Glofitamab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma and ≥2 Prior Therapies: Results From a Pivotal Phase II Expansion Study

To be presented by Brannon Flores on behalf of the authors

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Summary

Glofitamab is a T-cell engaging bispecific antibody with a novel 2:1 configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells)

We present pivotal Phase II expansion results for glofitamab in patients with R/R DLBCL and ≥2 prior therapies

Although the patient population was heavily pre-treated and highly refractory to previous therapies, fixed-duration glofitamab induced durable complete remissions in patients with R/R DLBCL, including those with prior exposure to CAR T-cell therapy

Glofitamab is the first T-cell engaging bispecific antibody to demonstrate clinically meaningful outcomes for patients with R/R DLBCL in a pivotal Phase II setting

Glofitamab is a promising new therapy for patients with heavily pre-treated and/or highly refractory DLBCL

Glofitamab was well tolerated, with a low discontinuation rate. CRS was mostly low grade and predictable, with most events occurring during Cycle 1

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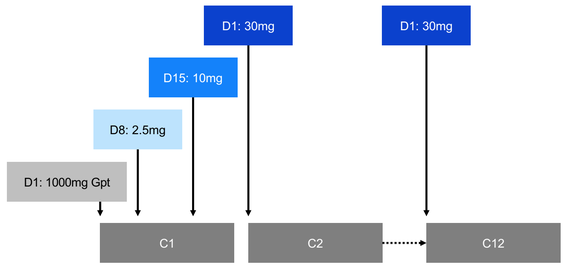
Background

- Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have a poor prognosis.[1,2]
- Glofitamab is a T-cell engaging bispecific antibody with a novel 2:1 configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells).[3]
- In a Phase I/II study (NCT03075696), escalating glofitamab doses were highly active and well tolerated in patients with R/R B-cell lymphomas, with obinutuzumab pre-treatment and Cycle (C) 1 step dosing providing effective cytokine release syndrome (CRS) mitigation.[4]
- Here we present pivotal Phase II expansion results for glofitamab in patients with R/R DLBCL and ≥2 prior therapies.

Methods

- All patients had DLBCL and had received ≥2 prior regimens, including ≥1 anti-CD20 antibody and ≥1 anthracycline.
- Intravenous (IV) obinutuzumab pre-treatment (1000mg) was given on Day (D) 1 of C1 (**Figure 1**). IV glofitamab was then given as step-up doses on D8 (2.5mg) and D15 (10mg) of C1 and at the target dose (30mg) on D1 of C2–12 (21-day cycles).
- The primary endpoint was complete response (CR) rate assessed by Independent Review Committee (IRC) using Lugano 2014 criteria. CRS was assessed using American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[5]

Figure 1. Glofitamab treatment schedule



Gpt, obinutuzumab pre-treatment.

Baseline characteristics

- As of March 14, 2022, 154 patients had received ≥1 dose of study treatment (safety evaluable population). Median age was 66 years and 75% had Ann Arbor stage III–IV disease (**Table 1**).
- The patient population was heavily pre-treated and highly refractory to previous therapies.

Table 1. Baseline characteristics

	N=154
Median age, years (range)	66 (21–90)
Male, n (%)	100 (64.9)
ECOG PS, n (%)	
0	69 (44.8)
1	84 (54.5)
2	1 (0.6)
Ann Arbor stage, n (%)	
I	10 (6.5)
II	25 (16.2)
III	31 (20.1)
IV	85 (55.2)
NHL subtype, n (%)	
DLBCL	110 (71.4)
trFL	27 (17.5)
HGBCL	11 (7.1)
PMBCL	6 (3.9)
Bulky disease, n (%)	
>6cm	64 (41.6)
>10cm	18 (11.7)

	N=154
Median prior lines, n (range)	3 (2–7)
Prior lines, n (%)	
2	62 (40.3)
≥3	92 (59.7)
Prior therapies, n (%)	
Anti-CD20 antibody	154 (100.0)
Anthracycline	149 (96.8)
CAR T-cell therapy	51 (33.1)
ASCT	28 (18.2)
Refractory to any prior therapy, n (%)	139 (90.3)
Refractory to last prior therapy, n (%)	132 (85.7)
Primary refractory, n (%)	90 (58.4)
Refractory to prior CAR T-cell therapy, n (%)	46 (29.9)
Refractory to any prior anti-CD20 antibody, n (%)	128 (83.1)

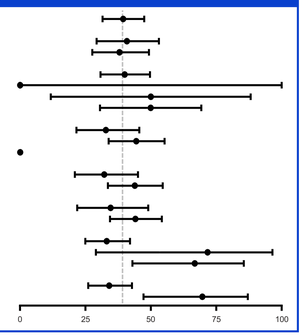
ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

Clinical response

- After a median follow-up of 12.6 months (range: 0–22), the intent-to-treat population (n=155) had an objective response rate (ORR) of 51.6% (95% confidence interval [CI]: 43.5–59.7) and a CR rate of 39.4% (95% CI: 31.6–47.5), both based on best responses.
- The primary endpoint was met in the primary efficacy population (n=108), with a significantly greater CR rate (by IRC) than the historical control (35.2% vs 20%; p<0.0001).
- Responses were achieved early (median time to first CR: 42 days; 95% CI: 42–44).
- CR rates were consistent in patients with and without prior CAR T-cell therapy (35% vs 42%; **Figure 2**).

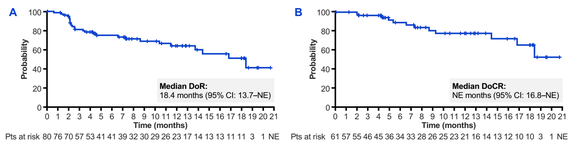
Figure 2. CR rates by IRC in pre-specified subgroups

Subgroups	N of patients	CR (95% CI) by IRC
Overall	155 (100%)	39% (32–48)
Age group		
<65	71 (46%)	41% (29–53)
≥65	84 (54%)	38% (28–49)
NHL subtype at study entry		
DLBCL	110 (71%)	40% (31–50)
HGBCL	11 (7%)	0%
PMBCL	6 (4%)	50% (12–88)
trFL	28 (18%)	50% (31–69)
Bulky disease >6cm		
Yes	64 (41%)	33% (22–46)
No	90 (58%)	44% (34–55)
Unknown/missing	1 (1%)	0%
Number of prior line of therapies		
2	62 (40%)	32% (21–45)
≥3	93 (60%)	44% (34–55)
Prior CAR T-cell therapy		
Yes	52 (34%)	35% (22–49)
No	103 (66%)	42% (32–52)
Post ASCT		
No	127 (82%)	33% (25–42)
Refractory	7 (5%)	71% (29–96)
Relapsed	21 (14%)	67% (43–85)
R/R to last prior therapy		
Refractory	132 (85%)	34% (26–43)
Relapsed	23 (15%)	70% (47–87)



- Durable responses were maintained after cessation of therapy (**Figure 3**). Duration of CR in earlier cohorts showed durable responses beyond 24 months.

Figure 3. DoR by IRC (A) and DoCR by IRC (B)



	N=80
Median DoR follow-up, months (range)	10.6 (0–21)
12-month DoR, % (95% CI)	63.6 (51.1–76.2)
Response ongoing at CCOD, n (%)	53 (66.3)

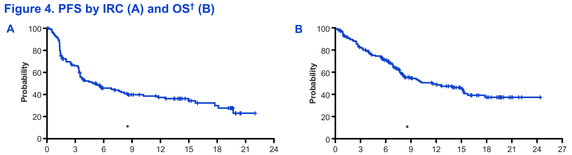
	N=61
Median DoCR follow-up, months (range)	10.6 (0–21)
12-month DoCR, % (95% CI)	77.6 (64.3–90.8)
CR ongoing at CCOD, n (%)	49 (80.3)

CCOD, clinical cut-off date; DoR, duration of response; DoCR, duration of complete response; NE, not estimable.

Time-to-event endpoints

- Clinically significant progression-free survival at 12 months and long-term overall survival were observed (**Figure 4**).

Figure 4. PFS by IRC (A) and OS[†] (B)



	N=155
Median PFS follow-up, months (range)	12.6 (0–22)
Median PFS, months (95% CI)[‡]	4.9 (3.4–8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2–53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5–45.8)

	N=155
Median OS, months (95% CI)[‡]	11.5 (7.9–15.7)
12-month OS rate, % (95% CI)	49.8 (41.1–58.5)

*Maximum treatment length; †includes 5 deaths due to COVID-19; ‡Kaplan–Meier estimates; OS, overall survival; PFS, progression-free survival.

Safety

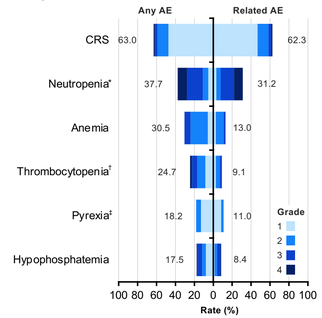
- Glofitamab was well tolerated, with a favorable safety profile (**Table 2** and **Figure 5**), including a low rate of treatment-related adverse events leading to discontinuation (**Table 2**).
- The Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) event rate was also low (any Grade [Gr]: n=12, 7.8%; Gr ≥3: n=4, 2.6%). Gr ≥3 ICANS events were: Gr 3 somnolence (n=1), Gr 3 agitation (n=1), Gr 3 delirium (n=1), and Gr 5 delirium (n=1).

Table 2. Glofitamab safety profile

	N=154
Median cycles received, n (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
Any Gr AEs, n (%)	152 (98.7)
Related	140 (90.9)
Gr 3–4 AEs, n (%)	87 (56.5)
Related	64 (41.6)
Serious AEs, n (%)	73 (47.4)
Related	46 (29.9)
Gr 5 (fatal) AEs, n (%)	8 (5.2)*
Related	0
AEs leading to treatment discontinuation, n (%)	14 (9.1)
Related	5 (3.2)

*COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1); AE, adverse event; Gr, Grade.

Figure 5. AEs (≥15%) by Grade and relationship with glofitamab



*Includes neutrophil count decreased; †Includes platelet count decreased; ‡Pyrexia events separate from CRS.

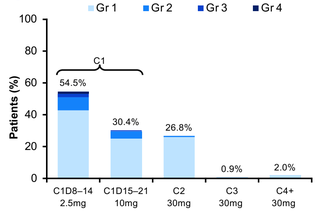
Cytokine release syndrome

- CRS was mostly low grade; time of onset was predictable, and most events occurred during C1 (**Table 3** and **Figure 6**).

Table 3. CRS

	N=154
CRS, n (%)	
Any Gr	97 (63.0)
Gr 1 (fever)	73 (47.4)
Gr 2	18 (11.7)
Gr 3	4 (2.6)
Gr 4	2 (1.3)
Median time to CRS onset from C1D8 dose (range), hours	13.6 (6.2–51.8)
CRS management, n (%)	
Corticosteroids	27/97 (27.8)
Tocilizumab	31/97 (32.0)

Figure 6. CRS by Cycle and Grade*



*One patient had Gr 1 CRS following obinutuzumab pre-treatment due to CAR T-cell re-expansion.

- CRS rates were lower in patients who received mandatory dexamethasone versus patients who received any corticosteroid (47.5% vs 68.4%, respectively). Severity of CRS was also lower with mandatory dexamethasone versus any corticosteroid.
- There were some Gr 4 CRS events at the 2.5mg glofitamab dose when any corticosteroid was given (and none for mandatory dexamethasone). There were no Gr ≥2 CRS events with 10mg or 30mg glofitamab and mandatory dexamethasone (but some for any corticosteroid).

Conclusions

- The primary efficacy endpoint was met, with a CR of 39.4% reported in heavily pre-treated, highly refractory patients with DLBCL
  - CR rates were consistent in patients with prior CAR T-cell therapy
  - CRs were achieved early and were durable after the fixed treatment duration.
- Glofitamab was well tolerated, with a low rate of treatment-related discontinuations.
- CRS was predictable, mostly low grade, and the incidence was lower with mandatory dexamethasone.
- Glofitamab is the first T-cell engaging bispecific antibody to demonstrate clinically meaningful outcomes for patients with R/R DLBCL in a pivotal Phase II setting.

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References

1. Chien HC, et al. *Future Oncol* 2021;17:411–22.
2. Crump M, et al. *Blood* 2017;130:1800–8.
3. Bacac M, et al. *Clin Cancer Res* 2018;24:4785–97.
4. Hutchings M, et al. *J Clin Oncol* 2021;39:1959–70.
5. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625–38.

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