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ORIGINAL REPORT

Obinutuzumab (GA101) Monotherapy in Relapsed/Refractory Diffuse Large B-Cell Lymphoma or Mantle-Cell Lymphoma: Results From the Phase II GAUGUIN Study

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ABSTRACT

Purpose
Obinutuzumab (GA101), a type II, glycoengineered, humanized anti-CD20 monoclonal antibody, was superior to rituximab in human diffuse large B-cell lymphoma (DLBCL) and mantle-cell lymphoma (MCL) xenograft models. In phase I of our study, obinutuzumab (GA101) exhibited encouraging activity but no clear dose-response relationship, and few patients had aggressive histologies. The efficacy and safety of two doses of obinutuzumab (GA101) were explored in our randomized phase II trial in patients with heavily pretreated DBLCL and MCL.

Patients and Methods
Patients were randomly assigned to receive eight cycles of obinutuzumab (GA101) either as a flat dose of 400 mg for all infusions (days 1 and 8 of cycle 1; day 1 of cycles 2 to 8) or 1,600 mg on days 1 and 8 of cycle 1 and 800 mg on day 1 of cycles 2 to 8.

Results
Forty patients were enrolled: 21 patients in the 400/400-mg treatment arm (DLBCL, n = 10; MCL, n = 11) and 19 patients in the 1,600/800-mg arm (DLBCL, n = 15; MCL, n = 4). End-of-treatment response was 28% (32% and 24% in the 1,600/800-mg and 400/400-mg study arms, respectively). Best overall response rates were 37% in the 1,600/800-mg arm and 24% in the 400/400-mg study arm (DLBCL, eight [32%] of 25 patients; MCL, four [27%] of 15 patients). Five (20%) of 25 rituximab-refractory patients exhibited treatment response, including four of 12 in the 1,600/800-mg group. The most common adverse events were infusion-related reactions (IRRs), which were manageable. Three patients had grade 3/4 IRRs. Grade 3/4 neutropenia was seen in only one patient.

Conclusion
Obinutuzumab (GA101) 1,600/800 mg achieves early steady-state concentration and clinical activity with an acceptable safety profile in relapsed/refractory DLBCL and MCL, supporting further exploration.

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INTRODUCTION

Despite the proven clinical efficacy of first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with diffuse large B-cell lymphoma (DLBCL),[1] some patients' disease relapse after first-line therapy or are refractory. Relapsed/refractory disease is associated with poor prognosis,[2-5] even relapsed DLBCL treated with high-dose therapy and autologous stem-cell transplantation.[6] Though rituximab is not currently approved for patients with mantle-cell lymphoma (MCL), rituximab-based induction and maintenance therapies have been shown to improve survival.[7] Despite these improvements, MCL remains incurable. There is, therefore, an unmet medical need for therapies that will further improve outcomes for patients with DLBCL and MCL.

The success of rituximab in treating CD20-positive malignancies has fueled development of novel anti-CD20 antibodies, with different functional activity and potential improvement on rituximab's efficacy. Anti-CD20 antibodies have been divided into two subtypes based on their mechanism

of action and mode of CD20 binding. Type I antibodies, such as rituximab and most anti-CD20 antibodies in clinical development (eg, ocrelizumab, veltuzumab, ofatumumab), act via multiple mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), and direct induction of cell death.[8-10] The glycoengineered type II antibody obinutuzumab (GA101) induces cell death and ADCC.[8,11,12] Obinutuzumab (GA101) –induced cell death differs from type I–induced apoptosis by being associated with actin reorganization and homotypic adhesion,[13] followed by induction of direct cell death via pathways distinct from classical apoptosis. These pathways are independent of BCL2 overexpression and caspase activation and involve lysosomal rupture[13] and reactive oxygen species.[14] Obinutuzumab (GA101) has been glycoengineered by reduction in fucose content of the Fc region, which increases its affinity for Fcγ receptors on effector cells and confers greater ADCC compared with nonglycoengineered antibodies.[15]

Obinutuzumab (GA101) has been shown to be superior to rituximab in preclinical studies using whole-blood depletion assays and human DLBCL and MCL xenograft models.[15] Evaluation of obinutuzumab (GA101) in patients with CD20-positive malignancies has demonstrated good tolerability, encouraging efficacy in the phase I (dose-escalating) part of the GAUSS study (BO21003, NCT00576758) and phase I of our study (GAUGUIN). In the GAUSS study, 32% of patients with heavily pretreated CD20-positive disease responded to four once-weekly, fixed doses of 200-2,000 mg of obinutuzumab (GA101). The maximum-tolerated dose was not identified.[16] In the dose-finding, phase I part of the GAUGUIN study, 43% of 21 heavily pretreated patients with non-Hodgkin's lymphoma (NHL) achieved disease response to eight 21-day cycles of obinutuzumab (GA101).[17] However, neither phase I study showed a clear dose-response relationship. Phase I pharmacokinetic (PK) data indicated that obinutuzumab (GA101) serum concentrations increased with higher doses and that a dose of at least 400/800 mg was required to saturate CD20 (and minimize drug clearance).[18] The 400/400-mg dose was considered to be the minimally effectively dose. Consequently, this and the highest dose explored in the phase I studies were selected for evaluation in the randomized phase II portion of the GAUGUIN study. In both the GAUSS study and phase I of the GAUGUIN study, most patients had indolent NHL; there was therefore a need to assess obinutuzumab (GA101) activity in a larger population with aggressive subtypes. We report in this article results from phase II of the GAUGUIN study in patients with heavily pretreated DLBCL and MCL treated with obinutuzumab (GA101).

PATIENTS AND METHODS

Patients

This was an open-label, multicenter, randomized, phase II study designed to investigate the efficacy and safety of two doses of obinutuzumab (GA101) monotherapy in patients with CD20-positive aggressive NHL for whom no therapy of higher priority was available.

Patients with DLBCL or MCL were randomly assigned to receive eight cycles of obinutuzumab (GA101) as a flat dose of 400/400 mg or 1,600/800 mg. There were to be $\geq$ 10 patients with DLBCL and 10 with MCL, but without stratification by dose arm. With 20 patients per dose group, the response rate would be estimated with a precision of 14% (80% CIs), assuming a response rate of 40%.

Eligible patients were ages 18 years or older, with relapsed/refractory CD20-positive DLBCL or MCL, at least one bidimensionally measurable lesion ($>$ 1.5 cm), life expectancy of more than 12 weeks, and an Eastern Cooperative Oncology Group performance status of 0 to 2.

Patients had to have adequate renal (creatinine clearance $>$ 50 mL/min) and liver function (ALT and AST $\leq$ 2.5$\times$ upper limit of normal) and normal hematologic parameters (platelets $\geq 75 \times 10^9$/L, neutrophils $\geq 1.5 \times 10^9$/L, hemoglobin $\geq$ 10 g/dL, unless owing to lymphoma). Patients positive for hepatitis B (DNA, surface, or core antigen), hepatitis C (serum antibody), or HIV were excluded.

The study was reviewed and approved by ethics review boards of the relevant institutions and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Treatment

Patients were randomly assigned to receive eight cycles of obinutuzumab (GA101) as a flat dose of 400/400 mg or 1,600/800 mg. Obinutuzumab (GA101) was administered on days 1 and 8 of cycle 1 and day 1 of subsequent 21-day cycles, for a total of nine infusions. In the 400/400-mg group, patients received 400 mg for all infusions (total dose, 3,600 mg). In the 1,600/800-mg group, patients received 1,600 mg for both infusions in cycle 1, then 800 mg for subsequent cycles (total dose, 8,800 mg). Obinutuzumab (GA101) was diluted to 10 mg/mL, administered at an initial rate of 50 mg/hour, and increased by 50 mg/hour every 30 minutes in the absence of infusion-related reactions (IRRs) to a maximum of 400 mg/hour. Patients were premedicated with oral acetaminophen or paracetamol (650 to 1,000 mg) and an antihistamine 30 minutes before first infusion. For subsequent infusions, the antihistamine could be omitted if no IRRs requiring medication or infusion interruption were seen with first infusion. Premedication with corticosteroids was recommended for patients at high risk of severe IRRs (eg, those with high circulating lymphocyte counts or those previously requiring corticosteroid premedication before rituximab infusion). Patients who had experienced severe IRRs with rituximab infusion were excluded.

Treatment with granulocyte colony-stimulating factor was permitted for patients with severe neutropenia. General prophylactic use of granulocyte colony-stimulating factor was not permitted unless indicated by standard institutional guidelines. Antibiotic prophylaxis was permitted as applicable.

Assessments

The primary end point was overall response rate (ORR), which was defined in two ways: end-of-treatment response (ETR) rate (assessed 4 weeks after last obinutuzumab (GA101) infusion) and best ORR (BOR, assessed at any time before new lymphoma treatment). Tumor response was assessed by computed tomography scan and International Workshop criteria.[19] Confidence interval analyses of response rates for the total aggressive NHL population and DLBCL and MCL subpopulations were prespecified in the analysis plan. Secondary end points were complete response (CR) and partial response (PR) rates, progression-free survival (PFS), safety, and PK. Safety, including full blood counts, serum chemistry, and renal and hepatic function, was assessed at screening, on days 1 and 8 of cycle 1, and on day 1 of subsequent cycles. Adverse events (AEs) were graded per National Cancer Institute Common Terminology Criteria for AEs, version 3.0.

For PK analyses, serial serum samples were taken after both infusions in cycle 1, before and after each infusion in cycles 2 to 7, and after final infusion (cycle 8). Blood samples were taken for genotypic analysis of FcγR polymorphisms at baseline.

RESULTS

Forty patients with aggressive NHL (DLBCL or MCL) were recruited between December 2008 and June 2009 from 11 centers in France; 21 patients were randomly assigned to the 400/400-mg study arm and 19 patients were randomly assigned to the 1,600/800-mg arm. All patients received at least one dose of obinutuzumab (GA101) and were included in the efficacy and safety analyses. Patients were not stratified for histologic disease type/subtype and were thus unevenly distributed between treatment

Table 1. Patient Characteristics

Characteristic	400/400 mg (n = 21)		600/800 mg (n = 19)		Total (N = 40)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	70		72		71	
Range	43-80		22-85		22-85	
Histology						
DLBCL	10		15		25	
MCL	11		4		15	
Percent male patients		62		74		68
IPI at diagnosis						
No. of patients*	19		18		37	
Low	8	42	11	61	19	51
Medium	9	47	4	22	13	35
High	2	11	3	17	5	14
Ann Arbor stage at diagnosis						
No. of patients*	21		17		38	
I	1	5	1	6	2	5
II	3	14	3	18	6	16
III	6	29	1	6	7	18
IV	11	52	12	71	23	61
Active bone marrow disease						
No. of patients*	14		15		29	
Yes	5	36	2	13	7	24
No	9	64	13	87	22	76
SPD mm^2						
Median	5,096		1,950		3,519	
Range	513-20,032		160-11,760		160-20,032	
At least 1 lesion ≥ 5 cm	14	67	6	32	20	50
FcγRIIa genotype						
No. of patients*	19		15		34	
131HH	7	37	5	33	12	35
131HR	8	42	5	33	13	38
131RR	4	21	5	33	9	26
FcγRIIIa genotype						
No. of patients*	15		13		28	
158FF	6	40	3	23	9	32
158FV	8	53	8	62	16	57
158VV	1	7	2	15	3	11
Prior autologous stem-cell transplantation	2	10	6	32	8	20
Prior therapies						
Median	4		3		3	
Range	1-17		1-6		1-17	
Prior rituximab therapies						
Median	2		2		2	
Range	1-6		1-4		1-6	
Refractory to last therapy	12	57	9	47	21	53
Response to last therapy						
CR/CRu	8	38	8	42	16	40
PR	5	24	3	16	8	20
SD	2	10	3	16	5	13
PD	5	24	4	21	9	23
Unknown	1	5	1	5	2	5
Duration of last response, months						
No. of patients*	13		11		24	
< 6	5	38	2	18	7	29
6-12	4	31	4	36	8	33
> 12	4	31	5	45	9	38
Rituximab refractory†	13	62	12	63	25	63

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; MCL, mantle-cell lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of product diameters.

*Data are not available for all 40 patients.

†No response or response lasting < 6 months to a prior rituximab-containing therapy.

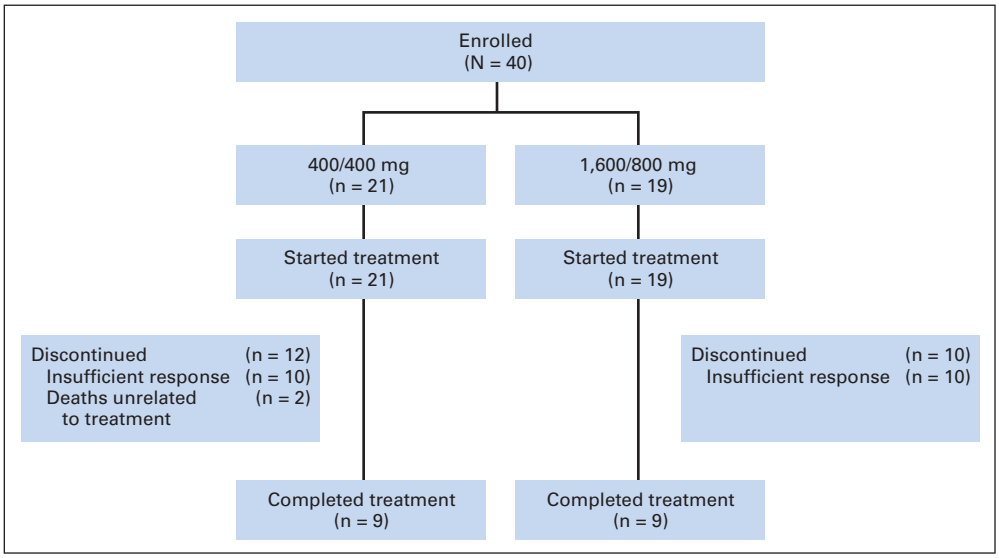

Fig 1. CONSORT diagram.

arms (Table 1). All patients were previously treated with rituximab, and 25 patients were rituximab-refractory (no response or response lasting < 6 months to a previous rituximab-containing therapy).

Eighteen patients completed treatment: nine patients in the 1,600/800-mg arm and nine in the 400/400-mg arm (Fig 1). Nine and six patients in the 400/400-mg and 1,600/800-mg treatment arms, respectively, received corticosteroids before infusion, with two and three patients, respectively, receiving corticosteroids for symptomatic treatment of IRRs. The most common reason for discontinuation was insufficient response (20 patients). One patient with a number of preexisting concurrent conditions (eg, hypertension, arrhythmia, morbid obesity, exertional dyspnea, atrial fibrillation, cardiac insufficiency) randomly assigned to the 400/400-mg arm died 8 days after first infusion from cardio-respiratory arrest that was probably as a result of ventricular arrhythmia in the context of recurrent bacteremia. No IRRs were associated with first infusion of obinutuzumab (GA101), and the second infusion was delayed because of the recurrence of bacteremia. The investigator considered the patient's bacteremia and cardio-respiratory arrest to be unrelated to obinutuzumab (GA101). An additional two patients died during follow-up, one patient in the 400/400-mg arm from allograft-mediated stem cell toxicity 10 months after last treatment dose and one patient in the 1,600/800-mg arm. This latter patient withdrew from treatment because of progressive disease and received further lymphoma treatment, but died 220 days after the last dose of obinutuzumab (GA101) as a result of respiratory distress. In Figure 1, the reason for this patient's discontinuation is listed as "insufficient response" versus "death."

Efficacy

All 40 patients were evaluable for response at end of treatment, with an ETR rate of 28% (CR, 5%). Six patients showed disease response in the 1,600/800 mg arm (all PRs; ORR, 32%; 80% CI, 18% to 49%); five patients showed disease response, including two CRs and one unconfirmed CR (CRu), in the 400/400-mg arm (ORR, 24%; 80% CI, 12% to 40%; Table 2).

BOR was 30% (CR, 13%) for all patients. In the 1,600/800-mg arm, BOR was 37% (seven of 19 patients; 80% CI, 22% to 54%), with one patient with DLBCL whose disease had a CR at day 80 but relapsed by end of treatment. Two patients in the 1,600/800-mg arm (both with DLBCL) improved from PR to CR at 3 and 8 months after end of treatment, for a best CR rate of 16% in this dose group (three of 19 patients). BOR was the same as the ETR rate in the 400/400-mg group.

Among DLBCL patients, BOR was 32% (five of 15 patients in the 1,600/800 mg group; three of 10 in the 400/400-mg group; 80% CI, 20% to 47%), with three patients with CRs in the 1,600/800-mg group and one with CRu in the 400/400-mg group. In patients with MCL, the

Table 2. Response Rates

Responders	400/400 mg (n = 21)		1,600/800 mg (n = 19)		Total (N = 40)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
ETR	5	24	6	32	11	28
CR	2	10	0	0	2	5
CRu	1	5	0	0	1	3
PR	2	10	6	32	8	20
BOR	5	24	7	37	12	30
CR	2	10	3	16	5	13
CRu	1	5	0	0	1	3
PR	2	10	4	21	6	15
DLBCL subset						
No. of patients	10		15		25	
ETR	3	30	4	27	7	28
CR/CRu	1	10	0	0	1	4
BOR	3	30	5	33	8	32
CR/CRu	1	10	3	20	4	16
MCL subset						
No. of patients	11		4		15	
ETR	2	18	2	50	4	27
CR/CRu	2	18	0	0	2	13
BOR	2	18	2	50	4	27
CR/CRu	2	18	0	0	2	13

Abbreviations: BOR, best overall response; CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; ETR, end-of-treatment response; MCL, mantle-cell lymphoma; PR, partial response.

Table 3. ETR by Baseline *FcγR* Subtypes

Subtype	400/400 mg			1,600/800 mg				
		Patients With Response			Patients With Response			
	No. of Patients	No. of Patients	%	No. of Patients	No. of Patients	%	OR	95% CI
FcγRIIa								
131HH	7	1	14.3	5	2	40.0	4.00	0.25 to 63.95
131HR	8	2	25.0	5	2	40.0	2.00	0.18 to 22.06
131RR	4	1	25.0	5	1	20.0	0.75	0.03 to 17.51
FcγRIIIa								
158FF	6	1	16.7	3	0		0.00	0.00 to > 1,000
158FV	8	3	37.5	8	4	50.0	1.67	0.23 to 12.22
158VV	1	0		2	1	50.0	> 100.00	0.00 to > 1,000

Abbreviations: ETR, end-of-treatment response; OR, odds ratio.

BOR was 27% (two of four patients in the 1,600/800-mg group; two of 11 in the 400/400-mg group), with two with CRs in the 400/400-mg group.

Among rituximab-refractory patients, ETR rate was 16% (four of 25 patients; DLBCL, three of 18; MCL, one of seven). One other DLBCL patient showed disease response during follow-up for a BOR of 20%. Four of the five rituximab-refractory patients whose disease responded at any time were in the 1,600/800-mg group.

In the 1,600/800-mg and 400/400-mg groups, responses were seen across different FcγR subtypes (FcγRIIa H/H, H/R, and R/R; FcγRIIIa V/V, V/F, and F/F). Half of the patients with a heterozygous genotype (V/F) responded, although the numbers in each group were too small to draw conclusions (Table 3).

Duration of Response and PFS

Median response duration was 9.8 months. For the five patients with DLBCL in the 1,600/800-mg arm who experienced disease response, response durations were 3.1, 5.8, and 19.5 months for three patients. One patient's disease was still in response at 26.9+ months, and one patient was censored after receiving additional radiotherapy while in PR at 3.1 months. For the three patients with DLBCL whose disease responded to treatment in the 400/400-mg arm, response durations were 6.3, 8.6, and 9.8 months. One patient with MCL had an ongoing response for 30.5+ months. The remaining three patients with MCL whose disease showed response had response durations of 29.8, 11.2, and 5.5 months.

After a median observation time of 14.2 months (range, 0.3 to 36.1 months), there was no significant difference in PFS between treatment arms. Median PFS was 2.7 months in the 1,600/800-mg arm (range, 0.2 to 32.7 months) and 2.6 months in the 400/400-mg arm (range, 0.3 to 32.7 months; Fig 2).

Of the patients who were rituximab-refractory, four had a response duration longer than 9 months: three patients in the 1,600/800-mg arm (DLBCL, one patient; MCL, one patient) and one patient with DLBCL in the 400/400-mg arm with response durations of 26.9+, 19.5, 29.8, and 9.8 months, respectively.

Safety

The most common AEs were IRRs, which were experienced by 81% of patients in the 400/400-mg arm and 68% in the 1,600/800-mg arm (Table 4). A majority of IRRs were grade 1/2. Three patients experienced grade 3/4 IRRs, two of whom were in the 400/400-mg arm and one of whom was in the 1,600/800-mg arm. The majority of patients were lymphopenic at baseline owing to their disease and previous treatments. Other grade 3/4 AEs occurring in more than one patient were thrombocytopenia (400/400-mg arm, n = 3), anemia (400/400-mg arm, n = 3; 1,600/800-mg arm, n = 1), cardiac failure (400/400-mg arm, n = 2), and tumor lysis syndrome (TLS; two patients with MCL in the 400/400-mg arm). Both patients with TLS had high circulating lymphocyte counts. All thrombocytopenic events occurred in patients with MCL, two of whom had low baseline platelet counts (48,000 and 81,000 platelets/μL). Only one grade 3/4 AE of neutropenia was reported (laboratory abnormalities were only reported when considered clinically relevant, ie, those requiring dose modification or treatment), with no infections of significance. A total of 19 grade 3/4 AEs experienced by 13 patients were considered to be related to treatment, five of which (26.3%) were in the 1,600/800-mg arm. Fourteen patients experienced 21 serious AEs during treatment, seven of which were considered to be treatment-related (three IRRs; two events of TLS; one bradycardia; one pyrexia). There were no treatment-related deaths.

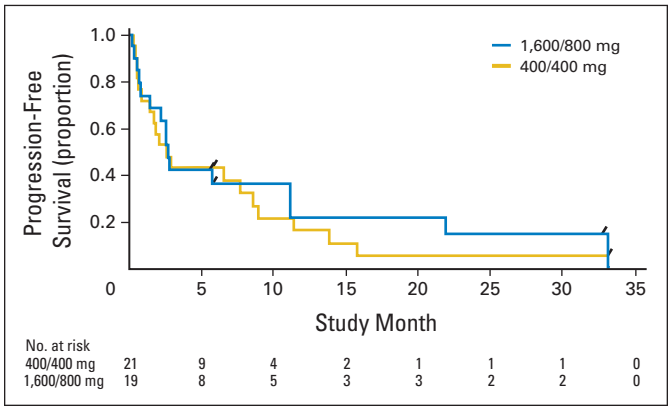

Fig 2. Progression-free survival by treatment cohort.

Table 4. AEs

AE	All Patients (N = 40)				Grade 3/4 by Cohort			
	All Grades		Grade 3/4		400/400 mg (n = 21)		1,600/800 mg (n = 19)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
IRR	30	75	3	8	2	10	1	5
Asthenia	7	18	1	3	1	5	—	
Anemia	6	15	4	10	3	14	1	5
Lymphopenia	6	15	6	15	3	14	3	16
Diarrhea	5	13	0		0		0	
Abdominal pain	4	10	0		0		0	
Constipation	4	10	0		0		0	
Cough	3	8	0		0		0	
Pain in extremity	3	8	0		0		0	
Peripheral edema	3	8	0		0		0	
Thrombocytopenia	3	8	3	8	3	14	0	
Tumor lysis syndrome	3	8	2	5	2	10	0	

NOTE. AEs occurring between first dose and last dose plus 28 days. Only events occurring in > two patients (all grades) or > 5% (grade 3/4) are listed.
Abbreviations: AE, adverse event; IRR, infusion-related reaction.

PKs

The number of patients with available PK data varied over time (cycle 1: 400/400-mg arm, 17 patients; 1,600/800-mg arm, 22 patients; cycle 8: 400/400-mg, 11; 1,600/800-mg, 19). In the 1,600/800-mg arm, serum concentrations of obinutuzumab (GA101) increased up to cycle 2 when steady-state seems to have been reached. In the 400/400-mg arm, serum concentrations of obinutuzumab (GA101) were lower, continued to increase between cycles 2 and 8, and did not reach steady-state (Fig 3).

B-Cell Depletion

Median baseline CD19-positive counts were 0.090×10^9/L in the 400/400-mg arm and 0.037×10^9/L in the 1,600/800-mg arm. Median CD19-positive cell counts decreased similarly during treatment in both arms. A total of 34 (89%) of 38 patients had a decrease in CD19-positive cell count to less than 5% of baseline and 40 of (100%) 40 had a CD19-positive cell count less than 0.04×10^9/L. Six patients experienced grade 3/4 lymphopenia (400/400-mg arm, three patients; 1,600/800-mg arm, three patients), Of the nine patients with available B-cell values more than 6 months after treatment, one had normal B-cell recovery to $\geq 0.07 \times 10^9$/L at 702 days after last obinutuzumab (GA101) dose. The other patients' disease progressed before B-cell recovery.

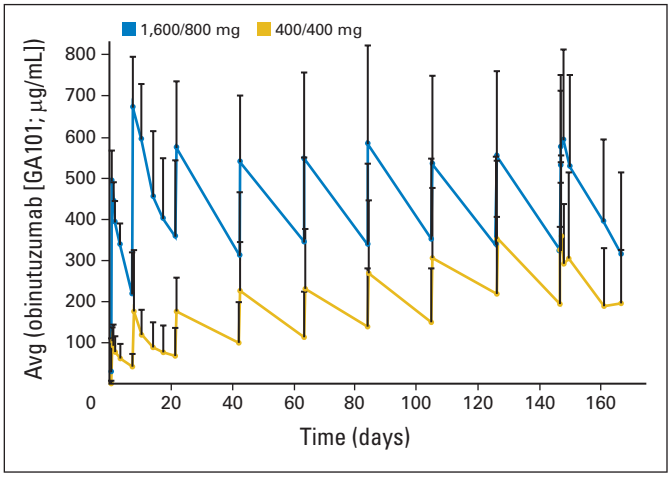

Fig 3. Serum concentrations of obinutuzumab (GA101) during the study. Avg, mean serum obinutuzumab (GA101) concentration.

DISCUSSION

In this phase II study, obinutuzumab (GA101) demonstrated encouraging efficacy in patients with previously treated DLBCL and MCL, with an ETR rate of 28% (32% and 24% in the 1,600/800-mg and 400/400-mg arms, respectively) and a BOR of 30% (37% and 24%, respectively). The BOR was 32% in patients with DLBCL and 27% in patients with MCL. In the MCL subpopulation, two of four patients responded to 1,600/800-mg obinutuzumab (GA101). In rituximab-refractory patients, BOR was 20%, with 12% CR/CRu. For the 1,600/800-mg study arm, the BOR was 33%, with 25% CR/CRu. Median response duration for all patients was 9.8 months, with three patients experiencing responses lasting longer than two years (MCL, n = 2; DLBCL, n = 1). Although numbers were small, median response duration in rituximab-refractory patients was longer than 6 months (ie, longer than their previous response, if any, to a rituximab-containing regimen). Median PFS was similar between dose groups. AEs were manageable and more common in the 400/400-mg arm. There were few grade 3/4 AEs. One patient had grade 3/4 neutropenia. Grade 3/4 IRRs occurred in three patients (400/400-mg arm, two patients; 1,600/800-mg arm, one patient).

In patients with DLBCL, the importance of achieving steady-state serum antibody concentrations early in treatment and maintaining exposure over a prolonged period has recently been suggested for rituximab.[20,21] In our study, higher obinutuzumab (GA101) serum concentrations were seen in the 1,600/800-mg group, with steady-state reached by cycle 2. Although less pronounced than in a parallel study conducted in patients with indolent NHL,[22] overall responses were numerically higher in the high-dose cohort and in the subset of rituximab-refractory patients treated in this group. The imbalance of

histologic subtypes and tumor burden between treatment arms possibly contributed to this nonstatistically determined higher response rate in the high-dose cohort. Patient numbers are too small to draw firm conclusions on the impact of dose on CR/CRu rates in both histologic subsets.

The challenges in treating patients with relapsed/refractory, aggressive subtypes of NHL are reflected in the lower response rates relative to patients with indolent disease. In our study of patients whose disease relapsed or failed after receiving a rituximab-containing regimen, obinutuzumab (GA101) response rates were comparable with those in trials of rituximab-naive patients with relapsed/refractory DLBCL (ORR, 37%) or MCL (ORR, 33% to 38%) treated with single-agent rituximab,[23-25] in which median time to progression ranged from 7.0 months (MCL)[24] to 8.2 months (DLBCL and MCL).[23] Response rates were also higher than those patients in a phase II study examining ofatumumab monotherapy in patients with pretreated DLBCL (ORR, 11%), none of whom were rituximab-refractory; the median PFS was 2.5 months.[26] In our study, median PFS in the 1,600/800-mg arm was 2.7 months.

Given the limited treatment options available for relapsed DLBCL and MCL, combining obinutuzumab (GA101) with other investigational agents may improve outcomes. Agents of possible interest to combine include the PI3 kinase inhibitor CAL-101,[27] lenalidomide,[28] inhibitors of Bruton tyrosine kinase[29] and mTOR,[30] anti-CD19 immunoconjugate SAR3419,[31] or agents such as vincristine that may potentiate obinutuzumab (GA101) –induced lysosome destabilization.[32] Some of these agents appear highly active in MCL, but obinutuzumab (GA101) achieves as good or better response rates in DLBCL, including rituximab-refractory DLBCL.

Our results demonstrate that obinutuzumab (GA101) monotherapy has promising activity in heavily pretreated DLBCL and MCL, warranting further study in both subtypes. Overall PK and efficacy data support further exploration of a higher obinutuzumab (GA101) dose. PK simulations have shown that use of 1,000 mg obinutuzumab (GA101) with an additional dose in cycle 1 on day 15 could achieve a PK profile similar to the 1,600/800-mg regimen used in this study.[33] On the basis of the combined phase I/II results and PK modeling, a flat dose of 1,000 mg, with three doses in cycle 1 (on days 1, 8, and 15) and one dose on day 1 of subsequent cycles, will be combined with CHOP in the GOYA study (NCT01287741) of patients with DLBCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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