waldenstrom's macroglobulinemia with Gr 2 CRS and Gr 3 tumor lysis syndrome.

Conclusions: Glofit-R-ICE demonstrated high response rates in pts with R/R DLBCL eligible for ASCT or CAR T-cell therapy. The safety profile was manageable with a low treatment discontinuation rate. Updated data will be presented.

haematologica

Haematologica. 2026 Mar 5. doi: 10.3324/haematol.2025.300086 [Epub ahead of print]

Epcoritamab plus rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin induces deep and durable responses in transplant-eligible patients with relapsed or refractory diffuse large B-cell lymphoma: results from the EPCORE NHL-2 trial

by Pau Abrisqueta, Yasmin H. Karimi, Daniel Morillo, Raúl Cordoba, Tycel Phillips, Sven de Vos, Marcel Nijland, Fritz Offner, Per-Ola Andersson, Joshua Brody, Chan Y. Cheah, Pilar Gomez Prieto, Mats Hellström, Judit Meszaros Jørgensen, David Lewis, Kim M. Linton, Gerardo Musuraca, Liwei Wang, Jennifer Marek, Kojo Osei-Bonsu, Malene Risum and Lorenzo Falchi

Twenty-nine patients received epcoritamab plus R-DHAX/C; 72% had stage IV disease; 66% had primary refractory disease. As of January 15, 2025 (median follow-up 40.4 months), overall response rate (primary endpoint) was 79%, and complete response rate was 69%. Sixteen

. At 36 months, an estimated 70% of responses were ongoing, 59% of patients were progression-free, and 76% were alive.

629. AGGRESSIVE LYMPHOMAS, IMMUNOTHERAPY INCLUDING BISPECIFIC ANTIBODIES

Safety and efficacy of CD3xCD20 bispecific antibody for the treatment of primary and secondary central nervous system lymphoma patients: A multicentric retrospective study

55 patients within 22 French and Belgium institutions were identified.

Thirty (73.2%) and eleven (26.8%) patients received epcoritamab and glofitamab respectively. Seven (23.3%) patients received epcoritamab as monotherapy. Twenty-three (76.7%) patients received epcoritamab in combination with lenalidomide (n=14, 46.7%), ibrutinib (n=5, 16.7%), pomalidomide (n=5, 16.7%), rituximab (n=4, 13.2%) or with polychemotherapies (n=3, 10.7%). One (9.1%) patient received glofitamab as monotherapy. Ten (90.9%) patients received glofitamab in combination with ibrutinib (n=7, 63.6%), lenalidomide (n=6, 54.5%) or pomalidomide (n=2, 18.1%). Patients received a median of 3 cycles of BsAbs (range, 1 to 12).

Overall response (ORR) and complete response (CR) rates were 65.9% (27/41) and 36.6% (15/41),

Cytokine release syndrome (CRS) developed in 19 (46.3%) patients including 4 grade 3/4 events. Nine (22.0%) patients experienced neurotoxicities including 3 grade 3/4 events. There were no grade 5 neurotoxicity event.

combination was 25% (2/8) and 39.4% (13/33), respectively. Nine responder patients received a subsequent treatment, with axicabtagene ciloleucel CAR-T cell therapy (n = 7 including 3 CR and 4 PR), thiotepa based IC + ASCT (n = 1 PR) and allogenic stem cell transplant (n = 1 CR). With a median follow-up of 6.7 months (range, 0.5 to 17.1), median PFS was 8.5 months

https://doi.org/10.1182/blood-2025-1018

Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy

blood* 18 APRIL 2024 | VOLUME 143, NUMBER 16

Drug	Epcoritamab[4]					Glofitamab[5]				
Structure	IgG-like anti-CD3×CD20 BsAb. Proprietary format, with point mutations in the Fab portion of the Fc of the antibody and heterodimerization.					Humanized mouse-derived BsAb with 1:2 CD3:CD20 ratio of Fab arms				
Route of administration	SC					IV				
Dosing schedule	C1-3: days 1, 8 ,15, and 22; C4-9: days 1 and 15; C10+: day 1, every 28 d until progression					C1: obin, day 1; glofit, days 8 and 15; C2-12: day 1, every 21 d				
CRS mitigation										
Step-up dosing	C1D1: 0.16 mg C1D8: 0.8 mg C1D15: 48 mg C1D22: 48 mg C2D1+: 48mg					C1D1: obin 1000 mg C1D8: 2.5 mg C1D15: 10 mg C2D1+: 30 mg				
Premedications	(1) A/P 650-1000 mg, 30-120 min before C1 treatments (2) Diphenhydramine 50 mg, 30-120 min before C1 treatments (3) Dexamethasone 15 mg, 30-120 min before C1 treatments and for 3 consecutive days after. Continue dexamethasone thereafter if G2 or G3 CRS with prior dose.					(1) A/P 500-1000 mg, 30 min before all treatments (2) Diphenhydramine 50 mg, 30 min before all infusions (3) Dexamethasone 20 mg, 1 h before treatment on C1D8, C1D15, C2D1, and C3D1. Continue if CRS with prior dose.				
Hospitalization	C1D15: 24-h admission					C1D8: 24-h admission				
CRS occurrence	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
	34%	15%	3%	0%	0%	47%	12%	3%	1%	0%
	Time course for CRS onset: C1D1: 5.8% C1D8: 11.8% C1D15: 42.8% C1D22: 4.9% C3+: 3%			Median time (h) to CRS onset: All doses: 24 C1D15: 20		Time course for CRS onset: C1D8: 42.8% C1D15: 25.2% C2: 26% C3+: 0.9%			Median time (h) to CRS onset: C1D8: 13.5 (range: 6-52)	
Median duration of CRS	2 d (range: 1-27 d)					30.5 h (range, 0.5-317 h)				
Neurotoxicity	G1	G2	G3	G4	G5	G 1-2		G 3-4		G5
	4.5%	1.3%	0%	0%	0.6%	5%		3%		0%

Clinical management of bispecific antibody therapy for lymphoma: A British Society for Haematology Good Practice Paper

Br J Haematol. 2025;207:1227–1241.

Grade 1 CRS	Grade 2 CRS	Grade 3 CRS	Grade 4 CRS
Fever (Temperature ≥ 38°C) No hypotension No hypoxia	Fever* (Temperature ≥ 38°C) AND Hypotension not requiring vasopressors AND/OR Hypoxia requiring low-flow nasal cannula or blow-by (O2 ≤ 6 L/min) to maintain O2 sats at >92-94%	Fever* (Temperature ≥ 38°C) AND Hypotension requiring vasopressor AND/OR Hypoxia Requiring high-flow nasal cannula (O2 > 6 L/min) , facemask, non-rebreather mask, or Venturi mask	Fever* (Temperature ≥ 38°C) AND Hypotension requiring multiple vasopressors AND/OR Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)
Supportive measures: Check FBC, U&Es, LFTs, Ca2+, uric acid, LDH, CRP, ferritin. Full infection screen. Antipyretics and IV fluids as needed. Check vital signs regularly until symptoms resolve. Initiate broad-spectrum IV antibiotics, especially if neutropenic and/ or CRS grade ≥2.			
Initiate **tocilizumab** 8 mg/kg IV or **dexamethasone** 10 mg OD PO x 1-2 days for persistent or recurrent fever after > 24 hours of antipyretics. For patients receiving ongoing steroid prophylaxis for CRS, tocilizumab is preferable. Earlier use of tocilizumab is recommended for high-risk† patients with CRS.	Consider IV fluid boluses of 500ml as needed. Administer oxygen as needed. Administer **tocilizumab** 8 mg/kg IV. Repeat every 8 hours if no response. Maximum 4 doses per CRS event, 2 doses in 24 hours. Start **dexamethasone** (if not already on this) 10 mg IV every 12 hours if no response after 1-2 doses of tocilizumab. Continue for 1-3 days until resolution to grade ≤1.	Critical care outreach referral. Transfer to ICU. Administer IV fluids, vasopressors and oxygen as needed. Continuous cardiac monitoring. Consider echo. Administer **tocilizumab 8 mg/kg IV.** Repeat every 8 hours if no response. Maximum 4 doses per CRS event, 2 doses in 24 hours. Start **dexamethasone** 10–20 mg IV every 6 hours if no response after 1-2 doses of tocilizumab. Continue for 1-3 days until resolution to grade ≤1. Consider **anakinra:** 100mg BD s/c if no improvement after tocilizumab and 24 hours of steroids. Anakinra can be continued for 3-7 days.	Administer **tocilizumab 8 mg/kg IV.** Repeat every 8 hours if not responsive; Maximum 4 doses per CRS event, 2 doses in 24 hours. Start **methylprednisolone** 1000 mg IV OD if no response after 1-2 doses of tocilizumab. Continue for 3 days and taper to 250 mg BD for 2 days, 125mg BD for 2 days, 60mg BD for 2 days. Consider **anakinra** 100mg BD s/c if no improvement after 24 hours of methylprednisolone. Anakinra can be continued for 3-7 days. Consider **Siltuximab** if no improvement after 2-3 days of high dose IV methylprednisolone.

†High-risk patients for CRS
High tumour burden
Renal and / or cardiac impairment
Frail patient

Tocilizumab: dose 8 mg /kg IV (not to exceed 800 mg). Can be repeated after at least 8 hours. Maximum 4 doses per CRS event.
Anakinra: not licensed for CRS. Needs funding. Dose can be increased to 200mg BD if no improvement after 24-48 hours.
Siltuximab: 11 mg/ Kg IV single dose. Not licensed for CRS. Needs funding.

If offering home management for CRS: Assess all patients for suitability prior to initiating BsAb therapy.
Patients with one or more risk factors# may not be suitable for home management and must be advised accordingly.
Pathway outlined below is an option for patients assessed as suitable for home management.

Patient contacts hospital triage line out of hours with
Fever (Temperature ≥ 38°C) within 24-48 hours of step up dose of BsAb

Otherwise feeling entirely well
No light headedness, dizziness, shortness of breath
Not neutropenic on the day of BsAb administration
Patient assessed as suitable for home management prior to starting BsAb

Yes

Antipyretics: Advise to take Paracetamol 1 g PO stat.
Hydration: drink oral fluids, around 1L every 8-12 hours.
Dexamethasone: 10 mg PO stat dose if persistent fever after >4-6 hours and 1 dose of paracetamol
Self-monitor: check temperature every 2-4 hours. Contact hospital immediately if begins to feel unwell at any stage or if no response in fever after paracetamol +/- dexamethasone.
If fever settles, ask to attend next day for hospital review.

Next day hospital review: Check FBC, U&Es, LFTs, Ca2+, uric acid, LDH, CRP, ferritin. Full infection screen. Arrange admission if any concerns on bloods or clinical assessment.

No

Arrange immediate assessment and admission to hospital.
Initiate management as per CRS management in hospital protocol.

ICE scoring system	
Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backward from 100 by 10	1 point

This pathway is only for hospitals able to offer remote, out-of-hospital management of low grade CRS. In all other cases, patients developing CRS symptoms at home must be asked to attend for immediate assessment and admission.
This pathway is outside the mandatory admission for each bispecific antibody.

Br J Haematol. 2025;207:1227–1241.

Features to Consider When Sequencing Salvage Therapies for R/R DLBCL

- Frailty assessment
- Comorbidities
- Organ function
- Ability to tolerate adverse events
- Disease burden
- Rate of disease progression
- Molecular/genetic features
- Baseline cytopenia
- Risk/benefit profile of regimen
- Documented response to therapy
- Duration of response to prior therapy
- Patient preferences
- Access to therapy
- Financial considerations

Grazie