MCL-553

Glofitamab induces high response rates and durable remissions in patients with heavily pretreated relapsed/refractory (R/R) mantle cell lymphoma (MCL), including those with a poor prognosis: Subgroup results from a Phase I/II trial

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Summary

NP30179 is an ongoing Phase I/II study evaluating fixed-duration glofitamab monotherapy in patients with relapsed/refractory mantle cell lymphoma (R/R MCL)

In the current analysis, high response rates and durable remissions were observed in patients with R/R MCL, including those with high-risk disease characteristics

In addition, most responders achieved undetectable minimal residual disease (MRD) at Cycle (C) 3, which is suggestive of a rapid and deep molecular response

Notably, most patients who were in complete response (CR) at the end of treatment (EOT) were progression-free and alive 18 months after the EOT

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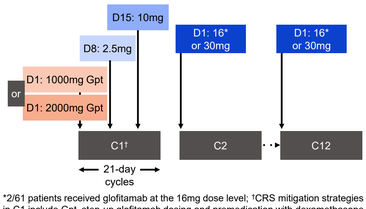
Background

- Patients with R/R MCL continue to have a poor prognosis, especially those whose disease has become R/R to Bruton's tyrosine kinase inhibitor (BTKi)-containing therapies. Novel and effective treatment options are needed.
- Glofitamab is a CD20xCD3 bispecific antibody that is approved for the treatment of patients with R/R diffuse large B-cell lymphoma who have received ≥2 prior lines of therapy.
- In an ongoing Phase I/II study (NP30179; NCT03075696), fixed-duration glofitamab monotherapy induced high response rates and durable remissions, and had a manageable safety profile, in a cohort of patients with heavily pretreated R/R MCL.[1]
- We report updated results for the R/R MCL cohort, including efficacy in clinically and/or histologically defined high-risk subgroups, and an exploratory analysis of MRD.

NP30179 is an ongoing Phase I/II study evaluating fixed-duration glofitamab monotherapy in patients with R/R MCL who have received ≥1 prior line of therapy

- Patients receive obinutuzumab pretreatment on C1 Day (D) 1 (**Figure 1**).
- Glofitamab is then given as step doses on C1D8 and C1D15 and at the target dose on D1 of each subsequent cycle (C2–12).

Figure 1. NP30179 dosing schedule.



*2/61 patients received glofitamab at the 16mg dose level; †CRS mitigation strategies in C1 include Gpt, step-up glofitamab dosing and premedication with dexamethasone. CRS, cytokine release syndrome; Gpt, obinutuzumab pretreatment.

- In the current analysis (data cut-off: May 17, 2024), tumor responses were assessed by investigators using Lugano 2014 criteria.[2]
- Formalin-fixed paraffin-embedded tumor biopsies were classified as classical, blastoid, or pleomorphic and analyzed by immunohistochemistry for Ki-67 or p53 expression.
- An exploratory analysis of MRD was carried out in genomic DNA (isolated from circulating tumor cells) or plasma DNA by clonoSEQ (Adaptive Biotechnologies).

At data cut-off, a total of 61 patients with R/R MCL had been enrolled

- Of these patients, all were included in the intent-to-treat (ITT) population, 60 received ≥1 dose of study medication and were included in the safety population, and 46 had an evaluable baseline biopsy and were included in the biomarker evaluable population (BEP).
- Notably, the majority of patients were heavily pretreated and refractory to BTKi-containing therapies at baseline (**Table 1**).

Table 1. Baseline characteristics in the safety population.

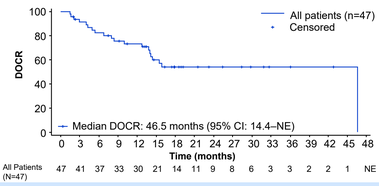
N (%) of patients in the safety population	n=60
Median age, years (range)	72 (41–86)
Male	44 (73.3)
Ann Arbor stage III/IV at study entry	52 (86.7)
Median number of prior lines of therapy, n (range)	2 (1–5)
Number of prior lines of therapy	
1	14 (23.3)
2	18 (30.0)
≥3	28 (46.7)
Prior BTKi therapy	33 (55.0)
Median time since last prior therapy, months (range)	2.4 (0.1–132.5)
Refractory to any prior therapy	50 (83.3)
Refractory to any prior BTKi	31 (51.7)
Refractory to last prior therapy	44 (73.3)
N (%) of patients in the BEP	**n=46**
≥1 high-risk histological feature	25 (53.0)
Blastoid morphology	5 (11.9)*
Ki-67 expression >50%	19 (41.3)
p53 expression >50%	9 (19.6)

*n=45.

High response rates and durable remissions were achieved

- Median follow-up in the ITT population was 24.2 months (range: 0–50).
- The overall response rate was 82% and CR rate was 77%. Median time to first response was 42 days (range: 29–164).
- At data cut-off, the median duration of CR (DOCR) was 46.5 months (95% confidence interval [CI]: 14.4–not estimable [NE]) and the event-free rate among complete responders was 73.3% at 12 months (95% CI: 60.3–86.2) (**Figure 2**).
- Median progression-free survival (PFS) was 18.0 months (95% CI: 11.3–NE) and median overall survival (OS) was NE (95% CI: 21.6–NE).
- Landmark analysis indicated that most patients who were in CR at end of treatment (EOT) were progression free and alive 18 months after the EOT (PFS rate: 71.8%; OS rate: 83.0%).

Figure 2. DOCR in the ITT population.



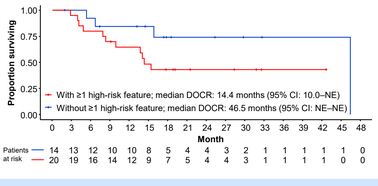
High response rates and durable remissions were also achieved in clinically and/or histologically defined high-risk subgroups (Table 2 and Figure 3)

Table 2. CR rates in subgroups of the ITT and BEP.

N (%) of patients achieving CR in subgroups of the ITT population	N=61
All patients (N=61)	47 (77)
Age (years)	
<70 (n=25)	19 (76)
≥70 (n=36)	28 (78)
Prior lines of therapy	
1 (n=15)	12 (80)
2 (n=18)	14 (78)
≥3 (n=28)	21 (75)
Prior BTKi exposure	
Yes (n=34)	24 (71)
No (n=27)	23 (85)
Refractory to last prior therapy	
Yes (n=45)	34 (76)
No (n=16)	13 (81)
N (%) of patients achieving CR in subgroups of the BEP	**n=46**
≥1 high-risk histological feature	
Yes (n=31)	20 (65)
No (n=15)	14 (93)
Blastoid morphology*	
Yes (n=5)	3 (60)
No (n=40)	30 (75)
Ki-67 expression >50%	
Yes (n=30)	20 (67)
No (n=16)	14 (88)
p53 expression >50%	
Yes (n=9)	6 (67)
No (n=37)	28 (76)

*n=45.

Figure 3. DOCR in patients with and without ≥1 high-risk feature in the BEP.



No new safety signals were reported (Table 3)

Table 3. Adverse event (AE) summary in the safety population.

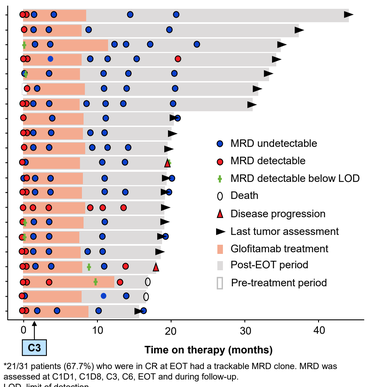
n (%)	N=60
Any AE	60 (100)
Gr 3–5 AE	48 (80.0)
Any SAE	47 (78.3)
Any Gr 5 (fatal) AE	9 (15.0)*
AE leading to withdrawal from glofitamab	5 (8.3)
Related to glofitamab	1 (1.7)
Any CRS†	42 (70.0)
Gr 3–4	7 (11.7)
Any ICANS	7 (11.7)‡
Gr 1	4 (6.7)
Gr 2	3 (5.0)

*COVID-19/COVID-19 pneumonia (n=5), post-acute COVID-19 syndrome (n=1), pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1); †CRS reported using ASTCT criteria according to Lee et al. 2019[3]; ‡three patients experienced glofitamab-related ICANS (Gr 1 confusional state [1000mg Gpt], Gr 2 disorientation [1000mg Gpt], and Gr 1 mental status changes [2,000 mg Gpt]); all were resolved and considered nonserious.
Gr, Grade; ICANS, immune effector cell-associated toxicity syndrome; SAE, serious adverse event.

MRD kinetics

- 14/15 (93.3%) patients with evaluable samples had undetectable MRD at C3 (**Figure 4**).
- Most patients who achieved undetectable MRD maintained molecular remissions after EOT (**Figure 4**).

Figure 4. Evolution of MRD over time.*



*21/31 patients (67.7%) who were in CR at EOT had a trackable MRD clone. MRD was assessed at C1D1, C1D8, C3, C6, EOT and during follow-up.
LOD, limit of detection.

Immune recovery after EOT

- Between 12–18 months after EOT, 4/10 (40%) patients with ongoing remissions and evaluable samples had B-cell counts above the lower limit of normal (LLN; ≥70cells/μL).
- Between 12–18 months after EOT, 9/10 (90%) patients with ongoing remissions and evaluable samples had IgG levels above the LLN (≥5g/L).

Conclusions

- Glofitamab induced high response rates and durable remissions in patients with R/R MCL, including those with high-risk disease characteristics.
- Notably, most patients who were in CR at EOT were progression free and alive 18 months after the EOT.
- Most responders rapidly achieved undetectable MRD, which was sustained after the EOT.
- B-cell recovery was observed starting from 12–18 months after EOT.
- GLOBRYTE (NCT06084936) is an ongoing, open-label, multicenter, randomized Phase III trial of glofitamab monotherapy versus rituximab (R) plus bendamustine or R plus lenalidomide that is currently recruiting patients with R/R MCL.

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1. Phillips, et al. ASCO 2024.
2. Cheson, et al. J Clin Oncol 2014;32:3059-67.
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Disclosures

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