

Optimized Glofitamab Schedule Halves Mortality Risk After CAR T Failure in Diffuse Large B-Cell Lymphoma: A Phase 2 Trial with External Control Arm Conducted by The LYSA Group

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Abstract

Background

Failure after anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in diffuse large B-cell lymphoma (DLBCL) is associated with poor survival and no established standard of care. We previously reported the phase 2 LYSA BiCAR trial of short-ramp-up glofitamab after CAR T-cell failure. Here, we present the final survival results and a pre-specified external comparative effectiveness analysis against a contemporary control arm constructed from academic data.

Methods

BiCAR is a multicenter, single-arm trial in adults with CD20-positive DLBCL refractory to, or in first relapse/progression after anti-CD19 CAR T-cell therapy. Participants received obinutuzumab pretreatment followed by intravenous glofitamab with an accelerated step-up to 30 mg within 8 days, then 30 mg every 21 days for up to 11 cycles. For comparative analyses, we constructed an external control arm from patients included in the French DESCAR-T registry and the ALYCANTE phase 2 trial who experienced CAR T-cell failure, who subsequently started non-bispecific systemic therapy, met key BiCAR eligibility criteria, and initiated treatment within a ± 1 -month window around the BiCAR treatment period. To minimise datasource bias, both arms, glofitamab (BiCAR) and control, were constructed from individual patient data from the DESCAR-T registry and the ALYCANTE trial. A propensity score including major prognostic variables was estimated and applied using stabilized inverse probability of treatment weighting with multiple imputation. Additional weighting schemes and restrictions were applied in sensitivity analyses, and restricted mean survival time (RMST) was evaluated by treatment arm.

Results

Among 47 enrolled BiCAR patients, 46 received glofitamab. At a median follow-up of 30.4 months, median overall survival (OS) was 17.3 months, and the 2-year OS rate was 38.3%. For comparative effectiveness, 45 glofitamab-treated patients and 133 controls formed the analysis cohort. In the primary weighted analysis, median OS was 19.6 months for glofitamab and 7.6 months for controls, with a hazard ratio for death of 0.49 (95% CI, 0.31–0.79; $P=0.007$). Multiple sensitivity analyses yielded consistent estimates. Glofitamab significantly improved the RMST of 5 months ($P=0.007$) over a 2-year follow-up.

Conclusions

In this robust comparative effectiveness study, short-ramp-up glofitamab immediately after CAR T-cell failure significantly increases the chance of survival compared to contemporaneous non-bispecific salvage therapies, supporting its use as a preferred option for eligible patients with DLBCL who fail anti-CD19 CAR T-cell therapy.

Trial registration.ClinicalTrials.gov identifier NCT04703686.

Background

Anti-CD19 CAR T-cell therapies have transformed outcomes for patients with relapsed or refractory (R/R) large B-cell lymphomas (LBCL), but 50–60% ultimately experience primary refractory disease or relapse after infusion. The median overall survival (OS) is then approximately 6 months once CAR T-cell failure occurred, regardless of whether CAR T-cells were infused in second-line [1, 2], or in third-line or more [3–6]. In this setting, there is no established standard of care, and clinicians commonly use heterogeneous combinations of chemo-immunotherapy, antibody-based, small-molecule, or investigational regimens, generally with limited efficacy.

CD20×CD3 bispecific antibodies (BsAbs), including glofitamab, have demonstrated substantial activity in R/R LBCL, with high response rates and durable remissions, including among patients previously treated with CAR T-cells [7–10]. However, those phase I/II studies enrolled heterogeneous populations including patients both with and without prior CAR T-cell exposure and were not specifically designed for the immediate post-CAR T-cell setting. Furthermore, they lacked direct comparisons between BsAbs and alternative salvage therapies following CAR T-cell failure. Consequently, the use of CD20×CD3 BsAbs as the preferred strategy for patients relapsing after CAR T-cell therapy remains largely empirical. The LYSA BiCAR trial is a prospective multicenter phase 2 study specifically dedicated to adults with CD20-positive DLBCL who are refractory to, or in first relapse/progression immediately after anti-CD19 CAR T-cell therapy and evaluates glofitamab using an intensified “short ramp-up” schedule that reaches the full 30-mg dose within one week. In the primary analysis (median follow-up 15.3 months), short-ramp-up glofitamab yielded a median OS of 14.7 months, a best overall metabolic response (OR) rate of 76.1%, and a best complete metabolic response (CR) rate of 45.7%, with no grade ≥ 3 cytokine release syndrome (CRS) or neurotoxicity [11]. Beyond demonstrating feasibility and clinical activity, a central clinical question remains whether glofitamab improves survival relative to the non-BsAbs regimens actually used in practice after CAR T-cell failure. While indirect comparisons suggest that bispecific antibodies are at least as effective as conventional salvage therapies [3, 5, 12], robust comparative effectiveness data are scarce, and no prospective randomized trial will answer this question in the future.

Here, we report the final survival results of BiCAR, together with a robust pre-specified external comparative effectiveness analysis of glofitamab against contemporaneous non-bispecific salvage strategies. This analysis is based on data from the DESCAR-T national CAR T-cell registry [13] and the ALYCANTE phase 2 trial [14].

Methods

Study design

This study combines the BiCAR trial (NCT04703686), a prospective, multicenter, single-arm phase 2 study of short-ramp-up glofitamab after CAR T-cell failure conducted by LYSA/LYSARC [11], and an external comparative effectiveness analysis of glofitamab against contemporaneous non-bispecific salvage strategies after CAR-T cell failure. To minimise datasource bias, the two arms, the glofitamab arm (BiCAR patients) and the control arm, are built from

individual patient data in the DESCAR-T registry and ALYCANTE trial. The comparative endpoint was OS from initiation of post-CAR T therapy. All comparative analyses were planned in the protocol and prespecified in a dedicated statistical analysis plan.

Populations, endpoints and setting

BiCAR trial

Eligibility criteria

BiCAR enrolled adults (≥ 18 years) with biopsy-proven CD20-positive DLBCL who were refractory to, or in first relapse/progression after, anti-CD19 CAR T-cell therapy given ≥ 1 month before enrolment; had ECOG performance status 0–1; at least one measurable lesion > 1.5 cm on PET-CT; adequate hepatic, renal and hematologic function; and life expectancy ≥ 3 months. Patients with CD20-negative disease, primary CNS lymphoma or CNS involvement, relapse within 30 days of CAR T infusion, uncontrolled infection or prior allogeneic transplant were excluded [11]. All participants provided written informed consent.

Treatment and assessments

Patients received obinutuzumab 1,000 mg intravenously on day – 3, followed by glofitamab intravenously with a short ramp-up during cycle 1 (14 days): 2.5 mg on day 1, 10 mg on day 3, and 30 mg on day 8. From cycle 2 onward, glofitamab 30 mg was given every 21 days for up to 11 cycles. Baseline Positron Emission Tomography-Computed Tomography (PET-CT) and subsequent scans after cycles 2, 4, 6, 9, and 11 were centrally reviewed using Lugano 2014 criteria. Adverse events were graded with Common Terminology Criteria for Adverse Events (CTCAE) v5.0; CRS and neurotoxicity with American Society for Transplantation and Cellular Therapy (ASTCT) criteria. The BiCAR full analysis set (BiCAR-FAS) comprised all patients who received at least one glofitamab dose [11].

BiCAR endpoints and data cutoff

The BiCAR primary endpoint was the OS measured from the date of the first glofitamab infusion to the date of death from any cause, censoring participants who were still alive at the last contact date. Secondary endpoints included progression-free survival (PFS), OR and CR rates, duration of response (DoR) and duration of complete response (DoCR), and safety [11]. The present final analysis uses a BiCAR database export dated June 13th, 2025, with a data cutoff on May 21st, 2025.

Comparative effectiveness analysis

External data sources

The DESCAR-T registry (NCT04328298) is a nationwide French observational database designed to capture real-world data on adults eligible for commercial anti-CD19 CAR T-cell therapy. The registry provides comprehensive longitudinal data, including baseline patient characteristics, infusion parameters, post-infusion clinical outcomes, and details on subsequent therapeutic interventions. This analysis utilized a data export dated March 13th, 2025

The ALYCANTE trial (NCT04531046) is a multicenter phase 2 trial evaluating axicabtagene ciloleucel (axi-cel) as second-line therapy in transplant-ineligible patients with large B-cell lymphoma. The dataset used here was exported on October 30th, 2024.

BiCAR clinical data were used to identify BiCAR participants within DESCAR-T and ALYCANTE via matching of birth month/year, initials, and CAR T infusion dates.

Comparative effectiveness populations

Glofitamab arm: The glofitamab arm for comparative analyses included BiCAR participants who: 1/ received obinutuzumab and at least one glofitamab dose; 2/ were confidently identified in DESCAR-T or ALYCANTE; 3/ were not treated with CAR T-cells in another clinical trial with unknown details. Of 46 treated BiCAR patients, 45 were identified in external databases (8 from ALYCANTE, 37 from DESCAR-T), and one treated in an unknown trial was excluded, yielding 45 patients in the glofitamab comparative arm.

Control arm: The control arm comprised DESCAR-T and ALYCANTE patients who: 1/ had DLBCL and received commercial axi-cel or tisagenlecleucel (tisa-cel); 2/ had stable disease (SD) or progression/relapse from month 1 after CAR T infusion; 3/ started systemic post-CAR T treatment other than a CD20 $\times$ CD3 bispecific antibody; 4/ met main BiCAR inclusion criteria (DLBCL, ECOG 0–1, adequate organ function). To ensure contemporaneity and comparable follow-up durations, DESCAR-T control patients were further required to have initiated their first post-CAR T regimen within a ± 1 -month window around the date of glofitamab initiation in the BiCAR trial. This alignment of treatment timelines was implemented to minimize temporal bias and provide contemporaneous data for the analysis.

Comparative full analysis set

Covariates and endpoint

Covariates available in all datasets and considered for propensity-score (PS) estimation were: sex; age at CAR T-cells infusion; number of prior treatment lines including CAR T-cell (L2 vs $\geq$ L3); time from CAR T-cells infusion to first progression/stable disease; Ann Arbor stage (I–II vs III–IV); lactate

dehydrogenase (normal vs > ULN-upper limit normal) at or just before CAR T-cell infusion (or at lymphodepletion if missing); CAR T-cell product (axi-cel vs tisa-cel); response to bridging therapy (CR/partial response-PR vs stable disease-SD/progression disease-PD vs no bridging); prior autologous stem-cell transplant (yes/no). For the comparative analysis, OS was defined as the time from first glofitamab infusion (glofitamab arm) or first non-bispecific post-CAR T regimen (control arm) to death from any cause; survivors were censored at last contact.

Analysis sets and missing data

Three analysis sets were defined: 1/ cFAS, all 178 patients fulfilling comparative criteria; 2/ complete case set (CC-set), cFAS patients without missing values in planned PS covariates (n = 165); 3/ Weighted pseudo-populations, created by applying PS-based weights (stabilized inverse probability of treatment weighting (sIPTW) [15], standardized mortality ratio weighting (SMRW) [16]) to the cFAS.

Missing covariates were handled by complete case analysis using the CC-set and multiple imputation (MI) via MICE with 15 imputations and 100 iterations, generating 15 completed datasets for the primary analysis and pooled using Rubin's rules.

Propensity score and weighting

The propensity score (probability of receiving glofitamab vs control given covariates) was estimated using logistic regression, including all listed variables, with continuous covariate effects modeled using spline functions. Two weighting schemes were prespecified: 1/ sIPTW, targeting the average treatment effect (ATE) in the overall population, with weights of $w_i = P/PS_i$ for treated, and $w_i = (1 - P)/(1 - PS_i)$ for controls with P for proportion of patients in the glofitamab arm and PS of propensity score and; 2/ SMRW, targeting the average treatment effect in the control population (ATC), reweighting treated patients to resemble controls. Patients with extreme propensity scores, defined as PS values below 0.025 or above 0.95, were excluded from weighted analyses to avoid undue influence of extreme weights on treatment. effect estimates.

Survival analysis

BiCAR trial final analysis

Within the BiCAR-FAS population, OS, PFS, DoR, and DoCR were estimated using Kaplan–Meier methods.

External control comparisons

Primary analysis: For the comparative effectiveness analysis, OS Kaplan-Meier curves were generated for the cFAS and for the weighted pseudo-populations (sIPTW and SMRW sets). The primary analysis was based on MI-sIPTW weighting including all data sources. Survival probabilities, median survival, and quartiles were estimated (if reached) with their 95% CIs. Cox models provided hazard ratios (HR) and 95% CIs for glofitamab versus control; proportional hazards assumptions were checked using Schoenfeld residuals. Differences between arms were tested with log-rank tests. The robustness of observed associations to unmeasured confounding was assessed using the E-value, which quantifies the minimum strength of association that a hypothetical unmeasured confounder would need to have with both the treatment arm and OS to fully explain away the observed HR of glofitamab versus non-BsAbs regimens [17].

Secondary and sensitivity analyses : As a secondary analysis, restricted mean survival time (RMST) over a 2-year follow-up period was calculated as the area under the weighted Kaplan-Meier curve, with between-group comparisons performed using the difference in RMST and its 95% confidence interval estimated via bootstrap with 500 replicates [18]. Pre-specified sensitivity analyses included: 1/ MI-SMRW analysis; 2/ sIPTW and SMRW on complete-case PS sets; 3/ MI-based analyses restricted to DESCAR-T patients only; 4/ MI-sIPTW restricted to Ann Arbor stage III–IV patients. Because weighting reduces the contribution of some patients, the effective sample size was calculated after analysis with sIPTW on complete case set, to reflect the equivalent sample size contributing information to the analysis.

Analyses were performed using SAS 9.4 and R 4.4.2.

Results

BiCAR final survival outcomes

Of the 47 enrolled BiCAR cohort-1 patients, 46 received glofitamab and formed the BiCAR-FAS. Patient and disease characteristics have already been published and are summarized in Table 1.

Table 1. Patient demographic and disease characteristics at inclusion in the BiCAR trial

	BiCAR FAS (N=46)
Median (min-max) age at enrollment, years	64 (30-77)
Sex, <i>n</i> (%)	
Female	15 (32.6)
Male	31 (67.4)
ECOG performance status, <i>n</i> (%)	
0	23 (50.0)
1	23 (50.0)
Ann Arbor stage, <i>n</i> (%)	
I-II	8 (17.4)
III-IV	38 (82.6)
IPI, <i>n</i> (%)	
0-2	19 (42.2)
3-4	26 (57.8)
Missing	1
LDH status: >ULN	35 (76.1)
Presence of at least one extranodal site, <i>n</i> (%)	35 (76.1)
Median number of previous lines of lymphoma treatment (minimum–maximum)	3 (2–5)
≥3 lines of treatment, <i>n</i> (%)	37 (80.4)
Previous autologous or allogeneic transplant, <i>n</i> (%)	8 (17.4)
Previous CAR-T cell therapy, <i>n</i> (%)	
Experimental CAR-T cell product (in clinical trial)	3 (6.5)
Tisa-cel	17 (37.0)
Axi-cel	26 (56.5)
Patient status at screening, <i>n</i> (%)	
Refractory ^a	14 (30.4)
Relapse/progression ^b	32 (69.6)
Time between CAR-T cell therapy and relapse/progression, <i>n</i> (%)	
1–3 months	9 (28.1)
3–6 months	8 (25.0)
>6 months	15 (46.9)

Missing data are specified for any variable for which *n* (%) does not add up to N.

^aRefractory: designates patients who never experienced a metabolic response (i.e., stable or progressive disease) after CAR-T cell therapy.

^bRelapse/progression designates patients who experienced response (PR or CR) after CAR-T cells then relapse/progression on subsequent PET-CT.

Abbreviations: Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor-T; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IPI, international prognostic index; PR, partial response; SD, standard deviation; tisa-cel, tisagenlecleucel; ULN, upper limit of normal.

At the final analysis (data cutoff: 21 May 2025), the median follow-up from first glofitamab infusion was 30.4 months (95% CI, 23.0–31.4). Median OS was 17.3 months (95% CI, 9.0–28.4), with a 2-year OS rate of 38.3% (95% CI, 26.1–50.4) (Figure 1A). Median PFS was 3.8 months (95% CI, 2.4–15.9) with a 2-year PFS rate of 29.1% (95% CI, 16.5–43.0) (Figure 1B). Median DoR among responders was 16.1 months (95% CI, 4.0–NR), and median DoCR was not reached (95%CI: 19.7; NR) (Figure 1C-1D).

Outcomes remained strongly associated with the timing of CAR T-cell failure (Figure 2A). Median OS was not reached (95% CI: 10.2- NR) in patients with late relapse (> 6 months post-infusion), compared with 11.1 months (95% CI: 5.5–20.0) in those with refractory or early-relapsing disease (≤6 months; log-rank *P*=0.01). Response after two cycles of glofitamab also predicted outcome; median OS was not reached in patients experiencing CR (95%CI, 27.4-not

estimable) versus 9.0 months (95% CI, 4.9-20.1) ($P=0.0015$) (Figure 2B). No new safety signals emerged, and safety details were unchanged from the primary report [11].

Comparative cohorts and baseline characteristics

Within the BiCAR-FAS, 45 patients were matched with the DESCART-T/ALYCANTE data sources and included in the glofitamab arm, while one patient was excluded as previously described. Out of 3,143 registry and trial-derived patients, 133 controls met the pre-specified eligibility criteria and temporal restrictions for the comparative analysis and received non-bispecific post-CAR-T therapy (Figure S1).

In the cFAS ($n=178$), 65.7% were male, with a median age of 63 years (range: 19–82) at the time of CAR T-cell infusion (Table 2). At CAR T-cells infusion, most patients presented with advanced disease, including 83.5% with Ann Arbor stage III–IV and 50.0% with LDH levels above the ULN. Most patients (84.8%) had received CAR T-cell therapy in the third-line setting or later, with 65.7% having received axi-cel. The median time from CAR T-cell infusion to treatment failure was 3.0 months (IQR 1.84–5.88). Baseline features were generally comparable between the glofitamab ($n=45$) and control ($n=133$) arms, with slightly more advanced disease (93.0% vs 80.3% stage III–IV), LDH within normal values (51.1% vs 42.1% normal LDH), no response after bridging (61.4% vs 50.4% no responder) and prior ASCT (18.2% vs 12.8%) in the glofitamab arm (Table 2). Control patients received a heterogeneous salvage therapy following CAR T-cell failure, including monoclonal antibodies (57.9%; among them 34.6% anti-CD20 and 18.8% anti-CD19), lenalidomide (48.1%), chemotherapy (31.6%), kinase inhibitors (12.0%, primarily ibrutinib), and radiotherapy (10.5%), and smaller proportions of other agents. All eight patients recorded as receiving corticosteroids also received at least one additional anti-lymphoma regimen. Best response in the control arm was complete response in 8.3% and partial response in 4.5%, while 72.0% had progressive disease.

Table 2. Patients’ characteristics from the control and BiCAR arm from the cFAS set and the CC-set.

	cFAS set N=178		CC-set N=165	
	Control N=133	Glofitamab N=45	Control N=125	Glofitamab N=40
Age at CAR-T infusion				
Median (range)	63 (19-82)	63 (30-77)	63 (19-82)	64 (30-77)
Sex				
Male, N (%)	87 (65.4)	30 (66.7)	83 (66.4)	27 (67.5)
Time between CAR-T and failure				
Median (Q1-Q3)	2.99 (1.22-5.68)	3.25 (2.07-6.64)	3.0 (1.2-5.7)	3.5 (2.1-8.0)
Ann Arbor Stage at CAR-T infusion				
Missing	6	2	6	1
I-II	25 (19.7)	3 (7.0)	25 (21.0)	2 (5.1)
III-IV	102 (80.3)	40 (93.0)	94 (79.0)	37 (94.9)
Prior ASCT				
Missing	0	1	-	-
Yes	116 (87.2)	36 (81.8)	16 (12.8)	7 (17.5)
No	17 (12.8)	8 (18.2)	109 (87.2)	33 (82.5)
Response After Bridging				
Missing	2	1	-	-
No bridge	18 (13.5)	4 (9.1)	16 (12.8)	3 (7.5)
Response (CR/PR)	46 (34.6)	13 (29.5)	45 (36.0)	12 (30.0)
No response (SD/PD)	67 (50.4)	27 (61.4)	64 (51.2)	25 (62.5)
Bulk at lymphodepletion				
Missing	10	9	10	8
Yes	26 (21.1)	10 (27.8)	26 (22.6)	10 (31.3)
No	97 (78.9)	26 (72.2)	89 (77.4)	22 (68.8)
LDH (IU/L) at CAR-T infusion				
> Upper limit	71 (53.4)	18 (40.0)	70 (56.0)	17 (42.5)
CAR-T product				
Tisa-cel	44 (33.1)	17 (37.8)	42 (33.6)	16 (40.0)
Axi-cel	89 (66.9)	28 (62.2)	83 (66.4)	24 (60.0)
Line of CAR-T infusion				
2L	17 (12.8)	10 (22.2)	16 (12.8)	9 (22.5)
3L+	116 (87.2)	35 (77.8)	109 (87.2)	31 (77.5)

Abbreviations: ASCT : autologous stem cell transplantation; CAR-T, chimeric antigen receptor-T; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IPI, international prognostic index; IPTW: Stabilized inverse probability of treatment weighting ; LDH : lactate dehydrogenase; PD, progressive disease; PR, partial response; PS, propensity score; SD, standard deviation; tisa-cel, tisagenlecleucel; ULN, upper limit of normal.

Covariate balance after weighting

PS weighting aimed to balance covariates between the control arm and the glofitamab arm to account for measured confounding variables (Table S1) that have been shown to impact PFS and OS after CAR T-cell failure [2, 5, 19, 20].

Primary analysis (MI-sIPTW)

In the primary MI-sIPTW analysis including all patients, except 11 patients with extreme propensity, adequate covariate balance was achieved after stringent adjustment on 9 parameters (Table S1). All absolute standardized mean differences (SMDs) were < 0.2 across the 15 imputed datasets (Figure S2).

Sensitivity analyses

In the MI-SMRW analysis, all SMDs were < 0.2, except for Ann Arbor stage where 1 out of 15 imputed datasets showed an SMD > 0.2. In the complete-case set (5 patients excluded for extreme PS, n=160), both sIPTW and SMRW reduced imbalances, with SMDs < 0.1 for all covariates except Ann Arbor stage, which could not be included due to very few stage I–II cases, and number of previous treatment lines for SMRW (SMD 0.15). After adjustment, patients in the glofitamab arm had more advanced disease (95.7% vs 78.6% Ann Arbor stage III–IV). For sIPTW, the effective sample size was 142. In MI-based analyses restricted to DESCAR-T patients, the number of previous treatment lines could not be included in the propensity score, but all SMDs were < 0.2. In MI-based analyses restricted to Ann Arbor stage III–IV patients, all covariates could be included and all SMDs were < 0.2.

Primary analysis

Primary weighted analysis (MI-sIPTW)

In the primary MI-sIPTW analysis (all data sources), weighted median OS was 19.6 months (95% CI, 10.2–not reached) in the glofitamab arm versus 7.6 months (95% CI, 5.5–9.8) in the control arm (Figure 3). The pooled HR for death across imputed datasets was 0.49 (95% CI, 0.31–0.79; *P*=0.0072). The E-value was 2.65 (1.31 for the lower CI bound), indicating that one or several unmeasured confounders would need to be strongly associated with both treatment and survival to fully explain the observed effect.

Secondary and sensitivity analysis

Restricted Mean Survival Time

The mean survival time restricted at 24 months of follow-up was 15.6 months (95% CI, 12.3 - 18.9) in the glofitamab arm versus 10.6 months (95% CI, 9.0 - 12.2) in the control arm, corresponding to an average RMST difference of 5.0 months (95% CI, 1.4–8.6; *P*=0.007) favouring glofitamab.

Sensitivity analyses

In the unweighted cFAS, median OS from the start of post-CAR T therapy was 6.5 months (IQR, 3.2–18.9; 95% CI, 4.8–8.1) in the control arm versus 17.3 months (IQR, 5.7–28.4; 95% CI, 8.8–not estimable) in the glofitamab arm. Sensitivity analyses across various statistical models yielded consistent results (Table 3). Under the MI-SMRW model (all data), glofitamab was associated with a significant survival benefit (HR 0.46; 95% CI: 0.33–0.66; *P*=0.0087; E-value: 2.78). Similar findings were observed using complete-case sIPTW and SMRW (HR 0.51, 95%CI: [0.31 – 0.82], *P*=0.0089 and HR 0.46, 95% CI: [0.33-0.65], *p*=0.0062 respectively). When restricting the control group to DESCAR-T registry patients only (n=162), the benefit remained robust (MI-sIPTW: HR 0.44, 95% CI: 0.26–0.74, *P*=0.0057; MI-SMRW: HR 0.41, 95% CI: 0.29–0.59, *P*=0.0067). Finally, an analysis restricted to stage III–IV disease (n=142) confirmed these results (MI-sIPTWHR 0.52; 95% CI: 0.33–0.81; *P*=0.0069). Across all analytic approaches, HR estimates consistently clustered between 0.40 and 0.55, uniformly favoring the glofitamab arm.

Table 3. Sensitivity analysis of overall survival evaluated in the indirect comparison study

	Multiple Imputations	DESCAR-T population		Ann-Arbor Stage III-IV	Complete cases				Raw data
	SMRW	sIPTW	SMRW	SIPTW	SIPTW		SMRW		Control group (n=133)
					Control group (n=120)	Glofitamab group (N=40)	Control group (n=120)	Glofitamab group (N=40)	
Number of death, N (%)					91 (75.8)	22 (55)	91 (75.8)	22 (55)	99 (74.4)
mOS, months [IC _{95%}]					6.6 [5.2;9.7]	17.3 [6.1;28.4]	6.5 [4.8;8.1]	17.3 [-;-]	6.5 [4.8;8.1]
HR [IC _{95%}]	0.46 [0.326;0.659]	0.44 [0.264;0.741]	0.41 [0.286;0.591]	0.52 [0.33;0.809]	0.51 [0.331;0.819]		0.46 [0.334;0.645]		0.54 [0.348;0.84]
P value (Log-Rank)	0.0087	0.0057	0.0067	0.0069	0.0089		0.0062		0.0028
E-value	2.784	2.903	3.087	2.529	2.576		2.779		2.517
Overall survival rates									
9-months					41.1 [33.8;50.2]	65.0 [43.8;78.8]	39.1 [30.2;47.9]	66.0 [42.0;82.0]	39.7 [31.3;48.0]
12-months					33.8 [25.0;42.8]	59.9 [38.8;75.7]	31.0 [22.8;39.6]	60.0 [36.2;77.4]	31.5 [23.6;39.7]
18-months					27.3 [19.0;36.3]	48.7 [27.6;67.0]	25.2 [17.6;33.6]	49.3 [25.5;69.4]	26.3 [18.9;34.3]
24-months					19.7 [12.1;28.7]	46.5 [25.3;65.2]	18.6 [11.5;27.0]	47.5 [23.7;68.1]	20.2 [13.2;28.3]

Abbreviations: OS: overall survival, SMRW: Standardized Mortality Ratio Weighting, sIPTW: Stabilized Inverse Probability of Treatment Weighting

Discussion

In this comparative effectiveness study combining the BiCAR phase 2 trial with a pre-specified external control arm, short ramp-up glofitamab after anti-CD19 CAR T-cell failure was associated with a 51% reduction in the risk of death compared with contemporaneous non-bispecific salvage therapies. Weighted median OS increased from 7.6 months in the control arm to 19.6 months with glofitamab; a secondary RMST analysis confirmed a 5-month survival gain over 2 years. These findings were consistent across alternative weighting schemes, data-source restrictions, and stage-restricted analyses, with hazard ratio estimates ranging from 0.40 to 0.55.

The primary BiCAR publication established the feasibility and activity of accelerated glofitamab dosing after CAR T-cell failure [11]. The present work extends these findings with longer follow-up (median 30.4 months), showing that OS benefit is maintained over time (median 17.3 months, 2-year OS 38.3%). Our control cohort, selected using strict eligibility criteria and contemporaneity constraints, had a median OS of 6.5–7.6 months, consistent with previous DESCAR-T analyses and other post-CAR T series [2–5], supporting the external validity of our findings.

This study represents the first prospective phase II trial designed to evaluate a CD20×CD3 bispecific antibody exclusively in patients with DLBCL failing anti-CD19 CAR T-cell therapy. With a complete response rate of 45.7% and a median overall survival of 19.6 months in the weighted analysis, these results can be compared with outcomes reported for other bispecific platforms in this population. Four other CD20×CD3 bispecific antibodies have demonstrated activity in post-CAR T relapsed/refractory DLBCL. In the pivotal glofitamab study (NP30179) using standard ramp-up, 52 patients with prior CAR T-cell therapy achieved a 37% complete response rate with a median duration of complete response of 22.0 months at 32 months median follow-up [7]. For epcoritamab (EPCORE NHL-1), 61 post-CAR T patients (38.9% of the total cohort) achieved a 36% complete response rate at 25 months median follow-up [8]. Odronextamab demonstrated a 31.7% complete response rate in a dedicated post-CAR T expansion cohort of 60 patients, with a median OS of 10.2 months at 16.2 months follow-up [9]. Mosunetuzumab showed a 24% complete response rate in 30 post-CAR T patients [10]. Although response rates are lower than BiCAR trial (45.7%), they appear comparable across these bispecific platforms (24% to 37%). However, several methodological and design differences distinguish BiCAR from existing studies.

First, BiCAR is the only prospective phase II study enrolling exclusively patients in immediate relapse or progression after CAR T-cell therapy. In contrast, glofitamab, epcoritamab, and mosunetuzumab included post-CAR T patients as subgroups within larger heterogeneous cohorts of relapsed/refractory DLBCL, while odronextamab, though conducted in a dedicated post-CAR T cohort, was an expansion arm of a phase I dose-finding study. The design of our study ensures population homogeneity and reduces selection biases that can occur when post-CAR T patients represent a subset of a broader trial. Second, BiCAR employed standardized dosing, a unified treatment schedule, and prespecified endpoints, in contrast to the dose-escalation designs and heterogeneous dosing cohorts in phase I/II studies. This consistency improves the reliability and reproducibility of efficacy estimates. Third, OS was the

primary endpoint of our comparative effectiveness analysis. While complete response rates are informative, they do not fully capture clinical benefit in heavily pretreated populations where durability of response and survival prolongation are relevant outcomes. The observed doubling of median overall survival (19.6 vs 7.6 months, HR 0.49) against contemporaneous external controls provides comparative evidence that is not available for other bispecific antibodies in the post-CAR T setting, as mosunetuzumab, epcoritamab, and odronextamab have not reported survival comparisons with contemporary controls in their post-CAR T cohorts.

The external control arm was constructed from individual patient data in the French national DESCAR-T registry and the ALYCANTE trial, using propensity score weighting and sensitivity analyses. Given the difficulty of conducting randomized controlled trials comparing bispecific antibodies to salvage therapies in post-CAR T patients, this methodology provides an alternative approach to generate comparative evidence. The consistency of hazard ratio estimates across weighting schemes (sIPTW, SMRW), data source restrictions (DESCAR-T only analysis), stage-restricted analyses, and methods for handling missing data (complete-case and multiple imputation) supports the robustness of the findings. E-values exceeded 2.5, indicating that an unmeasured confounder would need to have an association of at least this magnitude with both treatment assignment and overall survival to fully explain the observed hazard ratio.

This study has limitations. The non-randomized design and sample size in the glofitamab arm (n=45) preclude definitive causal inference, and residual confounding cannot be excluded despite propensity score adjustment. However, E-value (2.5) supports that it is unlikely that these potential confounders would substantially change the study conclusions. The heterogeneity of control treatments—spanning immunochemotherapy, lenalidomide-based regimens, targeted agents, and radiotherapy—reflects real-world practice but precludes conclusions regarding the comparative efficacy of glofitamab versus any single alternative strategy. Generalizability is limited to patients meeting BiCAR eligibility criteria, including ECOG performance status 0–1, adequate organ function, and CAR T-cell failure occurring at least one month after infusion.

The fixed 11-cycle treatment protocol with short ramp-up schedule (8 days to full dose vs 15 days in standard glofitamab dosing), and in contrast to treatment until progression for epcoritamab [8] and odronextamab [9]) may offer practical advantages for patients requiring rapid disease control. The safety profile showed no grade ≥ 3 cytokine release syndrome or neurotoxicity.

Conclusion

Short-ramp-up glofitamab after anti-CD19 CAR T-cell failure produces durable survival in a subset of patients with DLBCL and, in a pre-specified comparative effectiveness analysis using an academic external control arm, is associated with substantially longer OS than contemporaneous non-bispecific therapies. These findings support glofitamab as a preferred post-CAR T option for eligible patients and highlight the value of registry-based external controls to inform treatment decisions when randomised trials are not feasible.

Abbreviations

- ATE: average treatment effect
- ATC: average treatment effect in the control population
- CAR: chimeric antigen receptor
- CI: confidence interval
- CR: complete response
- CRS: cytokine release syndrome
- DLBCL: diffuse large B-cell lymphoma
- DoR: duration of response
- ECOG: Eastern Cooperative Oncology Group
- FAS: full analysis set
- HR: hazard ratio
- LDH: lactate dehydrogenase
- MI: multiple imputation
- OS: overall survival
- PD: progressive disease
- PFS: progression-free survival
- PR: partial response
- PS: propensity score
- RMST: restricted mean survival time
- SD: stable disease
- sIPTW: stabilized inverse probability of treatment weighting
- SMRW: standardized mortality ratio weighting
- ULN: upper limit of normal

Declarations

Ethics approval and consent to participate.

BiCAR was approved by the Comité de Protection des Personnes Ile-de-France X and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice; all participants provided written informed consent. DESCAR-T and ALYCANTE were approved by the appropriate institutional ethics committees. Use of de-identified registry and trial data for the external control analysis complied with applicable data-protection regulations.

Consent for publication

Not applicable (no identifiable individual patient data are presented).

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy and regulatory restrictions but are available from the corresponding author on reasonable request and with permission from LYSARC and the DESCAR-T/ALYCANTE data-holding institutions.

Competing interests

P.S. has received honoraria, and advisory/consultancy fees from Janssen, Roche, Bristol-Myers Squibb, AbbVie, AstraZeneca, Chugai, Novartis, and Kite/Gilead. R.H. has received honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, and Roche; and is a member on an entity's Board of Directors or advisory committees of Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte and Miltenyi. L.Y. has received honoraria, and advisory/consultancy fees from AbbVie, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Gilead/Kite, Janssen, and Roche. S.C. has received honoraria, and advisory/consultancy fees from AbbVie, AstraZeneca, Atara, BeiGene, Gilead/Kite, Janssen, Novartis, Pierre Fabre, and Takeda. F.J. has received honoraria, and advisory/consultancy fees from Roche, Bristol-Myers Squibb, Novartis, Kite/Gilead, Takeda, AbbVie, and Janssen. F-X.G. has received honoraria, and advisory/consultancy fees from Bristol-Myers Squibb, Novartis, Kite/Gilead, AstraZeneca, Janssen, and Miltenyi. F.M. has received consultancy fees from AbbVie, Bristol-Myers Squibb, Gilead, Novartis, and Roche, serves as an advisor for AbbVie, Gilead and Roche and received honoraria from Chugai and Kaleida for scientific lectures. C.Ro. has received honoraria, and advisory/consultancy fees from Roche, Takeda, Gilead/Kite, Bristol-Myers Squibb, MSD, AbbVie, BeiGene, Janssen, Lilly. T.G. has received travel and accommodation expenses from Roche. C.T. has received honoraria, and advisory/consultancy fees from Roche, Bristol-Myers Squibb, Novartis, Kite/Gilead, Takeda, AbbVie, Janssen. L.D.L.R. has received honoraria, and advisory/consultancy fees from Gilead/Kite, Novartis, Bristol-Myers Squibb, Janssen, Takeda. P.F. has received honoraria, and advisory/consultancy fees from, BeiGene, Kite/Gilead, AstraZeneca, AbbVie, Janssen. S.G. is an employee of LYSARC. G.C. has received honoraria, and advisory/consultancy fees from Roche, Bristol-Myers Squibb, BeiGene, Novartis, Kite/Gilead, Takeda, AstraZeneca, AbbVie, Janssen, Onward Therapeutics, Incyte and Mabqi. Y.A.T., M.J., C.L., F.L.B., A.M., J-O.B., C.R., L.R., and K.T. declare that they have no conflict of interest.

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Authors' contributions

G.C., P.S., Y.A.L., K.T. and C.L. contributed to the conception, design, and planning of the study. G.C., R.H., Y.A.L., F.L.B., L.Y., S.C., F.J., J-O.B, F-X.G., F.M., C.Ro., T.G., C.T., M.J., L.R., C.R., L.D.L.R., P.F., A.M., S.G., K.T., C.L., and P.S. contributed to the acquisition and analysis of data. G.C., R.H., Y.A.L., F.L.B., L.Y., S.C., F.J., J-O.B, F-X.G., F.M., C.R., T.G., C.T., M.J., L.R., C.Ro., L.D.L.R., P.F., A.M., S.G., K.T., C.L., and P.S. contributed to the critical review and revision of the manuscript. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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Figures

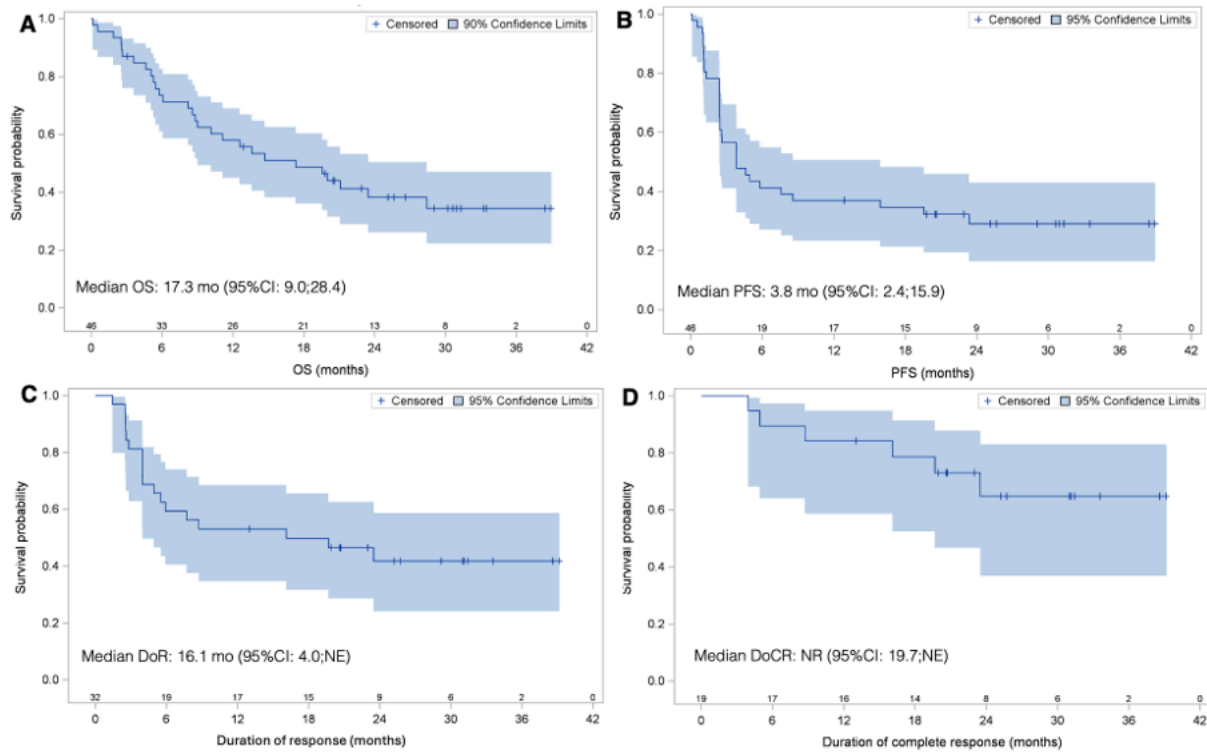


Figure 1

Kaplan-Meier curve for overall survival (A), progression-free survival (B), duration of response (C) and duration of complete response (D).

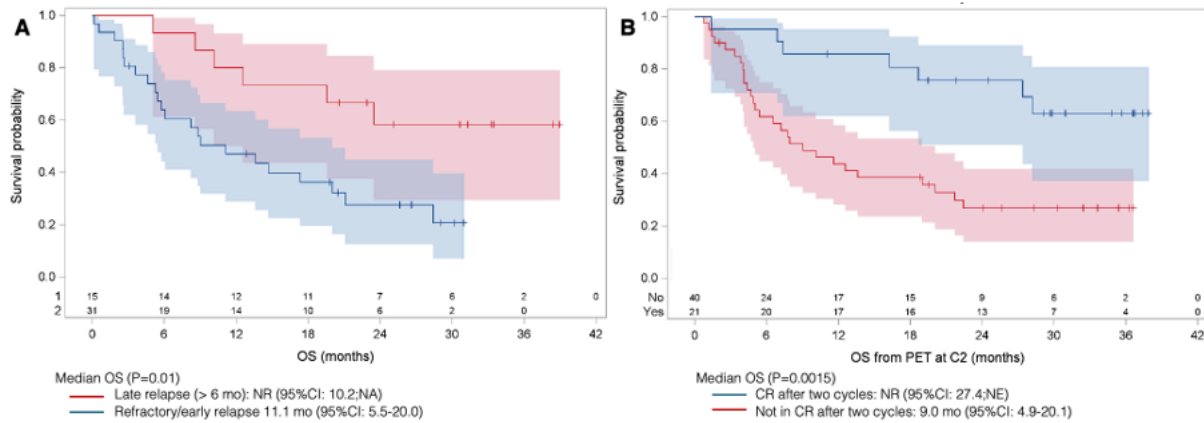


Figure 2

Kaplan-Meier curves of overall survival according to patient status (late relapse vs refractory/early relapse) (A) and CR status after two cycles of glofitamab (B).

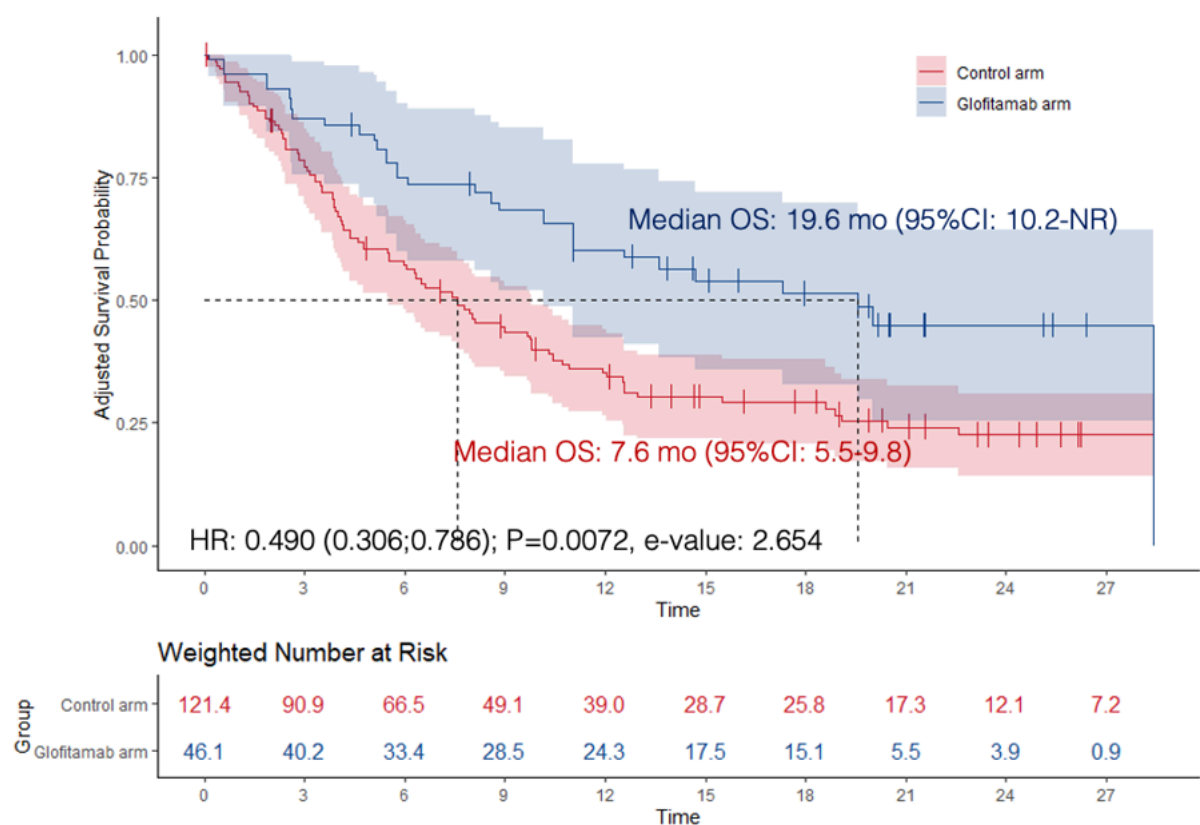


Figure 3

Survival according to post CAR-T regimens after multiple imputation-stabilized inverse probability of treatment weighting (MI-sIPTW)

Supplementary Files

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