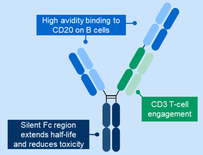
MCL-467

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma

Tycel Phillips,[1] Michael Dickinson,[2] Franck Morschhauser,[3] Emmanuel Bachy,[4] Michael Crump,[5] Marek Trněný,[6] Nancy L. Bartlett,[7] Jan Zaucha, [8] Tomasz Wrobel,[9] Fritz Offner,[10] Kathryn Humphrey,[11] Linda Lundberg,[12] James Relf,[11] Audrey Filezac de L'Etang,[12] David Carlile,[11] Ben Byrne,[11] Naseer Qayum,[11] Carmelo Carlo-Stella[13]

Summary

Glofitamab is a CD20xCD3 T-cell-engaging bispecific antibody with a 2:1 configuration for increased potency.



We present Phase I/II study (NCT03075696) results for glofitamab monotherapy in patients with relapsed/refractory mantle cell lymphoma (R/R MCL) and ≥1 prior therapy

A Phase III study with glofitamab monotherapy is planned for patients with R/R MCL

Although the patient population was heavily pre-treated and highly refractory to previous therapies, glofitamab induced high CR rates which were achieved early and were durable

Cytokine release syndrome (CRS), the most reported adverse event (AE), was manageable and predominantly low grade

[1]University of Michigan Medical School, Ann Arbor, MI, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [3]CHU Lille, Service des Maladies du Sang, Lille, France; [4]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France; [5]Princess Margaret Hospital, Toronto, ON, Canada; [6]1st Fac Medicine, Charles University, General Hospital, Prague, Czech Republic; [7]Siteman Cancer Center, Washington University, St. Louis, MO, USA; [8]Medical University of Gdańsk, Gdańsk, Poland; [9]Wroclaw Medical University, Wroclaw, Poland; [10]Dept Hematology Universitair Ziekenhuis, Gent, Belgium; [11]Roche Products Ltd, Welwyn Garden City, United Kingdom; [12]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [13]Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy

Background

- Patients with R/R MCL have a poor prognosis, especially those with progressive disease after Bruton's tyrosine kinase inhibitor (BTKi) therapy.[1]
- Chimeric antigen receptor (CAR) T-cell therapy is an option for patients with R/R MCL with prior BTK inhibitor treatment, but its use may be limited by logistical challenges.[2]
- Glofitamab is a CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate B cells, including those that cause malignant disease.[3]
- In an ongoing Phase I/II study (NCT03075696), glofitamab monotherapy with step-up dosing (SUD) and obinutuzumab pretreatment (Gpt) demonstrated high response rates and manageable CRS in patients with R/R MCL.[4]
  - Gpt reduces glofitamab receptor occupancy to mitigate CRS incidence and severity by competitive binding.[5]
- Here, we present updated efficacy and safety data for glofitamab monotherapy in patients with R/R MCL who had ≥1 prior therapy.

Methods

- Patients aged ≥18 years with histologically confirmed R/R MCL, ≥1 prior systemic therapy, and an Eastern Cooperative Oncology Group performance status ≤1 were included.
- Glofitamab was administered intravenously as a fixed-duration treatment to a maximum of 12 cycles; treatment schedule is presented in **Figure 1**.
- Safety was monitored with CRS events graded by ASTCT criteria.[6] Response rates were assessed per Lugano 2014 criteria.[7]

Figure 1. Glofitamab treatment schedule



*In the glofitamab SUD + 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose. C, cycle; D, Day.

Baseline characteristics

- At the clinical cut-off date (March 14, 2022), 37 patients had received glofitamab SUD (1000mg Gpt, n=16; 2000mg Gpt, n=21; **Table 1**).

Table 1. Baseline characteristics

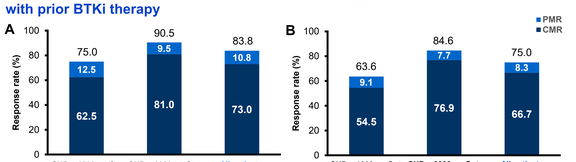
n (%) of patients unless stated		Glofitamab SUD + 1000mg Gpt (n=16)	Glofitamab SUD + 2000mg Gpt (n=21)	All patients (N=37)
Median age, years (range)		72.5 (57–83)	66.0 (41–84)	72.0 (41–84)
Male		13 (81.3)	14 (66.7)	27 (73.0)
Ann Arbor stage III–IV at study entry		16 (100)	18 (85.7)	34 (91.9)
MCL IPI score ≥6 at study entry		8 (50.0)	4 (19.0)	12 (32.4)
Prior therapy	Median time since last therapy, months (range)	2.20 (0.4–53.2)	1.40 (0.1–107.5)	1.90 (0.1–107.5)
	Prior lines of therapy, median (range)	3.0 (1–5)	2.0 (1–5)	3.0 (1–5)
	BTKi	11 (68.8)	13 (61.9)	24 (64.9)
	Lenalidomide	3 (18.8)	4 (19.0)	7 (18.9)
	CAR T	1 (6.3)	1 (4.8)	2 (5.4)
	ASCT	5 (31.3)	4 (19.0)	9 (24.3)
Refractory status*	Refractory to any prior therapy	15 (93.8)	18 (85.7)	33 (89.2)
	Refractory to first-line therapy	8 (50.0)	15 (71.4)	23 (62.2)
	Refractory to last prior therapy	12 (75.0)	15 (71.4)	27 (73.0)

*Patients who had no response or progression or relapse within 6 months of first anti-lymphoma therapy end date. Data on Ki-67 proliferation are pending. ASCT, autologous stem cell transplant; IPI, international prognostic index; PD, progressive disease; SD, stable disease.

Glofitamab monotherapy resulted in high response rates

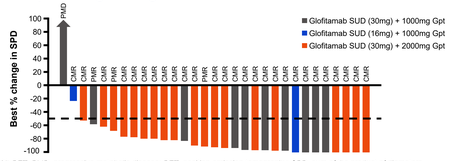
- After a median follow-up of 8.0 months, the overall response rate (ORR) and complete metabolic response (CMR) rate was 83.8% and 73.0%, respectively, across all patient groups (**Figure 2**).
- All glofitamab regimens investigated showed anti-tumor activity in R/R MCL (**Figure 3**).

Figure 2. Response rates by glofitamab regimen for (A) all patients* and (B) patients with prior BTKi therapy



*Efficacy results are reported for the secondary efficacy population (includes all patients who had a response assessment performed, withdrew early from treatment or study, or are on still on treatment at the time of their first scheduled response assessment). Prior lines of therapy ranged from 1–5 in both the responder and non-responder groups. PMR, partial metabolic response.

Figure 3. Best percentage change from baseline SPD*

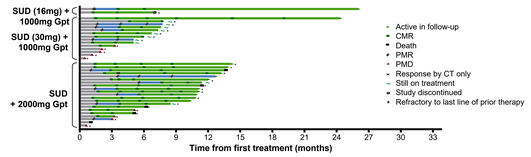


*Best response with PET. PMD, progressive metabolic disease; PET, position emission tomography; SPD, sum of the product of diameters.

Most responses were achieved early and were durable, with complete responses (CRs) maintained after cessation of therapy

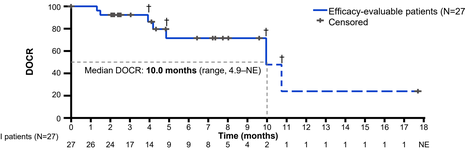
- Median time to first response was 51 days (range, 29–234); at first assessment, the CR rate was 48.6% and the ORR was 73.0% (**Figure 4**). No progressive disease was reported beyond end of treatment (EOT) in patients who had a response at EOT.
- Median duration of CR (DOCR) follow-up was 5.1 months (range, 0.0–18.0; **Figure 5**)
  - At data cut-off, 20/27 (74.1%) patients with CR remained in remission; with the four events due to COVID-19 deaths excluded, median DOCR was not reached and 87% of CRs were ongoing.

Figure 4. Time on glofitamab treatment and response in patients with R/R MCL



CT, computer tomography.

Figure 5. Kaplan-Meier plot for DOCR*



*DOCR is measured from the date of first complete response to the date of progression or death from any cause. †Death due to COVID. NE, not evaluable.

Higher Gpt (2000mg) was associated with lower incidences of serious AEs, Grade 3–4 AEs, and CRS

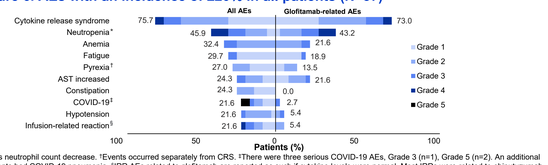
- Across all patients, no Grade 5 AEs related to glofitamab or AEs leading to treatment discontinuation were reported (**Table 2**)
- CRS was the most common AE overall (**Figure 6**); there were fewer CRS events, none of which were Grade 4, with the 2000mg Gpt regimen (**Figure 7**).

Table 2. Summary of AEs

n (%)	Glofitamab SUD + 1000mg Gpt (n=16)	Glofitamab SUD +2000mg Gpt (n=21)	All patients (N=37)
Any grade AE	16 (100)	21 (100)	37 (100)
Glofitamab related	16 (100)	19 (90.5)	35 (94.6)
Serious AE	13 (81.3)	16 (76.2)	29 (78.4)
Glofitamab related	12 (75.0)	11 (52.4)	23 (62.2)
Grade 3/4 AE	14 (87.5)	11 (52.4)	25 (67.6)
Glofitamab related	12 (75.0)	11 (52.4)	23 (62.2)
Grade 5 (fatal) AE˚	0	4 (19.0)	4 (10.8)
Glofitamab related	0	0	0
AE leading to treatment discontinuation	0	0	0
Deaths†	2 (12.5)	8 (38.1)	10 (27.0)

*COVID-19/pneumonia (n=3, days 154, 187 and 344), cardiac arrest (n=1, Day 29). †Reported deaths were considered unrelated to study treatment.

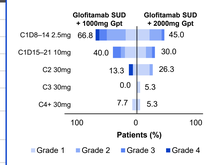
Figure 6. AEs with an incidence of ≥20% in all patients (N=37)



*Includes neutrophil count decrease. †Events occurred separately from CRS. ‡There were three serious COVID-19 AEs, Grade 3 (n=1), Grade 5 (n=2). An additional two patients had COVID-19 pneumonia. §IRR AEs related to glofitamab are reported as such if cytokine levels were normal. Most IRRs were related to obinutuzumab. AST, aspartate aminotransferase; IRR, infusion-related reaction.

Figure 7. CRS event summary and CRS by cycle, grade, and regimen

n (%) of patients with ≥1 AE unless stated	Glofitamab SUD + 1000mg Gpt (n=16)	Glofitamab SUD + 2000mg Gpt (n=21)	All patients (N=37)
Any CRS	14 (87.5)	14 (66.7)	28 (75.7)
Grade 1	4 (25.0)	7 (33.0)	11 (29.7)
Grade 2	6 (37.5)	5 (23.8)	11 (29.7)
Grade 3	2 (12.5)	2 (9.5)	4 (10.8)
Grade 4	2 (12.5)	0 (0.0)	2 (5.4)
Serious AE of CRS (any grade)	10 (62.5)	5 (23.8)	15 (40.5)
Median time to CRS onset, hours (range)	7.55 (4.4–14.0)	9.77 (5.0–20.8)	9.31 (4.4–20.8)
Tocilizumab for CRS management	11 (68.8)	6 (28.6)	17 (45.9)
Corticosteroid for CRS management	8 (50.0)	6 (28.6)	14 (37.8)



- One Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) event was reported for the Gpt (2000mg) cohort which resolved (**Table 3**).

Table 3. Other AEs of interest

AE, n (%)	All grades (N=37)	Grade ≥3 (N=37)
Infections and infestations	24 (64.9)	12 (32.4)*
Neutropenia	17 (45.9)	10 (27.0)
Febrile neutropenia	1 (2.7)	1 (2.7)
Tumor flare	5 (13.5)	0 (0.0)
Neurologic AEs	18 (48.6)	1 (2.7)
ICANS (derived)†	5 (13.5)‡	0 (0.0)‡
AEs leading to treatment discontinuation	0 (0.0)	0 (0.0)

*Includes one Grade 4 event (endocarditis) and three Grade 5 events (COVID-19, n=2; COVID-19 pneumonia, n=1). †Glofitamab-related neurologic AEs potentially consistent with ICANS; mental status changes (n=1), disorientation (n=1), confusional state, agitation and memory impairment (n=1), cognitive disorder and agitation (n=1), memory impairment and agitation (n=1, ongoing at CCOD). ‡CTCAE. CTCAE, common terminology criteria for AEs.

Conclusions

- Glofitamab monotherapy with fixed treatment duration of 12 cycles (approximately 8.3 months) induced high CR rates in heavily pretreated patients with MCL.
- CRs were achieved early and were durable.
- Glofitamab was well tolerated and there were no treatment discontinuations due to AEs.
- CRS events were manageable and were predominantly low grade
  - A higher dose of Gpt (2000mg) was associated with lower any grade and Grade ≥2 CRS events compared with a lower dose of Gpt (1000mg).
- A Phase III study with glofitamab monotherapy is planned for patients with R/R MCL.

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Disclosures

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