# Glofitamab monotherapy induces high complete response rates and manageable safety in Chinese patients with heavily pretreated relapsed or refractory diffuse large B-cell lymphoma

Current standard-of-care for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) comprises chemotherapy and autologous stem cell transplantation (ASCT).[1] Patients who are ineligible for ASCT/who relapse shortly after ASCT have a poor prognosis.[2]

Chimeric antigen receptor (CAR) T-cell therapy has recently been approved for treatment of R/R DLBCL following ≥2 prior lines of therapy. However, CAR T-cell therapy may be complicated by severe toxicities and logistical challenges which can delay treatment initiation, and access may be restricted to specialist treatment centers. Furthermore, patients who fail CAR T-cell therapy have extremely limited treatment options and inferior outcomes.[3,4] Tolerable treatments with increased efficacy and off-the-shelf availability are needed to improve outcomes for these patients.

Glofitamab is a CD20xCD3 bispecific antibody with a novel 2:1 format that engages and redirects T cells to eliminate B cells.[5] As an off-the-shelf treatment, glofitamab can be initiated without delay. In pivotal cohorts of the global NP30179 phase I/II study (*clinicaltrials gov. Identifier: NCT03075696*), 155 patients with R/R DLBCL who had received ≥2 prior therapies were administered fixed-duration glofitamab monotherapy. Glofitamab demonstrated a manageable and well tolerated safety profile, with high response rates (objective response rate [ORR]: 52%; complete response [CR]: 39%) and durable CR.[6] Only a small number of Asian patients were enrolled in the study (2 centers in Taiwan) and limited information is known about the impact of racial differences on the outcomes of patients with R/R DLBCL treated with glofitamab. We report data from a multicenter, open-label, phase I study (*clinicaltrials gov. Identifier: NCT04657302*), where pharmacokinetics (PK), efficacy, and safety of glofitamab were investigated in Chinese patients with R/R DLBCL after ≥2 prior lines of therapy including ≥1 anti-CD20 antibody-containing and ≥1 anthracycline-containing regimen. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable laws. The protocol was approved by the Institutional Review Board and/or the Independent Ethics Committee, and written informed consent was provided by all patients. Patients aged ≥18 years with histologically confirmed DLBCL-not otherwise specified (NOS), high-grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL), or transformed follicular lymphoma (trFL) were included. Patients received obinutuzumab pretreatment (1,000 mg) on cycle (C) 1 day (D) 1, followed by step-up dosing of intravenous glofitamab during C1 (2.5 mg D8, 10 mg D15), then the target dose (30 mg) on D1 of C2–12 (21-day cycles) for up to 12 cycles or until disease progression (PD) or unacceptable toxicity. Premedication with corticosteroids before each infusion of obinutuzumab and glofitamab was mandatory in C1 and

**Table 1.** Demographic and baseline clinical characteristics (safety population).

| Characteristics | N=30 |
|---|---|
| Median age in years (range) | 57.5 (20-82) |
| Male sex, N (%) | 13 (43.3) |
| ECOG performance status, N (%) | |
| 0 | 15 (50.0) |
| 1 | 15 (50.0) |
| Ann Arbor stage at study entry, N (%) | |
| II | 3 (10.0) |
| III | 3 (10.0) |
| IV | 24 (80.0) |
| NHL subtype, N (%) | |
| Diffuse large B-cell lymphoma NOS | 20 (66.7) |
| Primary mediastinal B-cell lymphoma | 5 (16.7) |
| High-grade B-cell lymphoma | 3 (10.0) |
| Transformed follicular lymphoma | 2 (6.7) |
| Bulky disease at study entry, N (%) | |
| <6 cm | 19 (63.3) |
| ≥6 and <10 cm | 6 (20.0) |
| ≥10 cm | 5 (16.7) |
| Prior lines of therapy | |
| Number, median (range) | 2 (2-6) |
| 2 prior lines, N (%) | 17 (56.7) |
| ≥3 prior lines, N (%) | 13 (43.3) |
| Prior CAR T-cell therapy, N (%) | 6 (20.0) |
| Prior autologous stem cell transplant , N (%) | 3 (10.0) |
| Relapsed/refractory status, N (%) | |
| Refractory to any prior therapy | 28 (93.3) |
| Refractory to last prior therapy | 27 (90.0) |
| Refractory to first-line therapy | 20 (66.7) |
| Refractory to prior CAR T-cell therapy | 4 (13.3) |

CAR: chimeric antigen receptor; ECOG: Eastern Cooperative Oncology Group; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified.

C2 but optional thereafter in patients not considered high risk for cytokine release syndrome (CRS).

Efficacy endpoints included response, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Response was assessed by an Independent Review Committee (IRC) and by investigators according to Lugano 2014 criteria.[7]

The safety analysis included patients who received ≥1 dose of glofitamab or obinutuzumab; the efficacy analysis included all patients who received ≥1 glofitamab dose.

As of December 2, 2022, 30 patients (12 in the PK cohort; 18 in the expansion cohort) were enrolled at five sites across China (27 received ≥1 glofitamab dose; 3 patients received obinutuzumab pretreatment alone and discontinued). At data cutoff, 12 patients had completed treatment and 18 had discontinued (discontinuations due to: PD, N=9; patient withdrawal, N=4; physician's decision, N=2; adverse events [AE], N=2; other, N=1).

Median age was 57.5 years (range, 20-82). Two-thirds of patients had DLBCL-NOS (Table 1). All patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 and most had advanced disease (Ann Arbor stage III–IV: 90.0%). Median number of prior thera-

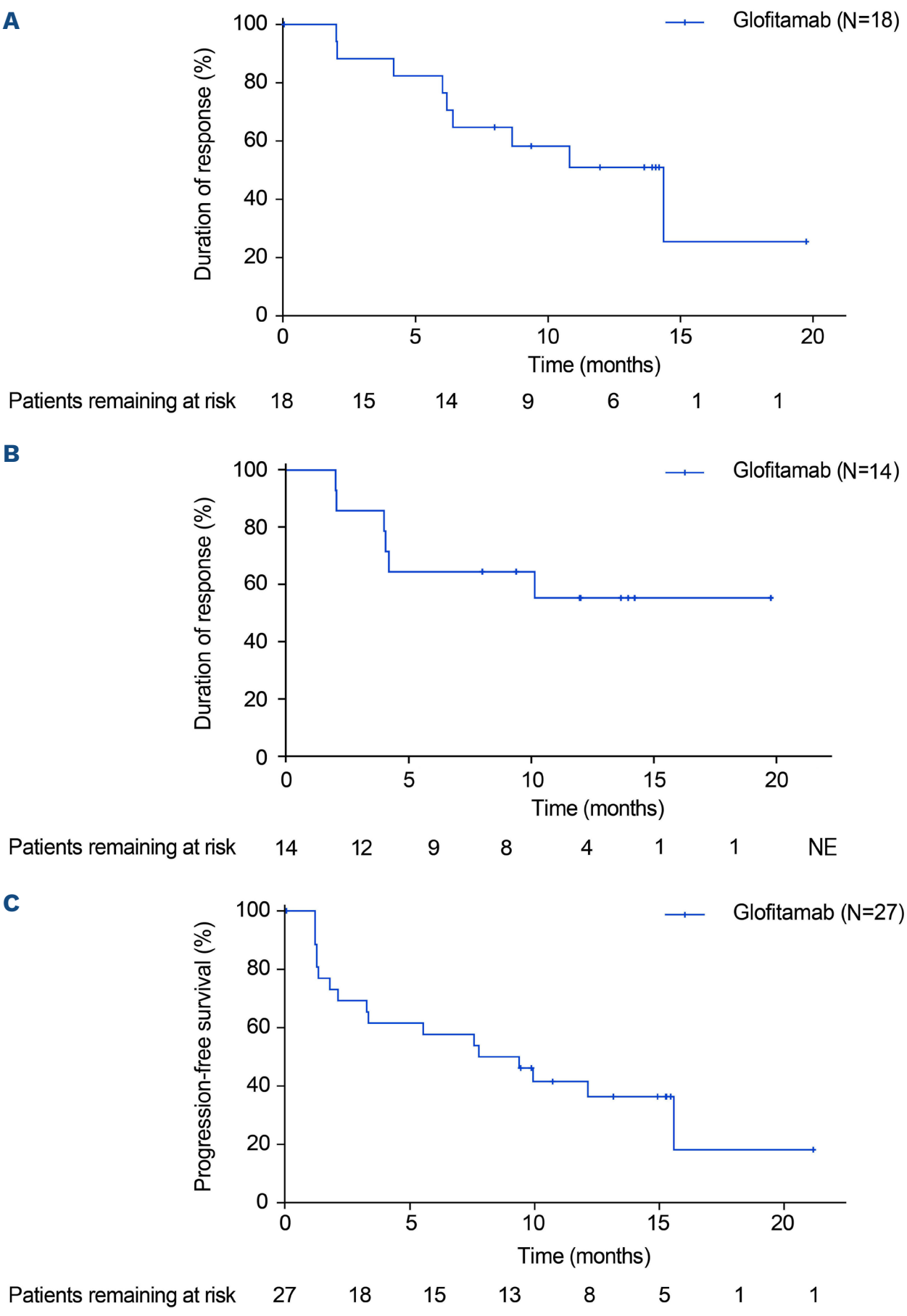


**Figure 1. Kaplan-Meier plots for efficacy outcomes.** (A) Duration of response. (B) Duration of complete response. (C) Progression-free survival (as assessed by independent review committee). NE: not evaluable.

pies was 2 (range, 2-6); 43.3% of patients had received ≥3 prior lines. Two-thirds of patients were refractory to first-line treatment, 90.0% were refractory to their most recent regimen, and 20.0% had received CAR T-cell therapy (13.3% of enrolled patients were refractory to CAR T-cell therapy; Table 1). Median duration of glofitamab treatment was 7.2 months (range, 0.3-8.8); median number of cycles received was 11 (range, 1-12).

Serum concentrations of glofitamab increased in an approximately dose-proportional manner (*Online Supplementary Figure S1*). The PK profile of glofitamab appeared bi-phasic with an apparent half-life of 5 days. Mean maximum concentration (coefficient of variation %) following dosing on C2D1 was 10.5 μg/mL (28.9%). No post-dose anti-glofitamab antibodies were identified in the PK cohort (0/11 evaluable patients).

After a median follow-up of 15 months (range, 0-23), CR rate and ORR (as best response) by IRC were 51.9% (95% confidence interval [CI]: 32.0-71.3; 14/27 patients) and 66.7% (95% CI: 46.0-83.5; 18/27), respectively. Anti-tumor activity was observed in most patients, with similar activity seen in different DLBCL subtypes and in patients with/without prior CAR T-cell therapy (*Online Supplementary Figure S2*). Median time to CR was 43 days (95% CI: 40.0-104.0). Median DOR was 14.4 months (95% CI: 6.2-not reached [NR]) and median duration of CR was NR (Figure 1A, B, respectively). A total of 57.1% of CR (8/14 patients) and 50.0% of objective responses (9/18) were ongoing at data cutoff. By DLBCL subtype, IRC-assessed CR rate and ORR, respectively, were: DLBCL-NOS, 52.9% (9/17 patients) and 58.8% (10/17); PMBCL, 40.0% (2/5) and 80.0% (4/5); HGBCL, both 66.7% (2/3); trFL, 50.0% (1/2) and 100.0% (2/2). IRC-assessed CR rate and ORR were 50.0% (2/4 patients) in patients refractory to prior CAR T-cell therapy, and 100.0% (2/2) in those who relapsed after prior CAR T-cell therapy.

IRC-assessed median PFS was 8.6 months (95% CI: 3.3-15.6) (Figure 1C). IRC-assessed 12- and 15-month PFS rates were 41.5% (95% CI: 22.3-60.8) and 36.3% (95% CI: 17.0-55.7), respectively. Median OS was NR (95% CI: 9.5-NR). The estimated 15-month OS rate was 61.3% (95% CI: 42.5-80.1).

The most common AE were CRS (63.3%), anemia (56.7%), and decreased white blood cell count (53.3%) (*Online Supplementary Table S1*). The most frequent grade 3/4 AE (76.7% overall) was neutropenia (30.0%). Serious AE occurred in 43.3% of patients; there were no grade 5 AE (Table 2). AE leading to treatment discontinuation were reported in two patients (6.7%): acute myocardial infarction in one patient, and anemia, pancreatitis, CRS, and peritonitis in the other. CRS events were predominantly low grade per ASTCT criteria (any grade: 63.3%; grade 1: 56.7%; grade 2: 3.3%; grade 3: 3.3%) and all resolved. CRS events primarily occurred during C1; no grade ≥2 CRS events occurred after C2. Following the first dose of glofitamab, CRS events were reported in 13 of 27 (48.1%) patients. Median time to CRS onset after the start of the first glofitamab infusion was 18.3 hours (range, 9.3-35.9) and median duration of CRS was 14.3 hours (range, 0.0-456.0). Following the second dose of glofitamab, CRS events were reported in 11 of 27 (40.7%) patients. Median time to CRS onset after the start of the second glofitamab infusion was 23.8 hours (range, 12.9-36.1) and median duration of CRS was 15.6 hours (range, 1.4-623.6). CRS man-

**Table 2.** Adverse events (safety population)

| Adverse events, N (%) | N=30 |
|---|---|
| Any AE | 30 (100.0) |
| Most common AE (occurring in ≥20% of patients) | |
| CRS | 19 (63.3) |
| Anemia | 17 (56.7) |
| Decreased white blood cell count | 16 (53.3) |
| Neutropenia | 15 (50.0) |
| Thrombocytopenia | 15 (50.0) |
| Hypoalbuminemia | 10 (33.3) |
| Pyrexia | 9 (30.0) |
| Increased ALT | 9 (30.0) |
| Decreased lymphocyte count | 8 (26.7) |
| Increased AST | 8 (26.7) |
| Increased C-reactive protein | 8 (26.7) |
| Hypertriglyceridemia | 7 (23.3) |
| Hypocalcemia | 6 (20.0) |
| Cytokine increased | 6 (20.0) |
| Hypertension | 6 (20.0) |
| Infusion-related reaction | 6 (20.0) |
| Any glofitamab-related AE | 27 (90.0) |
| Any grade 3/4 AE | 23 (76.7) |
| Most common grade 3/4 AE (occurring in ≥5% of patients) | |
| Neutropenia | 9 (30.0) |
| Decreased lymphocyte count | 6 (20.0) |
| Anemia | 6 (20.0) |
| Thrombocytopenia | 4 (13.3) |
| Decreased white blood cell count | 4 (13.3) |
| Hypertension | 2 (6.7) |
| Infection | 2 (6.7) |
| Any glofitamab-related grade 3/4 AE | 17 (56.7) |
| Any serious AE | 13 (43.3) |
| Most common serious AE (occurring in ≥5% of patients) | |
| CRS | 3 (10.0) |
| Herpes zoster | 2 (6.7) |
| Anemia | 2 (6.7) |
| Any glofitamab-related serious AE | 10 (33.3) |
| AE of special interest | |
| Neurologic AE (grade ≥2) | 3 (10.0) |
| AST, ALT, or total bilirubin elevation (grade ≥2) | 3 (10.0) |
| CRS (ASTCT grade ≥2) | 2 (6.7) |
| Any grade 5 AE | 0 (0.0) |
| Any AE leading to withdrawal of glofitamab | 2 (6.7) |
| Any glofitamab-related AE leading to withdrawal of glofitamab | 2 (6.7) |
| Any AE leading to glofitamab dose interruption | 10 (33.3) |
| Any glofitamab-related AE leading to glofitamab dose interruption | 8 (26.7) |

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ASTCT: American Society for Transplantation and Cellular Therapy; CRS: cytokine release syndrome.

agement included tocilizumab (8/19 [42.1%] patients with CRS), corticosteroids (31.6%), single pressors (5.3%), low-flow oxygen (5.3%), and high-flow oxygen (5.3%); intensive care unit admission or multiple pressors were not used. One (3.3%) patient experienced a CRS event that led to glofitamab discontinuation.

Neurologic AE occurred in 26.7% (8/30) of patients (grade 1: 16.7%; grade 2: 6.7%; grade 3: 3.3%) and were most commonly *Herpes zoster* infection (13.3%), headache (6.7%), and post-herpetic neuralgia (6.7%). Neurologic AE potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were not reported.

Infections were observed in 43.3% of patients (18 events), the most frequent being *Herpes zoster* (13.3%). Three serious infections were reported: grade 3 infection in one patient concurrent with grade 1 CRS but with no clear infectious focus (the event resolved after treatment with antibiotics), and two cases of *Herpes zoster* (grades 2 and 3; 1 unresolved and 1 resolved at data cutoff).

Ten patients had hepatitis B virus (HBV) infection that resolved before enrollment (defined as hepatitis B surface antigen-negative and hepatitis B core antibody positive, at baseline). Two patients received prophylactic nucleos(t)ide analogs. One patient, who did not receive prophylaxis, developed HBV reactivation (grade 2, non-serious) on D197. This resolved on D204 after treatment with entecavir. No patients developed HBV-related hepatitis. Glofitamab should not be administered to patients with an active infection; anti-infective prophylaxis and treatment for viral, fungal, bacterial, or pneumocystis infections are permitted and should be administered per institutional practice or investigator preference on the basis of individual patient risk factors.

Nine patients died due to PD; three died due to other reasons after PD (one cardiac arrest) and following initiation of a new anti-lymphoma treatment (one unknown; one sudden cardiac death) beyond the AE reporting period.

This analysis is limited by the small patient number. The PK profile of glofitamab in Chinese patients was similar to that reported in the NP30179 study.[8] The CR rate was also comparable with that of the global population (CR 39%)[6] and glofitamab had a manageable safety profile with no major differences *versus* the NP30179 study.[6] Low rates of HBV reactivation in patients with prior HBV infection, and those considered at risk of developing HBV reactivation, were reassuring.

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**Disclosures**

CWa is an employee and holds stock in Roche. CWu is an employee and holds stock in Roche. D-HL is an employee of Roche. YD is an employee of Roche. KH is an employee and holds stock in Roche. All other authors have no conflicts of interest to disclose.

**Contributions**

Y-QS, CWa, CWu, D-HL, KH, and JZ were involved in conception and design of the study. Y-QS, H-LZ, H-QH, Q-YZ, HM-J, and JZ provided study materials or patients. Y-QS, H-LZ, H-QH, Q-YZ, HM-J, CWa, CWu, D-HL, YD, and JZ participated in collection and assembly of data. Y-QS, H-LZ, H-QH, Q-YZ, HM-J, CWa, CWu, D-HL, YD, KH, and JZ were involved in data analysis and interpretation. All authors were involved in manuscript writing and provided final approval for submission and publication. All authors are accountable for all aspects of the work.

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**Data-sharing statement**

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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