Glofitamab plus Gemcitabine and Oxaliplatin (Glofit-GemOx) for Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL): Results of a Global Randomized Phase III Trial (STARGLO)

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Summary

Glofitamab is a CD20xCD3 T-cell engaging bispecific antibody that is approved as monotherapy for the treatment of patients with R/R large B-cell lymphoma (LBCL) after ≥2 prior therapies

We present efficacy and safety results of Glofit-GemOx versus rituximab (R)-GemOx in patients with R/R DLBCL after ≥1 prior line of therapy from the global, randomized, Phase III STARGLO trial

Fixed duration Glofit-GemOx demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit versus R-GemOx in patients with R/R DLBCL

Glofit-GemOx was tolerable; adverse events (AEs) were consistent with the known risks of the study drugs

Glofitamab is the first CD20xCD3 bispecific antibody to demonstrate a survival benefit in DLBCL in a randomized Phase III trial; these results support the use of Glofit-GemOx for the treatment of R/R DLBCL

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Background

- Glofitamab is a T-cell engaging bispecific antibody with a 2:1 (CD20:CD3) format that is administered as an off-the-shelf, fixed duration treatment for R/R LBCL[1,2]
- Phase I/II pivotal trial experience in R/R DLBCL after ≥2 prior therapies:[2]
  - Glofitamab step-up dosing schedule and target dose (30mg) were established in patients with B-cell non-Hodgkin lymphoma (NHL)[3]
  - High complete response (CR) rates, with the majority of CRs lasting >2 years[2,4]
  - Effective cytokine release syndrome (CRS) risk mitigation
  - Glofitamab is approved as monotherapy for the treatment of patients with R/R LBCL after ≥2 prior therapies
- We report the efficacy and safety of Glofit-GemOx versus R-GemOx in patients with R/R DLBCL after ≥1 prior therapy from the Phase III STARGLO trial (GO41944; NCT04408638)

STARGLO is a global, randomized, Phase III trial in ASCT-ineligible patients with R/R DLBCL (Figure 1)

Figure 1. STARGLO study design

- **Primary analysis** (cut-off: **Mar 29, 2023**): prespecified interim analysis after 70% OS events (n=101), study met interim threshold for significance
- **Updated analysis** (cut-off: **Feb 16, 2024**): follow-up until all patients had finished therapy

Gemcitabine 1000mg/m² and oxaliplatin 100mg/m².
*In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m². ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. §Hierarchical.
ASCT, autologous stem cell transplant; C, cycle; D, day; DoCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; IRC, independent review committee; NOS, not otherwise specified; PFS, progression-free survival; R 2:1, patients randomized in a 2:1 ratio.

Between February 2021–March 2023, 274 patients were enrolled

- Baseline characteristics are reported in **Table 1**

Table 1. Baseline characteristics

n (%), unless otherwise stated		R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years	Median (range)	68.0 (20–84)	68.0 (22–88)
	≥65 years	56 (61.5)	116 (63.4)
Sex	Male	53 (58.2)	105 (57.4)
Race	Asian	51 (56.0)	86 (47.0)
	Black or African American	1 (1.1)	2 (1.1)
	White	33 (36.3)	82 (44.8)
	Unknown	6 (6.6)	13 (7.1)
ECOG PS	0	44 (50.0)	72 (40.0)
	1	36 (40.9)	89 (49.4)
	2	8 (9.1)	19 (10.6)
Ann Arbor stage	I–II	20 (22.0)	60 (32.8)
	III–IV	70 (76.9)	123 (67.2)
Number of prior lines of therapy	1	57 (62.6)	115 (62.8)
	≥2	34 (37.4)	68 (37.2)
Primary refractory	Yes	47 (51.6)	106 (57.9)
R/R to last prior therapy	Relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Bulky disease (≥10cm)	Present	14 (15.4)	23 (12.6)
Cell of origin at initial diagnosis	GCB	29 (31.9)	60 (32.8)
	Non-GCB (including ABC)	50 (54.9)	103 (56.3)
	Unknown	12 (13.2)	20 (10.9)
Prior CAR T-cell therapy	Received	8 (8.8)	13 (7.1)

ABC, activated B-cell-like; CAR, chimeric antigen receptor; GCB, germinal center B-cell-like.

A statistically significant and clinically meaningful benefit in OS, PFS, and CR rate observed with Glofit-GemOx versus R-GemOx

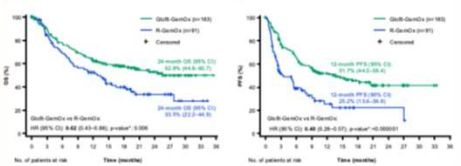
- Significant and clinically meaningful benefits in OS and PFS were observed at the primary analysis and continued at the updated analysis (**Table 2** and **Figure 2**)
- Response rates at the updated analysis:
  - IRC-assessed CR rate was significantly better with Glofit-GemOx vs R-GemOx (58.5% vs 25.3%, respectively [descriptive p-value <0.0001]); the difference in CR rate between treatment arms was 33.2% (95% CI: 19.7–44.5)
  - ORR was 68.3% with Glofit-GemOx and 40.7% with R-GemOx

Table 2. OS and IRC-assessed PFS at the primary and updated analysis

	R-GemOx (n=91)	Glofit-GemOx (n=183)	R-GemOx (n=91)	Glofit-GemOx (n=183)
	Primary OS analysis (median follow-up: 11.3 months)		Updated OS analysis (median follow-up: 20.7 months)	
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.59** (0.40–0.89)		**0.62** (0.43–0.88)	
p-value*	0.011		0.006	
	Primary PFS analysis (median follow-up: 9.6 months)		Updated PFS analysis (median follow-up: 16.1 months)	
PFS, median (95% CI); months	3.3 (2.5–5.6)	12.1 (6.8–18.3)	3.6 (2.5–7.1)	13.8 (8.7–20.5)
HR (95% CI)	**0.37** (0.25–0.55)		**0.40** (0.28–0.57)	
p-value*	<0.000001		<0.000001	

p-value is alpha controlled at the primary analysis and descriptive at the updated analysis.

Figure 2. A) OS (primary endpoint) and B) PFS (by IRC assessment) at the updated analysis

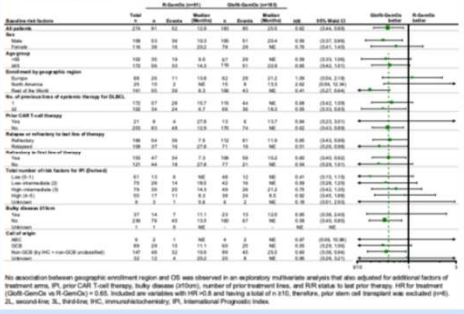


24-month OS and 12-month PFS not reported at the primary analysis as data were not sufficiently mature.
*p-value is descriptive at the updated analysis.

Comparable OS was observed in clinically relevant stratified subgroups (relapsed vs refractory and 2L vs 3L+)

- Regional inconsistencies were observed, but interpretation was limited by wide CI and small patient numbers (**Figure 3**)

Figure 3. OS in pre-specified subgroups: exploratory analysis



No association between geographic enrollment region and OS was observed in an exploratory multivariate analysis that also adjusted for additional factors of treatment arms, IPI, prior CAR T-cell therapy, bulky disease (≥10cm), number of prior treatment lines, and R/R status to last prior therapy. HR for treatment (Glofit-GemOx vs R-GemOx) = 0.65, including 2 new variables with HR <0.6 and having a total of n ≥10, therefore, prior stem cell transplant was excluded (n=6).
2L, second-line; 3L, third-line; IHC, immunohistochemistry; IPI, International Prognostic Index.

The safety profile of Glofit-GemOx is consistent with the known risk of the individual study drugs (Table 3)

Table 3. Safety profile summary

n (%), unless otherwise stated	R-GemOx (n=88)	Glofit-GemOx (n=180)
Number of cycles,* median (range)	4 (1–8)	11 (1–13)
Any grade AEs	84 (95.5)	180 (100)
Rituximab/glofitamab related	58 (65.9)	149 (82.8)
Serious AEs	15 (17.0)	98 (54.4)
Rituximab/glofitamab related	7 (8.0)	62 (34.4)
Grade 3–5 AEs	36 (40.9)	140 (77.8)
Rituximab/glofitamab related	20 (22.7)	85 (47.2)
Grade 5 (fatal) AEs	4 (4.5)	15 (8.3)
Rituximab/glofitamab related	1 (1.1)	5 (2.8)
AE leading to any treatment discontinuation	11 (12.5)	48 (26.7)

Includes any patient who received any study treatment including obinutuzumab pretreatment, rituximab, glofitamab, gemcitabine, or oxaliplatin.
*Number of cycles refers to either rituximab or glofitamab cycles.

- CRS mainly occurred during Cycle 1 and was predominantly low grade (**Table 4**)
- Neurologic AEs potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were reported in 2% of patients receiving Glofit-GemOx (n=4/172) and were mostly low grade
- Grade ≥3 infections were higher with Glofit-GemOx (23.3%) than R-GemOx (12.5%)
- Other AEs of interest were consistent with the known risk of the individual drugs

Table 4. CRS summary

n (%) of patients with ≥1 CRS AE*	Glofit-GemOx (Glofit exposed) (n=172)
Any grade†	76 (44.2)
Grade 1 / Grade 2 / Grade 3	54 (31.4) / 18 (10.5) / 4 (2.3)‡
Median time to CRS onset, hours (range)	
2.5mg glofitamab (C1D8) / 10mg glofitamab (C1D15)	13.5 (4.4–134.9) / 32.4 (7.4–564.3)
Median CRS duration, hours (range)	
2.5mg glofitamab (C1D8) / 10mg glofitamab (C1D15)	22.7 (0.0–168.0) / 24.0 (0.0–248.5)
Tocilizumab for CRS management, n / n (%)	28 / 76 (36.8)
Corticosteroids for CRS management, n / n (%)	39 / 76 (51.3)

Dexamethasone premedication was mandated to prevent/mitigate CRS prior to step-up doses and prior to at least two 30mg doses of glofitamab, until no additional CRS was observed.*Unless otherwise specified. †No Grade 4 or 5 CRS events were reported. ‡One patient had a Grade 3 CRS event confounded by a concurrent Grade 5 Septic Shock that required multiple pressors.

- The COVID-19-related AE profile is shown in **Table 5**. These data should be contextualised considering the rapidly changing landscape of the COVID-19 pandemic and management during the STARGLO study

Table 5. COVID-19 AEs

COVID-19 AE, n (%)	R-GemOx (n=88)	Glofit-GemOx (n=180)
Any grade COVID-19 AE	8 (9.1)	33 (18.3)
Grade ≥3 AE	2 (2.3)	11 (6.1)
Grade 5 (fatal) AEs associated with COVID-19*	0	7 (3.9)
AE leading to treatment discontinuation†	5 (5.7)	22 (12.2)

*Four instances of COVID-19, one respiratory tract infection, one neutropenic sepsis, one acute respiratory distress syndrome.
†COVID-19 events that led to treatment discontinuation following Independent Data Monitoring Committee recommendations occurred in five patients in the R-GemOx arm and 14 patients in the Glofit-GemOx arm.
COVID-19, coronavirus-19.

Conclusions

- Fixed duration glofitamab added to GemOx demonstrated a statistically significant and clinically meaningful OS benefit in patients with R/R DLBCL, who are ineligible for ASCT
  - Median OS of 25.5 months with Glofit-GemOx compared with 12.9 months with R-GemOx (HR 0.62)
  - Glofit-GemOx improved median PFS (13.8 vs 3.6 months) and CR rate (58.5 vs 25.3%) vs R-GemOx
- Glofit-GemOx was tolerable; AEs were consistent with the known risks of the study drugs. CRS primarily occurred in C1 and was mostly low grade
- Glofitamab is the first CD20xCD3 bispecific antibody to demonstrate a survival benefit in DLBCL in a randomized Phase III trial; these results support the use of Glofit-GemOx for the treatment of R/R DLBCL

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