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ORIGINAL ARTICLE

Glofitamab in relapsed/refractory diffuse large B-cell lymphoma: Real-world data

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Abstract

Glofitamab is a CD3xCD20 bi-specific antibody with two fragments directed to the CD20 antigen and a single CD3-binding fragment. Encouraging response and survival rates were recently reported in a pivotal phase II expansion trial conducted in patients with relapsed/refractory (R/R) B-cell lymphoma. However, the real-world data of patients of all ages with no strict selection criteria are still lacking. Herein, this retrospective study aimed to evaluate the outcomes of diffuse large B-cell lymphoma (DLBCL) patients who received glofitamab via compassionate use in Turkey. Forty-three patients from 20 centers who received at least one dose of the treatment were included in this study. The median age was 54 years. The median number of previous therapies was 4, and 23 patients were refractory to first-line treatment. Twenty patients had previously undergone autologous stem cell transplantation. The median follow-up time was 5.7 months. In efficacy-evaluable patients, 21% and 16% of them achieved complete response and partial response, respectively. The median response duration was 6.3 months. The median progression-free survival (PFS) and overall survival (OS) was 3.3 and 8.8 months, respectively. None of the treatment-responsive patients progressed during the study period, and their estimated 1-year PFS and OS rate was 83%. The most frequently reported toxicity was hematological toxicity. Sixteen patients survived, while 27 died at the time of the analysis. The most common cause of death was disease progression. One patient died of cytokine release syndrome during the first cycle after receiving the first dose of glofitamab. Meanwhile, two patients died due to glofitamab-related febrile neutropenia. This is the largest real-world study on the effectiveness and toxicity of glofitamab treatment in R/R DLBCL patients. The median OS of 9 months seems promising in this heavily pretreated group. The toxicity related mortality rates were the primary concerns in this study.

KEYWORDS
bispecific antibodies, glofitamab, relapsed/refractory diffuse large B-cell lymphoma

1 | INTRODUCTION

The standard therapeutic strategy for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) if the patient is eligible for transplant.[1] The prognosis of DLBCL patients who are unresponsive to R-CHOP therapy, are refractory to salvage regimen, or experience relapse within ≤12 months after high-dose chemotherapy and ASCT is unfavorable if standard chemotherapy options are used.[2] The treatments that have been approved for R/R DLBCL after at least two lines of therapy include antibody–drug conjugates,[3,4] tafasitamab with lenalidomide,[5] selinexor,[6] and chimeric antigen receptor (CAR) T-cell therapies.[7–9] Although CAR T-cell therapies appear to be the most effective, their long manufacturing time and restricted accessibility due to high cost and logistic constraints can be an issue.

Bispecific antibodies (BsAbs) are monoclonal antibodies (moAbs) that recognize two specific antigens or epitopes, thus redirecting autologous T-cells against tumor cells.[10] Recently, different anti-CD20 BsAbs (polatuzumab vedotin and loncastuximab tesirine) showed promising activity against R/R DLBCL.[11] Glofitamab is a CD3xCD20 BsAb with a 2:1 structure composed of two fragments directed to the CD20 antigen and a single CD3-binding fragment. A phase I trial on heavily pretreated patients with B-NHL subtypes showed the considerable activity of glofitamab in R/R DLBCL, with an overall response rate (ORR) of 41.1% (complete response [CR]: 28.8%) globally and an ORR of 55% (CR: 42.1%) at a dose of ≥10 mg. The median duration of response (DOR) of the entire cohort was 5.5 months, which was not reached by those patients who achieved CR. The median follow-up time was 27.4 months.[12] Epcoritamab, another CD3xCD20 BsAb, was also used in R/R patients with DLBCL in a phase I/II study. Results revealed that epcoritamab administered subcutaneously led to deep and durable responses in highly

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refractory patients with DLBCL, including those who previously used CAR T-cell therapies. At a median follow-up of 10.7 months, the ORR was 63.1%, while the complete response rate was 38.9%. Although the median DOR was 12.0 months for all patients, it was not reached by patients who showed CR.[13]

Current knowledge regarding the outcomes of R/R DLBCL cases is based on the results of clinical trials or studies conducted in academic centers using selected cases. Therefore, real-world data involving patients of all ages with no strict selection criteria are lacking. This retrospective study aimed to determine the outcomes of patients with DLBCL who received glofitamab via compassionate use in Turkey.

2 | METHODS

Forty-six patients from 20 Turkish institutions were included in this study. Glofitamab was available via compassionate use between March 2021 and September 2022 for patients aged >18 years and with R/R DLBCL, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma who had previously received at least three lines of treatment. Patients received 1000 mg of obinutuzumab 7 days prior to the first dose of glofitamab. Glofitamab was administered intravenously at a fixed dose of 2.5/10/30 mg on cycle (C) 1 day (D) 1 and D8, and at the target dose from C2D1 q3w, for up to 12 cycles. It took approximately 10–30 days to seek approval from regulatory authorities for the use of glofitamab, as it was part of a compassionate use program. In accordance with the regulations of the Compassionate Use Program, glofitamab therapy was only applied as an inpatient treatment, and the patient had to stay at the hospital for 24 h after the completion of the infusion at each application.

The primary endpoint of the study was the response rate. The secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety. The PFS and OS were calculated on the first day of the first cycle of glofitamab treatment. PFS was defined as the period from glofitamab treatment until disease progression or death, while OS was defined as the period from glofitamab treatment until death. Both OS and PFS were censored at the last day of the study for which these information were available. Response to therapy was evaluated by performing positron emission tomography/computed tomography (PET/CT) and based on the Lugano criteria.[14] Response assessments were carried out after 2–4 cycles of treatment at the discretion of the treating physician.

Safety and tolerability were assessed prior to each cycle of glofitamab according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.19.[15] The median DOR, PFS, and OS rates, along with their two-sided 95% confidence intervals (CIs), were estimated using the Kaplan–Meier method. Survival functions were compared using the log-rank test. All data analyses were performed using SPSS version 21.

The compassionate use program of glofitamab was organized following the ethical approval of the central authority, with the supervision of the Ministry of Health.

3 | RESULTS

3.1 | Patients

As of 1 July 2022, 46 patients had been admitted for glofitamab treatment via compassionate use. Three patients died prior to glofitamab use and were excluded from the analysis. The results of 43 patients from 20 centers who received ≥1 dose of this treatment were presented in this study. The patients' characteristics, number of previous treatment lines, and responses are summarized in Table 1. The patients' median age was 54 years (range, 20–81 years), and 28 (65.1%) patients were men. Two patients had transformed follicular lymphoma, while 41 patients had DLBCL. At the initiation of glofitamab therapy, 7 patients (16.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≥2, and 13 patients (30.2%) had bulky disease (>5 cm). The median number of previous therapies was 4 (range, 3–6), and 23 patients (53.5%) were refractory to first-line treatment. Twenty patients (47.6%) had previously undergone an ASCT.

Some patients required hospitalization longer than 24 h during the course of glofitamab treatment. The median number of hospitalization days for the first cycle was 2 (2–21). Three patients were hospitalized for 7–12 days due to the occurrence of cytokine release syndrome (CRS) after the first cycle of treatment. One of the patients required intensive care unit admission due to CRS. Five patients had been hospitalized for at least once during their glofitamab treatment due to fever and infection, which lasted for 3–38 days. Six patients received all cycles as inpatient and died due to disease progression during the early cycles of treatment. The patient died due to disease progression during the early cycles of treatment.

3.2 | Response to treatment

The patients received a median of four cycles (1–12) of glofitamab. Five patients (11%) died prior to the response evaluation (2 patients died due to coronavirus disease 2019 [COVID-19], one patient died due to CRS, one patient died due to disease progression, and one patient died due to arrhythmia). Among the efficacy-evaluable patients, 21% achieved CR (8/38), while 16% (6/38) achieved partial remission (PR). After glofitamab treatment, 3 patients (8%) had stable disease (SD), while 21 patients (55%) had progressive disease (PD) (Figures 1 and 2). The median time to response was 84 days (range, 42–252) or after four cycles of treatment. Six patients underwent stem cell transplantation following glofitamab treatment. Three patients underwent allogeneic stem cell transplantation (AlloSCT). Two of these patients achieved CR after 4 and 11 cycles of glofitamab, respectively; one patient survived and achieved CR within 3 months after AlloSCT, while the second patient died due to sepsis and graft versus host disease within 101 days after AlloSCT. The 3rd patient achieved PR after undergoing AlloSCT following 12 cycles of glofitamab and died of sepsis within 9 days after AlloSCT.

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TABLE 1 Demographic and clinical characteristics of the patients at the initiation of glofitamab treatment.

Characteristics	*N*: 43 patients
Age, years, median (range)	54 (20–81)
Male sex, no. (%)	28 (65.1%)
ECOG performance status, no. (%)	
0	20 (47.6%)
1	15 (35.7%)
2	4 (9.5%)
3	3 (7.1%)
Ann Arbor staging, no. (%)	
I and II	11 (25.6%)
III and IV	32 (74.4%)
Bulky disease, 5 cm, no. (%)	13 (30.2%)
Histology subtype, no. (%)	
DLBCL	41 (95.4%)
Transformed FL	2 (4.6%)
COO	
GCB	19 (44.2%)
ABC	11 (25.6)
Unknown	13 (30.2)
Prior autologous stem cell transplant, no. (%)	20 (47.6%)
Previous lines of therapy; median (range)	4 (3–6)
Refractory to first-line therapy, no. (%)	23 (53.5%)
LDH level prior to glofitamab therapy	34
Normal	9 (26%)
>ULN	25 (74%)
Median follow-up, months	5.7 (0.3–14.19)
Cycles of glofitamab; median (range)	4 (1–12)
Response	
CR	8 (21%)
PR	6 (16%)
SD	3 (8%)
PD	21 (55%)
Died prior to the response assessment	5 patients

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper limit of normal.

Three patients underwent ASCT, two achieved CR after four and twelve cycles of glofitamab, and both were still alive with CR within 11 and 4 months after ASCT, respectively. The 3rd patient had SD after undergoing ASCT following 10 cycles of glofitamab and eventually died due to disease progression within 4 months after ASCT.

Results of the univariate analysis of the clinical and treatment-associated factors affecting the treatment response are shown in Table 2, and only advanced stage has been shown to predict poor response to glofitamab treatment.

3.3 | Survival outcomes

3.3.1 | Progression-free survival

The median follow-up time was 5.7 (range, 0.30–14.9) months. The median DOR was 6.3 months (range, 0.3–12). The median PFS was 3.3 months (95% CI: 2.34–4.35). The estimated 1-year PFS rate was 29.6% (Figure 3). Results of the univariate analyses of the clinical and treatment-associated factors affecting PFS are shown in Table 2. Poor PS (ECOG 3), advanced stage, and unresponsiveness to glofitamab were the risk factors significantly associated with worse PFS (Table 2). The median PFS was not reached in stage 1 and 2 patients, whereas the median PFS in stage 3 and 4 patients was 2.8 months (95% CI: 0.01–7.07) and 2.4 months (95% CI: 1.26–3.60), respectively ($p = 0.03$). Only three patients had an ECOG PS score of 3, and their median PFS time was only 0.5 months (95% CI: 0.42–0.63), which was shorter than that of patients with an ECOG PS score of ≤2 (3.3 months (95% CI: 0.01–7.48), $p < 0.001$).

Although the median PFS of patients who achieved CR with glofitamab treatment was not reached, those who achieved PR after glofitamab treatment had a median PFS of 13.8 months. None of the treatment-responsive patients (who achieved CR or PR) progressed during the study period, and the estimated 1-year PFS rate of this group was 83%. Among the three patients who had SD after glofitamab treatment, two (one completed 12 cycles, while the other completed five cycles) were still alive.

3.3.2 | Overall survival

The median OS was 8.8 months (95% CI: 4.85–12.89). The estimated 1-year OS was 29.6% (Figure 3). Results of the univariate analysis of the clinical and treatment-associated factors affecting OS are shown in Table 2. Poor PS (ECOG PS: 3), advanced stage, and unresponsiveness to glofitamab treatment were the risk factors that were significantly associated with lower OS. Although the median OS was not reached in stage 1 and 2 patients, the median OS in stage 3 and 4 patients was 13.8 and 5 months, respectively ($p = 0.02$). The median OS of patients with an ECOG PS score of 3 was only 1 month (95% CI: 0.23–1.80), which was shorter than that of patients with an ECOG PS score of ≤2 (8.9 months (95% CI:4.70–13.23), $p = 0.005$). Patients who achieved CR after glofitamab treatment did not reach the median OS (1-year OS rate: 83%), while patients who achieved PR after glofitamab treatment had a median OS time of 13.8 months (1-year OS rate: 83%). For patients with PD despite receiving glofitamab treatment, the median OS time was 5 months (95% CI: 2.71–7.33) ($p < 0.001$).

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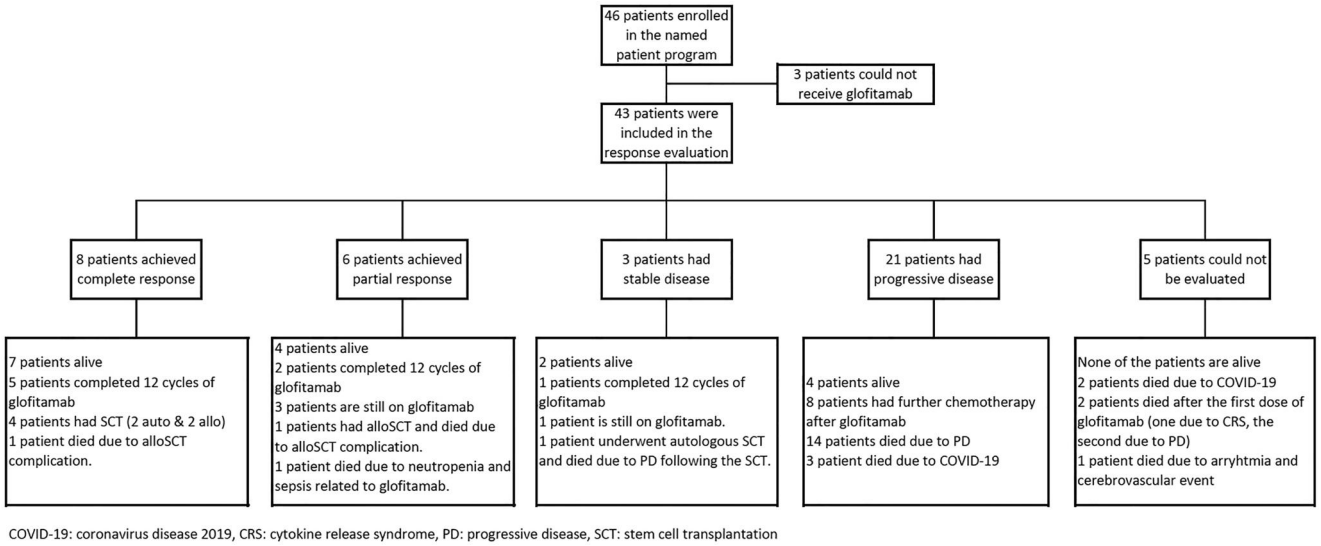


FIGURE 1 Flowchart of patients according to their glofitamab treatment-related response.

3.4 | Safety and causes of death

The most frequently reported toxicities were hematological problems; neutropenia was observed in 17 patients (39.5%), and ≥grade 3 neutropenia developed in 10 patients (23.2%). Granulocyte colony-stimulating factor (G-CSF) was administered in 12 patients (27.9%). Glofitamab-related febrile neutropenia was observed in 8 patients (18.6%). Anemia was observed in 16 patients (37.2%) and it was ≥grade 3 in 8 of them (18.6%). Thrombocytopenia was observed in 12 patients (27.9%), reported to be ≥grade 3 in 8 cases (18.6%). Thrombocytopenia was observed in 12 patients (27.9%), while ≥ grade thrombocytopenia occurred in 3 of 8 patients (18.6%). CRS developed in 12 patients (27.9%), grade ≥3 CRS in 4 cases, and grade 5 CRS in 1 patient. Neurological toxicity was observed in only three patients (7%), while ≤ grade 2 neurological toxicity occurred in all patients. This compassionate use program was conducted during the COVID-19 pandemic era, and nine patients (20.9%) acquired COVID-19 during the treatment period. The adverse events are summarized in Table 3.

Sixteen patients survived, while 27 died at the time of the analysis. Four patients died due to COVID-19; two of these patients died after the first cycle, and the remission status of these patients remained unknown. The other two patients who died after the 2nd and 5th cycles were unresponsive to glofitamab treatment. In the first cycle, 30 h after administering the first dose of glofitamab, one patient developed hypotension. The patient received dexamethasone, was transferred to the intensive care unit, and was treated with vasopressors. As anuria occurred, hemofiltration was performed. However, 7 h after admission to the intensive care unit, the patient experienced cardiopulmonary arrest and eventually died, which was considered by the treating physician as death due to cytokine release syndrome (CRS) related to glofitamab treatment. Unfortunately, tocilizumab could not be obtained or used in this patient. Two patients who underwent AlloSCT died due to transplantation-related complications; one of them achieved CR, while the other achieved PR prior to transplantation. Two patients died due to febrile neutropenia which was related to Glofitamab treatment; one of these patients was in PR after 2 cycles of treatment and the other had PD after 2 cycles of treatment. The first patient who was 61 years old was primary refractory and had received Glofitamab as the 5th line of therapy while his performance status was good (ECOG:0). He had neutropenia, anemia and thrombocytopenia (all Grade 3) and CRS grade 4 requiring tociluzumab and G-CSF application during the first cycle, but all resolved. After the 2nd cycle he again had neutropenia, anemia and thrombocytopenia. However, in the neutropenic period, although he was receiving G-CSF he had Gram (–) septicemia due to extended spectrum beta lactamase resistant Escherichia coli and died 24 days after the 2nd cycle of Glofitamab. The second patient who was 26 years old had received Glofitamab as the 4th line of treatment and his ECOG performance status was 3 at the start of Glofitamab treatment. He was already leukopenic (WBC: 1100/mm^3) at the start of Glofitamab.

4 | DISCUSSION

Glofitamab can prolong the PFS and OS and provide a durable response in treatment-responsive patients in a heavily treated and highly refractory DLBCL cohort. In this study, the patients were pretreated with a median of four lines of therapy, and all available treatment options were exhausted. The CR rate was 21%, the PR rate was 16%, and the SD rate was 8%. Only advanced stage was considered as a prognostic factor for treatment response. The estimated 1-year PFS and OS was 83% in patients who achieved CR or PR after glofitamab. None of the responders showed PD during the follow-up period. Among the responders (CR and PR), the median

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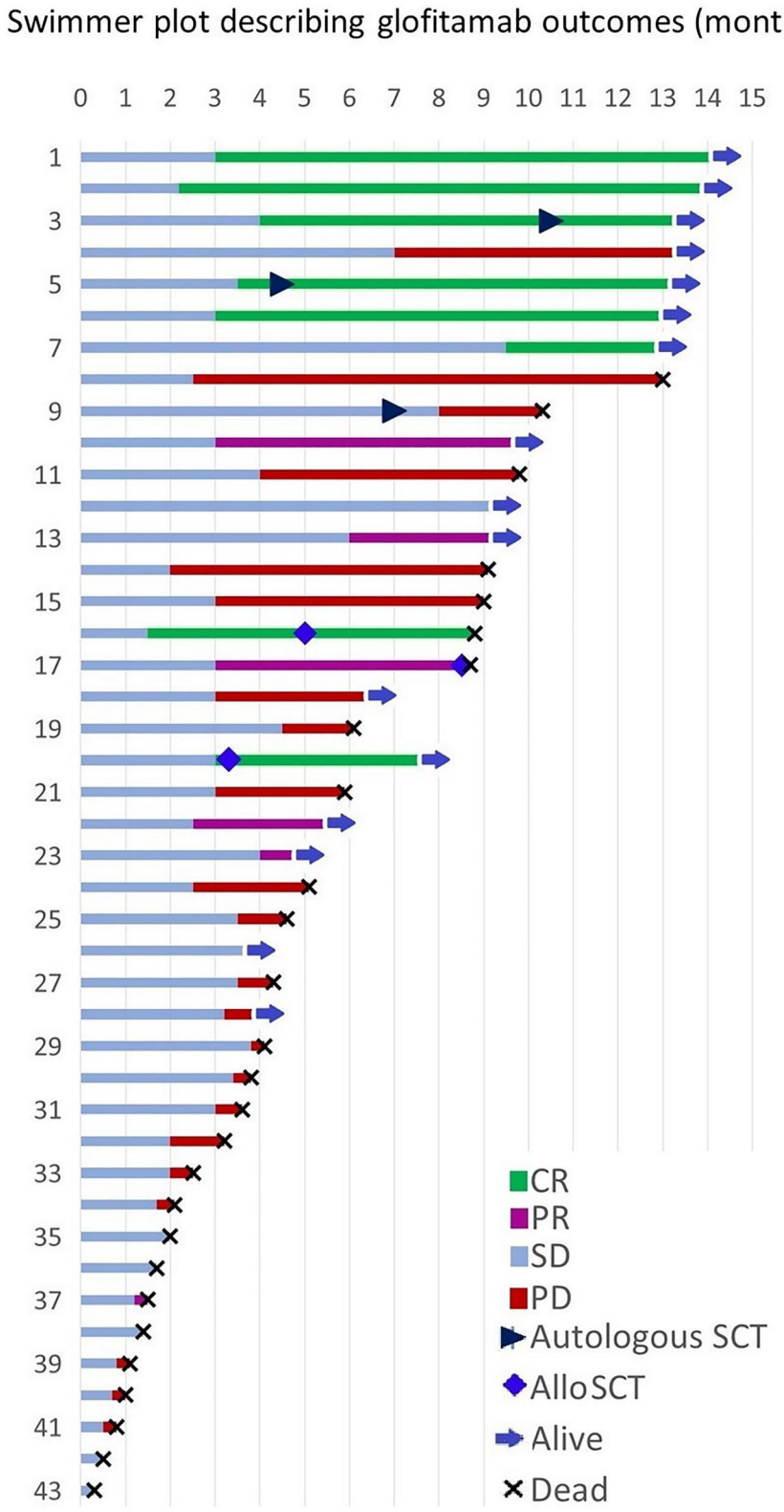


FIGURE 2 Graph of the patients' response characteristics. AlloSCT, allogeneic stem cell transplantation; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

DOR was not reached at the time of the analysis. Only 3 patients had SD. One of these three patients underwent ASCT after 10 cycles of glofitamab, showed PD at 4 months after ASCT, and eventually died.

In phase I/II study (NCT03075696), glofitamab was well tolerated in patients with R/R B cell lymphomas.[16] The differences between our study and the phase II study are summarized in Table 4. The RRs were lower in our study compared with that in a previous pivotal study (ORR: 37% vs. 52%, CR: 21% vs. 39%, respectively), and the median follow-up time was shorter (5.8 vs. 12.6 months). The patients received more lines of treatment, and a higher proportion of

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TABLE 2 Results of the univariate analysis according to the associations of patients' clinical characteristics with glofitamab treatment and progression-free survival and overall survival.

		n	PFS (months; median, 95% CI)	*p*	OS (months; median, 95% CI)	*p*	CR/PR versus non-responding	*p*
Age	<60 years	31	3.58 (0.01–8.01)	0.72	8.96 (4.20–13.73)	0.56	35.7%/64.3%	0.80
	≥60 years	12	1.70 (0.31–3.10)		4.53 (1.08–7.98)		40%/60%	
Gender	Female	15	10.11 (0.01–23.98)	0.39	10.11 (0.01–20.26)	0.31	50%/50%	0.25
	Male	28	3.22 (2.49–3.94)		8.67 (3.34–13.99)		30.8%/69.2%	
Primary refractory	Yes	23	3.38 (0.01–7.19)	0.46	8.96 (4.44–13.49)	0.09	39.1%/60.9%	0.98
	No	20	2.43 (1.63–3.22)		3.61 (0.44–6.78)		33.3%/66.7%	
Ann-Arbor stage	I and II	11	NR	**0.004**	NR	**0.01**	70%/30%	**0.01**
	III and IV	32	2.62 (1.60–3.65)		5.84 (3.56–8.13)		25%/75%	
Bulky disease (≥5 cm)	No	30	3.02 (0.01–8.19)	0.96	8.67 (3.02–14.32)	0.72	40%/60%	0.57
	Yes	13	3.35 (2.32–4.47)		8.87 (1.90–15.83)		30.8%/69.2%	
ECOG	0	21	3.38 (0.01–7.79)	**<0.001**	8.96 (7.74–10.19)	**0.03**	42.1%/57.9%	0.64
	1	15	3.22 (1.51–4.92)		4.20 (0.01–10.31)		38.5%/61.5%	
	2	4	10.11 (0.01–21.06)		10.11 (2.03–18.20)		25%/75%	
	3	3	0.52 (0.42–0.63)		1.01 (0.23–1.80)		0%/100%	
Previous ASCT	Yes	20	3.02 (0.01–10.31)	0.40	12.78 (0.01–26.31)	0.44	41.2%/58.8%	0.51
	No	22	3.22 (1.93–4.50)		8.67 (4.78–12.55)		30%70%	
COO	GCB	19	2.43 (0.37–4.48)	0.74	8.67 (3.64–13.70)	0.83	40%/60%	0.86
	ABC	11	3.58 (1.59–5.56)		10.11 (1.02–19.21)		30%/70%	
	Unknown	13	3.35 (0.01–13.17)		12.78 (1.27–24.28)		38.5%/61.5%	
Previous lines of treatment	3	16	2.62 (1.39–3.86)	0.73	8.67 (3.96–13.38)	0.82	33.3%/66.7%	0.75
	4	15	3.58 (0.01–7.27)		8.96 (7.85–10.08)		46.2%/53.8%	
	5	10	1.93 (0.20–3.66)		4.04 (0.01–8.06)		25%/75%	
	6	2	2.43 (NA)		3.61		50%/50%	
LDH level before glofitamab treatment	Normal	9	3.38 (0.01–12.53)	0.70	8.67 (1.29–16.05)	0.83	41.7%/58.3%	0.13
	>ULN	25	2.82 (1.88–3.76)		5.84 (0.01–12.52)		18.2%/81.8%	
Response to glofitamab treatment	CR	8	NR	**<0.001**	NR	**<0.001**	NA	
	PR	6	13.88 (NA)		13.89 (NA)		NA	
	SD	3	10.11 (NA)		10.11 (NA)		NA	
	PD	21	2.43 (s1.84–3.02)		5.02 (2.71–7.33)		NA	

Note: Bold values point to statistically significant parameters affecting PFS and OS in the univariate analysis.

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper limit of normal.

patients in our cohort had previously undergone ASCT. None of the patients in the pivotal study had an ECOG PS score of ≥2, but 7 (16.6%) of our patients obtained this PS score. The times to response was 42 days in the pivotal study and 84 days in our study. Since our study used real-world data, the response evaluations were performed after 2–4 cycles of treatment at the discretion of the treating physician; however, the time to response could not be assessed properly, and it was longer in our study compared with that in the pivotal study. The estimated 1-year PFS and OS times were lower in our cohort compared with that in the pivotal phase II study; this finding can be explained by the fact that our patients were more heavily pre-treated and had poorer PS compared with those in the phase II study. However, the remission rates were similar in both studies.

The hematological toxicity profile in our study was similar to that observed in the phase I and phase II extension studies. Neutropenia was observed in 17 patients (39.5%), and ≥grade 3 neutropenia developed in 10 of these patients (23.2%). In the pivotal phase II

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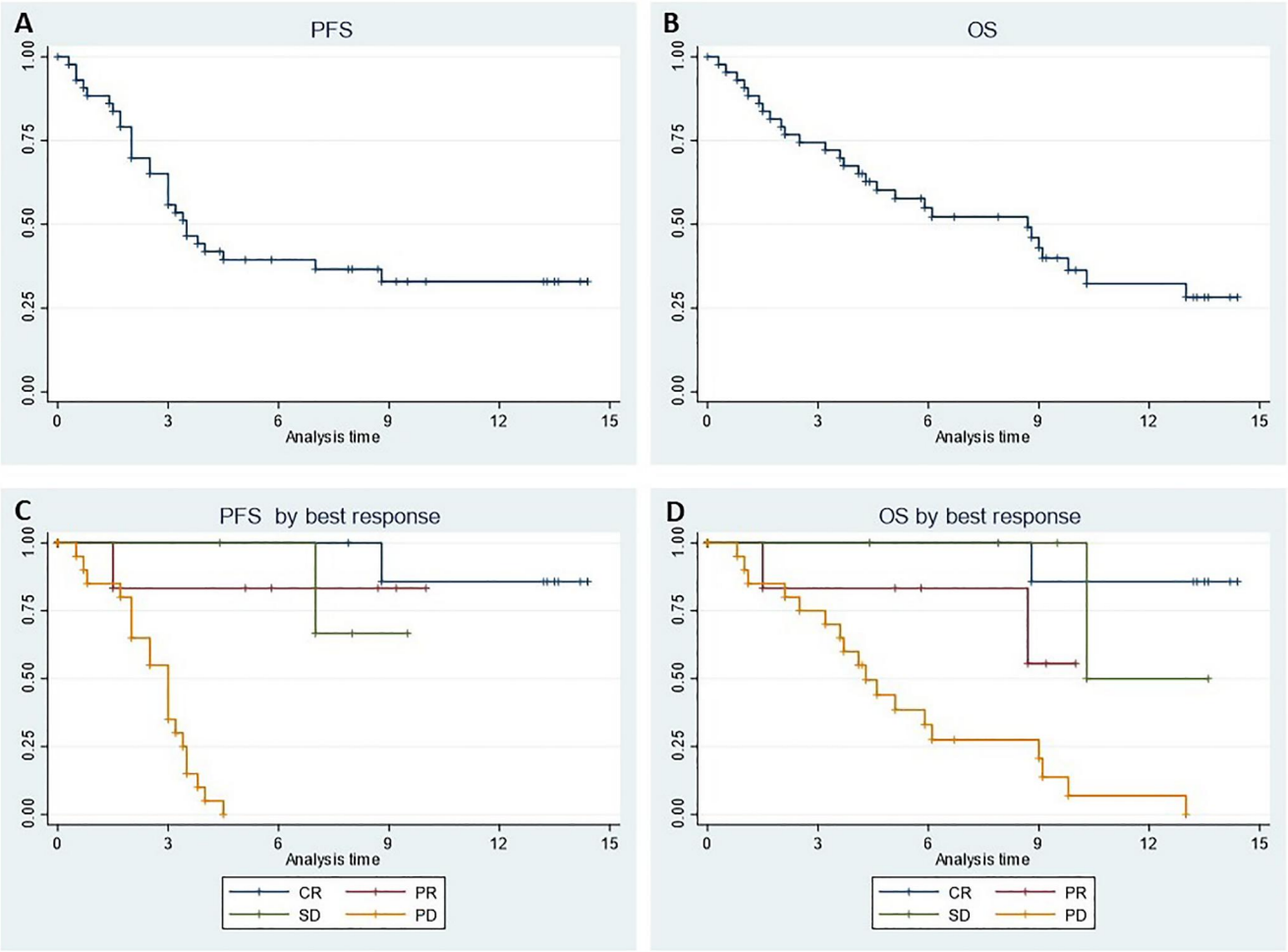


FIGURE 3 (A), PFS, (B) OS, (C) PFS, and (D) OS according to treatment response. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3 Adverse events that occurred in patients treated with glofitamab.

	All grades	≥Grade 3	Grade 5
Anemia	16 (37.2%)	8 (18.6%)	
Neutropenia	17 (39.5%)	10 (23.2%)	
Thrombocytopenia	12 (27.9%)	8 (18.6%)	
Fatigue	14 (32.6%)		
Nausea	9 (20.9%)		
Diarrhea	3 (7%)		
Fever	16 (37.2%)		
Febrile neutropenia	8 (18.6%)		2
COVID-19 infection	9 (20.9%)		4
Tumor flare	2 (4.7%)		
CRS	12 (27.9%)	4 (9.3%)	1
Neurologic adverse event	3 (7%)		

Abbreviation: COVID-19, coronavirus disease 2019.

study, neutropenia was observed in 38% of patients, and 27% of them reported ≥ grade 3 neutropenia. Glofitamab-related febrile neutropenia was observed in eight patients (18.6%) in our cohort, of whom two died (due to resistant *E. coli* and *Klebsiella* septicemia). In the phase II study, ≥grade 3 febrile neutropenia was reported in 4 patients (3%). Infection was observed in 38% of the patients in the phase II study, while sepsis was reported in 4% of the patients ($n = 6$).

CRS was observed in 12 patients (27.9%) in our cohort, and ≥grade3 CRS occurred in 4 patients (9.3%). One patient died in our study due to CRS within 2 days after the first dose of glofitamab owing to the unavailability of tocilizumab. Therefore, treatment with bispecific antibodies should be performed only at well-equipped facilities and by expert physicians. CRS was frequently encountered in pivotal phase II studies. All grades of CRS were reported in 63% of the patients, while ≥ grade 3 CRS was reported in 4% of the patients. Neurological toxicity was less commonly encountered in our cohort compared with that in the pivotal study (7%, all < grade 3 vs. 8%, 3% ≥grade 3). The lower CRS and neurological toxicity rates may be due to the retrospective nature of our study.

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TABLE 4 Differences between phase II study and our study.

	Phase 2 trial (n = 154)[16]	Our study (n = 43)
Non-Hodgkin's lymphoma subtype		
Diffuse large B-cell lymphoma, not otherwise specified	110 (71%)	41 (95.4%)
Transformed follicular lymphoma	27 (18%)	2 (4.6%)
High-grade B-cell lymphoma	11 (7%)	-
Primary mediastinal B-cell lymphoma	6 (4%)	-
Median number of previous lines of treatment	3 (2–7)	4 (3–6)
ECOG performance status	All 0 or 1	0–1: 83.4%
		2–3: 16.6% (n = 7)
Stage III–IV disease	75%	74.4%
Previous ASCT	18%	47.6%
Response assessment	CR: 61/155 (39%)	CR: 8/38 (21%)
	PR: 19/155 (13%)	PR: 6/38 (16%)
	ORR: 52%	ORR: 37%
Median duration of follow-up	12.6 months (0–22)	5.7 months (0.3–14.19)
Median time to response	42 days	84 days; at a median of 4 cycles
1-year PFS	37%	29.6%
1-year OS		
All	50%	29.6%
Patients with an objective response	74%	83%

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Grade 5 (fatal) adverse events occurred in 8 patients in the phase II study; the occurrence of these events was triggered by either COVID-19–related pneumonia or COVID-19 itself in 5 patients, sepsis in 2 patients, and delirium in 1 patient. None of the death cases were considered to be related to glofitamab therapy in the phase II study. Although the toxicity rate was in accordance with that reported in the phase 2 extension study, the toxicity-related mortality rate was higher in our real-life cohort. This may be related to the fact that the centers chosen for the trials were more experienced in the management of drug-related toxicities.

With the application of CAR T-cell therapies, a prolonged response duration can be achieved; at 2 years of treatment, 38%–40% of the patients can survive without a disease. However, CAR T-cell therapy can be difficult to apply in standard practice, especially for patients with PD as it takes a few weeks to months to manufacture this drug. Moreover, CAR T-cell therapies are not available in all countries, including Turkey, and their cost is relatively high.

On the contrary, off-the-shelf T-cell-engaging bispecific antibodies can be used as alternative treatment options for these patients. As already discussed, a phase II study of glofitamab in R/R DLBCL and a phase I/II trial of epcoritamab in R/R DLBCL patients reported a CR rate of 39%, which is comparable to the CR rates with CAR T-cell therapies.[12,13,16] Epcoritamab is administered until disease progression or unacceptable toxicity occurs. Although the median DOR was not reached among complete responders, all patients achieved a median DOR of 12.0 months; approximately 88.7% of the patients who achieved CR still exhibited the same response at 6 and 9 months.[13] Glofitamab was administered for 12 cycles. At 12 months, CR was achieved in 78% of the patients. Data from a longer follow-up in a cohort of patients who were treated with lower doses of glofitamab (10–25 vs. 30 mg) showed a median duration of complete response of 34.2 months.[12] This result indicates that CR can be maintained after the completion of glofitamab therapy. Although these results are promising, the follow-up duration of patients treated with bispecific antibodies was relatively short; moreover, it is still too early to estimate the curative potential of glofitamab.

To our knowledge, this is the largest real-world study examining the effectiveness and toxicities of glofitamab treatment in R/R DLBCL patients. The response rates were lower than those reported in the pivotal phase II study; this finding may be related to the higher median number of previous lines of therapy, higher proportion of patients with a history of ASCT, poor PS, and higher proportion of patients who were refractory to first-line treatment. However, the high toxicity-related mortality rate remains a concern in this real-life

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study. The median OS of 9 months in this heavily pretreated group seems promising.

AUTHOR CONTRIBUTIONS

Elif Birtas Atesoglu and Burhan Ferhanoglu coordinated the study; Elif Birtas Atesoglu, Murat Ozbalak and Burhan Ferhanoglu wrote the manuscript; Elif Birtas Atesoglu and Murat Ozbalak performed the statistical evaluations; Elif Birtas Atesoglu, Zafer Gulbas, Ant Uzay, Muhit Ozcan, Fahir Ozkalemkas, Mehmet Sinan Dal, Hakan Kalyon, Olga Meltem Akay, Burak Deveci, Huseyin Bekoz, Omur Gokmen Sevindik, Tayfur Toptas, Fergun Yilmaz, Derya Koyun, Nihan Alkis, Inci Alacacioglu, Mehmet Sonmez, Irfan Yavasoglu, Anil Tombak, Ozgur Mehtap, Fatih Kurnaz, Orhan Kemal Yuce, Volkan Karakus, Mehmet Turgut, Derya Deniz Kurekci, Mesut Ayer, Muzaffer Keklik, Deram Buyuktas and Burhan Ferhanoglu contributed data; Burhan Ferhanoglu served as the principal investigator. All participants read and approved the current manuscript.

CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

PUBLICATION

Our study was presented in American Society of Hematology 2022 Annual Meeting.

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PEER REVIEW

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REFERENCES

1. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540-1545. https://doi.org/10.1056/nejm199512073332305
2. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. https://doi.org/10.1182/blood-2017-03-769620
3. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2020;38(2):155-165. https://doi.org/10.1200/jco.19.00172
4. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, singlearm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790-800. https://doi.org/10.1016/s1470-2045(21)00139-x
5. Salles G, Duell J, Gonzalez Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective,single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978-988. https://doi.org/10.1016/s1470-2045(20)30225-4
6. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational,multicentre, open-label, phase 2 trial. *Lancet Haematol*. 2020;7(7):e511-e522. https://doi.org/10.1016/s2352-3026(20)30120-4
7. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42. https://doi.org/10.1016/s1470-2045(18)30864-7
8. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56. https://doi.org/10.1056/nejmoa1804980
9. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852. https://doi.org/10.1016/s0140-6736(20)31366-0
10. Gonzalez Barca E. Role of bispecific antibodies in relapsed/refractory diffuse large B-cell lymphoma in the CART era. *Front Immunol*. 2022;13:909008. https://doi.org/10.3389/fimmu.2022.909008
11. Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns and opportunities. *Blood*. 2022;141(5):467-480. blood.2021011994. https://doi.org/10.1182/blood.2021011994
12. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol*. 2021;39(18):1959-1970. https://doi.org/10.1200/jco.20.03175
13. Thieblemont C, Phillips T, Ghesquieres H, et al. 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. *J Clin Oncol*. 2022;22:JCO2201725.
14. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068. https://doi.org/10.1200/jco.2013.54.8800

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15. Common Terminology criteria for adverse events (CTCAE) version 4.05. November 27, 2017. Accessed December 31, 2016.
16. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(24):2220-2231. https://doi.org/10.1056/NEJMoa2206913

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