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Outcomes of real-world complete responders after fixed-duration glofitamab in relapsed/refractory large B-cell lymphoma

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Author Contributions

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Letter to the Editor

CD20×CD3 bispecific antibodies (BsAbs) induce complete remissions (CR) in a substantial number of relapsed/refractory large B-cell lymphoma (r/r LBCL) patients [1, 2], yet outcomes of real-world complete responders remain insufficiently characterized. We retrospectively analyzed 52 consecutive patients with r/r LBCL who achieved CR after glofitamab monotherapy at 25 centers across Germany, Austria, Switzerland and Italy between August 2021 and February 2025 (data cut-off: February 1, 2026). All patients received glofitamab as standard of care or compassionate use outside interventional clinical trials and provided consent per local regulations. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (IRB) of the University of Muenster (2024-317-f-S). Most patients maintained durable remissions with favorable survival and limited late relapse. A CONSORT diagram summarizing patient selection is provided in **Supplemental Figure S1**. Overall, 232 patients with r/r LBCL received glofitamab monotherapy during the study period, corresponding to a CR rate of 22.4% (52/232).

The cohort of collected patients had received a median of three prior lines of therapy, with 63.5% having received a prior chimeric antigen receptor T-cell (CAR-T) therapy. Radiographic/metabolic CRs were confirmed by investigators based on Lugano response criteria, including Deauville assessment.

The most common LBCL entities were *de novo* diffuse large B-cell lymphoma (DLBCL) (35/52), transformed indolent lymphoma (11/52) and high-grade B-cell lymphoma (6/52) (**Table 1**). Median age at BsAb initiation was 67 years. Thirty-eight percent of patients received BsAb in third line (3L) and 62% in later lines (4L+). At treatment initiation 51.6% had a high-intermediate or high international prognostic index (IPI). Because this cohort includes only CR patients, baseline features describe the responding population and are not intended to imply prognostic enrichment.

Baseline clinical parameters among complete responders were moderate. Almost 77% presented with an elevated LDH (40/52), 34.6% refractoriness to last therapy, and late relapse (>6 months) among those previously exposed to CAR-T in 48.5% of patients. CR was documented by positron emission tomography-computed tomography (PET-CT) in 63.5% of cases and in 36.5% by radiologic imaging (CT) (**Table 1 and S1**).

At the time of last follow-up, no patients were receiving ongoing glofitamab therapy. Thirty-six patients (69.2%) completed 12 cycles without any subsequent consolidation, 5 (9.6%) discontinued due to toxicity, and one (1.9%) due to secondary malignancy. Three (5.8%)

underwent CAR-T consolidation and four (7.7%) underwent allogeneic stem cell transplantation as consolidation after the maximum of 5 cycles of glofitamab. One more patient (1.9%) underwent allogeneic stem cell transplantation after completing 12 cycles of glofitamab. Two patients (3.8%) distontinued treatment due to progression (**Table S1**).

Median time to documented CR was 136 days (range, 17-360). At a median follow-up (FU) of 21.2 months after BsAb initiation, 8 patients (15.4%) experienced relapse or progression and thirteen (25%) died, including four due to r/r disease and nine from non-relapse reasons (infection, n=5; bleeding, n=1; secondary malignancy, n=1; unknown, n=2, all in CR). Of those relapsing, 2 relapsed during ongoing BsAb therapy and 6 relapsed after end of treatment (EOT) (five after 12 cycles, one after 7 cycles of glofitamab discontinued due to a COVID-19 infection). Four patients died from r/r disease at data cut-off. Notably, 4 of 5 fatal infections occurred in patients in sustained CR after regular EOT with 12 cycles of glofitamab, with one, six, eight and 10 months from EOT to death. This corresponds to a relapse-related mortality of 7.7% and a non-relapse mortality (NRM) rate of 17.3%.

Overall, 24 out of 52 patients experienced any infection (46%) with a grade ≥ 3 documented in 13 patients (25%). Infectious complications included mostly bacterial (n=15; 29.8%) and viral (n=16; 30.8%), with COVID-19-related events observed in 12 patients (23.1%). One additional patient also had a fungal infection in addition to bacterial and viral infections. Acyclovir (400 mg twice daily) and cotrimoxazole (960 mg twice daily two days a week or 960mg once daily three days per week) were used as prophylaxis. Immunoglobulin Replacement Therapy (IgRT) could be employed in cases where patients exhibited serum IgG levels below 4 g/l and experienced recurrent or severe infections; 21 of 52 patients (40.4%) received IgRT. Kaplan-Meier estimates showed a 1-year PFS of 90% and 1-year OS of 94% after BsAb initiation in patients achieving CR (**Figure 1A/B**). Among patients who completed all 12 glofitamab cycles (n = 36; 69.2%), the 1-year PFS and OS after EOT were 69.0% and 83.0%, respectively (**Figure 1C/D**). Patients with early treatment termination for non-relapse causes (n = 7; 13.4%) showed a 1-year PFS of 71.0% and OS of 71.0% after EOT. Those who underwent consolidation with either CAR-T therapy or allogeneic HSCT (n = 7; 13.4%) demonstrated a 1-year PFS and OS of 86% after consolidation. Accordingly, the median duration of CR was not reached.

The individual patient trajectories are shown in the swimmer plot (**Figure 2)**.

Overall, CR remains a key prerequisite for achieving durable disease control in r/r LBCL. The introduction of BsAbs has revolutionized treatment and prognosis in heavily pretreated

patients. As BsAb development followed the clinical introduction of CAR-T therapies, their curative potential in the real-world setting is still being defined. In the last FU of the glofitamab pivotal study, the median CR duration was 29.8 months, with 2-year PFS and OS rates of 57% and 77% in patients with CR at EOT respectively [3]. Although the FU in our analysis is shorter, and patients were more heavily pretreated (2/3 vs. 1/3 post-CAR-T treatment), our data are so far in line with the above-mentioned studies, with most patients maintaining durable remissions with favourable survival and limited late relapse, supporting the potential for sustained, treatment-free disease control after fixed-duration bispecific antibody therapy. However, given the retrospective design and limited follow-up of this analysis, so far cure cannot be reliably inferred, and longer observation will be required to define long-term outcomes.

In our previous real-world analyses, CR rates with BsAbs reached up to 27.1% in patients with a median of 4 prior therapy lines [4, 5]. A further real-world analyses by Brooks et al. showed a CR-rate of 30% [6]. In the present analysis, the CR rate was 22.4%. So far, combinations of BsAbs with chemotherapy or biologicals show improved efficacy - albeit in indirect comparisons - compared with BsAb monotherapy. Despite short FU, CR- and survival rates of such combination studies in patients who had failed at least one previous treatment line are promising and approach responses of patients treated with CAR-T (**Table S2**) [1-3, 7-14]. In the STARGLO trial, glofitamab plus gemcitabine/oxaliplatin (GemOx) achieved a 58.5% metabolic CR rate and a median OS of 25.5 months in transplant-ineligible patients after at least one prior therapy line [8]. In patients with a CR at EOT (n= 82), the 1-year PFS and -OS rates were 82.4% and 89.3% respectively[15]. The EPCORE NHL-2 study evaluated epcoritamab in combination with GemOx in transplant-ineligible patients after at least two prior lines of therapy, reporting a CR rate of 61% and a median OS of 21.6 months[16]. At present, whether BsAb combinations should bridge to or even replace CAR-T therapies remains an open question, and no direct comparison between BsAb-based combinations and CAR-T efficacy can be made based on this analysis. Notably, patients with early BsAb termination due to toxicity or who were consolidated also demonstrated excellent outcomes in our cohort.

Beyond efficacy, our analyses highlight the still inadequately recognized risk of infection-related mortality in patients treated with BsAbs. Our data are in line with the infection rates reported in the pivotal trials [1, 2], indicating the need for close follow-up even in patients with ongoing CR. Immune profiling including IgG levels, but possibly also biomarkers of the patients' cellular immune status such as CD4+ T-cell subsets, T-cell receptor repertoire diversity, or delayed CD19+ recovery may identify patients early which are at risk of developing serious infections. Subsequent measures can include immunoglobulin substitution, antibiotic and

antiviral prophylaxis, as well as vaccination strategies to mitigate the risk of preventable infections.

In summary, BsAb monotherapy with glofitamab can induce durable CRs in heavily pretreated r/r LBCL patients. The limitations of our study are a relative short median follow-up, the retrospective design, investigator-assessed response evaluation, the lack of standardized imaging schedules across centers and a relatively small cohort size. However, this is reflective of the infrequent occurrence of complete remissions in the real-world setting and the exploratory nature of this analysis is acknowledged.

NRM rather than relapse mortality was the leading cause of death among our patients in CR after BsAb. To this end, infection-related NRM, especially after EOT, poses a critical challenge. As bispecific antibodies will move into earlier lines of treatment of patients with aggressive B-cell lymphomas, long-term risk mitigation with improved anti-infectious prophylactic and therapeutic strategies should become a key element of clinical development to unlock their full therapeutic potential.

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Table 1. Patient characteristics of the study cohort.

Parameters	**n (%)**
Patients	52 (100)
Median age at lymphoma diagnosis, [IQR]	62 [54-72]
Median age at Glo administration, [IQR]	67 [57-76]
Sex, male	22 (42.3)
Lymphoma types	
DLBCL *de novo*	35 (67.3)
- GCB (Hans et al.)	10 (19.2)
- Non-GCB (Hans et al.)	13 (25.0)
- Unclassifiable	12 (23.1)
DLBCL transformed from any indolent lymphoma	11 (21.2)
HGBL w/ *MYC & BCL2* rearr.	5 (9.6)
HGBL, NOS	1 (1.9)
Median time from dx to Glo, mo, [IQR]	26 [17-55]
BsAb in 3L	20 (38.5)
BsAb in 4L+	32 (61.5)
Therapies prior to Glo	
Median number of lines, range	3 (2-6)
Anti-CD20/anthracycline-based	45 (86.5)
Platinum-based salvage	34 (65.4)
Benda/ritux +/- polatuz.	13 (25)
- Benda w/in last 6 mo prior Glo	3 (5.8)
Tafasitamab / lenalidomide	13 (25)
PD-1 inhibitor	3 (5.8)
Ibrutinib	1 (1.9)
Cellular therapies prior Glo	
CAR-T	33 (63.5)
- Early CAR-T failure (0-3 mo.)	8 (24.2)
- Intermediate CAR-T failure (4-6 mo.)	9 (27.3)
- Late CAR-T failure (>6 mo.)	16 (48.5)
Auto-HSCT	14 (26.9)
Allo-HSCT	4 (7.7)
Disease features prior Glo	
Bulky (>7.5 cm)	7 (13.5)
Extranodal lesions	31 (59.6)
Median LDH U/L prior to Glo, [IQR]	289 [239-372]
LDH U/L > upper limit of normal, prior to Glo	40 (76.9)
Secondary IPI at Glo initiation, n = 48	
IPI low (0-1)	8 (16.7)
IPI low-int. (2)	15 (31.1)
IPI high-int. (3)	12 (24.5)
IPI high (4-5)	13 (27.1)
Refractory to last tx	18 (34.6)

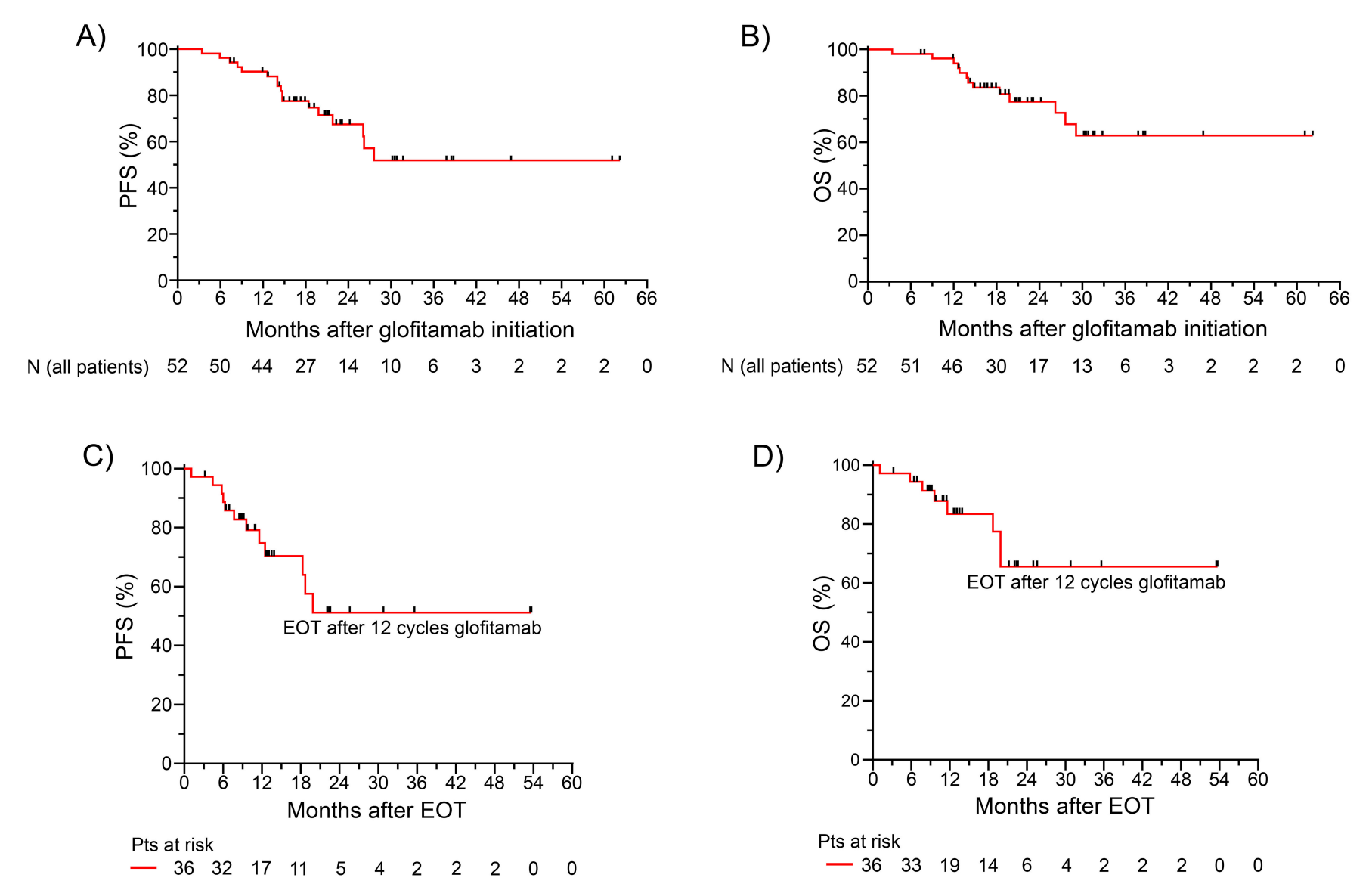
Types of BsAb administered	
Glofitamab	52 (100)

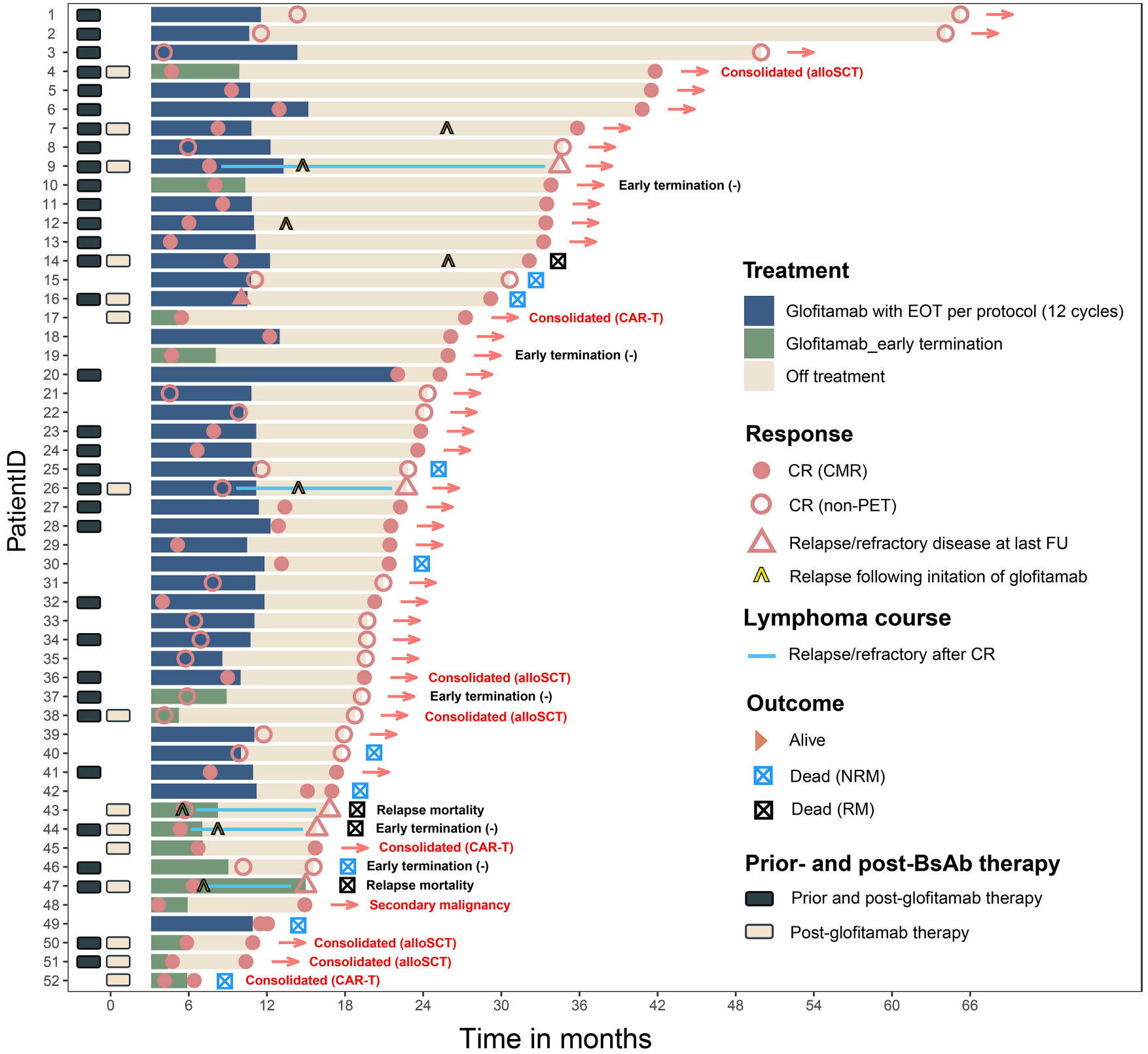
Percentages refer to total number of events scored. Glo, glofitamab; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell like-type; NOS, not otherwise specified; trans, transformed; HGBL, high-grade B-cell Lymphoma; w/, with; rearr. rearrangement; dx, diagnosis; mo., months; 3L, third line; 4L+, fourth line or later; Benda, bendamustine; ritux, rituximab; polatuz, polatuzumab vedotin; PD-1, programmed cell death protein 1; Auto-HSCT, autologous hematopoietic stem cell transplantation; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T-cells; LDH, lactate dehydrogenase; IPI, international prognostic index; int., intermediate; Tx, therapy.

Figures

Figure 1. Survival outcomes of the patients with r/r LBCL in CR following a treatment with glofitamab. (A) PFS for all patients; (B) OS for all patients; (C) PFS for patients after EOT; (D) OS for patients after EOT. The p-values are obtained using a logrank test and patients at risk are highlighted below the Kaplan-Meier plot. r/r, relapsed/refractory; LBCL, large B-cell lymphoma; CR, complete remission; PFS, progression-free survival; OS, overall survival; Pts., patients; EOT, end of treatment.

Figure 2. Swimmer plot visualizing the timing and durability of responses and highlights treatment in all patients of this cohort. CR, complete remission; CMR, complete metabolic remission; CAR-T, chimeric antigen receptor T-cell; alloSCT, allogeneic stem cell transplantation; PD, progressive disease; NRM, non-relapse mortality; RM, relapse-related mortality; EOT, end of treatment; PET, positron emission tomography.


A)
PFS (%)
Months after glofitamab initiation
N (all patients) 52 50 44 27 14 10 6 3 2 2 2 0
B)
OS (%)
Months after glofitamab initiation
N (all patients) 52 51 46 30 17 13 6 3 2 2 2 0
C)
PFS (%)
EOT after 12 cycles glofitamab
Months after EOT
Pts at risk
36 32 17 11 5 4 2 2 2 0 0
D)
OS (%)
EOT after 12 cycles glofitamab
Months after EOT
Pts at risk
36 33 19 14 6 4 2 2 2 0 0


PatientID
Time in months
0
6
12
18
24
30
36
42
48
54
60
66
Consolidated (alloSCT)
Early termination (-)
Consolidated (CAR-T)
Early termination (-)
Consolidated (alloSCT)
Early termination (-)
Consolidated (alloSCT)
Relapse mortality
Early termination (-)
Consolidated (CAR-T)
Early termination (-)
Relapse mortality
Secondary malignancy
Consolidated (alloSCT)
Consolidated (alloSCT)
Consolidated (CAR-T)
Treatment
Glofitamab with EOT per protocol (12 cycles)
Glofitamab_early termination
Off treatment
Response
CR (CMR)
CR (non-PET)
Relapse/refractory disease at last FU
Relapse following initation of glofitamab
Lymphoma course
Relapse/refractory after CR
Outcome
Alive
Dead (NRM)
Dead (RM)
Prior- and post-BsAb therapy
Prior and post-glofitamab therapy
Post-glofitamab therapy

Outcomes of real-world complete responders after fixed-duration glofitamab in relapsed/refractory large B-cell lymphoma

Supplemental Table S1. Efficacy and outcomes of glofitamab therapy in CR patients with r/r LBCL.

Parameters	**n (%)**
Patients	52 (100)
Median days to BORR, range	136 (17-360)
Immunoglobulin replacement therapy	21 (40.4)
Documented CR type	
Metabolic	33 (63.5)
Radiologic	19 (36.5)
Relapse/PD rate following initiation of Glo	8 (15.4)
Median time to relapse/PD following first Glo administration, mo, range	11 (IQR 10; 7-17)
Reason for EOT with Glo	52 (100)
- completion of 12 cycles glofitamab and no any subsequent consolidation	36 (69.2)
- treatment toxicity	5 (9.6)
- secondary malignancy	1 (1.9)
- CAR-T consolidation	3 (5.8)
- Allo-HSCT consolidation after maximum of 5 cycles glofitamab	4 (7.7)
- Allo-HSCT consolidation after 12 cycles glofitamab	1 (1.9)
Relapse under glofitamab	2 (9.6)
Ongoing therapy	0
Median FU from Glo initiation, mo, range	19 (IQR 15; 29-14)
Remission state at last FU	
CR	47 (90.4)
r/r disease	5 (9.6)
Status at last FU	
Alive	39 (75)
Dead	13 (25)
Cause of death, n = 10	
r/r lymphoma	4 (7.7)
non-lymphoma reasons	9 (17.3)
- Infection	5 (9.6)
- unknown	2 (3.8)
- bleeding	1 (1.9)
- secondary malignancy	1 (1.9)

Percentages refer to total number of events scored. Glo, glofitamab; CR, complete response; r/r, relapsed/refractory; LBCL, large B-cell lymphoma; PD, progressive disease; mo, months; EOT, end of treatment; CAR-T, chimeric antigen receptor T-cell therapy; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; FU, follow-up. * one patient underwent allo-HSCT consolidation following regular EOT after 12 cycles of glofitamab

Supplemental Table S2. Efficacy of CAR-T cell therapies and of bispecific antibodies applied in combination with other agents in relapsed/refractory LBCL patients.

Study name; investigated product	**Prior therapies**	**Patient population (n)**	**ORR**	**CRR**	**PFS**	**OS**	**Reference**
ZUMA-1 Axicabtagene ciloleucel	≥2, including DLBCL patients who failed HDCT/ASCT	n=111 (n=101 treated with axi-cel), median 3 prior lines of therapy	83%	58%	2-year PFS 39%; mPFS 5.9 mo.	2-year OS 50.5%; mOS 25.8 mo.	1,2
ZUMA-7 Axicabtagene ciloleucel vs. second line HDCT/ASCT	1, only primary refractory or relapse ≤12 months, eligible for HDCT/ASCT	n=180 (in the axi-cel arm) and n=179 (in the SOC arm), 1 prior line of therapy	83% vs. 50%	65% vs. 32%	2-year PFS 46% vs. 27%; mPFS 14.7 vs. 3.7 mo.	2-year OS 60% vs. 51% (*crossover in SOC); mOS not reached vs. 31.1 mo (*crossover in SOC)	3,4
TRANSCEND NHL001 Lisocabtagene maraleucel	≥2, including those who failed HDCT/ASCT	n=270, median 3 prior lines of therapy	73%	53%	2-year PFS 40.6%; mPFS 6.8 mo.	2-year OS 50.5%; mOS 27.3 mo.	5
TRANSFORM Lisocabtagene maraleucel vs. second line HDCT/ASCT	1, only primary refractory or relapse ≤12 months, eligible for HDCT/ASCT	n=92 (in the liso-cel arm) and n=92 (in the SOC arm), 1 prior line of therapy	87% vs. 49%	74% vs. 43%	3-year PFS 50.9% vs. 26.5%; Not reached vs. 6.2 mo.	3-year OS 62.8% vs. 51.8% (**crossover in SOC); mOS not reached for both (**crossover in SOC)	6,7
STARGLO Glofitamab - GemOx vs. R-GemOx	≥1, HDCT/ASCT ineligible	n=183 (in the glofitamab - GemOx arm)	68.3% vs. 40.7%	58.5% vs. 25.3%	2-year PFS not available;	2-year OS 52.8% vs. 33.5%; mOS	8,9

		and n=91 (in the R-GemOx arm), median 1 prior line of therapy			mPFS 13.8 vs. 3.6 mo.	25.5 vs. 12.9 mo.	
EPCORE NHL-2 Epcoritamab - GemOx	≥1, HDCT/ASCT ineligible	n=103, median 2 prior lines of therapy	85%	61%	mPFS 11.2 mo.	mOS 21.6 mo.	10
Phase 1b/2 Mosunetuzumab + polatuzumab vedotin	≥1, HDCT/ASCT ineligible	n=120, median 2 prior lines of therapy	59.2%	45.9%	mPFS 11.4 mo.	mOS 23.3 mo.	11
SUNMO Phase 3 Trial Mosunetuzumab + polatuzumab vedotin vs. R-GemOx	≥1, HDCT/ASCT ineligible	n=138 (in the mosunetuzumab - pola arm) and n=70 (in the R-GemOx arm), median 2 prior line of therapy	70.3% vs. 40%	51.4% vs. 24.3%	1-year PFS 48.5% vs. 17.8%; mPFS 11.5 vs. 3.8 mo.	1-year PFS 48.5% vs. 17.8%; mPFS 11.5 vs. 3.8 mo.	12
Phase 1 Trial BP41072 Englumafusp alfa (CD19-4-1BBL) combined with glofitamab in patients with r/r B-cell lymphoma	≥1, HDCT/ASCT ineligible	n=83 with aggressive lymphoma, median 3 prior lines of therapy	67.5%	56.6%	mPFS 9.7 mo.	mOS 20.9 mo.	13
LOTIS-7, arm E Loncastuximab tesirine combined with glofitamab in patients with agressive B-cell lymphoma	≥1, CAR-T and HDCT/ASCT eligible	n=30 with aggressive lymphoma	93.3%	86.7%	mPFS not reached	mOS not reached	14
Glofitamab, NP30179 Phase I/II Trial Glofitamab monotherapy	≥2, including patients who failed HDCT/ASCT and/or CAR-T cell therapy	N=154, median 3 prior lines of therapy	52%	39%	1-year PFS 37%; mPFS 4.9 mo.	1-year OS 50%; mOS 12 mo.	15,16

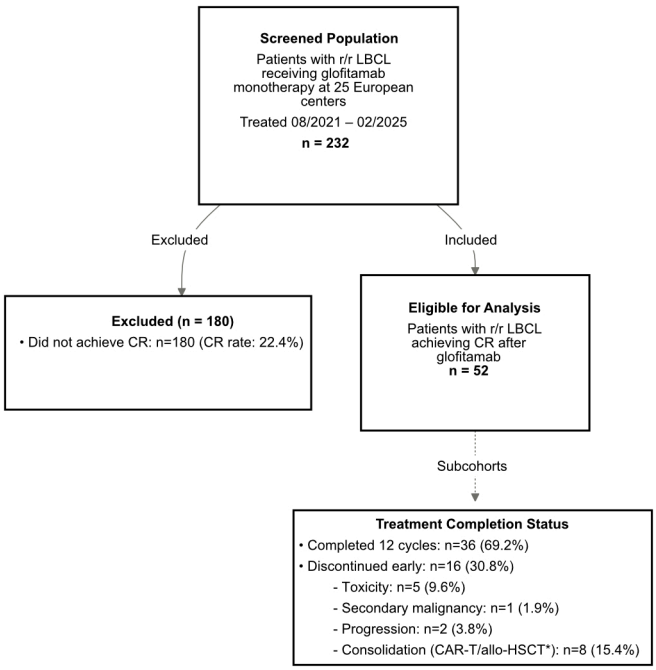
Epcoritamab, EPCORE™ NHL-1 trial Epcoritamab monotherapy	≥2, including patiens who failed HDCT/ASCT and/or CAR-T cell therapy	N=157, median 3 prior lines of therapy	63.1%	40.1%	2-year PFS 27.8%; mPFS 4.4 mo.	2-year OS 44.6%; mOS 18.5 mo.	17,18

CAR-T, chimeric antigen receptor T-cells; r/r, relapsed/refractory; LBCL, large B-cell lymphoma; ORR, overall response rate; CRR, complete response rate; PFS, progression-free survival; mPFS, median progression-free survival; OS, overall survival; mOS, median overall survival; HDCT/ASCT, high-dose chemotherapy/autologous stem cell transplantation; mo, months; SOC, standard of care; mo, months; GemOx, gemcitabine, oxaliplatin; R-GemOx, rituximab, gemcitabine, oxaliplatin; pts., patients; FU, follow-up; Pola, polatuzumab vedotin

*57% of HDCT/ASCT patients in ZUMA-7 received CAR-T cells in third-line;

**66% of HDCT/ASCT patients in TRANSFORM crossed over to receive lisocabtagene maraleucel in third-line.

Supplemental Figure S1. CONSORT diagram summarizing screening and inclusion of 52 patients achieving CR after monotherapy with glofitamab at 25 European centers (treatment Aug 2021–Feb 2025).



R/r LBCL, relapsed/refractory large B-cell lymphoma; CR, complete remission; CAR-T, chimeric antigen receptor T-cell therapy; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; *one patient underwent allo-HSCT after completion of 12 cycles glofitamab.

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