MCL-341

Glofitamab Monotherapy in Patients with Heavily Pretreated Relapsed/Refractory Mantle Cell Lymphoma: Updated Analysis From a Phase I/II Study

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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 updated efficacy and safety data from a Phase I/II study for patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) treated with glofitamab monotherapy

The majority of patients with a complete response (CR) at the end of therapy (EOT) remained progression-free and alive 15 months post-EOT

Glofitamab induced high response rates and durable responses in patients with R/R MCL, including patients with prior Bruton tyrosine kinase inhibitor (BTKi) therapy

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Background

- Treatment of R/R MCL remains a clinical challenge with decreasing response duration observed after each relapse[1]
  - Patients who relapse following BTKi treatment have a particularly poor prognosis[2–5]
  - Recent data support a role for BTKi-containing combinations in the first-line setting,[6] increasing the need for new treatment options for patients with R/R MCL, particularly those who have progressed following BTKi treatment
- Glofitamab is an off-the-shelf, fixed duration treatment, approved for patients with large B-cell lymphoma (LBCL) after ≥2 prior therapies[5]
- Glofitamab has shown high CR rates and durable responses with a manageable safety profile in patients with heavily pretreated R/R MCL in the Phase I/II NP30179 study (NCT03075696)[7]
- We report updated efficacy and safety data for patients with R/R MCL treated with glofitamab monotherapy after a median follow-up of 19.6 months

NP30179 Phase I/II study design

- NCT03075696 is a multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with obinutuzumab pretreatment (Gpt) in patients with R/R MCL (**Figure 1**)

Figure 1. Study overview.

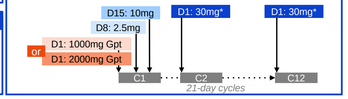
Key inclusion criteria
- Age ≥18 years
- R/R MCL
- ECOG PS 0–1
- ≥1 prior systemic therapy

Efficacy endpoints
- CR
- ORR
- DOCR
- DOR
- PFS
- OS

Glofitamab IV administration

Fixed-duration treatment
- Maximum 12 cycles (approximately 8.5 months)

CRS mitigation:
- Obinutuzumab IV pretreatment (1000mg or 2000mg)
- C1 step-up dosing



*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase. C, cycle; CRS, cytokine release syndrome; D, day; DOCR, duration of confirmed response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

As of September 4, 2023, 60 patients had received ≥1 dose of study treatment

- The efficacy-evaluable population included all patients who received ≥1 dose of study treatment (n=60) and the intent-to-treat population included all patients enrolled in the study (n=61)
- Patients with R/R MCL were heavily pretreated and highly refractory to their last prior therapy (**Table 1**)
- Approximately half of the patients (51.7%) had received prior BTKi therapy
  - A higher proportion of patients with prior BTKi therapy were refractory to their last prior therapy compared with BTKi-naïve patients (**Table 1**)

Table 1. Baseline characteristics in the efficacy-evaluable population.

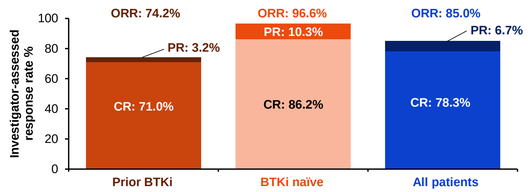
		Prior BTKi (n=31)	BTKi naïve (n=29)	All patients (N=60)
Median age, years (range)		70.0 (41–84)	72.0 (52–86)	72.0 (41–86)
Male, n (%)		23 (74.2)	21 (72.4)	44 (73.3)
Ann Arbor stage III/IV, n (%)		28 (90.3)	24 (82.8)	52 (86.7)
MIPI score ≥6, n (%)		7 (22.6)	8 (27.5)	15 (25.0)
Median number of prior lines (range)		3.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Median time since last prior therapy to first study treatment, months (range)		1.3 (0.1–53.2)	7.4 (1.1–132.5)	2.4 (0.1–132.5)
Median time since last anti-CD20 therapy to first study treatment, months (range)		15.1 (0.7–159.0)	25.1 (1.4–132.5)	16.3 (0.7–159.0)
Refractory status, n (%)	Refractory to any prior therapy	30 (96.8)	20 (69.0)	50 (83.3)
	Refractory to first-line therapy	17 (54.8)	14 (48.3)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)	44 (73.3)

MIPI, mantle cell lymphoma international prognostic index.

Glofitamab induced high response rates and durable responses in patients with R/R MCL

- High CR rates and ORRs were observed in the overall population and in both BTKi-naïve patients and those with prior BKTi therapy (**Figure 2**)
  - Median time to first response among responders (n=51) was 42 days (95% confidence interval [CI]: 42.0–45.0)
- With a median follow-up for CR of 17.2 months (95% CI: 9.5–22.6), fixed-duration glofitamab monotherapy achieved durable CRs (**Table 2**)

Figure 2. Response rates in patients with R/R MCL (efficacy-evaluable population).



PR, partial response.

Table 2. Duration of investigator-assessed response.

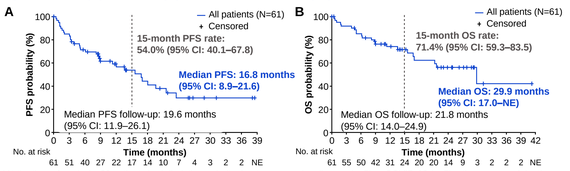
	Prior BTKi n=22	All patients n=47
Median DOCR, months (95% CI)	12.6 (5.4–NE)	15.4 (12.7–NE)
15-month DOCR rate, % (95% CI)	33.5 (10.6–56.4)	50.3 (32.0–68.6)
Ongoing CR, n (%)	10 (45.5)	28 (59.6)
	n=23	**n=51**
Median DOR, months (95% CI)	12.6 (7.4–NE)	16.2 (12.6–NE)
15-month DOR rate, % (95% CI)	38.0 (15.5–60.6)	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)

NE, not estimable.

Glofitamab induced clinically significant survival rates and most patients with a CR at EOT remained progression-free and were alive 15 months post-EOT

- Clinically significant PFS and OS at 15 months were achieved with fixed-duration glofitamab in all patients (**Figure 3**)
- In patients who received prior BTKi therapy (n=32), median PFS and OS follow-up was 26.1 months (95% CI: 13.5–31.2) and 24.7 months (95% CI: 13.6–28.8), respectively
  - Median PFS was 8.6 months (95% CI: 3.4–15.6) and median OS was 21.2 months (95% CI: 9.0–NE)
  - 15-month PFS and OS rates in these patients were 33.0% (95% CI: 14.8–51.1) and 55.0% (95% CI: 36.5–73.6), respectively

Figure 3. PFS (A) and OS* (B) in the intent-to-treat population.



*At the time of analysis, 22 patients had died, the majority due to progressive disease (n=7) or COVID-19 (n=7); other causes of death were pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1), and unknown/other (n=5). All patients who died due to COVID-19 had achieved a CR.

- Thirty patients had a CR at EOT and the majority of these patients remained progression-free and were alive at 15 months after EOT
  - Median PFS was NE (95% CI: 10.6–NE) and the 15-month PFS rate was 59.2% (95% CI: 35.5–83.0)
  - Median OS was NE and the 15-month OS rate was 72.7% (95% CI: 51.9–93.5)

The safety profile of glofitamab was consistent with previous analyses[8]

- In the 1000mg Gpt cohort, the most common adverse events (AEs) with an incidence of ≥15% were CRS (87.5%), neutropenia (56.3%) and pyrexia (37.5%)
  - In the 2000mg Gpt cohort, the most common AEs with an incidence of ≥15% were also CRS (63.6%), neutropenia (31.8%) and pyrexia (29.5%)
- The majority of CRS events were Grade 1/2, and a lower incidence of CRS was observed in the 2000mg vs 1000mg cohort (**Table 3**)
  - CRS events were predominantly in Cycle 1, and the median duration of CRS was shorter in patients pretreated with 2000mg obinutuzumab than 1000mg (**Table 3**)
- All immune effector cell-associated neurotoxicity syndrome (ICANS) events were resolved and considered non-serious (**Table 3**)
- All COVID-19-related events were observed during the pandemic (**Table 3**)
  - One additional patient died due to post-acute COVID-19 syndrome and one further patient died due to COVID-19/COVID-19 pneumonia outside of the AE reporting window
  - All patients who died due to COVID-19 had achieved a CR, and six remained in remission at the time of death

Table 3. Safety outcomes.

	1000mg Gpt (n=16)	2000mg Gpt (n=44)	All patients (N=60)
Safety summary, n (%)			
Any grade AE / Glofitamab related AE	16 (100) / 16 (100)	44 (100) / 39 (88.6)	60 (100) / 55 (91.7)
Serious AE / Glofitamab related Serious AE	15 (93.8) / 12 (75.0)	32 (72.7) / 24 (54.5)	47 (78.3) / 36 (60.0)
Grade 3/4 AE / Glofitamab Grade 3/4 related AE	13 (81.3) / 13 (81.3)	26 (59.1) / 22 (50.0)	39 (65.0) / 35 (58.3)
Grade 5 AE / Glofitamab related Grade 5 AE	2 (12.5) / 0	7 (15.9) / 0	9 (15.0) / 0
CRS summary, n (%)			
Any grade CRS*, n (%)	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1 / 2	4 (25.0) / 6 (37.5)	18 (40.9) / 7 (15.9)	22 (36.7) / 13 (21.7)
Grade 3 / 4	2 (12.5) / 2 (12.5)	3 (6.8) / 0	5 (8.3) / 2 (3.3)
Serious AE of CRS†, n (%)	11 (68.8)	12 (27.3)	23 (38.3)
CRS management, n (%)			
Tocilizumab / Corticosteroid	11 (68.8) / 8 (50.0)	11 (25.0) / 10 (22.7)	22 (36.7) / 18 (30.0)
Tocilizumab and corticosteroids	6 (37.5)	7 (15.9)	13 (21.7)
Intensive care unit admission	5 (31.3)	4 (9.1)	9 (15.0)
2.5mg glofitamab on Cycle 1 Day 8			
Median time to CRS‡ onset, hours (range)	6.1 (3.4–13.0)	17.5 (4.0–46.3)	9.7 (3.4–46.3)
Median CRS duration, hours, (range)	53.3 (9.0–171.2)	21.0 (2.0–692.7)	49.0 (2.0–692.7)
10mg glofitamab on Cycle 1 Day 15			
Median time to CRS‡ onset, hours (range)	17.5 (8.5–34.3)	20.6 (6.7–32.6)	20.6 (6.7–34.3)
Median CRS duration, hours, (range)	44.9 (1.0–625.5)	19.5 (1.5–83.0)	24.6 (1.0–625.5)
Other AEs of interest, n (%)			
Infections			
Any Grade	12 (75.0)	32 (72.7)	44 (73.3)
Grade 3/4 / Grade 5	4 (25.0) / 2 (12.5)	9 (20.5) / 6 (13.6)	13 (21.7) / 8 (13.3)
ICANS (derived) related to glofitamab			
Any Grade	2 (12.5)	1 (2.3)	3 (5.0)
Grade 1 / 2	1 (6.3)§ / 1 (6.3)¶	1 (2.3)# / 0	2 (3.3) / 1 (1.7)
COVID-19 / COVID-19 pneumonia			
Any Grade	4 (25.0)	15 (34.1)	19 (31.7)
Grade 3/4 / Grade 5	1 (6.3) / 0	4 (9.1) / 5 (11.4)	5 (8.3) / 5 (8.3)

*CRS by American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria[9]; †Serious AE of CRS is defined as per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ‡CRS by ASTCT consensus grading criteria[9]; §Confusional state; ¶Disorientation; #Mental state changes.

Conclusions

- Fixed duration glofitamab monotherapy induced high response rates and durable responses in heavily pretreated patients with R/R MCL, including patients with prior BTKi therapy
- The majority of patients with a CR at EOT remained progression-free and alive 15 months post-EOT
- The safety profile was manageable and consistent with the known profile of glofitamab
  - CRS events were predominantly Grade 1/2 and most occurred during Cycle 1
  - A lower incidence of CRS was observed following glofitamab treatment in the higher obinutuzumab dose cohort (2000mg vs 1000mg); this 2000mg Gpt dose is being used in the ongoing Phase III GLOBRYTE study (NCT06084936)
  - Strategies to minimize COVID-19-related events have been implemented
- Glofitamab monotherapy is a promising treatment option for patients with R/R MCL
- Based on these data, glofitamab received Breakthrough Therapy Designation status from the US Food and Drug Administration on May 31, 2024 for the treatment of patients with R/R MCL after at least two systemic therapies

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