Glofitamab in Relapsed/Refractory Mantle Cell Lymphoma: Results From a Phase I/II Study

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ABSTRACT

PURPOSE Patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) have a poor prognosis. The phase I/II NP30179 study (ClinicalTrials.gov identifier: NCT03075696) evaluated glofitamab monotherapy in patients with R/R B-cell lymphomas, with obinutuzumab pretreatment (Gpt) to mitigate the risk of cytokine release syndrome (CRS) with glofitamab. We present data for patients with R/R MCL.

METHODS Eligible patients with R/R MCL (at least one previous therapy) received Gpt (1,000 or 2,000 mg) 7 days before the first glofitamab dose (single dose or split over 2 days if required). Glofitamab step-up dosing was administered once a day on days 8 (2.5 mg) and 15 (10 mg) of cycle 1, with a target dose of 16 or 30 mg once every 3 weeks from cycle 2 day 1 onward, for 12 cycles. Efficacy end points included investigator-assessed complete response (CR) rate, overall response rate (ORR), and duration of CR.

RESULTS Of 61 enrolled patients, 60 were evaluable for safety and efficacy. Patients had received a median of two previous therapies (range, 1-5). CR rate and ORR were 78.3% (95% CI, 65.8 to 87.9) and 85.0% (95% CI, 73.4 to 92.9), respectively. In patients who had received previous treatment with a Bruton tyrosine kinase inhibitor (n = 31), CR rate was 71.0% (95% CI, 52.0 to 85.8) and ORR was 74.2% (95% CI, 55.4 to 88.1). CRS after glofitamab administration occurred in 70.0% of patients, with a lower incidence in the 2,000 mg (63.6% [grade ≥2, 22.7%]) versus 1,000 mg (87.5%; grade ≥2, 62.5%) Gpt cohort. Four adverse events led to glofitamab withdrawal (all infections).

CONCLUSION Fixed-duration glofitamab induced high CR rates in heavily pretreated patients with R/R MCL; the safety profile was manageable with appropriate support.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Mantle cell lymphoma (MCL), a rare type of B-cell lymphoma comprising approximately 6% of all non-Hodgkin lymphomas,[1] is characterized by a variable disease course and the existence of both indolent and aggressive subtypes.[2] Chemoimmunotherapy remains the standard first-line treatment for patients with nonindolent MCL; however, recent data support a role for Bruton tyrosine kinase inhibitor (BTKi)–containing combinations as a first-line therapy.[3] Treatment of relapsed disease represents a clinical challenge, with decreasing duration of response (DoR) typically observed after each relapse.[4] Prognosis is particularly unfavorable in patients with progressive disease (PD) after treatment with BTKis.[5-8]

Chimeric antigen receptor (CAR) T-cell therapy and pirtobrutinib are the only approved therapies for patients with relapsed/refractory (R/R) MCL who have progressed after treatment with a BTKi; notably, there are no approved drugs that are administered with curative intent. The use of CAR T-cell therapy may be complicated by potentially severe toxicities, including high-grade immune effector cell–associated neurotoxicity syndrome (ICANS).[9-11] Furthermore, high production costs, logistical challenges, and the need for caregiver support and to remain close to the treatment center may limit patients' access to CAR T-cell therapy.[12,13]

Glofitamab is a CD20 × CD3 bispecific antibody with a novel 2:1 tumor-T-cell binding configuration that confers bivalent

CONTEXT

Key Objective

Treatment of relapsed/refractory (R/R) mantle cell lymphoma (MCL) remains a clinical challenge. This phase I/II NP30179 study investigated the efficacy and safety of glofitamab, a T-cell–engaging CD20 × CD3 bispecific antibody, for the treatment of patients with R/R MCL.

Knowledge Generated

Fixed-duration glofitamab monotherapy achieved high complete and overall response rates in heavily pretreated patients with R/R MCL, with durable responses beyond the end of treatment. The incidence and severity of adverse events (AEs) was consistent with the known safety profile of glofitamab, with cytokine release syndrome reported as the most common AE.

Relevance *(S. Lentzsch)*

These promising results support a planned phase III trial of glofitamab in patients with MCL who have received a Bruton tyrosine kinase inhibitor.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

binding to CD20 on B cells and monovalent binding to CD3 on T cells, leading to the engagement and redirection of T cells to eliminate malignant B cells.[14] Glofitamab is currently approved in >30 countries for the treatment of patients with R/R diffuse large B-cell lymphoma (DLBCL) after two or more previous therapies.[15-18]

In the phase I/II NP30179 trial (ClinicalTrials.gov identifier: NCT03075696), glofitamab monotherapy with obinutuzumab pretreatment (Gpt) demonstrated promising efficacy with frequent and durable complete responses (CRs), and a manageable safety profile (with appropriate support), in patients with R/R B-cell lymphomas, including MCL.[19,20] Cytokine release syndrome (CRS) risk was reduced with the use of Gpt and glofitamab step-up dosing (SUD). Obinutuzumab mitigates CRS through direct competition with glofitamab for the CD20 binding site, independent depletion of B cells, and reduction of overall antigen burden.[14] Patients with MCL have a two-fold higher clearance of obinutuzumab at the start of treatment than patients with other B-cell lymphomas.[21] A higher Gpt dose may be important to further reduce the risk of CRS in patients with MCL; therefore, two different Gpt doses were investigated in this study.

We report data from the phase I/II NP30179 study in patients with R/R MCL who received either 1,000 or 2,000 mg Gpt before glofitamab monotherapy.

METHODS

Study Design and Patient Population

NP30179 is a multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with Gpt in patients with R/R B-cell lymphomas, including MCL. Dose-escalation data from this study have been reported previously,[19] including for six patients with MCL who are described herein.

Patients age 18 years and older with histologically confirmed MCL and at least one previous treatment regimen were included. Full eligibility criteria are listed in the Data Supplement (online only).

All enrolled patients provided written informed consent. The study was approved by each center's ethics committee or institutional review board, and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council for Harmonization, and applicable laws.

Treatment

Patients received 1,000 or 2,000 mg intravenous Gpt on cycle (C) 1 day (D) 1, 7 days before the first glofitamab dose. Gpt was administered as a single dose or split over 2 days for the management of infusion-related reactions (IRRs) if required. SUD with intravenous glofitamab was administered once a day on C1D8 (2.5 mg) and C1D15 (10 mg), with a target dose of 16 mg (dose-escalation phase) or 30 mg once every 3 weeks from C2D1 onward for 12 cycles (approximately 8.5 months). Accrual to the 16- and 30-mg target dose cohorts was sequential. Patients were hospitalized to receive glofitamab SUD on C1D8 and C1D15, and for 24 hours after infusion. For patients who experienced a CRS event during C1, hospitalization was mandatory for 36 hours after completion of the 16- or 30-mg dose on C2D1. Patients who repeated SUD because of toxicity were considered to have received an extra cycle (Data Supplement, Methods). Premedications to reduce the risk of IRRs and CRS are detailed in the Data Supplement.

TABLE 1. Baseline Characteristics in the Overall Populations and in Patients With and Without Previous BTKi Treatment

Characteristic	Previous BTKi (n = 31)	No Previous BTKi (n = 29)	All Patients (N = 60)
Age, years, median (range)	70.0 (41-84)	72.0 (52-86)	72.0 (41-86)
Male sex, No. (%)	23 (74.2)	21 (72.4)	44 (73.3)
ECOG PS, No. (%)			
0	14 (45.2)	14 (48.3)	28 (46.7)
1	17 (54.8)	15 (51.7)	32 (53.3)
Ann Arbor stage at study entry, No. (%)			
I	1 (3.2)	2 (6.9)	3 (5.0)
II	2 (6.5)	3 (10.3)	5 (8.3)
III	5 (16.1)	6 (20.7)	11 (18.3)
IV	23 (74.2)	18 (62.1)	41 (68.3)
MCL IPI score ≥6, No. (%)	7 (22.6)	8 (27.6)	15 (25.0)
Extranodal disease present, No. (%)	20 (64.5)	19 (65.5)	39 (65.0)
Bulky disease, cm, No. (%)			
>6	7 (22.6)	6 (20.7)	13 (21.7)
>10	2 (6.5)	3 (10.3)	5 (8.3)
Time since last previous therapy to first study treatment, months, median (range)	1.3 (0.1-53.2)	7.4 (1.1-132.5)	2.4 (0.1-132.5)
Time since last anti-CD20 therapy to first study treatment, months, median (range)	15.1 (0.7-159.0)	25.1 (1.4-132.5)	16.3 (0.7-159.0)
No. of previous lines of therapy, median (range)	3.0 (1-5)	2.0 (1-4)	2.0 (1-5)
Previous therapy for lymphoma, No. (%)			
CAR T-cell therapy	1 (3.2)	1 (3.4)	2 (3.3)
ASCT	7 (22.6)	9 (31.0)	16 (26.7)
Refractory status, No. (%)			
Any previous therapy	30 (96.8)	20 (69.0)	50 (83.3)
First-line therapy	17 (54.8)	14 (48.3)	31 (51.7)
Last previous therapy	27 (87.1)	17 (58.6)	44 (73.3)
Progress or relapse ≤24 months after first-line treatment start, No. (%)	17 (54.8)	14 (48.3)	31 (51.7)
Ki-67 index, No. (%)			
High (≥30%)	16 (51.6)	12 (41.4)	28 (46.7)
Low (<30%)	4 (12.9)	2 (6.9)	6 (10.0)
Missing	5 (16.1)	8 (27.6)	13 (21.7)
Not done	6 (19.4)	7 (24.1)	13 (21.7)
TP53-mutated, No. (%)			
Missing[a]	16 (51.6)	12 (41.4)	28 (46.7)
Mutation abnormality	5 (16.1)	0	5 (8.3)
Unknown[b]	9 (29.0)	17 (58.6)	26 (43.3)
Wild-type	1 (3.2)	0	1 (1.7)

Abbreviations: ASCT, autologous stem-cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; MCL, mantle cell lymphoma.
[a]*TP53* mutation status was not reported for these patients.
[b]*TP53* mutations status reported as unknown.

End Points and Assessments

Efficacy end points included investigator-assessed CR rate and overall response rate (ORR) by Lugano 2014 criteria,[22] duration of CR (DoCR), DoR, progression-free survival (PFS), and overall survival (OS). Safety end points were assessed using Common Terminology Criteria for Adverse Events version 4.03. CRS grades were derived according to the American Society for Transplantation and Cellular Therapy criteria.[23] Efficacy- and safety-evaluable populations are defined in the Data Supplement.

Tumor assessments using computed tomography (CT) and positron emission tomography-CT were performed at

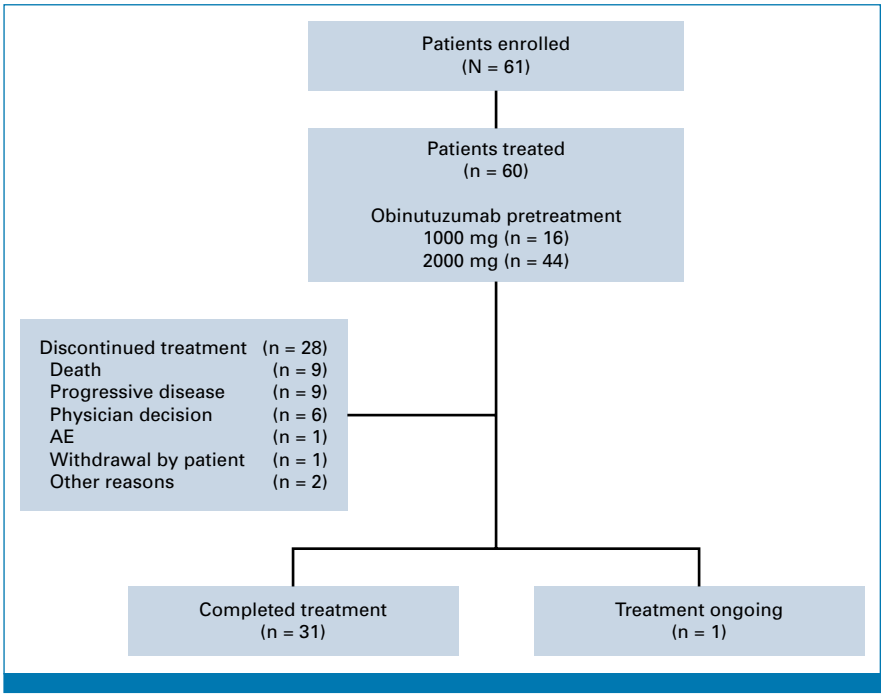

FIG 1. Patient disposition. AE, adverse event.

screening; after C2, C5, C8, and end of treatment; then every 3 months until PD.

Statistical Analyses

The MCL population was enrolled primarily to evaluate the efficacy of the recommended phase II dosing schedule for glofitamab and optimize the safety of this regimen. Comparisons between the two Gpt dose cohorts are descriptive. PFS was defined as the time from first study drug to the first occurrence of PD or death. Patients who did not experience an event were censored at their last adequate response assessment. OS was defined as the time from first study drug to death from any cause. Patients still alive at the clinical cutoff date were censored at the date of last follow-up. Further information on the statistical analyses conducted are included in the Data Supplement and have been previously reported.[19]

RESULTS

Patients

As of September 4, 2023, 61 patients with R/R MCL were enrolled. Sixty patients had received study treatment: 16 received 1,000 mg Gpt (glofitamab target dose: 16 mg, n = 2; 30 mg, n = 14) and 44 received 2,000 mg Gpt (all 30 mg

TABLE 2. Efficacy in the Overall Population (efficacy-evaluable population), and in Patients With and Without Previous BTKi Treatment

	Glofitamab SUD		All Patients		
Efficacy (INV-assessed)	1,000 mg Gpt Cohort (n = 16)	2,000 mg Gpt Cohort (n = 44)	Previous BTKi (n = 31)	No Previous BTKi (n = 29)	All Patients (N = 60)
Complete response rate					
No. (%)	11 (68.8)	36 (81.8)	22 (71.0)	25 (86.2)	47 (78.3)
95% CI	41.3 to 89.0	67.3 to 91.8	52.0 to 85.8	68.3 to 96.1	65.8 to 87.9
Partial response rate					
No. (%)	1 (6.3)	3 (6.8)	1 (3.2)	3 (10.3)	4 (6.7)
95% CI	0.2 to 30.2	1.4 to 18.7	0.1 to 16.7	2.2 to 27.4	1.9 to 16.2
Overall response rate					
No. (%)	12 (75.0)	39 (88.6)	23 (74.2)	28 (96.6)	51 (85.0)
95% CI	47.6 to 92.7	75.4 to 96.2	55.4 to 88.1	82.2 to 99.9	73.4 to 92.9

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; Gpt, obinutuzumab pretreatment; INV, investigator; SUD, step-up dosing.

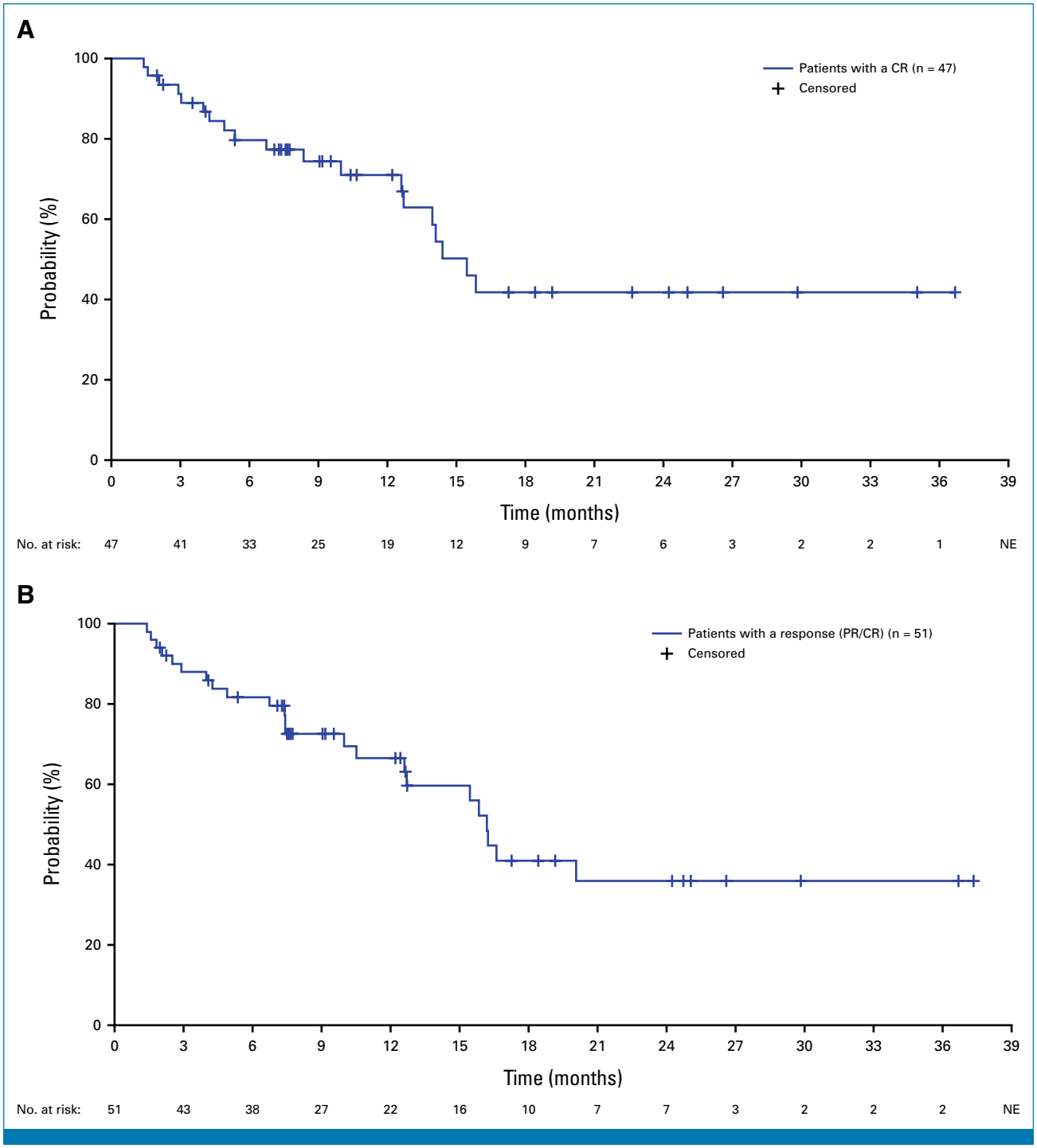

FIG 2. (A) Duration of CR, (B) duration of response, and (C) time on treatment. CR, complete response; CT, computed tomography; NE, not estimable; PD, progressive disease; PR, partial response. (continued on following page)

glofitamab target dose). Median age was 72.0 (range, 41-86) years, 53.3% of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, and 86.7% had Ann Arbor stage III/IV disease. The median number of previous lines of therapy received was two (range, 1-5); 51.7% had previously received a BTKi (58.1% of whom received it as their last previous therapy); and 73.3% were refractory to their last line of previous therapy (Table 1; Data Supplement, Table S1). Twenty-two patients (36.7%) received previous treatment with bendamustine, nine within the previous 12 months, and four within the previous 6 months.

At data cutoff, 31/60 (51.7%) patients had completed planned study treatment and remained on study, 28/60 (46.7%) had discontinued treatment early, and one patient was on study treatment (Fig 1).

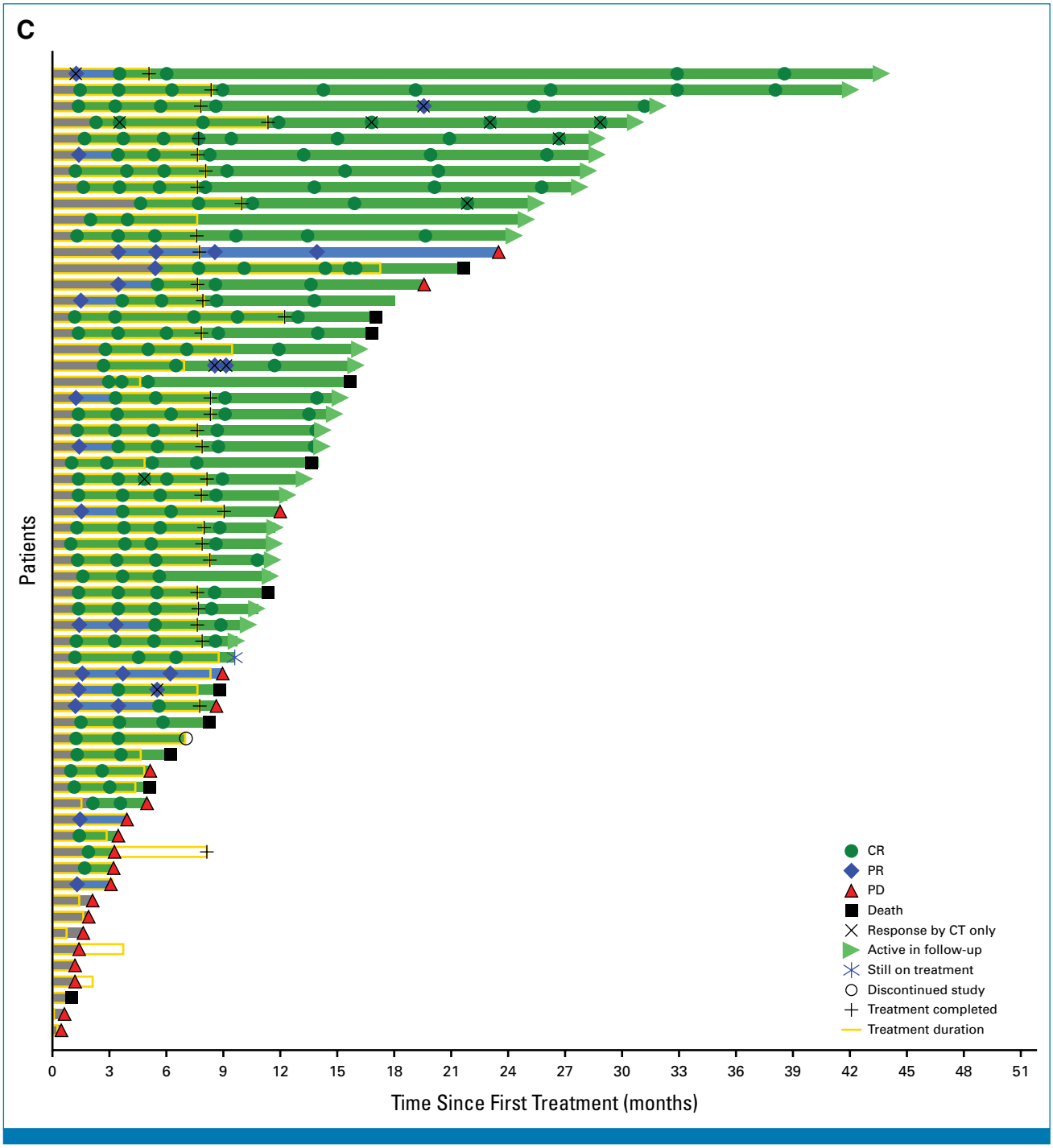

FIG 2. (Continued).

The median duration of glofitamab treatment was 7.4 (range, 0.0-17.0) months; the median number of glofitamab cycles received was 12 (range, 1-13; Data Supplement, Table S2).

Efficacy

After a median follow-up of 19.6 (range, 0-39) months, 60 patients were efficacy-evaluable (one patient received no study treatment). Investigator-assessed CR rate and ORR were 78.3% (95% CI, 65.8 to 87.9) and 85.0% (95% CI, 73.4 to 92.9), respectively (Table 2). Median time to first response was 42.0 (range, 29.0-164.0) days. Eleven patients converted from partial response (PR) to CR eight at the second response assessment and three at the third response assessment (two after consecutive PRs, one after a PR at the second response assessment only).

Median DoCR was 15.4 months (n = 47; 95% CI, 12.7 to not estimable [NE]), with a 12-month DoCR rate of 71.0% (95% CI, 56.8 to 85.2); median DoR was 16.2 months (n = 51; 95%

TABLE 3. PFS and Durability of Response in the Overall Population and in Patients With Previous BTKi Treatment

Efficacy (INV-assessed)	Previous BTKi (n = 32)	All Patients (N = 61)
Median PFS, months	8.6	16.8
95% CI	3.4 to 15.6	8.9 to 21.6

Efficacy (INV-assessed)	Previous BTKi (n = 22)	All Patients (n = 47)
Median DoCR, months	12.6	15.4
95% CI	5.4 to NE	12.7 to NE

Efficacy (INV-assessed)	Previous BTKi (n = 23)	All Patients (n = 51)
Median DoR, months	12.6	16.2
95% CI	7.4 to NE	12.6 to NE

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; DoCR, duration of complete response; DoR, duration of response; INV, investigator; NE, not estimable; PFS, progression-free survival.

CI, 12.6 to NE), with a 12-month DoR of 66.6% (95% CI, 52.3 to 80.8; Fig 2; Table 3; Data Supplement, Table S3). Median PFS was 16.8 months (95% CI, 8.9 to 21.6); 12-month PFS rate was 56.7% (95% CI, 43.2 to 70.1; Table 3; Data Supplement, Table S3). Median OS was 29.9 months (95% CI, 17.0 to NE); 12-month OS rate was 73.9% (95% CI, 62.4 to 85.4; Data Supplement, Table S3). At the time of analysis, 22 patients (36.7%) had died, most due to PD (n = 7) or COVID-19 (n = 7; Data Supplement, Table S4). All patients who died due to COVID-19 had achieved a CR, and six remained in remission at the time of death.

Among patients who had received previous BTKi treatment (n = 31), the CR rate was 71.0% (95% CI, 52.0 to 85.8) and ORR was 74.2% (95% CI, 55.4 to 88.1; Table 2). Median DoCR was 12.6 months (n = 22; 95% CI, 5.4 to NE); median DoR was 12.6 months (n = 23; 95% CI, 7.4 to NE). Median PFS was 8.6 months (95% CI, 3.4 to 15.6; Table 3). The CR rate and ORR in BTKi-naïve patients (n = 29) were 86.2% (95% CI, 68.3 to 96.1) and 96.6% (95% CI, 82.2 to 99.9), respectively (Table 2). Response rates were similar in patients who received a BTKi as their last previous therapy (n = 18; ORR, 72.2% [all CRs]) or as any other previous line (n = 13; CR, 69.2%; ORR, 76.9%). Efficacy data for patients with high-risk disease characteristics (high Ki-67 and *TP53* mutational status) are reported in the Data Supplement (Table S5). In patients who had received previous bendamustine, CR rate and ORR were 68.2% (95% CI, 45.1 to 86.1) and 77.3% (95% CI, 54.6 to 92.2), respectively. Of nine patients who received bendamustine within the previous 12 months, seven achieved a response (CR, n = 5; PR, n = 2). Two patients had received previous CAR T-cell therapy, one achieved a CR and one a PR.

TABLE 4. Summary of Safety in the Overall Population and by Cohort (safety-evaluable population)

	Glofitamab SUD, No. (%)		
AE	1,000 mg Gpt Cohort (n = 16)	2,000 mg Gpt Cohort (n = 44)	All Patients (N = 60)
Any AE	16 (100.0)	44 (100.0)	60 (100.0)
Grade 3/4 AE	13 (81.3)	26 (59.1)	39 (65.0)
SAE	15 (93.8)	32 (72.7)	47 (78.3)
AE leading to glofitamab withdrawal[a]	1 (6.3)	3 (6.8)	4 (6.7)
AE leading to glofitamab dose interruption	10 (62.5)	26 (59.1)	36 (60.0)
AE related to glofitamab	16 (100.0)	39 (88.6)	55 (91.7)
AE related to glofitamab leading to glofitamab withdrawal	0	1 (2.3)	1 (1.7)
AE related to glofitamab leading to glofitamab dose interruption	7 (43.8)	15 (34.1)	22 (36.7)
Grade 3/4 AEs related to glofitamab	13 (81.3)	22 (50.0)	35 (58.3)
SAE related to glofitamab	12 (75.0)	24 (54.5)	36 (60.0)
Grade 5 AE	2 (12.5)	7 (15.9)	9 (15.0)
Grade 5 AE related to glofitamab	0	0	0

Abbreviations: AE, adverse event; Gpt, obinutuzumab pretreatment; SAE, serious adverse event; SUD, step-up dosing.
[a]AEs leading to glofitamab withdrawal: COVID-19, n = 2; laryngitis, n = 1; otitis media, n = 1; pneumonia, n = 1; sinusitis, n = 1.

TABLE 5. Summary of CRS Events and Their Management in the Overall Population and by Cohort (safety-evaluable population)

	Glofitamab SUD, No. (%)		
CRS Event/Management	1,000 mg Gpt Cohort (n = 16)	2,000 mg Gpt Cohort (n = 44)	All Patients (N = 60)
Any CRS	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
Serious AE of CRS	11 (68.8)	12 (27.3)	23 (38.3)
Fatal CRS event	0	0	0
CRS management			
Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Corticosteroid	8 (50.0)	10 (22.7)	18 (30.0)
Tocilizumab and corticosteroids	6 (37.5)	7 (15.9)	13 (21.7)
Low flow oxygen	6 (37.5)	4 (9.1)	10 (16.7)
ICU stay	5 (31.3)	4 (9.1)	9 (15.0)
Fluid support	4 (25.0)	5 (11.4)	9 (15.0)
Single-pressor therapy	4 (25.0)	3 (6.8)	7 (11.7)
Multiple-pressor therapy	2 (12.5)	0	2 (3.3)
High-flow oxygen	1 (6.3)	0	1 (1.7)
Mechanical ventilation	1 (6.3)	0	1 (1.7)

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; Gpt, obinutuzumab pretreatment; ICU, intensive care unit; SUD, step-up dosing.

Safety

In the safety-evaluable population (N = 60), all patients experienced ≥one adverse event (AE; Table 4), most commonly CRS (70.0%), neutropenia (38.3%), COVID-19 (31.7%), and pyrexia (31.7%; Data Supplement, Table S6). Grade 3/4 AEs were reported in 65.0% of patients, most commonly neutropenia (23.3%), pneumonia (11.7%), anemia (11.7%), and CRS (11.7%). Serious AEs were reported in 78.3% of patients, most commonly CRS (36.7%) and infections (33.3%). Eight patients (13.3%) had a grade 5 infection AE (n = 1 septic shock; n = 5 COVID-19/COVID-19 pneumonia; n = 1 post-acute COVID-19 syndrome; n = 1 pneumonia). One additional patient died due to COVID-19 outside of the AE reporting window. One other grade 5 AE, considered unrelated to glofitamab, was reported (cardiac arrest [2,000 mg Gpt] occurring after CRS resolution). AEs leading to glofitamab dose interruption were reported in 36/60 (60.0%) patients (most commonly COVID-19/COVID pneumonia [15.0%], neutropenia [15.0%], CRS [10.0%], and pneumonia [10.0%]), and 4/60 (6.7%) patients were withdrawn from glofitamab treatment due to AEs (all infections). Safety data by Gpt cohort are reported in the Data Supplement (Results).

CRS events were reported in 87.5% of patients in the 1,000 mg Gpt cohort (grade 1, 25.0%; grade 2, 37.5%; grade 3, 12.5%; grade 4, 12.5%) and in 63.6% in the 2,000 mg Gpt cohort (grade 1, 40.9%; grade 2, 15.9%; grade 3, 6.8%; Table 5). No CRS-related deaths were reported. One patient (1,000 mg Gpt) died due to PD while a CRS event was ongoing; all other events had resolved. CRS events occurred primarily during C1 and C2 (Data Supplement, Table S7).

After the first glofitamab dose (C1D8-C1D14), CRS events were reported in 29 (48.3%) patients (1,000 mg Gpt, n = 10/16 [62.5%]; 2,000 mg Gpt, n = 19/44 [43.2%]). Median time to CRS onset after the start of glofitamab infusion was 9.7 (range, 3.4-46.3) hours, and median duration of CRS was 49.0 (range, 2.0-692.7) hours (Data Supplement, Table S7). After the second glofitamab dose (C1D15-C1D21), CRS events were reported in 20 (33.3%) patients (1,000 mg Gpt, n = 6/16 [37.5%]; 2,000 mg Gpt, n = 14/44 [31.8%]). Median time to CRS onset was longer (20.6 [range, 6.7-34.3] hours) and median duration of CRS was shorter (24.6 [range, 1.0-625.5] hours) than after the first glofitamab dose.

CRS events were mainly managed symptomatically, with tocilizumab in 22/60 (36.7%) patients (1,000 mg Gpt, 11/16 [68.8%]; 2,000 mg Gpt, 11/44 [25.0%]) and corticosteroids in 18/60 (30.0%) patients (1,000 mg Gpt, 8/16 [50.0%]; 2,000 mg Gpt, 10/44 [22.7%]). Both tocilizumab and corticosteroid therapy were required by 13/60 (21.7%) patients (1,000 mg Gpt, 6/16 [37.5%]; 2,000 mg Gpt, 7/44 [15.9%]). Intensive care unit (ICU) admission for CRS management was required for 9/60 (15.0%) patients (1,000 mg Gpt, 5/16 [31.3%]; 2,000 mg Gpt, 4/44 [9.1%]; Table 5). IRRs were reported in 10 patients (16.7%) and considered related to Gpt and glofitamab in eight (13.3%) and two patients (3.3%), respectively.

Neurologic AEs potentially consistent with ICANS were reported in seven patients (11.7%; grade 1, n = 5; grade 2, n = 2). Events were considered glofitamab-related in three patients (grade 1 confusional state [1,000 mg Gpt], grade 2 disorientation [1,000 mg Gpt], and grade 1 mental status changes [2,000 mg Gpt]); all were resolved and considered nonserious.

DISCUSSION

In patients with heavily pretreated R/R MCL, fixed-duration glofitamab monotherapy achieved a high CR rate (78.3%) and ORR (85.0%), with durable responses (median DoCR, 15.4 months; median DoR, 16.2 months; upper bounds were NE). The median PFS was 16.8 months. When patients with COVID-19 were censored, the median DoR and PFS were 20.0 months and 19.6 months, respectively. High response rates were observed in both BTKi-naïve patients (CR, 86.2%; ORR, 96.6%) and patients who had received previous BTKi therapy (CR, 71.0%; ORR, 74.2%), supporting future evaluation of bispecific antibodies before and after BTKi therapy. Patients treated with previous BTKis had poorer outcomes compared with patients who were BTKi-naïve. However, these populations are not directly comparable because of baseline differences. High response rates were also observed in patients who had received previous bendamustine (CR, 68.2%; ORR, 77.3%).

Cross-trial comparisons should be made with caution because of differences in study populations and trial designs; however, the CR rate achieved with glofitamab compares favorably with those observed with therapies approved for R/R MCL, pirtobrutinib (20%) and lenalidomide (5%),[24,25] and is similar to those achieved with the CAR T-cell therapies brexucabtagene autoleucel (68%)[26] and lisocabtagene maraleucel (72%).[27] The median PFS of 16.8 months (19.6 months when censoring COVID-19) reported here with fixed-duration glofitamab compares favorably with pirtobrutinib (7.4 months) and lenalidomide (8.7 months), both administered until PD, and was similar to that observed with lisocabtagene maraleucel (15.3 months).[24,25,27] A longer median PFS (25.8 months) was reported with brexucabtagene autoleucel.[26]

Several novel regimens are under investigation in R/R MCL. In BTKi-naïve patients with R/R MCL, CR rates of 54% and 56% were reported with ibrutinib plus venetoclax and ibrutinib plus lenalidomide and rituximab, respectively (both administered until PD); median PFS was 31.9 and 16.0 months, respectively.[28,29]

The safety profile reported with glofitamab monotherapy was manageable with appropriate support; the incidence and severity of AEs were consistent with its known safety profile.[19,20] AEs were predominantly managed with interruption of glofitamab treatment; the rate of withdrawal from glofitamab due to AEs was low. Seven patients died due to COVID-19/COVID-19 pneumonia (all had achieved a CR; 6/7 remained in remission at the time of death). We acknowledge that B-cell–depleting agents have been associated with higher rates of COVID-19 complications, and factors such as treatment era and vaccination status affect complication rates after COVID-19 infection.[30] As a fixed-duration treatment, glofitamab may be less likely to induce infection-related complications in the longer term versus bispecific antibodies administered until progression. CRS was the most common AE (70.0%), with most events occurring during C1 and C2. No grade 5 (fatal) events were reported. Overall, 36.7% of patients received tocilizumab for CRS management and 15.0% were admitted to ICU.

Although the trial was not designed to compare rates between the two obinutuzumab doses, 2,000 mg Gpt (*v* 1,000 mg Gpt, respectively) appeared to be associated with a lower incidence of any-grade CRS events (63.6% *v* 87.5%), grade ≥2 CRS events (22.7% *v* 62.5%), a longer time to CRS onset, and a shorter duration of CRS. Therefore, the recommended phase II dosing schedule was confirmed as 2,000 mg Gpt on C1D1, followed by glofitamab 2.5 mg on C1D8, 10 mg on C1D15, to a target dose of 30 mg from C2D1 onward for a maximum of 12 cycles, in line with the glofitamab target dose approved for use in patients with R/R DLBCL.[15-18]

Neurologic AEs potentially consistent with ICANS were uncommon with glofitamab, reported in seven (11.7%) patients (all grade 1/2). Events were considered glofitamab-related in three patients (all resolved). The incidence of neurologic AEs with the CAR T-cell therapies brexucabtagene autoleucel and lisocabtagene maraleucel has been reported to be 63% and 31%, respectively, with grade 3/4 events in 31% and 9% of patients.[9,27]

Although all patients in the study have finished treatment, the upper limits on DoR were NE. Our ability to comment on long-term end points, such as survival, is therefore limited. Further potential limitations include the single-arm design, modest sample size, selection of fitter patients (ECOG PS 0 or 1), and limited data on *TP53* deletions and/or mutations.

In conclusion, fixed-duration treatment with off-the-shelf glofitamab monotherapy achieved high CR rates in heavily pretreated patients with R/R MCL, including patients previously treated with a BTKi. Responses were highly durable beyond end of treatment, and a fixed treatment duration (approximately 8.5 months) may help reduce the treatment burden for patients with R/R MCL. The safety profile of glofitamab was predictable and manageable with appropriate support, with a lower rate of CRS events observed with 2,000 mg versus 1,000 mg Gpt. Glofitamab represents a new active therapy for patients with R/R MCL. A phase III study (ClinicalTrials.gov identifier: NCT06084936) will further evaluate the efficacy and safety of glofitamab monotherapy versus rituximab with investigator's choice of either bendamustine or lenalidomide for patients with R/R MCL previously treated with a BTKi.

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