REGULAR ARTICLE

blood advances

Safety and efficacy of glofitamab for relapsed/refractory large B-cell lymphoma in a multinational real-world study

Evgenii Shumilov,[1,*] Rebecca Wurm-Kuczera,[2,*] Andrea Kerkhoff,[1,*] Meng Wang,[2] Thomas Melchardt,[3-6] Udo Holtick,[7] Ulrike Bacher,[8] Philipp Staber,[9] Paolo Mazzeo,[10] Corinna Leng,[2] David Böckle,[2] Alexander Hölscher,[11] Joseph Kauer,[12] Natalia Rotter,[13] Vladan Vucinic,[14] Jakob Rudzki,[15] David Nachbaur,[15] Veit Bücklein,[16] Ulf Schnetzke,[17] Isabelle Krämer,[12] Kai Wille,[18] Alexander Hasse,[19] Bastian von Tresckow,[20,21] Mathias Hänel,[22] Christian Koenecke,[23] Giuliano Filippini Velazquez,[24] Andreas Viardot,[25] Christoph Schmid,[24] Lorenz Thurner,[19] Dominik Wolf,[15] Marion Subklewe,[16,26] Martin Dreyling,[16] Peter Dreger,[12] Sascha Dietrich,[11] Ulrich Keller,[2,27] Ulrich Jäger,[9] Richard Greil,[3-6] Thomas Pabst,[28] Georg Lenz,[1,†] and Björn Chapuy[2,27,†]

[1]Department of Medicine A, Hematology, Oncology, and Pneumology, University Hospital Muenster, Münster, Germany; [2]Department of Hematology, Oncology, and Cancer Immunology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]Salzburg Cancer Research Institute, Center for Clinical Cancer and Immunology Trials, Salzburg, Austria; [4]Austrian Group for Medical Tumor Therapy Study Group, Vienna, Austria; [5]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [6]Cancer Cluster, Salzburg, Austria; [7]Department I of Internal Medicine, Medical Faculty and University Hospital of Cologne, University of Cologne, Cologne, Germany; [8]Department of Hematology, University Hospital Inselspital and University of Bern, Bern, Switzerland; [9]Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; [10]Department of Hematology and Medical Oncology, and INDIGHO Laboratory, University Medical Center Göttingen, Göttingen, Germany; [11]Department of Hematolgy, Oncology and Immunology, University Hospital of Düsseldorf, Düsseldorf, Germany; [12]Department of Hematology and Oncology, University Hospital Heidelberg, Heidelberg, Germany; [13]Internal Medicine I: Medical Oncology and Hematology, Ordensklinikum Linz GmbH, Elisabethinen, Linz, Austria; [14]Department of Hematology, Cell Therapy, Hemostaseology and Infectious Diseases, University Hospital Leipzig, Leipzig, Germany; [15]Clinic for Hematology and Oncology, Comprehensive Cancer Center Innsbruck, Tyrolean Cancer Research Institute, Medical University Innsbruck, Innsbruck, Austria; [16]Department of Medicine III, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; [17]Hematology and Medical Oncology, University Hospital Jena, Jena, Germany; [18]University Clinic for Haematology, Oncology, Hemostaseology and Palliative Care, Johannes Wesling Medical Center Minden, University Hospital of the University of Bochum, Minden, Germany; [19]Department of Internal Medicine 1-Oncology, Hematology, Clinical Immunology, and Rheumatology, Saarland University Medical School, Homburg, Germany; [20]Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [21]German Cancer Consortium (DKTK), Essen, Germany; [22]Department of Internal Medicine III, Klinikum Chemnitz, Chemnitz, Germany; [23]Department of Hematology and Oncology, University Hospital Hannover, Hannover, Germany; [24]Department of Hematology, University Hospital Augsburg, Augsburg, Germany; [25]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [26]German Cancer Consortium (DKTK), Munich, Germany; [27]German Cancer Consortium (DKTK), Berlin, Germany; and [28]Department of Oncology, University Hospital Inselspital and University of Bern, Bern, Switzerland

Key Points

- Glofitamab has a 46% ORR (27% CR; 19% PR) and a manageable safety in heavily pretreated patients with r/r LBCL.
- Increased lactate dehydrogenase is the strongest predictor of dismal PFS and overall survival after glofitamab.

Glofitamab, a bispecific antibody targeting CD20 and CD3, is approved for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) after at least 2 prior treatment lines, but real-world data are scarce. In this retrospective, multicenter, multinational study, we evaluated the outcomes of 70 patients with r/r DLBCL treated with glofitamab as part of the compassionate use patient program in Germany, Austria, and Switzerland. The median number of prior treatment lines was 4, with 71% of patients refractory to their last treatment. Cytokine release syndrome was observed in 40% of patients (grade 3-4 in 2%), immune effector cell–associated neurotoxicity syndrome in 10% (grade 3 in 1%), and infections in 31% (grade 5 in 3%). The overall response rate was 46%, with 27% achieving complete responses (CR) and 19% partial responses. The median progression-free survival (PFS) was 3.6 months, whereas the median overall survival was 5.7 months. Notably, 13 patients (19%) were in CR 6 months after initiating glofitamab and exhibited durable responses. Elevated lactate dehydrogenase is the most robust predictor of inferior outcome.

Submitted 23 September 2024; accepted 2 December 2024; prepublished online on *Blood Advances* First Edition 11 December 2024. https://doi.org/10.1182/bloodadvances.2024014903.

*E.S., R.W.-K., and A.K. contributed equally as first authors to this study.

†G.L. and B.C. contributed equally as last authors to this study.

Original data are available on request from the corresponding author, Björn Chapuy (bjoern.chapuy@charite.de).

The full-text version of this article contains a data supplement.

Patients pretreated with bendamustine within 6 months prior to glofitamab initiation exhibited significantly reduced PFS, suggesting that bendamustine may impair T-cell fitness and hence glofitamab efficacy. In summary, glofitamab demonstrates promising efficacy and a manageable safety profile in heavily pretreated patients with r/r DLBCL in a real-world scenario and the optimal sequence of treatments should use T-cell–depleting agents before glofitamab with caution.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma, in which R-CHOP (rituximab, cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisone)–like frontline immunochemotherapy cures approximately two-thirds of patients.[1] The remaining patients either experience primary refractory or relapsed (r/r) DLBCL.[2,3] Despite recent advances in the treatment of r/r DLBCL, these patients still are characterized by a dismal prognosis[2] underscoring the medical need to establish effective treatment options for this challenging patient population.

Standard-of-care treatment for patients who experience r/r DLBCL <12 months after the end of first-line treatment (early relapse) is the application of chimeric antigen receptor T-cell (CAR-T) therapy with either axicabtagene ciloleucel or lisocabtagene maraleucel. This recommendation is based on 2 positive randomized phase 3 trials, in which both CAR-T products have demonstrated improved event-free survival against the prior standard-of-care of high-dose chemotherapy and autologous stem cell transplantation (SCT).[4-8]

Patients with primary refractory disease, ineligibility to CAR-T therapy, or those who experience relapsed disease after previous CAR-T therapy, face poor prognosis when treated with conventional therapies.[2,8-10] Specifically, patients not responding to second-line therapy have long-term overall survival (OS) rates of <20% at 2 years.[2,10] The prognosis is even worse for patients, who experience disease progression or relapsed disease after CAR-T treatment, with a median OS of ~5 months.[11]

Several bispecific antibodies (bsABs) have been developed for the treatment of patients with r/r DLBCL.[11-13] Mechanistically, bsABs with binding sites for CD20 and CD3 (CD20×CD3) or CD19 and CD3 (CD19×CD3) bridge the immunologic synapse between B-cell lymphoma cells and T-effector cells to expand and activate autologous effector T cells close to the target cell thereby fostering an antilymphoma attack.[14]

Notably, glofitamab, a CD20×CD3 bsAB with 2 CD20 binding sites, has recently received approval for the treatment of adult patients with r/r DLBCL not otherwise specified (NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma (FL), after ≥2 lines of systemic therapy based on the results of the phase 1/2 NP30179 trial.[11] In this trial, 155 patients with r/r DLBCL, who had previously received at least 2 lines of therapy (1/3 with prior CAR-T therapy), were treated with 12 cycles of glofitamab monotherapy after a mandatory pretreatment with a single dose of obinutuzumab to attenuate cytokine release syndrome (CRS). After a median follow-up of 12.6 months, the complete response (CR) rate was 39%. Importantly, these CRs were durable and persisted in 78% of patients at 12 months. After a median follow-up of 25.8 months, 40% of patients had a CR with a median duration of response (DOR) of complete CRs of 26.9 months; an estimated 67% of patients with a CR at any time remained in remission at 18 months.[15]

Importantly, glofitamab exhibits a favorable safety profile making it applicable to heavily pretreated patients. Specifically, grade ≥3 toxicities occurred in 62% of patients, with 5% grade 5 toxicities (fatal, excluding progressive disease [PR]). The most commonly observed adverse event was CRS in 63% of patients. Only 4% had CRS grade ≥3 and immune effector cell–associated neurotoxicity syndrome (ICANS) events of grade ≥3 were recorded in 3% of patients. The risk of CRS was reduced by administration of dexamethasone during the pretherapy period, so that no CRS grade >1 occurred in the study from the second glofitamab administration onward.[11]

Despite its frequent use, there is still a notable scarcity of systematic real-world data concerning the use of glofitamab for patients with r/r DLBCL. Collecting data from patients who have received glofitamab outside a controlled clinical trial setting can offer valuable insights into its clinical applicability, treatment duration, effectiveness, and safety when used for patients with r/r DLBCL. Here, we present the findings of a retrospective, multicenter, real-world data analysis (RWA). This study comprises 70 patients with r/r DLBCL who underwent treatment with glofitamab as part of the compassionate use patient program (CUP) in Germany, Austria, and Switzerland.

Patients, materials, and methods

This investigator-initiated, retrospective, multicenter, multinational study enrolled consecutive patients from 20 study sites, with r/r DLBCL treated with glofitamab between September 2020 and August 2023 as part of the National CUP in Germany, Austria, and Switzerland. This program allowed administration of glofitamab to patients with r/r DLBCL before its approval and market availability by the European Medicines Agency in July and August 2023, respectively. Patients were eligible for treatment through the CUP, if they had experienced treatment failure after ≥3 lines of therapy or were ineligible for next-in-line therapy, including autologous/allogeneic SCT or CAR-T therapy. Each patient within the CUP provided informed consent before treatment initiation. This study was approved by the internal review board of the University Münster (2023-267-f-N). All study protocols and procedures adhered to pertinent guidelines, including the Declaration of Helsinki and local regulations. After approval from the internal review board, clinical data were extracted locally from medical records, electronic patient files, and databases. Patient data were locally pseudonymized, and summary statistics and endpoint analyses were performed centrally.

Glofitamab dosing and infectious prophylaxis

Glofitamab was administered as recommended in the CUP and as previously reported.[11,16,17] Briefly, to mitigate CRS, all patients received on day 1, cycle 1 pretreatment with 1000 mg obinutuzumab, administered IV 7 days before their first dose of glofitamab. Glofitamab was administered IV in a step-up dosage regimen, with 2.5 mg on day 8 cycle 1 and 10 mg on day 15 cycle 1 followed by a 30 mg flat dose on day 1, cycles 2 through 12, with each cycle spanning 21 days. Standard infectious prophylaxis for patients treated with glofitamab included acyclovir and cotrimoxazole. Granulocyte colony-stimulating factors were supplemented if the absolute neutrophil count was <1000/μL. Immunoglobulin replacement therapy was recommended for patients with serum immunoglobulin G levels <4 g/L and recurrent or severe infections.

Response assessment and adverse event grading

Adverse events during glofitamab therapy were assessed according to recommendations outlined in the Common Terminology Criteria for Adverse Events, version 5.0.[18] The grading of CRS and ICANS was conducted following the consensus grading criteria established by the American Society for Transplantation and Cellular Therapy.[19] Response to glofitamab therapy was categorized following the Lugano response criteria[20]: CR, partial response, stable disease (SD), and progressive disease (PD). The best overall response rate (BORR) was defined as the proportion of patients achieving CR or PR as their best response. Response assessment was based on radiological criteria using computed tomography and/or positron emission tomography scans performed after initiating glofitamab therapy. The data cutoff for the evaluation of outcomes was October 2023.

Clinical end points and statistical analysis

The end points of this study were BORR, progression-free survival (PFS), and OS in patients who received glofitamab. Additionally, secondary end points included the assessment of incidence and severity of CRS, ICANS, and other nonhematologic toxicities after glofitamab therapy. To facilitate comparative analysis, the patients included in this study were also categorized into 2 cohorts based on whether they had previously undergone CAR-T therapy at the time of their first glofitamab treatment.

For categorical data, the Fisher's exact test was used, whereas the unpaired *t*-test was used for normally distributed metric data. In cases in which metric data did not follow a normal distribution, the Mann-Whitney *U* test was applied. Time-to-event analyses for PFS and OS used the Kaplan-Meier method, and statistical significance was tested with a log-rank test (significance threshold of $P < 0.05$). In the context of PFS calculations, events were defined as either disease progression or death; whereas for OS, only death was considered an event. DOR was defined as the time from onset of response to progression or death due to any cause, whichever occurred earlier. Univariable and multivariable Cox regression analyses were performed for potential risk factors. Cox regression models were reported using the model coefficients (as hazard ratios) with 95% confidence intervals and corresponding *P* values. Potential risk factors that did not show any association in univariable screening ($P > 0.05$, likelihood ratio test) were not considered for multivariable modeling. Descriptive statistics were executed using GraphPad Prism 9.0.1 for Windows, developed by GraphPad Software in San Diego, CA. Kaplan-Meier plots, Cox regression, and swimmer plots were generated in R (version 4.3.2) using the following R packages: survival (3.7.0), ggplot2 (3.5.0), swimplot (1.2.0), and ggsci (3.0.3).

Results

Patient characteristics

The study enrolled 70 patients and represents a typical r/r DLBCL cohort, with a median age of 62 years (range, 23-94), a male predominance, and 40% of patients having an Eastern Cooperative Oncology Group performance status of ≥2. Overall, 58% of patients had de novo DLBCL (41/70), including 1 with T-cell/histiocyte-rich LBCL, 26% (18/70) had transformed DLBCL from indolent lymphoma, and 16% (11/70) had high-grade B-cell lymphoma (HGBL; Table 1). Median lactate dehydrogenase (LDH) before glofitamab application was 400 U/L (range, 157-1799) with 73% of patients (46/63) exhibiting a high-intermediate or high International Prognostic Index, and 32% (22/69) having bulky disease (>7.5 cm). The median time from diagnosis of aggressive lymphoma to glofitamab application was 20 months (range, 7-295; Table 1). Patients in this cohort were heavily pretreated, with a median of 4 prior lines (range, 2-14) of treatment, including 71% of patients that received a CAR-T therapy and 10% an allogeneic SCT; 71% of patients were refractory to the prior line of treatment (Table 1).

To explore the role of prior CAR-T treatment in the efficacy and toxicity of glofitamab, we analyzed all parameters in the CAR-T–exposed and –naive cohorts, respectively. Both cohorts exhibited similar baseline characteristics, including gender, age, lymphoma type, prior therapies, and International Prognostic Index distributions, but the median time from diagnosis of aggressive lymphoma to initiation of glofitamab treatment was significantly shorter in the CAR-T naive than the CAR-T–exposed cohort (14 months vs 30 months; $P = .010$; Table 1). Additionally, although 60% of patients (30/69) in the CAR-T–exposed cohort had refractory disease in response to the last lymphoma treatment before glofitamab, all patients in the CAR-T naive (19/19 [100%]) had documented refractory disease before glofitamab initiation ($P = .0002$). These data suggest that the CAR-T–naive cohort represents a selection of patients with high disease burden and refractory disease, for whom the local physician may have selected glofitamab instead of CAR-T therapy due to its off-the-shelf availability to control the disease and/or bridge to CAR-T treatment. In fact, 16% of patients (3/19) from this cohort received CAR-T treatment as the subsequent line of treatment.

Time-to-response and response rates

The median number of glofitamab cycles administered was 4 (range, 1-12) with significantly fewer cycles in the CAR-T–naive cohort (2 vs 5; $P = .013$). Median follow-up time from the first glofitamab treatment was 5 months (range, 0.5-35) with no significant difference between the CAR-T–naive and CAR-T–exposed groups (3 months vs 5 months; $P = .109$). Best overall response in the full cohort after glofitamab treatment occurred at a median of 54 days (range, 29-337). Overall, 47% of patients (33/70) exhibited a response to glofitamab; 27% (19/70) achieved a CR, and 20% (14/70) a PR (supplemental Figure1A; Table 2). Although CAR-T–naive and CAR-T–pretreated patients showed no statistically significant differences in the BORR (Fisher's exact test,

Table 1. Patient characteristics of the study cohort

Parameters	All patients	CAR-T naive	CAR-T exposed	*P* value
Patient number, %	70 (100%)	20 (29%)	50 (71%)	–
Age at lymphoma diagnosis, (R), y	62 (23-94)	65 (23-94)	62 (27-77)	.668
Gender, n (%)				
Male	41 (59%)	12 (60%)	29 (58%)	1.000
Female	29 (41%)	8 (40%)	21 (42%)	–
Lymphoma types				
DLBCL de novo, n (%)	40 (57%)	12 (60%)	28 (56%)	.796
GCB	13 (19%)	1 (5%)	12 (24%)	.091
Non-GCB	16 (23%)	7 (35%)	9 (18%)	.206
NOS	11 (16%)	4 (20%)	7 (14%)	.717
DLBCL transformed from Ig-NHL, n (%)	18 (26%)	5 (25%)	13 (26%)	1.000
HGBL with *MYC* and *BCL2/BCL6* rearrangement, n (%)	9 (13%)	2 (10%)	7 (14%)	.707
HGBL NOS, n (%)	2 (3%)	1 (5%)	1 (2%)	–
TCRLBCL, n (%)	1 (1%)	–	1 (2%)	–
Median time from dx to glo, mo (R)	20 (7-295)	14 (6-47)	30 (9-296)	**.003**
Therapies before glo				
Median therapy lines prior glo, n (R)	4 (2-14)	4 (2-13)	4.5 (2-14)	**.042**
Anti-CD20/anthracycline-based reg., n (%)	67 (96%)	18 (90%)	49 (98%)	.194
Platinum-based salvage reg., n (%)	63 (90%)	16 (80%)	47 (94%)	.097
Benda/ritux ± polatuz. ved., n (%)	49 (70%)	16 (80%)	33 (66%)	.387
Benda w/in last 6 mo before glo, n (%)	24 (34%)	11 (55%)	13 (26%)	.072
Tafasitamab/lenalidomide, n (%)	24 (34%)	9 (45%)	15 (30%)	.272
PD-1 inhibitor, n (%)	6 (9%)	1 (5%)	5 (10%)	.666
Ibrutinib, n (%)	4 (6%)	1 (5%)	3 (6%)	1.000
Prior autologous SCT, n (%)	22 (31%)	4 (20%)	18 (36%)	.259
Prior allogeneic SCT, n (%)	7 (10%)	2 (10%)	5 (10%)	1.000
Bulky disease (>7.5 cm) before glo, avail. for 69/70 pts	22 (32%)	9 (45%)	13 (27%)	.161
Extranodal lesions before glo, avail. for 64/70 pts	23 (36%)	7 (37%)	16 (36%)	.161
Median LDH U/L before glo, n (R)	400 (157-1799)	468 (157-1644)	388 (172-1799)	.406
IPI before glo, avail. for 63/70 pts				
IPI low (0-1)	8 (13%)	2 (11%)	6 (14%)	1.000
IPI low-int. (2)	9 (14%)	4 (21%)	5 (11%)	.434
IPI high-int. (3)	26 (41%)	8 (42%)	18 (41%)	1.000
IPI high (4-5)	20 (32%)	5 (26%)	15 (34%)	.769
Dx confirming bx before glo, n (%)	38 (54%)	5 (25%)	33 (66%)	**.003**
CD20 positivity by IHC before glo				
$CD20^+$ lymphoma	35/38 (92%)	4/5 (80%)	31/33 (94%)	–
$CD20^-$ lymphoma	3 (8%)	1/5 (20%)	2/31 (6%)	–
Refractory to last tx, % (avail. for 69/70 pts)	49 (71%)	19 (100%)	30 (60%)	**.0002**

The *P* values are obtained using Fisher's exact test for categorical data and Mann-Whitney *U* test for metric data. Significant *P* values are set in bold.

avail, available; Benda, bendamustine; BCL2/BCL6, B-cell lymphoma 2/B-cell lymphoma 6; bx, biopsy; dx, diagnosis; dz, disease; GCB, germinal center B-cell–like type; glo, glofitamab; IHC, immunohistochemistry; int., intermediate; IPI, International Prognostic Index; Ig-NHL, low-grade Non-Hodgkin lymphoma; MYC, myelocytomatosis oncogene; polatuz. ved, polatuzumab vedotin; PD-1, programmed death protein-1; pts, patients; R, range; reg., regimen; ritux, rituximab; TCRLBCL, T-cell/histiocyte-rich LBCL; tx, therapy.

$P = .116$; supplemental Figure 1B), there was a considerable numerical difference, with BORR being 30% in CAR-T–naive patients compared with 52% in CAR-T–pretreated patients. In this series, we documented 7 PRs that converted to CRs, with a median of 210 days (range, 73-307; Figure 1). Two patients with SD documented 3 and 6 weeks after initiation of glofitamab improved to CR in subsequent 69 and 35 days, respectively. Notably, the median DOR in this cohort was 3.2 months (range,

Table 2. Efficacy of glofitamab therapy and outcomes

Parameters	All patients, n = 70	Patients without prior CAR-Ts, n = 20	Patients with prior CAR-Ts, n = 50	*P* value
Median time to best response, (range), d	54 (6-337)	27 (6-300)	59 (7-337)	**.044**
Best response under glofitamab, n (%)				
ORR, n (%)	32 (46%)	6 (30%)	26 (52%)	.117
CR	19 (27%)	2 (10%)	17 (34%)	.072
PR	13 (19%)	4 (20%)	9 (18%)	1.000
SD	6 (9%)	1 (5%)	5 (10%)	.666
PD	31 (44%)	13 (65%)	18 (36%)	.035
Median DOR, mo, range	3.2 (0.4-34)	2.8 (1.8-11)	3.6 (0.4-34)	.900
Relapse/PD rate after initiation of glofitamab, n (%)	47 (67%)	16 (80%)	31 (62%)	.172
Median time to relapse/PD after first glofitamab administration, range, y	60 (6-371)	27 (6-149)	75 (7-371)	.064
Reason for ending glofitamab				
PD	45 (64%)	16 (80%)	29 (58%)	.252
EOT	9 (13%)	1 (5%)	8 (16%)	.430
Hypersensitivity pneumonitis	1 (1%)	-	1 (2%)	-
Death due to nonlymphoma reason	3 (4%)	2 (10%)	1 (2%)	.226
Consolidation of PR by allo-SCT	3 (4%)	1 (5%)	2 (4%)	1.000
Ongoing	9 (13%)	0 (0%)	9 (18%)	.052
Median time follow-up from glofitamab initiation, (range), mo	5 (0.5-35)	3 (0.5-15)	5 (0.5-35)	.090
Remission status at last follow-up (available for 69/70 cases)				
CR	16 (23%)	2 (10%)	14 (29%)	.127
PR	8 (12%)	3 (15%)	5 (10%)	.682
SD	4 (6%)	0 (0%)	4 (8%)	.319
r/r disease	41 (59%)	15 (75%)	26 (53%)	.108
Consolidative therapy after glofitamab				
Allo-SCT, n (%)	4 (6%)	1 (5%)	3 (6%)	-
Survival status at last follow-up				
Alive	27 (39%)	3 (16%)	24 (55%)	**.010**
Dead	43 (61%)	17 (84%)	26 (45%)	
Mortality reasons				
r/r lymphoma	39 (56%)	15 (75%)	24 (48%)	**.040**
Nonlymphoma reasons	4 (6%)	2 (10%)	2 (4%)	.572
Infection	2 (3%)	1 (5%)	1 (2%)	1.000
Other reasons	2 (3%)	1 (5%)	1 (2%)	.493

Significant *P* values are set in bold.
Allo-SCT, allogeneic SCT; EOT, end of treatment.

0.4-34; Figure 1; Table 2) and at the last follow-up, 39% of patients (27/70) were alive, of whom 56% patients (15/27) remained in CR (13/15 achieved with glofitamab) and 26% (7/27) in PR (Figure 1). The remaining 5 patients presented either with SD or PD (2/27 for each; 15%); for 1 patient (3%) remission status was unavailable at the last follow-up.

In our cohort, 67% of patients (47/70) experienced documented relapse or PD, with a median time to relapse of 60 days (range, 6-371). Although the rate of relapse or PD was similar in both groups, the median time to relapse or PD tended to be shorter in the CAR-T–naive group (27 days vs 75 days; $P = .069$) further supporting the notion that the CAR-T–naive group was selected for more aggressive diseases (Table 2).

At the last follow-up, 13% of patients (9/70) still received glofitamab. The reasons for discontinuing glofitamab included end of treatment as planned in 13% (9/70), consolidation of PR with allogeneic SCT in 4% (3/70), relapsed or PD in 64% (45/70), and death due to nonlymphoma reasons in 4% (3/70; Table 2). Of patients in this series, 51% had no further treatment after glofitamab, whereas 36% received additional treatments, including

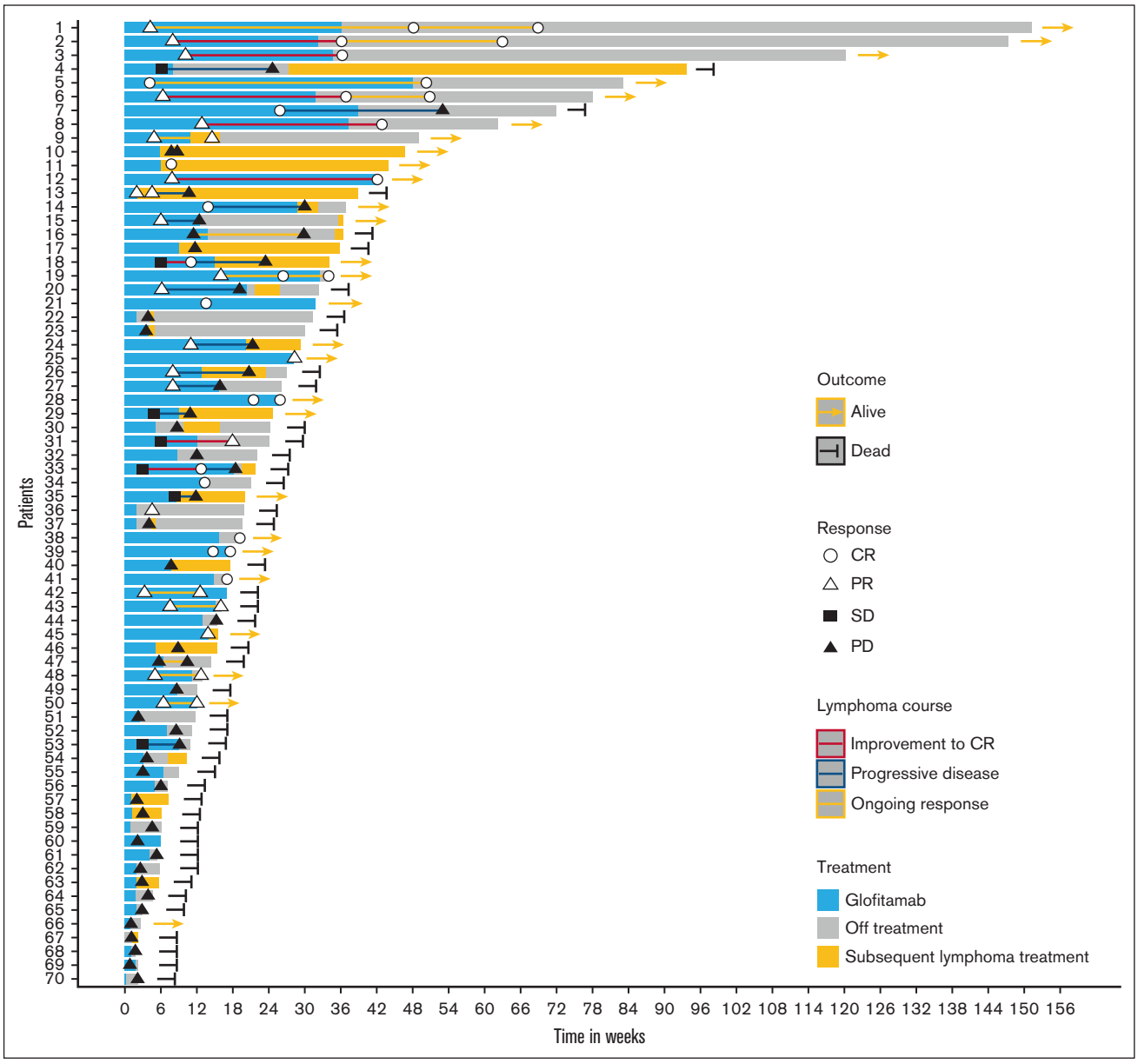


Figure 1. Patient trajectories. Swimmer plot visualizes timing of response and DOR and highlights treatment in all patients of this cohort.

immunochemotherapy, combination of targeted agents (venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide, and polatuzumab vedotin),[21] CAR-Ts, allogeneic SCT, palliative radiation, among others, whereas 9 patients received ongoing treatment with glofitamab (supplemental Table 1).

Nonhematological toxicity

In total, 6% of patients (4/70) succumbed to nonlymphoma-related causes, with 3% of patients (2/70) attributed to infections (grade 5 toxicities) and 3% of patients (2/70) to other reasons (fall-related injury, treatment-related mortality after allogeneic SCT; Tables 2 and 3). Despite routine infectious prophylaxis and limited duration of glofitamab treatment, infections occurred in 31% of patients (22/70), with grades ≥3 in 12% of patients (8/21; grade unknown for 1 patient; Table 3). Notably, half of the infections were viral (11/22; 4/22 severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and 7/22 other viral), 41% (9/22) bacterial, and 9% (2/22) fungal (Table 3). In this series, only 3% of patients (2/70) experienced tumor lysis syndrome (Table 3). The frequency of CRS was 40% (28/70), with grades 3 to 4 documented only in 3% of patients (2/70). Eight patients (11%) presented with ICANS, of which only 1 patient (1%) had grade 3 and the remainder grade 1 to 2 (Figure 2; Table 3). Treatment of CRS and ICANS included mainly steroids alone or in conjunction with tocilizumab, and if needed, infrequently vasopressors; admission to intermediate care or intensive care units was necessary for treatment of CRS/ICANS in 10% of patients (7/70; Table 3). Importantly, there were no patient fatalities related to CRS or ICANS.

Table 3. Toxicities of glofitamab therapy in patients of this study

Parameters	All patients, n = 70	Patients without prior CAR-Ts, n = 20	Patients with prior CAR-Ts, n = 50	*P* value
Median number of glofitamab cycles administered, n (range)	4 (1-12)	2 (1-12)	5 (1-12)	**.013**
CRS after glofitamab, n (%)				
CRS (grade 1-4)	28 (40%)	9 (45%)	19 (38%)	1.000
Grade 0	42 (60%)	11 (55%)	31 (62%)	1.000
Grade 1	17 (25%)	5 (25%)	12 (24%)	1.000
Grade 2	9 (13%)	3 (15%)	6 (12%)	.708
Grade 3	1 (1%)	1 (5%)	-	-
Grade 4	1 (1%)	-	1 (2%)	-
ICANS after glofitamab, n (%)				
ICANS (grade 1-3)	8 (11%)	3 (15%)	5 (10%)	.708
Grade 0	62 (89%)	17 (85%)	45 (90%)	.708
Grade 1	4 (6%)	1 (5%)	3 (6%)	1.000
Grade 2	3 (4%)	2 (10%)	1 (2%)	.194
Grade 3	1 (1%)	-	1 (2%)	-
Treatment of CRS (available for 24/28 cases)				
Symptomatic (eg, antipyretics, volume), n (%)	10 (36%)	3 (33%)	7 (47%)	-
Steroids, n (%)	1 (4%)	1 (11%)	-	-
Steroids/tocilizumab, n (%)	11 (39%)	4 (44%)	7 (47%)	-
Steroids/tocilizumab/vasopressor, n (%)	2 (7%)	1 (11%)	1 (7%)	-
Treatment of ICANS (available for 6/8 cases)				
Supportive measures only, n (%)	2 (33%)	1 (33%)	1 (33%)	-
Steroids, n (%)	2 (33%)	1 (33%)	1 (33%)	-
Steroids/tocilizumab, n (%)	1 (17%)	1 (33%)	-	-
Steroids/tocilizumab/vasopressor, n (%)	1 (17%)	-	1 (33%)	
Admission to IMC/ICU because of CRS and/or ICANS, n (%)	7 (10%)	4 (20%)	3 (2%)	.135
Infection incidence under glofitamab, n (%)	22 (31%)	8 (40%)	14 (28%)	.397
Infection type under glofitamab, n (%)				
Bacterial	9 (13%)	6 (30%)	3 (6%)	**.013**
Fungal	2 (3%)	-	2 (4%)	1.000
Viral non-SARS-CoV-2	7 (10%)	1 (5%)	6 (12%)	.664
SARS-CoV-2	4 (6%)	2 (10%)	2 (4%)	.572
Infection grade (CTCAE) under glofitamab, n (%) (n = 21)				
Grade 1	8 (11%)	2 (10%)	6 (12%)	1.000
Grade 2	5 (7%)	1 (5%)	4 (8%)	1.000
Grade 3	6 (9%)	3 (15%)	3 (6%)	.097
Grade 5	2 (3%)	1 (5%)	1 (2%)	.493
Tumor lysis syndrome under glofitamab, n (%)	2 (3%)	1 (5%)	1 (2%)	.493

Significant *P* values are set in bold.
CTCAE, common terminology criteria for adverse events; ICU, intensive care unit; IMC, intermediate care.

Outcome

Overall, 61% of patients (43/70) died, underscoring that these patients represent a difficult-to-treat cohort, with a higher mortality rate in the CAR-T–naive patients than CAR-T–exposed patients (84% vs 45%; $P = .010$). Disease progression was the primary cause of mortality, accounting for 56% of all patients (39/70), and was significantly higher in CAR-T–naive patients than CAR-T–exposed patients (75% vs 48%; $P = .040$). Among the entire patient cohort treated with glofitamab, the median PFS (mPFS) was 3.6 months and the median OS (mOS) was 5.7 months (Figure 3A-B). The estimated mPFS was better in the CAR-T–exposed than in the CAR-T–naive group (4.50 vs 1.15 months; log-rank $P = .006$), which also extended to OS

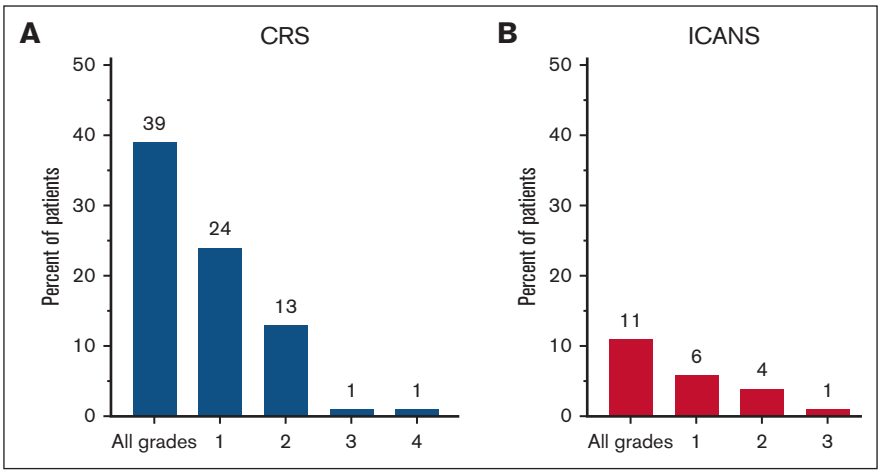


Figure 2. CRS and ICANS after glofitamab. Incidence of CRS (A) and ICANS (B) in all patients by grades.

advantages (8.2 vs 3.4; log-rank $P = .004$; Figure 3C-D). As detailed above, the median time to relapse was 60 days and 34 of 38 patients with PD/SD died at the last follow-up, with a median of 3 months after initiation of glofitamab. We also conducted a landmark analysis at day 180 after the start of glofitamab treatment, as this was the time point with the most response data available in our real-world cohort, in which imaging studies were not conducted at uniform intervals across all patients. This analysis was performed on all patients alive at day 180 after the start of glofitamab and revealed a significant PFS ($P = .011$) and an OS ($P = .0005$) advantage for patients in CR at this time point (Figure 3E-F).

Next, we analyzed the outcomes of patients treated with glofitamab based on pathological subtypes, including DLBCL NOS, transformed DLBCL (83%, n = 15 from FL; 17%, n = 3 from marginal zone lymphoma), and HGBL. Interestingly, patients with transformed DLBCL demonstrated significantly better survival outcomes in comparison with DLBCL NOS and HGBL (mPFS: not reached vs 4.3 vs 2.5 months; $P = .014$; mOS: not reached vs 5.1 vs 4.7 months; $P = .020$), accordingly (Figure 4). Yet, there were no significant differences between transformed DLBCL, DLBCL NOS, and HGBL considering baseline parameters before glofitamab (supplemental Table 4). We did not see any survival differences between germinal center B-cell–like type and non–germinal center B-cell–like DLBCL-type patients with respect to mPFS or mOS after glofitamab (supplemental Figure 2).

The univariate and multivariate Cox proportional hazards models identified key prognostic factors for PFS and OS in patients treated with glofitamab (Table 4). The univariate analysis revealed that recent exposure to bendamustine (hazard ratio [HR], 2.00; $P = .02$), CAR-T naivety (HR, 1.97; $P = .03$), refractoriness to the last therapy (HR, 2.62; $P = .01$), bulky disease (>7.5 cm; HR, 2.78; $P = .009$), and elevated LDH (HR, 1.89; $P = .03$) were significantly associated with inferior PFS. However, when controlling for multiple variables in the multivariate model, only elevated LDH remained a significant predictor of PFS (HR, 1.83; $P = .05$), underscoring its strong predictive value.

For OS, univariate analysis identified CAR-T naivety (HR, 2.17; $P = .02$), refractoriness to the last therapy (HR, 2.58; $P = .02$), and elevated LDH (HR, 2.10; $P = .03$) as significant factors. However, with the exemption of elevated LDH, these factors did not remain significant in the multivariate model. Elevated LDH levels were associated with worse OS (HR, 1.98; $P = .04$), highlighting its role as a key prognostic marker across both survival outcomes.

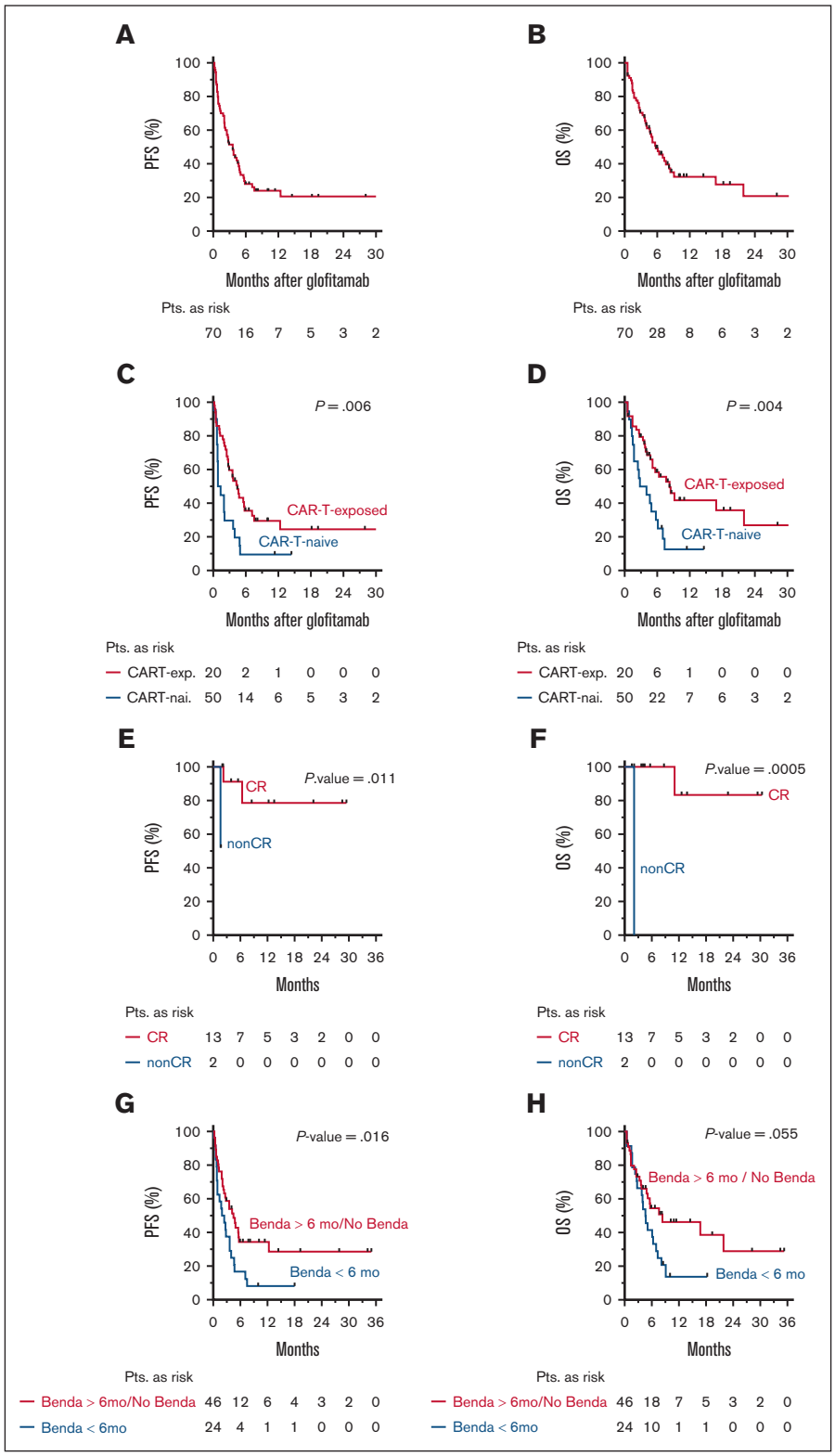
Although bendamustine exposure did not retain significance in the multivariate analysis, it may still be an important factor, particularly because of its negative effects on T-cell fitness. Bendamustine is known to deplete T cells, which could influence the efficacy of T-cell–engaging therapies such as glofitamab. In our data, patients who received bendamustine within 6 months before glofitamab treatment experienced significantly reduced PFS and showed a trend toward lower OS than those who had either been treated with bendamustine >6 months earlier or had no prior exposure to the drug (Figure 3G-H). Notably, no differences were observed in outcomes between patients who were completely naive to bendamustine and those who had no recent exposure within the last 6 months (supplemental Figure 3). To ensure that patients receiving bendamustine did not have more aggressive or higher-risk lymphoma, we compared relevant risk factors between groups and found no significant differences (supplemental Table 5).

In summary, besides the fitness of the T cells, the actual biology of the tumor seems to be the most important factor determining glofitamab efficacy.

Discussion

Here, we report, to the best our knowledge, the largest RWA studying the efficacy and safety of glofitamab treatment in patients with r/r DLBCL. We enrolled 70 patients, who were treated with glofitamab within the CUP, which made glofitamab available to patients without any other treatment options before formal approval by the authorities. To this end, the cohort herein represents an extremely heavily pretreated selection of r/r DLBCL patients with a median of 4 (range, 2-14) prior lines of treatment, including 71% of patients with prior CAR-T therapy and 10% with prior allogeneic SCT. In addition, 71% of patients were refractory to the last line of treatment (Table 1). Despite this challenging patient population, we

Figure 3. Survival proportions after treatment initiation with glofitamab and outcomes for clinically relevant patient (pt) subsets. (A) PFS for all pts; (B) OS for all pts; (C) PFS in CAR-T–naive (blue) and CAR-T–exposed (red) pts; and (D) OS in CAR-T–naive (blue) and CAR-T–exposed (red) pts. (E-F) Landmark analysis for PFS (E) and OS (F) in pts depending on response 180 days after start of glofitamab (CR, red; non-CR, blue). (G-H) PFS (G) and OS (H) for pts treated before glofitamab with Benda-containing regimes (red, >6 months; blue, ≤6 months). The *P* values are obtained using a log-rank test and pts at risk are highlighted below the Kaplan-Meier plot. Benda, bendamustine; exp., exposed; nai., naive.



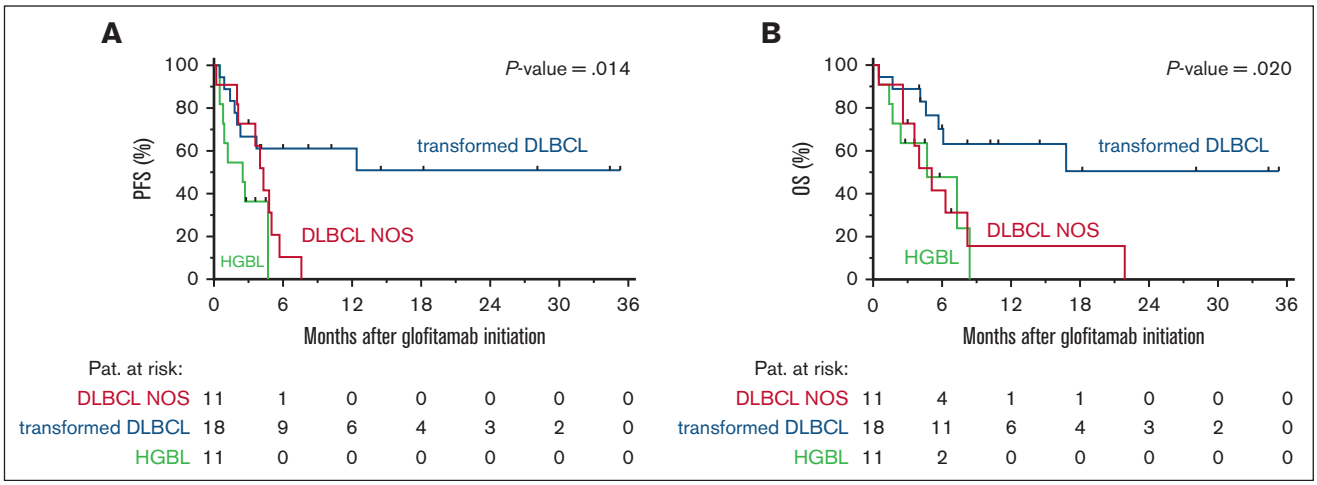


Figure 4. Survival proportions stratified by pathological subtypes. PFS (A) and OS (B) for patients stratified by DLBCL NOS (red), transformed DLBCL (blue), and HGBL (green). The *P* values are obtained using a log-rank test and patients at risk are highlighted below the Kaplan-Meier plot.

observed an encouraging ORR of 46%, with 27% CRs and 19% PRs (Figure 1). The ORR in our study was higher than those recently reported from a smaller Turkish analysis (37% ORR, with 21% CRs and 16% PRs; supplemental Tables 2 and 3)[22] but lower than the results from the pivotal trial that demonstrated a better ORR (52%) and CR rate (39%; supplemental Tables 2 and 3). The lower ORR in our study than in the pivotal trial can be explained by the significantly more pretreated patient cohort in comparison to the approval study: 4 vs 3 median prior lines of therapy; 71% vs 33% prior CAR-T therapies. Moreover, 71% of patients in this cohort were refractory to the last treatment before glofitamab (supplemental Table 2).

In addition to the observed ORR, another notable aspect of glofitamab is the short median time to best response, reported as 42 days in the pivotal trial and 54 days in our RWA (supplemental Tables 2 and 3).[11] It is important to acknowledge that in this RWA imaging was not conducted at uniform intervals across all patients as in clinical trials. Furthermore, some patients, particularly those with PD in a palliative setting were not further evaluated with imaging. Despite these limitations, we obtained imaging-based response assessments for 87% of patients (61/70), which is a considerable proportion. Although this variability in imaging timing and availability may introduce some imprecision in our time-to-response data, the findings nonetheless provide valuable insights into the efficacy and underline the high clinical activity of glofitamab even in this last line treatment of patients. Thus, our data support its use in the licensed indication and its exploration in earlier lines of treatment.

Because of the quick response rate and chemotherapy-independent mechanisms of action, some clinical investigators in our RWA used the off-the-shelf available glofitamab as a bridging strategy to CAR-T therapies in those patients with an unfavorable

Table 4. Univariate and multivariate Cox proportional hazards models

		PFS		OS	
Variable before Glo	**Category**	**HR (univariate)**	**HR (multivariate)**	**HR (univariate)**	**HR (multivariate)**
Age at Glo infusion	Continuous variable	*P* = .93	–	*P* = .44	–
Gender	Male/female	0.99 (0.55-1.78; *P* = .97)	–	0.89 (0.47-1.68; *P* = .71)	–
DLBCL, de novo	Yes vs no	1.45 (0.77-2.72; *P* = .25)	–	1.56 (0.78-3.11; *P* = .21)	–
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements	Yes vs no	1.65 (0.72-3.76; *P* = .24)	–	1.60 (0.66 -3.88; *P* = .29)	–
Treatment lines before Glo	Continuous variable	*P* = .73	–	*P* = .81	–
Bendamustine within last 6 mos vs >6 mos/never	Yes vs no	**2.00 (1.11-3.62; *P* = .02)**	1.53 (0.79-2.97; *P* = .21)	1.81 (0.95-3.47; *P* = .07)	–
CAR-T naive	Yes vs no	**1.97 (1.06-3.63; *P* = .03)**	1.57 (0.80-3.06; *P* = .19)	**2.17 (1.12-4.20; *P* = .02)**	1.62 (0.79-3.31; *P* = .19)
Refractoriness to last therapy	Yes vs no	**2.62 (1.26-5.48; *P* = .01)**	1.59 (0.69-3.67; *P* = .28)	**2.58 (1.12-5.92; *P* = .03)**	1.97 (0.79-4.90; *P* = .14)
Bulky disease (>7.5 cm)	Yes vs no	**2.78 (1.51-5.09; *P* = .0009)**	1.83 (0.93-3.58; *P* = .08)	1.69 (0.87-3.26; *P* = .12)	–
LDH >400 U/L	Yes vs no	**1.89 (1.05-3.40; *P* = .03)**	**1.83 (1.00-3.35; *P* = .05)**	**2.10 (1.09-4.05; *P* = .03)**	**1.98 (1.02-3.83; *P* = .04)**

Bold indicates significance. Only variables found to be significant in the univariate analysis were tested in the multivariate model; for variables not tested in the multivariate model. "–" is used to indicate unavailable data.

Glo, glofitamab.

tumor biology (LDH of >400 U/L, and a higher number of refractory patients; above referred to as CAR-T–naive group; Table 1). In fact, 3 of 12 patients for whom this strategy was intended were eventually treated with CAR-Ts, suggesting that bsABs might be used for bridging to CAR-Ts. However, in this RWA most patients received glofitamab as a salvage treatment after CAR-T therapies (above referred to as CAR-T exposed; Table 1) with even better ORR of 54% (34% CR and 20% PR).

In the full cohort, the median PFS after glofitamab application was 3.6 months, slightly shorter but comparable with the 4.9 months reported in the pivotal trial.[11] Notably, 19% of patients in CR 6 months after starting glofitamab maintained their responses until the end of the observation period. This underscores that glofitamab can induce durable remissions even when no other treatment options are available. Conversely, all patients who did not achieve a CR eventually succumbed to their disease, highlighting that obtaining a CR with glofitamab is the most critical predictor of long-term outcomes.

Not surprisingly, and in line with response analyses to other treatments for LBCL, certain clinical factors reflecting aggressive tumor biology, such as elevated LDH, refractoriness to the last therapy, and recent bendamustine exposure, were significant predictors of poor outcomes in the univariate Cox regression analysis. However, in the multivariate Cox regression model, only elevated LDH remained a statistically significant predictor of both worse PFS and OS, underscoring its role as a dominant prognostic marker.

Bendamustine, frequently used in combination with polatuzumab and rituximab, is the most common long-term T-cell–depleting agent in treatment of r/r DLBCL.[23,24] Given glofitamab's mechanism of action, we believe that the timing of bendamustine, which depletes host T cells and affects their fitness, remains important for optimizing treatment outcomes.

In our cohort, patients who received bendamustine within 6 months before glofitamab treatment experienced significantly reduced PFS and showed a trend toward lower OS, suggesting that bendamustine should be used cautiously, particularly within 6 months of anticipated glofitamab treatment. This finding is consistent with the mechanism of action and recent reports that find decreased CAR-T activity for patients exposed to bendamustine.[25] The apparent lack of significance in the multivariate analysis suggests that LDH, as a key marker of aggressive disease, may have a stronger overall influence on survival outcomes.

Notably, transformed DBLCL, demonstrated the best survival outcomes under glofitamab among all analyzed LBCLs (compared with DLBCL NOS or HGBL), which is interesting because commonly transformed DLBCL is characterized by inferior outcomes in comparison with de novo DLBCL with conventional immunochemotherapies. However, this cohort was too small and heterogeneous to draw more biological conclusions and requires validation in larger patient cohorts with deeper molecular profiling.

Importantly, the nonhematological toxicity profile in our RWA was similar to the profile observed in the pivotal trial (supplemental Table 3).[11] We found CRS of any grade in 40% of patients (only 2% grade 3/4, no grade 5), compared with the 63% reported frequency in the pivotal trial (4% grade 3/4, no grade 5). All patients with CRS were manageable with the application of steroids, tocilizumab, and/or a combination of both. The frequency of patients with ICANS was comparable with that reported in the pivotal trial (11% vs 8% in our RWA vs pivotal trial, respectively). Importantly, except 1 ICANS case of grade 3, the remainder of ICANS cases were of grades 1 to 2. Also, the frequency of patients that required admission to the intensive care unit during their treatment to treat CRS or ICANS was similar (10%) in our cohort, compared with 7% in the pivotal trial. Despite rapid responses, we noted only infrequent tumor lysis syndromes in 2 patients (3%; supplemental Table 3).[11]

Overall, the rate of infections was 31% in our RWA, slightly lower than the 38% frequency in the pivotal trial. Fatal infections (common terminology criteria for adverse events grade 5) were infrequent and comparable with the pivotal trial (RWA, 2 patients [3%], Dickinson et al, 2 patients [1%]; supplemental Table 3).[11] The infections were mainly viral (50%, 11/22) and bacterial (9/22 [41%]), whereas fungal infections were rare (9%, 2/22). Of note, only 6% of patients (4/70) experienced a SARS-CoV2 infection, similar to that in the pivotal trial (6%). Overall, glofitamab showed an expected and manageable safety profile in the RWA, very similar to the safety data in the pivotal trial (supplemental Table 3).[11]

In summary, our RWA of glofitamab showed good efficacy paired with an expected and overall manageable safety profile in highly pretreated patients with r/r DLBCL, reinforcing glofitamab's potential to contribute to the therapeutic armamentarium for patients with DLBCL. Although our data suggest that patients pretreated with bendamustine-containing regimens tended to respond less well to glofitamab, the small size of our cohort limits our ability to conclusively demonstrate this effect. Nonetheless, the potential impact of bendamustine or other agents affecting the T-cell fitness warrants careful consideration of the treatment sequence, particularly within a 6-month window before bsAb treatment. Because of its off-the-shelf availability, ongoing prospective clinical trials will redefine the optimal application and sequence of glofitamab in the treatment of patients suffering from DLBCL.

Acknowledgment

This study was supported by institutional funds as part of a recruiting package from Charité Universiätsmedizin Berlin and Berlin Institute of Health (B.C.).

Authorship

Contribution: B.C. and G.L. conceived the project and provided leadership; E.S., R.W.-K., A.K., T.M., U.H., U.B., P.S., A. Hölscher, J. K., N.R., V.V., J.R., D.N., V.B., U.S., C.L., D.B., I.K., K.W., A. Hasse, B.v.T., M.H., C.K., G.F.V., A.V., C.S., L.T., D.W., M.S., M.D., P.D., S.D., U.K., U.J., R.G., T.P., G.L., and B.C. provided patient data; E.S., R.W.-K., A.K., M.W., P.M., G.L., and B.C. analyzed the data; E.S., R.W.-K., A.K., G.L., and B.C wrote the manuscript; and all authors approved the final manuscript.

Conflict-of-interest disclosure: B.C. is an inventor on patent applications related to molecular subtyping of diffuse large B-cell lymphoma, including DLBc*lass*; has received research funding from Gilead Sciences in 2021 (unrelated to this manuscript); served on advisory boards for AbbVie, ADC Therapeutics, Bristol Myers

Squibb (BMS), Incyte, Janssen, Regeneron, Roche, and Sobi (not related to this manuscript); received honoraria for talks from AbbVie, Ars Tempi, AstraZeneca, BMS, Incyte, Janssen, Gilead, Kompetenznetzwerk Maligne Lymphome, Roche, Sandoz, Sobi, and Ono (not related to this manuscript); received travel support from Sobi and Roche (not related to this manuscript); and is the lead investigator on the R-Pola-Glo clinical trial, which is indirectly funded by Roche. G.L. received research grants from Agios, AQUINOX, AstraZeneca, Bayer, Celgene, Gilead, Janssen, MorphoSys, Novartis, Roche, and Verastem, and received honoraria from ADC Therapeutics, AbbVie, Amgen, AstraZeneca, Bayer, BMS, Celgene, Constellation, Genase, Genmab, Gilead, Hexal-Sandoz, Immagene, Incyte, Janssen, Karyopharm, Lilly, Miltenyi, Morphosys, NanoString, Novartis, PentixaPharm, Roche, Sobi, and Takeda (unrelated to this manuscript). M.H. received travel support from AbbVie and served on advisory boards for Sobi, Novartis, Gilead, BMS, Pfizer, Incyte, Sanofi, Roche, Janssen, and Amgen (unrelated to this manuscript). U.J. received honoraria for consultancy or advisory roles from AbbVie, Roche, Novartis, Gilead, BMS, Janssen, and Miltenyi (unrelated to this manuscript). A.V. received honoraria for consultancy or advisory roles from AbbVie, BMS, Novartis, Gilead, and Roche, and travel support from Sobi, Janssen, and Gilead (unrelated to this manuscript). J.R. received honoraria for consultancy or advisory roles from AbbVie, Roche, Novartis, Gilead-Kite, BMS-Celgene, Takeda, Janssen, and Miltenyi (unrelated to this manuscript). U.H. has served on advisory boards for BMS, Johnson & Johnson, Kite Gilead, and Roche, and received honoraria for talks from AbbVie, BeiGene, BMS, Johnson & Johnson, Kite Gilead, and Miltenyi Biotec (unrelated to this manuscript). I.K. received honoraria for talks from AbbVie, Lilly, and Incyte, and travel support/congress participation fee from Janssen, Lilly, and Sobi (unrelated to this manuscript). D.W. received sponsorship for clinical trials or research funding from Ariad, Pfizer, Novartis, BMS, Roche, AOP, Merck Sharp and Dohme (MSD), Gilead, Miltenyi, Bexalta, and Incyte, and speakers' honorary/travel support from Ariad, Pfizer, Novartis, BMS, Roche, Amgen, Incyte, Lilly, Takeda, Jazz, AbbVie, and Bexalta (unrelated to tis manuscript). T.M. received honoraria from AbbVie, BMS, Incyte, Janssen, Regeneron, and Roche, not related to this manuscript. B.v.T. is an adviser or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead-Kite, Incyte, IQVIA, Janssen-Cilag GmbH, Lilly, MSD, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, Sobi, and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead-Kite, Incyte, Lilly, MSD, Novartis, Roche Pharma AG, and Takeda (unrelated to this manuscript); reports research funding unrelated to this manuscript from Esteve (institutional), MSD (institutional), Novartis (institutional), and Takeda (institutional); and reports travel support from AbbVie, AstraZeneca, Gilead-Kite, Lilly, MSD, Pierre Fabre, Roche, Takeda, and Novartis (not manuscript related). N.R. received honoraria from AbbVie, AstraZeneca, BeiGene, Gilead, Incyte, Janssen, Merck, Novartis, Roche, Sandoz, and Takeda (not related to this manuscript). V.V. received honoraria for consultancy or advisory roles from AbbVie, Novartis, Gilead, BMS, Janssen, Sobi, Incyte, AstraZeneca, Amgen, and MSD, unrelated to this manuscript. U.S. received honoraria for consultancy, travel support, or advisory from AbbVie, Novartis, Kite Gilead, BMS, Janssen, Sobi, Takeda, and BeiGene (not related to this manuscript). The remaining authors declare no competing financial interests.

ORCID profiles: E.S., 0000-0003-0178-1729; A.K., 0000-0001-6904-2821; M.W., 0009-0006-1426-4594; T.M., 0000-0002-0122-3631; U.H., 0000-0002-5543-0257; U.B., 0000-0001-8771-947X; P.S., 0000-0001-6729-7708; P.M., 0000-0001-6317-0216; C.L., 0009-0006-4007-9122; D.B., 0000-0002-1783-9641; A. Hölscher, 0009-0004-8994-1137; J.K., 0000-0003-1632-0167; N.R., 0009-0009-9813-5344; V.V., 0000-0002-8398-285X; J.R., 0000-0001-7963-3385; D.N., 0009-0006-6243-915X; V.B., 0000-0001-7391-7280; U.S., 0000-0001-7455-8988; I.K., 0000-0003-1667-4109; K.W., 0000-0002-7682-8563; B.v.T., 0000-0003-1410-4487; M.H., 0000-0002-4767-3275; C.K., 0000-0001-7025-1735; G.F.V., 0000-0003-2884-3432; A.V., 0000-0001-9593-6327; C.S., 0000-0001-7070-487X; L.T., 0000-0002-8167-2989; D.W., 0000-0002-4761-075X; M.S., 0000-0001-9154-9469; M.D., 0000-0002-0358-5249; P.D., 0000-0002-7429-8570; S.D., 0000-0002-0648-1832; U.K., 0000-0002-8485-1958; U.J., 0000-0001-9826-1062; R.G., 0000-0002-4462-3694; T.P., 0000-0002-6055-5257; G.L., 0000-0002-4728-1693; B.C., 0000-0002-6485-8773.

Correspondence: Björn Chapuy, Charité-University Medical Center, Berlin Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany; email: bjoern.chapuy@charite.de.

References

1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 5th ed. International Agency for Research on Cancer; 2008.
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.
3. Frontzek F, Karsten I, Schmitz N, Lenz G. Current options and future perspectives in the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma. *Ther Adv Hematol*. 2022;13:20406207221103321.
4. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654.
5. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
6. 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.

7. 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.
8. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.
9. Di Blasi R, Le Gouill S, Bachy E, et al. Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis. *Blood*. 2022;140(24):2584-2593.
10. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016;51(1):51-57.
11. 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.
12. 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*. 2023;41(12):2238-2247.
13. Ayyappan S, Kim WS, Kim TM, et al. Final Analysis of the Phase 2 ELM-2 study: odronextamab in patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *Blood*. 2023;142(suppl 1):436.
14. Brinkmann U, Kontermann RE. The making of bispecific antibodies. *mAbs*. 2017;9(2):182-212.
15. Hutchings M, Carlo-Stella C, Morschhauser F, et al. Glofitamab monotherapy in relapsed or refractory large B-cell lymphoma: extended follow-up from a pivotal phase II study and subgroup analyses in patients with prior chimeric antigen receptor T-cell therapy and by baseline total metabolic tumor volume. *Blood*. 2023;142(suppl 1):433.
16. Roche. Pharmacy Manual Glofitamab CUP v4.0.pdf. 2023.
17. Roche. Glofitamab Compassionate Use Program for 4L+ DLBCL-patients. 2023.
18. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.
19. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
20. 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.
21. Melani C, Lakhotia R, Pittaluga S, et al. Phase Ib/II study of multi-targeted therapy with venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (ViPOR) in relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *Blood*. 2023;142(suppl 1):434.
22. Birtas Atesoglu E, Gulbas Z, Uzay A, et al. Glofitamab in relapsed/refractory diffuse large B-cell lymphoma: real-world data. *Hematol Oncol*. 2023;41(4):663-673.
23. 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.
24. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood Adv*. 2022;6(2):533-543.
25. Iacoboni G, Navarro V, Martin-Lopez AA, et al. Recent bendamustine treatment before apheresis has a negative impact on outcomes in patients with large B-cell lymphoma receiving chimeric antigen receptor T-cell therapy. *J Clin Oncol*. 2024;42(2):205-217.