# CORRESPONDENCE

# CD20 xCD3 bispecific antibodies for large B cell lymphoma: latest updates from 2024 ASH annual meeting

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# Abstract

Bispecific antibodies (BsAbs) represent an innovative class of off-the-shelf T-cell redirecting agents and are considered among the most promising immunotherapeutic strategies for the treatment of lymphoma. Notably, anti-CD20 × CD3 BsAbs have exhibited substantial monotherapy efficacy in patients with heavily pretreated B-cell non-Hodgkin lymphoma (B-NHL), showing a tolerable toxicity profile predominantly associated with T-cell activation-related side effects. In this study, we summarized several latest reports on CD20  $\times$  CD3 bsAbs for the therapy of Large B Cell Lymphoma (LBCL), also in first line, from the ASH 2024 annual meeting (ASH 2024).

# To the Editor,

This article presents a comprehensive overview of the most recent clinical data on CD20×CD3 BsAbs for LBCL, as showcased at the 2024 ASH Annual Meeting (Table 1).

# BsAbs in the setting of first line fit treatment patients

Patients with LBCL experience a relapse rate of 40% after first-line treatment, with OS and PFS rates decreasing as the IPI increases, suggesting the need for novel treatments to improve outcomes. Falchi et al. reported results from the EPOCORE-NHL 2 trial involving 47 previously untreated patients with LBCL (IPI $\geq$ 3) who received epcoritamab (epcor) [1] plus R-CHOP. At the median follow-up the ORR was 100%, with a CR rate of 87%. The estimated OS and PFS at 24 months were 87% and

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74%, respectively. The most frequent treatment-related AEs were neutropenia (70%), anemia (68%), and CRS (60%), with CRS all being Grade 1-3 and occurring after the first full dose. ICANS was reported in 2 patients and resolved.

In a multicenter trial comparing glofitamab (glofit)-R-CHOP (arm A) and glofit-pola-R-CHP (arm B) for highrisk LBCL patients (IPI $\geq$ 3, NCCN-IPI $\geq$ 4, or HGBL with MYC and BCL2 and/or BCL6 rearrangements) [2], 80 patients were randomized. After induction, CR/PR rates were 70%/29% in arm A and 80%/18% in arm B. Grade  $\ge$  3 AEs occurred in 22/40 patients in each arm, with CRS Grade 1 in 7/40 (18%) in arm A and 8/40 (20%) in arm B. One Grade 2 CRS event occurred in each arm, with no Grade 3-5 CRS events.

## BsAbs in the setting of first line unfit treatment patients

The EPCORE® DLBCL-3 trial (Arm A) [3] enrolled 45 patients aged over 75 years, anthracycline-ineligible due to advanced age, comorbidities, or cardiac toxicity risk, all with newly diagnosed LBCL. These patients received epcor for a fixed duration of up to one year. Among 39 evaluable patients, the ORR was 74% (29/39) and the

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Agent	Format	CD20:CD3 ratio	Administration	FC silencing mutations	Dosing	Approved indications
Epcoritamab <sup>1</sup>	lgG1	1:1	SC	L234F, L235E, D265A (no FcyR, C1q binding)	Step-wise	LBCL and FL R/R after 2 or more lines
Glofitamab <sup>2</sup>	lgG1	2:1	IV	lgG1-P329G-LALA (no FcγR binding)	Step-wise	LBCL after 2 or more lines
Odronextamab <sup>5</sup>	lgG4	1:1	IV	Modified IgG4 (no FcyRIII binding)	Step-wise	Non approved for now
Mosunetuzumab <sup>12</sup>	lgG1	1:1	IV/SC	N297G (no FcγR binding)	Step-wise	R/R FL after 2 or more lines
Plamotamab <sup>8</sup>	lgG1	1:1	IV/SC	G236R, L328R (no FcyR binding)	Step-wise	Non approved for now

Table 1 Characteristics of CD20×CD3 bispecifc antibodies

CR rate was 64% (25/39). The most common treatmentemergent AEs occurred in 20% of patients, with 68% of these being CRS. Despite advanced age and comorbidities, epcor demonstrated both efficacy and a favourable safety profile.

Another study explored the combination of epcor and R-mini-CHOP in first-line LBCL [4]. In arm 8 of the EPCORE<sup>™</sup> NHL-2 study, 28 patients with a median age of 81 years and cardiological comorbidities were enrolled. The median follow-up was 16.8 months, with an ORR of 89% (25/28) and a CR rate of 82% (23/28). The most common treatment-related AEs were CRS (45%), all resolved except for one case.

Given R-CHOP's high efficacy, BsAbs may be reserved for higher-risk or comorbid patients to enhance chemotherapy, without introducing new safety concerns.

### BsAbs in the setting of R/R patients

R/R LBCL patients have poor prognosis, with 50% failing salvage chemotherapy and ASCT. CAR-T achieves long-term remission in 40%, with some ineligible due to fitness, access, or cost, or needing bridging therapy.

In the setting of R/R LBCL, three groups presented long-term follow-up data on monotherapy with BaAbs. Allan et al. [5] reported pooled data from the ELM 1 and 2 studies using odronextamab (odro) monotherapy in hard-to-treat R/R LBCL populations. Epcore-NHL 1 [6] presented 3-year data from 157 patients treated with epcor monotherapy. Dickinson [7] presented 3-year results from 155 patients treated with 12 cycles of glofit. These three trials demonstrated similar efficacy in terms of ORR and comparable CRS rates (Table 2).

Riedell et al. [8] presented the first results from plamotamab, a novel CD20×CD3 BsAb administered subcutaneously in heavily pretreated NHL patients, including 14 with LBCL. The median number of prior lines was 4, compared to 3 for other BsAbs.

For combination therapies in R/R LBCL, Diefenbach et al. [9] explored the combination of glofit with R-ICE in patients eligible for ASCT or CAR-T therapy after one prior line. Gurion et al. [10] updated the Epcore-NHL-5 study, where 40 patients with R/R LBCL received epcor plus lenalidomide for 12 cycles, achieving an ORR/CR

rate of 67.6%/65%, this combination aim to restore the immune synapse and enhance cytotoxicity.

Both glofit and mosunetuzumab (mosu) have been combined with the anti-CD79b antibody-drug conjugate polatuzumab vedotin (pola) in R/R LBCL patients [11–12]. In the Chavez trials, patients were randomized to the M-Pola arm vs. the rituximab (R)-Pola arm. The ORR and CR rates for these combinations were 84% and 61% for glofit, and 78% and 58% for mosu, respectively. These results suggest an advantage for combination therapy while maintaining a similar safety profile (Table 2).

CD20×CD3 BsAbs are a major advance in LBCL treatment. While their CR rates match CAR-T, more data on long-term outcomes and DoRs are needed. The easiest accessibility to these drugs could represent an advantage to CAR-T and ensure better compared to ASCT in R/R patients.

First         Fir prs         NCT04663347 <sup>1</sup> //1         Epor+R-CHOP         47         66         LBCL         /         100/76           Line         NCT04914741 <sup>2</sup> I         Epor+R-CHOP         47         66         LBCL         /         100/76           Line         NCT04914741 <sup>2</sup> I         Epor+R-CHOP         80         58         High-risk         /         100/76           Alss         Cloff+pola-R-CHP         Alss         Cloff+pola-R-CHP         80         58         High-risk         /         100/76           Alss         Cloff+pola-R-CHP         Alss         Cloff+pola-R-CHP         80         58         High-risk         /         100/76           Alss         Cloff+pola-R-CHP         Alss         Cloff+pola-R-CHP         8         31         100/76         31           Alss         Cloff+pola-R-CHP         24-65         BCL         100/76         31         31           Alss         NCT02560967 <sup>3</sup> I         Epocr/R-minICHOP         28         31         100/76         32         36         31           RR         Monotherapy         NCT02320376         I         Epocr/R-minICHOP         28         BCL         100/76 <th>Setting</th> <th>Type of pts</th> <th>Trial</th> <th>Phase</th> <th>Regimen</th> <th>N° pts</th> <th>Median age (y)</th> <th>Histology</th> <th>Prior CAR-T</th> <th>ORR/ CR %</th> <th>OS/PFS %</th> <th>% to remain CR</th> <th><u>CRS/</u> ICANS %</th> <th>-<u>Iol</u> (mo) (mo)</th>	Setting	Type of pts	Trial	Phase	Regimen	N° pts	Median age (y)	Histology	Prior CAR-T	ORR/ CR %	OS/PFS %	% to remain CR	<u>CRS/</u> ICANS %	- <u>Iol</u> (mo) (mo)
NCT04914741 <sup>2</sup> II         Giorth-R-CHOP (arm A)vs         S8         High risk LBCL         /         100700 (arm B)           Alvs         Giorth-Dola-R-CHOP (arm B)         Alvs         C24-65         LBCL         (P12-3)-LGBU         Alvs         100700           Alvs         Giorth-Dola-R-CHOP (arm B)         NCT05660967 <sup>3</sup> II         Epcor fixed dose         45         81         LBCL         100700           NCT04663347 <sup>4</sup> //I         Epcor fixed dose         45         81         LBCL         74/64         74/64           NCT03688105 <sup>5</sup> //I         Epcor fixed dose         45         81         LBCL         74/64         74/64           NCT030388105 <sup>5</sup> //I         Epcor fixed dose         45         12         24-65         24/64           NCT030388105 <sup>5</sup> //I         Epcor fixed dose         15         64         LBCL         16         59/41           NCT030388105 <sup>5</sup> //I         Epcor fixed dose         15         64         LBCL         16         59/41           NCT030388105 <sup>5</sup> //I         Epcor fixed         15         64         LBCL         16         59/41           NCT0305050 <sup>6</sup> //I         Epcor fixed	First Line	Fit pts	NCT04663347 <sup>1</sup>		Epcor + R-CHOP	47	66 (19–82)	LBCL (IPI≥3)		100/87	87/74 at 24 mo (e)	83 CR at 24 mo (e)	60/4.3	27.6
			NCT04914741 <sup>2</sup>	=	Glofit-R-CHOP (arm A)vs Glofit-pola-R-CHP (arm B)	80	58 (24–65)	High risk LBCL (IPI ≥ 3, HGBL/ HGBL-double hit)	~	100/70 (arm A) <i>vs</i> 100/80	96/88(arm A) vs 97/95 (arm B) at 12 mo	NR	20(arm A) <i>v</i> s 22 (arm B)/0	14.6
RR         NCT04663347 <sup>4</sup> //1         Epcor+R-miniCHOP         28         81         B.C.         99/82           RR         Monotherapy         NCT02290951-         1         Odro         187         65         B.C.         Kes         50/31.           setting         NCT02290951-         1         Odro         187         65         B.C.         Kes         50/31.           NCT03550376         /11         Epcor         157         64         B.C.L.HGBL, mediastinal LBCL         Yes         59/41           NCT030756967         11         Gloft         155         66         LBCL.HGBL, mediastinal LBCL         Yes         59/41           NCT029244028         1         Oloft         155         66         LBCL.HGBL         Yes         59/41           NCT029244028         1         Plamo         22         67         LBCL/HGBL         Yes         53/40           NCT029341249         1b/1         Plamo         22         67         LBCL/HGBL         Yes         53/40           NCT053332311         b/11         Epcor+Hena         40         71-50         Other*         Yes         57/65           NCT0533323231         b/11         Epcor+Hena		Older/unfit	NCT05660967 <sup>3</sup>	=	Epcor fixed dose	45	81 (77 05)	LBCL (and multiple comprision)	~	(arm b) 74/64	76 at 6 mo/NR	88 CR at 6	13/15	9
R/R         Monotherapy         NCT0229051-         1         Odro         187         6.5         LBCL         Ves         508/31           setting         NCT03388105 <sup>5</sup> V/I         Epcor         157         6.4         LBCL, HGBL, mediastinal LBCL         Yes         59/41           NCT03305505 <sup>6</sup> II         Gloft         157         6.4         LBCL, HGBL, mediastinal LBCL         Yes         59/41           NCT03075506 <sup>7</sup> II         Gloft         155         6.6         LBCL         Yes         52/40           NCT032924402 <sup>8</sup> I         Plamo         22         6.7         LBCL/HGBL/         Yes         52/40           NCT032924429 <sup>8</sup> I         Plamo         22         6.7         LBCL/HGBL/         Yes         52/40           NCT05283370 <sup>10</sup> B/II         Epcor+Hena         40         71.5         LBCL/HGBL/         Yes         67/6/51           NCT05283370 <sup>10</sup> B/II         Epcor+Hena         40         71.5         LBCL         Yes         67/6/51           NCT052833203 <sup>11</sup> B/II         Gloff+Pola         57         59         LBCL/HGBL/         Yes         67/6/51           NCT052833203 <sup>11</sup> <td< td=""><td></td><td></td><td>NCT04663347<sup>4</sup></td><td></td><th>Epcor + R-miniCHOP</th><td>28</td><td>(ce-77) 81 (74-90)</td><td>(age, muriple comorportes) LBCL (age, cardiological comorbidities)</td><td>~</td><td>89/82</td><td>96/88 at 12 mo (e)</td><td>91 CR at 12 mo (e)</td><td>45/0</td><td>16.8</td></td<>			NCT04663347 <sup>4</sup>		Epcor + R-miniCHOP	28	(ce-77) 81 (74-90)	(age, muriple comorportes) LBCL (age, cardiological comorbidities)	~	89/82	96/88 at 12 mo (e)	91 CR at 12 mo (e)	45/0	16.8
NCT036250376         I/I         Epcor         157         64         LBCL, HGBL, mediastinal LBCL         Yes         59/41           NCT030756967         I         Gloft         155         66         LBCL         Yes         52/40           NCT029244028         I         Plamo         22         67         LBCL/HGBL/         Yes         43/14           NCT029244028         I         Plamo         22         67         DLC/HGBL/         Yes         43/14           NCT029244028         I         Plamo         22         67         DLC/HGBL/         Yes         52/40           NCT029244028         I         Plamo         22         67         Nec         71/4         Yes         43/14           Recurrention         NCT0533232010         Ib/II         Epcor+lena         40         71/5         LBCL         Yes         67/651.           NCT0528372010         Ib/II         Epcor+lena         40         71/5         LBCL         Yes         67/651.           NCT05283328311         Ib/II         Gloff+Pola         71/5         LBCL/HGBL/         Yes         67/651.           NCT0353328311         Ib/II         Gloff+Pola         71/5         LBCL/HGBL/	R/R setting	Monotherapy	NCT02290951- NCT03888105 <sup>5</sup>	_	Odro	187	65 (24–88)	LBCL	Yes	50.8/31.6	27/17.5 at 36 mo (e)	51 at 36 mo	52.9/0	23
NCT030756967         II         Gloft         155         66         LBCL         Yes         52/40           NCT02924402 <sup>8</sup> I         Plamo         22         67         LBCL         Yes         43/14           NCT02924402 <sup>8</sup> I         Plamo         22         67         LBCL         Yes         43/14           Combination         NCT05364424 <sup>9</sup> Ib         Glofit+R·ICE         41         66         LBCL/HGBL         Yes         78.1/68.1           NCT05383720 <sup>10</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51.           NCT05333283 <sup>11</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51.           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL         Yes         67.6/51.           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL         Yes         67.6/51.           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL         Yes         67.6/51.	'n		NCT03625037 <sup>6</sup>		Epcor	157	64 (20–83)	LBCL, HGBL, mediastinal LBCL	Yes	59/41	18.5 mo /4.2 mo (median)	36.1 mo (median)	51/0	37.1
NCT02924402 <sup>8</sup> I         Plamo         22         67         LBCL/HGBL/         Yes         43/14           Combination         NCT05364424 <sup>9</sup> Ib         Glofit+R-ICE         41         (27-90)         Other*         43/16           NCT05364424 <sup>9</sup> Ib         Glofit+R-ICE         41         66         LBCL/HGBL         No         78.1/68:           NCT05383720 <sup>10</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51:           NCT05333283 <sup>11</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51:           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL/         Yes         67.6/51:           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL/         Yes         84/61			NCT03075696 <sup>7</sup>	=	Glofit	155	66 (21–90)	LBCL	Yes	52/40	77/57 in CR pts	28.9 mo (median)	62/0	41
Combination         NCT05364424 <sup>9</sup> Ib         Glofit+R-ICE         41         66         LBCL/HGBL         No         78.1/68.           NCT05283720 <sup>10</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51.           NCT05283720 <sup>10</sup> Ib/II         Epcor+lena         40         71.5         LBCL         Yes         67.6/51.           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL/         Yes         84/61           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL/         Yes         84/61           NCT03533283 <sup>11</sup> Ib/II         Glofit+Pola         57         59         LBCL/HGBL/         Yes         84/61           Yes         EL         29-82         Mediastinal LBCL/transformed         PL			NCT02924402 <sup>8</sup>	_	Plamo	22 (14 LBCL)	67 (27–90)	LBCL/HGBL/ Other*	Yes	43/14	. N	5.5 mo (median)	6/69	11
NCT05283720 <sup>10</sup> Ib/li       Epcor+lena       40       71.5       LBCL       Yes       67.6/51.         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61         NCT03533283 <sup>11</sup> Ib/li       Glofit+Pola       57       59       LBCL/HGBL/       Yes       84/61		Combination	NCT05364424 <sup>9</sup>	q 	Glofit + R-ICE	41	66 (41–78)	LBCL/HGBL	No	78.1/68.8	NR	NR	48.8/0	3#
NCT03533283 <sup>11</sup> Ib/II <b>Glofit+Pola</b> 57 59 LBCU/HGBL/ Yes 84/61 (LBCL) (29–82) Mediastinal LBCL/transformed FL FL			NCT05283720 <sup>10</sup>	ll/dl	Epcor + lena	40	71.5 (26–85)	LBCL	Yes	67.6/51.4	NR	NR	65/2.5	11.5
			NCT03533283 <sup>11</sup>	II/qI	Glofit + Pola	57 (LBCL)	59 (29–82)	LBCL/HGBL/ Mediastinal LBCL/transformed FL	Yes	84/61	39.2/12.3 mo (median *all pts)	31.8 mo (median *all pts)	43/3.1	23.5
NLIU36/IU18 <sup></sup> ID/II <b>M -POIAVS</b> &U /1V56/ LBLUFHGBL/ Yes /3/35 V R-Pola (40 vs Trasformed FL 50/35 An)			NCT03671018 <sup>12</sup>	II/qI	M -Polavs R-Pola	80 (40 vs	71 vs 67	LBCL/HGBL/ Trasformed FL	Yes	78/58 vs 50/35	nr/nr vs nr/6.4 mo	nr median	4/2.5	18

\*: T cell rich lymphoma, mantle cell lymphoma, Waldenstrom macroglobulinemia

#: period of interim efficacy evaluable populations

Abbreviations: CAR-T: Chimeric Antigen Receptor-T: CR: Complete Response; CRS: Cytokine Release Syndrome; Epcori Epcoritamab; E: estimated; FL: Follicular Lymphoma; ICANS: Immune effector Cell-Associated Neurotoxicity Syndrome; Glofi: Glofitamab; ICE: Ifosfamide, Carboplatin, Etoposide; IPI: International Prognostic Index; HBGL: High-Grade B-Lymphoma; LBCL: Large B-cell lymphoma; M: mosunetuzumb; Mo: Months; Nr: not reached; NR: not reported; Odro: odronextamab; OS: Overall Survival; ORR: Overall Response Rates; PFS: Progression-Free Survival; Plamo: plamotamab; Pola: Polazutumab; Pts: Patients; R: Rituximab; R/R: Relapsed/ Refractory; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

#### Abbreviations

AE	Adverse Events
ASH	American Society of Hematology
ASCT	Autologous Stem Cell Transplantation
BsAbs	Bispecific Antibodies
CAR-T	Chimeric Antigen Receptor
CR	Complete Response
CRS	Cytokine Release Syndrome
DoR	Duration of Response
FL	Follicular Lymphoma
IV	Intravenous
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	lfosfamide, Carboplatin, Etoposide
IPI	International Prognostic Index
HBGL	High-Grade B-Lymphoma
LBCL	Large B-cell lymphoma
Мо	Months
NCCN	National Comprehensive Cancer Network
NHL	Non Hodgkin Lymphoma
OS	Overall survival
ORR	Overall Response Rates
PFS	Progression-Free Survival
PR	Partial Response
Pts	Patients
R/R	Relapsed/Refractory
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and
	Prednisone
SC	Subcutaneous

#### Author contributions

VT, LR and OA drafted and revised the manuscript and prepared the tables. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

This is not applicable for this summary.

#### **Competing interests**

The authors declare no competing interests.

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