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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

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Summary

Glofitamab is a CD20xCD3 T-cell engaging bispecific antibody that is available as an off-the-shelf, fixed-duration treatment

We report an extended follow-up from a Phase II study in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL), along with subgroup analyses in patients with prior chimeric antigen receptor (CAR) T-cell therapy and by baseline total metabolic tumor volume (TMTV)

Higher baseline TMTV may be prognostic for lower progression-free survival (PFS) and was associated with an increased risk of experiencing cytokine release syndrome (CRS)

Complete response (CR) rate and duration of complete response (DoCR) in patients with prior CAR T-cell therapy were consistent with the overall population

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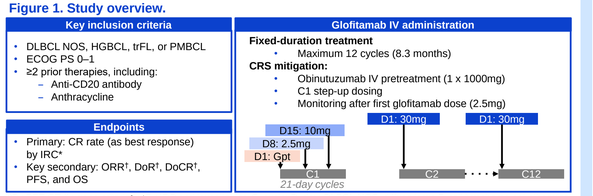
Background

- Patients with R/R diffuse large B-cell lymphoma (DLBCL) after ≥2 prior therapies have a poor prognosis[1,2]
  - CAR T-cell therapy has shown benefits in the third-line setting, however, ~50% of patients with a CR subsequently relapse[3]
  - Treatment options are limited for patients who experience disease progression while receiving CAR T-cell therapy[4]
- Glofitamab is a bispecific antibody that is available as an off-the-shelf, fixed-duration treatment[5]
  - Engages and redirects T cells to eliminate B cells
  - Is administered as a fixed-duration treatment and is approved in more than 30 countries for the treatment of patients with R/R LBCL after ≥2 prior therapies
- In a Phase II study (NCT03075696), glofitamab induced high CR rates with a manageable toxicity profile in patients with R/R DLBCL[6,7]
- Here, we present data with an extended follow-up, along with subgroup analyses, in patients with prior CAR T-cell therapy and by baseline TMTV

Study design: pivotal Phase II study in patients with R/R LBCL and ≥2 prior therapies

- Patients received 1000mg obinutuzumab pretreatment 7 days prior to the first glofitamab dose, followed by intravenous (IV) glofitamab (for up to 12 cycles; **Figure 1**)

Figure 1. Study overview.



*By PET-CT (Lugano criteria[8]); †By IRC and investigator. C, cycle; D, day; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

As of September 4, 2023, 154 patients had received ≥1 dose of study treatment

- Baseline characteristics were as previously reported;[6] the patient population was heavily pre-treated and highly refractory to prior therapy (**Table 1**)

Table 1. Baseline characteristics.

	All patients (N=154)*
Median age, years (range)	66.0 (21–90)
Male, n (%)	100 (64.9)
ECOG PS 1†, n (%)	84 (54.5)
Ann Arbor stage, n (%)	
III/IV	116 (75.3)
Non-Hodgkin lymphoma subtype, n (%)	
DLBCL	110 (71.4)
trFL	28 (18.2)
HGBCL	10 (6.5)
PMBCL	6 (3.9)
Median number of prior lines, n (range)	3 (2–7)
≥3 prior lines	93 (60.4)
Prior CAR-T, n (%)	51 (33.1)
Refractory to prior CAR-T‡, n (%)	46 (29.9)
Refractory to last prior therapy, n (%)	131 (85.1)
Refractory to first line of prior therapy, n (%)	90 (58.4)
Refractory to any prior anti-CD20, n (%)	128 (83.1)

*Safety-evaluable population; †ECOG PS 2, n=1 (0.6%); one patient had an ECOG PS of 1 at enrolment but deteriorated before the receipt of study treatment; ‡Patients who had no response or relapsed within 6 months.

Fixed-duration glofitamab provides long-lasting remissions for patients with R/R LBCL

- Median time on study was 32.1 months (range: 0–43)
- Glofitamab showed high response rates and durable remissions across subgroups and in the intent-to-treat population (**Table 2**)
  - ORR and CR rates in all patients were 52% and 40%, respectively; 34/62 (55%) CRs were ongoing at data cut-off
  - Median DoCR in all patients was 26.9 months and 24-month DoCR rate was 55.0%

Table 2. Response rates and DoCR.

IRC-assessed endpoints	All patients (N=155)*	R/R DLBCL / trFL (N=132)†,‡	Prior CAR-T (N=52)‡
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); †Primary efficacy population reported in the glofitamab US prescribing information, all patients received at least one dose of glofitamab;[9] ‡Patients in this subgroup had similar baseline characteristics to the overall population. CI, confidence interval; NE, not estimable; NR, not reached.

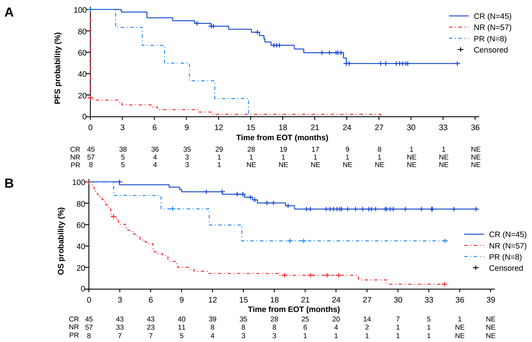
The majority of patients with a CR at EOT remained progression-free and alive at 18 months after end of treatment (EOT)

- A high proportion of patients with a CR at C3 remained progression-free and alive after 24 months (**Table 3**)
- Landmark analyses by response at EOT are shown in **Table 3** and **Figure 2**

Table 3. Landmark analysis by CR at C3 and EOT.

	PFS	OS
Landmark analysis from C3 in patients with CR at C3	n=44	n=44
Median, months (95% CI)	31.1 (22.4–NE)	NE (NE)
24-month rate, % (95% CI)	63.5 (47.5–79.6)	73.4 (59.9–87.0)
Landmark analysis from EOT in patients with CR at EOT	n=45	n=45
Median, months (95% CI)	24.0 (19.1–NE)	NE (NE)
18-month rate, % (95% CI)	66.6 (51.0–82.2)	80.7 (68.6–92.8)

Figure 2. PFS (A) and OS (B) in patients with CR at EOT.



PR, partial response.

Baseline TMTV may be prognostic for PFS

- Baseline TMTV was derived from baseline PET images using a semi-automated method with a threshold for TMTV of 2x the mean standardized uptake value (SUV) of the liver
  - Median baseline TMTV in patients who received at least one dose of glofitamab was 128.7mL (range: 0–3820; n=144)
- 24-month PFS rate for patients with baseline TMTV ≥ median was 11.8% (95% CI: 6.0–23.5) and 41.6% (95% CI: 31.1–55.6) for patients with baseline TMTV < median (hazard ratio: 2.4 [95% CI: 1.6–3.6])

The safety profile was consistent with previous analyses[6,7]

- The incidence of adverse events (AEs) and serious AEs (SAEs) were stable and no new AEs were reported (including immune effector cell-associated neurotoxicity syndrome, CRS, infections, or Grade 5 AEs)
- CRS remained the most common AE and occurred in 64% of patients
  - Most CRS events (by American Society for Transplantation and Cellular Therapy criteria) were Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon

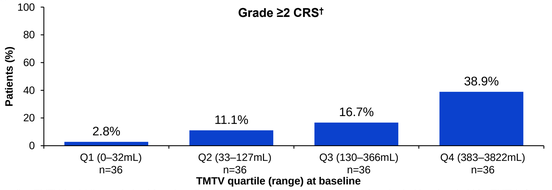
Table 4. Safety summary.

n (%)	All patients (N=154)*
AE / Glofitamab-related	152 (99) / 140 (91)
Grade ≥3 AE / Glofitamab-related	100 (65) / 69 (45)
SAE / Glofitamab-related	75 (49) / 46 (30)
Grade 5 AE / Glofitamab-related	11 (7) / 0
AE leading to treatment discontinuation / Glofitamab-related	14 (9) / 5 (3)
AE leading to dose modification/interruption of glofitamab / Glofitamab-related	29 (19) / 16 (10)

*Safety-evaluable population.

- Higher baseline TMTV was associated with an increased risk of experiencing a Grade ≥2 CRS event (**Figure 3**)
  - Most Grade ≥2 CRS events occurred with the first dose of glofitamab (C1D8, 2.5mg) and resolved before the next dose (C1D15, 10mg).

Figure 3. Association between baseline TMTV* and CRS.



*Baseline TMTV (n=144) was derived from baseline PET images using a semi-automated method with a threshold for TMTV of 2x the SUV_{mean} of the liver; †Chi-square=16.273; degrees of freedom=1; p<0.0001. Q, quartile.

Conclusions

- Glofitamab induces high CR rates in patients with R/R DLBCL, including those with prior CAR T-cell therapy
  - The majority of patients with a CR are in remission at 24 months' follow-up
  - CR rates and DoCR in patients with prior CAR T-cell therapy were consistent with the overall population
- The majority of patients with a CR at EOT were alive and event-free 18 months after EOT
- Higher baseline TMTV may be prognostic for lower PFS and was associated with an increased risk of experiencing Grade ≥2 CRS
- No new AEs were observed since the previous analysis, reflecting the advantage of the fixed duration of glofitamab treatment
- **Fixed-duration glofitamab provides long-lasting remissions for patients with R/R LBCL**

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