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ORIGINAL REPORT

Ofatumumab As Single-Agent CD20 Immunotherapy in Fludarabine-Refractory Chronic Lymphocytic Leukemia

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ABSTRACT

Purpose
New treatments are needed for patients with fludarabine- and alemtuzumab-refractory (FA-ref) chronic lymphocytic leukemia (CLL) or patients with fludarabine-refractory CLL with bulky (> 5 cm) lymphadenopathy (BF-ref) who are less suitable for alemtuzumab treatment; these groups have poor outcomes with available salvage regimens. Ofatumumab (HuMax-CD20) is a human monoclonal antibody targeting a distinct small-loop epitope on the CD20 molecule. We conducted an international clinical study to evaluate the efficacy and safety of ofatumumab in patients with FA-ref and BF-ref CLL.

Patients and Methods
Patients received eight weekly infusions of ofatumumab followed by four monthly infusions during a 24-week period (dose 1 = 300 mg; doses 2 to 12 = 2,000 mg); response by an independent review committee (1996 National Cancer Institute Working Group criteria) was assessed every 4 weeks until week 24 and then every 3 months until month 24.

Results
This planned interim analysis included 138 treated patients with FA-ref (n = 59) and BF-ref (n = 79) CLL. The overall response rates (primary end point) were 58% and 47% in the FA-ref and BF-ref groups, respectively. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48% of patients, respectively. Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. The most common adverse events during treatment were infusion reactions and infections, which were primarily grade 1 or 2 events. Hematologic events during treatment included anemia and neutropenia.

Conclusion
Ofatumumab is an active, well-tolerated treatment providing clear clinical improvements for fludarabine-refractory patients with very poor-prognosis CLL.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by progressive accumulation of mature B cells in the blood, lymph nodes, spleen, liver, and bone marrow and remains incurable with standard therapies. Fludarabine is a cornerstone of treatment and is most effective in combination regimens.[1-5] Patients who become refractory to fludarabine-based regimens have low response rates to salvage therapy and poor survival outcomes.[6,7] The CD52 monoclonal antibody (mAb) alemtuzumab is indicated as a single-agent therapy in CLL, producing a 33% response rate in fludarabine-refractory patients.[8] However, low response rates are generally seen with alemtuzumab monotherapy in relapsed/refractory patients with bulky (> 5 cm) lymph node involvement.[8-13] Patients with fludarabine-refractory CLL also refractory to alemtuzumab (FA-ref) or less suitable for alemtuzumab as a result of bulky lymphadenopathy (BF-ref) have a poor prognosis.[6,7] Therefore, new effective and well-tolerated treatments are needed for these patients.

The CD20 mAb rituximab, combined with fludarabine and cyclophosphamide, has substantially improved outcomes for patients with CLL.[2,5,14,15] However, single-agent, standard-dose rituximab has limited activity in relapsed/refractory CLL.[16,17] Higher response rates were seen with dose-intense rituximab (up to 2,250 mg/m^2), but refractoriness to

fludarabine was associated with a low response rate (20% in fludarabine-refractory patients *v* 56% in fludarabine-sensitive patients; $P = .02$).[18]

Ofatumumab (HuMax-CD20) is a human mAb that binds a distinct epitope composed of both small and large loops on the CD20 molecule.[19] Ofatumumab induces killing of a panel of tumor B-cell lines and primary tumor cells via activation of complement- and antibody-dependent, cell-mediated cytotoxicity in vitro.[20,21] Ofatumumab demonstrates increased binding of C1q and more potent complement-dependent cytotoxicity than rituximab, even in cells with low CD20 expression levels, including freshly isolated CLL cells and complement-resistant B-cell lines. The potent complement-dependent cytotoxicity with ofatumumab may be a result of the close proximity of the small-loop binding site to the cell surface, potentially leading to more effective deposition of complement on the cell surface.[19-22] In a phase I/II study, patients with relapsed or refractory CLL were treated with four weekly doses of single-agent ofatumumab (dose 1 = 500 mg; doses 2 to 4 = 2,000 mg). The overall response rate (ORR) was 50%, median duration of response was 3.7 months, median time to next CLL therapy was 12 months, and treatment was well tolerated.[23,24]

We conducted an international, multicenter study of ofatumumab in patients with FA-ref and BF-ref CLL. Here we report a planned interim analysis demonstrating efficacy, clinical improvement, and safety of single-agent ofatumumab.

PATIENTS AND METHODS

Patients

Patients (age ≥ 18 years) with active CLL (1996 National Cancer Institute Working Group [NCI-WG] criteria)[25] indicated for treatment, tumor immunophenotype of $CD5^+/20^+/23^+$, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and life expectancy of ≥ 6 months were eligible for enrollment. There were no restrictions based on blood counts or transfusion requirements. Patients were required to be refractory to at least one fludarabine-containing regimen and either refractory to at least one alemtuzumab-containing regimen (FA-ref) or considered less suitable for alemtuzumab as a result of bulky (> 5 cm) lymphadenopathy (BF-ref). Bulky lymphadenopathy was confirmed either by physical examination or computed tomography scan at screening. Refractoriness to fludarabine (at least two cycles) and alemtuzumab (at least 12 doses) was defined as failure to achieve at least partial response (PR) by 1996 NCI-WG criteria or disease progression during treatment or within 6 months of the last dose of each agent.

Exclusion criteria included CLL therapy within 4 weeks or autologous stem-cell transplantation within 6 months of study initiation, allogeneic stem-cell transplantation, Richter's transformation or CNS involvement, active infectious disease requiring systemic treatment, clinically significant cardiac disease, or positive hepatitis B serology. All patients provided signed informed consent at enrollment. Protocol, amendments, consent forms, and patient information were approved by health authorities and local independent ethics committees or institutional review boards. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. This study is registered at ClinicalTrials.gov (NCT00349349).

Study Design and Treatment

This is an international, single-arm study. Patients received eight weekly intravenous infusions of ofatumumab, followed by four monthly infusions (dose 1 = 300 mg; doses 2 to 12 = 2,000 mg). Patients received acetaminophen 1,000 mg and cetirizine 10 mg (or equivalent) before infusions. Patients also received glucocorticoid (prednisolone 100 mg or equivalent) before infusions 1, 2, and 9; if initial infusions were well tolerated, the glucocorticoid dose could be reduced to less than 100 mg for other infusions. Anti-infective prophylaxis was not mandated.

Baseline assessments included physical examination, hematology, biochemistry, evaluation of constitutional symptoms, ECOG performance status, prior treatments, and prognostic factors. Disease status and response were assessed (physical examination and blood counts) every 4 weeks until week 28 and every 3 months thereafter until month 24. After month 24, patients were monitored at 3-month intervals for survival and B-cell counts. Monitoring continued until the B-cell counts reached baseline level or above, alternative CLL therapy was initiated, or month 48 was reached.

Efficacy

The primary end point was ORR based on objective response (including complete response, nodular PR, and PR, defined by the 1996 NCI-WG criteria[25]) during the 24-week period from the start of treatment. Responses were assessed by an independent review committee (IRC). In accordance with the 1996 NCI-WG criteria, responses must have been maintained for ≥ 2 months, and computed tomography scans were not included for response assessment. Secondary end points included duration of response (time from the initial response to progression or death) and the following events calculated from time of first ofatumumab infusion: time to response, progression-free survival (PFS), and overall survival (OS).

Safety Evaluations

Severity of adverse events (AEs) was graded by investigators according to the NCI Common Terminology Criteria for Adverse Events (version 3.0). Serious AEs were monitored from the time informed consent was given until month 48 or until alternative CLL therapy was initiated. Major infections were defined as those requiring hospitalization for at least 48 hours and occurring during or within 4 weeks of completing treatment. Early deaths were defined as those occurring within 8 weeks from the start of treatment.

Blood samples were drawn at screening and at all visits during the study period (screening to month 24) for blood chemistry and hematology and at screening, week 12, and months 9, 12, 18, and 24 for evaluation of human antihuman antibodies (HAHAs). Blood chemistry and hematology samples were analyzed at central laboratories (Bio-Analytical Research Corporation, Lake Success, NY) in the United States and in Europe, and HAHA was analyzed at Charles River Laboratories (Margate, United Kingdom).

Statistical Analysis

This planned interim analysis was triggered when the primary end point data became available for 66 patients in the FA-ref group. Assuming a 30% ORR, data from 66 patients (per patient group) provide a two-sided exact 99% CI to exclude a 15% ORR (at a significance level of 1%) with 63% power. For the final primary end point analysis, 100 patients correspond to an increase of the statistical power to 92%. In the interim analysis, a superiority analysis (the 99% CI for ORR excludes 15%) and a futility analysis (the conditional power under the alternative hypothesis < 10%) were performed for both patient groups. The independent data monitoring committee (including an independent statistician) notified the sponsor that the criteria for futility or superiority had been met. Evaluation of all end points was based on the full analysis set, including all patients exposed to ofatumumab.

Duration of response, PFS, and OS were evaluated using Kaplan-Meier estimates. An exploratory analysis was conducted to evaluate the association between response and OS using a landmark analysis[26] at week 12. AEs and clinical safety data were summarized using descriptive statistics.

RESULTS

Patient Characteristics

Enrollment began on June 13, 2006; patients were enrolled from 41 centers in 10 countries. We report results from a planned interim analysis of data collected through May 19, 2008 (two thirds of planned enrollment). As a result of protocol amendments in the eligibility criteria that defined refractoriness to fludarabine and alemtuzumab

therapies, 16 of 154 treated patients with primary end point data did not qualify for either the FA-ref or BF-ref groups based on IRC assessment; data from those patients were analyzed separately. Thus, the current report includes 59 patients with FA-ref CLL and 79 patients with BF-ref CLL (Table 1). Of these patients, 91% received eight or more ofatumumab infusions, and 54% received all 12 infusions.

Efficacy

The ORR was 58% (99% CI, 40% to 74%) for the FA-ref group and 47% (99% CI, 32% to 62%) for the BF-ref group, surpassing the 15% criterion for superiority ($P < .001$ for both groups) and allowing for continued accrual. One complete response was observed in the BF-ref group, and all other responses were PRs. Stable disease was noted in 31% of patients with FA-ref CLL and 41% of patients with BF-ref CLL. Responses by baseline characteristics are listed in Table 2. The ORRs among patients previously treated with a rituximab-containing regimen were 54% and 44% in the FA-ref and BF-ref groups, respectively. The ORRs among patients refractory to fludarabine combined with cyclophosphamide and rituximab were 50% and 44% in the FA-ref and BF-ref groups, respectively. Among all characteristics evaluated, 17p deletion in the BF-ref group was the only factor associated with lower response rate (Table 2).

Measures of clinical improvement, based on components of the NCI-WG response criteria, are listed in Table 3. For patients who had baseline thrombocytopenia or anemia, improvements to normal values occurred by week 8 of treatment in approximately 50% of the patients (Appendix Figs A1A and A1B, online only). Furthermore, 45% of patients with decreased ECOG performance status at baseline (worse than 0) experienced an improvement during the treatment period.

Table 1. Baseline Characteristics of Patients With Refractory CLL Treated With Ofatumumab

Characteristic	FA-ref (n = 59) No. of Patients	%	BF-ref (n = 79) No. of Patients	%
Age, years				
Median	64		62	
Range	41-86		43-84	
Sex				
Male	44	75	57	72
Female	15	25	22	28
No. of prior treatments				
Median	5		4	
Range	1-14		1-16	
Duration of CLL, years				
Median	6		6	
Range	1-18.6		0.7-18.0	
Largest lymph node > 5 cm based on clinical evaluation	11	19	36	46
Largest lymph node > 5 cm by palpation or CT scan	55	93	79	100
Rai stage at screening				
0	1	2	0	0
I or II	26	44	24	30
III or IV	32	54	55	70
Binet stage at screening				
A	6	10	4	5
B	23	39	24	30
C	30	51	51	65
ECOG PS				
0	27	46	25	32
1-2	31*	53	54	68
Prior alkylating therapy	55	93	73	92
Prior rituximab-containing regimen	35	59	43	54

Abbreviations: CLL, chronic lymphocytic leukemia; FA-ref, fludarabine and alemtuzumab refractory; BF-ref, bulky fludarabine refractory; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*One patient in the FA-ref group had ECOG PS of 3 at baseline as a result of elbow surgery unrelated to CLL and was allowed to enroll onto the study.

Table 2. Response Rates According to Baseline Characteristics for Patients With Refractory CLL Treated With Ofatumumab

Baseline Characteristic	FA-ref No. of Patients	FA-ref ORR (%)	FA-ref *P**	BF-ref No. of Patients	BF-ref ORR (%)	BF-ref *P**
Age, years						
< 65	32	63	.4400	46	48	1.00
≥ 65	27	52		33	45	
< 70	49	57	1.00	60	48	.7929
≥ 70	10	60		19	42	
Prior rituximab						
Yes	35	54	.5984	43	44	.6553
No	24	63		36	50	
Prior FCR						
Refractory to FCR†	16	50	.5585	16	44	1.00
Other†	43	60		63	48	
Prior FC						
Refractory to FC‡	33	64	.4264	46	50	.6480
Other‡	26	50		33	42	
Palpable lymph node size, cm						
≤ 5	43	56	1.00	39	54	.1647
> 5	11	55		36	36	
Disease stage						
Rai stage I or II	26	58	1.00	24	54	.4654
Rai stage III or IV	32	56		55	44	
ECOG PS						
0-1	46	59	1.00	66	50	.2384
2	12	58		13	31	
FISH cytogenetic abnormalities§						
17p del	17	41	.1429	14	14	.0073
No 17p del	40	65		62	55	
11q del	24	63	.5963	22	64	.0838
No 11q del	33	55		56	41	
12q trisomy	3	33	.5669	8	38	.7147
No 12q trisomy	54	59		70	49	

Abbreviations: CLL, chronic lymphocytic leukemia; FA-ref, fludarabine and alemtuzumab refractory; BF-ref, bulky fludarabine refractory; ORR, overall response rate; FCR, fludarabine plus cyclophosphamide and rituximab; FC, fludarabine plus cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; PS, performance status; FISH, fluorescent in situ hybridization.
*Two-sided Fisher's exact test.
†Patients considered refractory to FCR, with or without other drugs; other represents patients refractory to a fludarabine-based regimen other than that containing FCR.
‡Patients considered refractory to FC, with or without other drugs; other represents patients refractory to a fludarabine-based regimen other than that containing FC.
§Categories adapted from Döhner hierarchical classification of FISH cytogenetic abnormalities.[27]

Table 3. Summary of Clinical Improvement for a Minimum Duration of 2 Months in Patients With Refractory CLL Treated With Ofatumumab

Improvement in Clinical Parameters	FA-ref			BF-ref		
	No. of Patients With Abnormal Clinical Parameters at Baseline	Patients With Improvement From Baseline to Week 24		No. of Patients With Abnormal Clinical Parameters at Baseline	Patients With Improvement From Baseline to Week 24	
		No.	%		No.	%
Complete resolution of constitutional symptoms	31	15	48	46	29	63
Complete resolution of lymphadenopathy (nodes < 1 cm)	55	9	16	74	8	11
Complete resolution of splenomegaly	30	14	47	46	16	35
Complete resolution of hepatomegaly	18	9	50	21	11	52
Normalization of neutrophil count (from $< 1.5 \times 10^9$/L to $\geq 1.5 \times 10^9$/L)	19	1	5	17	5	29
Improvement in hemoglobin level (from ≤ 11.0 g/dL to > 11.0 g/dL)	26	8	31	42	11	26
Improvement in platelet count (from $\leq 100 \times 10^9$/L to > 50% increase or $> 100 \times 10^9$/L)	29	12	41	44	17	39

Abbreviations: CLL, chronic lymphocytic leukemia; FA-ref, fludarabine and alemtuzumab refractory; BF-ref, bulky fludarabine refractory.

In responding patients, median time to response was 1.8 months for both the FA-ref and BF-ref groups. Approximately 80% of responses were observed within 2 months of initiating treatment. One patient in the BF-ref group had a delayed PR 9 months after initiating treatment. The median duration of response was 7.1 months (95% CI, 3.7 to 7.6 months) in the FA-ref group and 5.6 months (95% CI, 3.6 to 7.0 months) in the BF-ref group.

The median PFS time was 5.7 months (95% CI, 4.5 to 8.0 months) in the FA-ref group and 5.9 months (95% CI, 4.9 to 6.4 months) in the BF-ref group (Fig 1A). Median OS time was 13.7 months (95% CI, 9.4 months to not yet reached) in the FA-ref group and 15.4 months (95% CI, 10.2 to 20.2 months) in the BF-ref group (Fig 1B). On the basis of the landmark analysis at week 12, median OS time was significantly longer (by ≥ 10 months) among responding patients compared with nonresponders; the median OS time had not yet been reached for responders in both the FA-ref and BF-ref groups; whereas for nonresponders, the OS time was 9.8 months ($P = .0424$; Fig 1C) in the FA-ref group and 10.2 months ($P < .0001$; Fig 1D) in the BF-ref group.

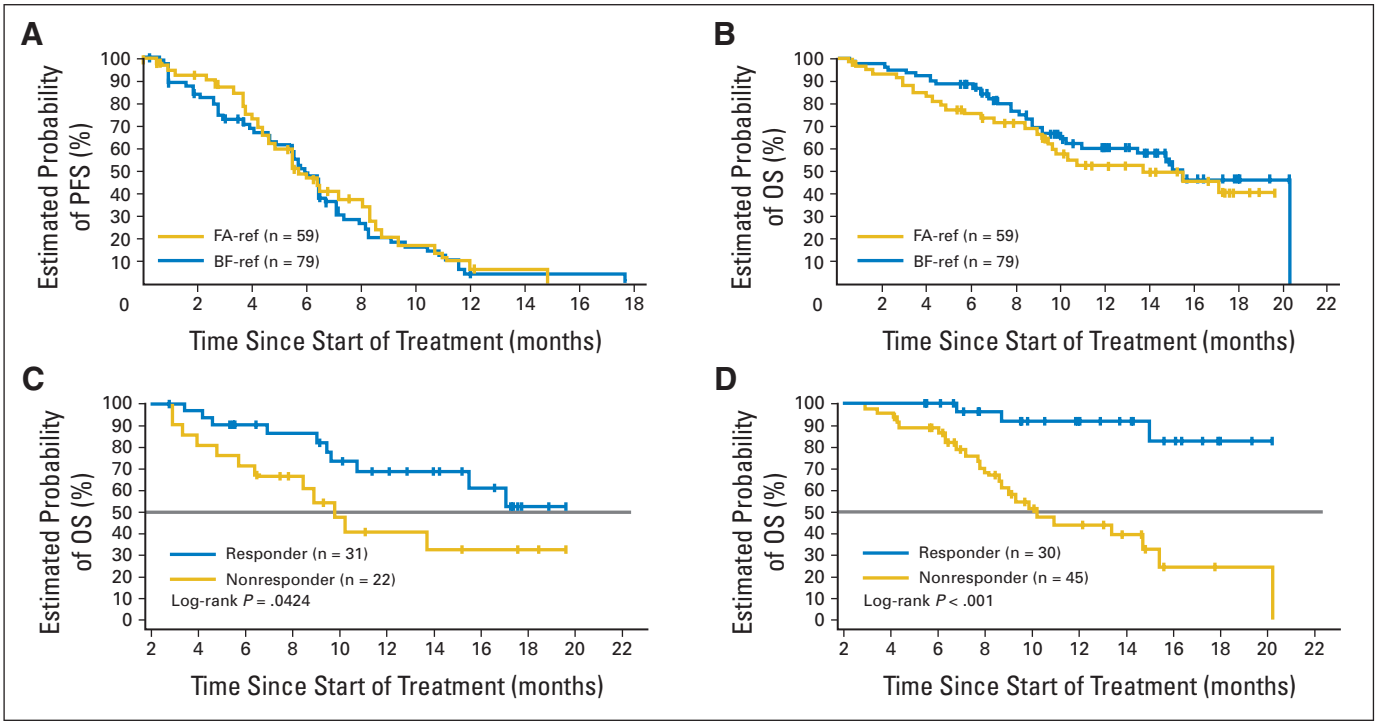
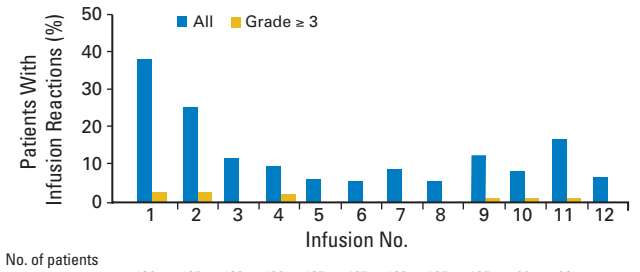


Fig 1. (A) Progression-free survival (PFS) by patient group. PFS was defined as time from baseline (week 0) to progression (assessed by independent end point review committee) or death. (B) Overall survival (OS) by patient group. OS was defined as time from baseline (week 0) to death. (C) OS according to response status in the fludarabine- and alemtuzumab-refractory (FA-ref) group. (D) OS according to response status in the bulky fludarabine-refractory (BF-ref) group. OS in panels C and D based on landmark analysis at week 12, which includes patients who were alive at the week 12 time point; *P* value derived from two-sided log-rank test.



No. of patients												
n	138	135	133	130	127	127	126	125	105	96	82	74
Count (all)	52	34	15	12	8	7	11	7	13	8	14	5
Percent (all)	38	25	11	9	6	6	9	6	12	8	17	7
Count (grade ≥ 3)	3	3	0	2	0	0	0	0	1	1	1	0
Percent (grade ≥ 3)	2	2	0	2	0	0	0	0	1	1	1	0

Fig 2. Infusion-related reactions by infusion number.

Table 5. Summary of Death With Ofatumumab Therapy

Death*	FA-ref (n = 59)		BF-ref (n = 79)	
	No. of Patients	%	No. of Patients	%
Total deaths	6	10	5	6
Cause of death				
Sepsis/septic shock	3	5	1	1
Pneumonia	2	3	2	3
CLL Richter's transformation	1	2	0	0
Myocardial infarction	0	0	1	1
Disease progression	0	0	1	1

Abbreviations: FA-ref, fludarabine and alemtuzumab refractory; BF-ref, bulky fludarabine refractory; CLL, chronic lymphocytic leukemia.
*Occurring within 30 days of the last ofatumumab infusion.

Safety

Overall, infusion-related reactions were seen in 64% of patients in the FA-ref group and 61% of patients in the BF-ref group, nearly all of which were grade 1 or 2 (Fig 2). These reactions predominantly occurred during the first and second infusions and subsided during the course of treatment, decreasing from 38% of patients at the first infusion to 7% at the 12th infusion. The most common AEs (≥ 10% of patients) occurring during treatment (between the first ofatumumab infusion and up to 30 days after the last infusion) were infections (67%), cough (18%), diarrhea (16%), anemia (16%), fatigue (15%), fever (15%), neutropenia (15%), dyspnea (13%), nausea (11%), and rash (10%). Among these AEs, those judged by investigators to be related to ofatumumab treatment are listed in Table 4. One patient with FA-ref CLL had grade 4 thrombocytopenia during treatment. In the BF-ref group, during treatment, one patient each experienced grade 3 febrile neutropenia, thrombocytopenia, and hemolytic anemia, and one patient experienced grade 4 hemolytic anemia. No HAHAs were detected in any of the evaluable patients.

During treatment, 189 infectious events were reported among 92 patients; 139 of these events (74%) were grade 1 or 2 in severity. Among 37 grade 3 or 4 infections, pneumonia (14 events) and other respiratory tract infections (six events) were the most common. Thirteen infections with onset during treatment led to death, including sepsis (n = 6), pneumonia (n = 5), *Fusarium* infection (n = 1), and progressive multifocal leukoencephalopathy (PML; n = 1). Among these grade 5 infections, eight infections (FA-ref, n = 5; BF-ref, n = 3) led to death within 30 days of the last ofatumumab infusion (Table 5). Other causes of death within 30 days of last infusion are listed in Table 5.

Early deaths (≤ week 8) occurred in four patients (7%) in the FA-ref group and two patients (3%) in the BF-ref group. Four of these deaths are listed in Table 5, including one death each as a result of pneumonia and sepsis in the FA-ref group and one death each as a result of sepsis and myocardial infarction in the BF-ref group. Two other early deaths were a result of *Fusarium* infection (mentioned earlier) and bronchopneumonia in the FA-ref group.

Table 4. Related Adverse Events With Ofatumumab Therapy

Adverse Events*	FA-ref (n = 59)				BF-ref (n = 79)			
	All Grades		Grade 3 or 4		All Grades		Grade 3 or 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Infection	12	20	7	12	17	22	6	8
Neutropenia	11	19	8	14	6	8	5	6
Fatigue	3	5	0	0	7	9	0	0
Cough	5	8	0	0	4	5	0	0
Anemia	2	3	0	0	7	9	4	5
Diarrhea	5	8	0	0	3	4	0	0
Dyspnea	5	8	1	2	3	4	0	0
Nausea	3	5	0	0	5	6	0	0
Rash	5	8	0	0	2	3	0	0
Fever	5	8	1	2	1	1	0	0

Abbreviations: FA-ref, fludarabine and alemtuzumab refractory; BF-ref, bulky fludarabine refractory.
*Adverse events judged by investigators to be related to ofatumumab among the most common adverse events that occurred in ≥ 10% of patients from the first infusion of ofatumumab to within 30 days of the last infusion.

DISCUSSION

Outcomes for patients with FA-ref or BF-ref CLL are poor with available salvage regimens, including intensive chemoimmunotherapy, with low response rates (23% ORR), short time to treatment failure (median, 2 to 3 months), and short survival (median, 9 months)[7]; new treatment options are needed for these patients. Comparisons with available historical data are limited; however, an ORR of 47% to 58% and a median PFS time of approximately 6 months with ofatumumab, as assessed by an IRC, clearly demonstrate clinical activity and are significant given outcomes reported with current salvage therapies.[7] Furthermore, the activity with single-agent ofatumumab is remarkable, given the ORR of 0% in 14 patients with FA-ref or BF-ref CLL treated with other types of mAb therapy in the retrospective report.[7] The median OS time with ofatumumab treatment was 14 to 15 months, and a significant survival benefit was observed in responding patients in both patient groups. The landmark method was used to minimize the survival bias in responders, which would otherwise occur when using a direct comparison of survival among all responders versus nonresponders.

In this study, treatment with ofatumumab was associated with considerable relief of disease-related constitutional symptoms and improvements in performance status, even among patients who did not qualify as responders strictly based on NCI-WG criteria. Complete

resolution of splenomegaly and hepatomegaly and/or substantial reduction in lymphadenopathy were observed in a large proportion of patients (Table 3), and patients with thrombocytopenia or anemia at baseline experienced improvements in hematologic parameters.

Response to ofatumumab was consistent across various subgroups based on pretreatment characteristics, except for 17p deletion, which was associated with lower ORR in the BF-ref group. This study was not powered to identify subgroup differences; however, it is encouraging to appreciate responses in patients who may be considered higher risk, such as those with advanced disease stage, age $\geq$ 70 years, 11q deletion, poor performance status, or large palpable lymph nodes ($>$ 5 cm). The dose of corticosteroid premedication used in this study has not been reported to have efficacy in refractory patients with CLL and was not likely to significantly affect the ORR.

With median response duration of 6 to 7 months, some patients experienced relapse soon after completing treatment. One possible explanation for this is the proliferative nature of disease in these refractory patients. Because all but one responder achieved PR, responders had residual disease that progressed after completion of ofatumumab treatment. The median number of malignant B cells in peripheral blood decreased rapidly with ofatumumab and remained depleted during the course of treatment (Appendix Fig A2, online only). The gradual disappearance of the tumor bulk during continued therapy was followed by a gradual return of the malignant clone after discontinuation of treatment (data not shown). Thus, loss of response did not seem to be a result of resistance to ofatumumab during active treatment; detailed pharmacokinetic and pharmacodynamic analyses may provide further insights.

Ofatumumab was well tolerated, there were no unexpected toxicities, and no formation of HAHAs was detected. The most common AEs were infusion reactions and infections, which were primarily grade 1 or 2 events; infusion reactions were common during the first two doses, as expected with this type of therapy, but largely subsided with subsequent infusions. The incidence of grade 3 or 4 infections was at an expected level, considering prior treatment, extent of disease, and immunosuppression among these patients.[28] One case of PML (resulting in death 63 days after last dose of ofatumumab) occurred in a patient with FA-ref disease who had received eight prior treatments and had a low CD4 count at baseline (data not shown). PML has been reported in patients with B-cell malignancies treated with rituximab-containing regimens.[29-31] The incidence of major infections (as previously defined by Tam et al[7]) in our patients with FA-ref and BF-ref CLL (32% and 23%, respectively; data not shown) compared favorably with that of similar patients treated with various other salvage regimens (60% and 45%, respectively)[7]; the incidence of early death in our patients with FA-ref and BF-ref CLL (7% and 3%, respectively) was also lower than that reported in the historical data (16% and 10%, respectively).[7] Although median neutrophil counts in our patient population decreased during the first 4 to 8 weeks of treatment, they remained greater than 1.5×10^9/L and were stable during the course of treatment (Appendix Fig A3A, online only). Median platelet and hemoglobin values rapidly improved during the study for patients who stayed on the study (Appendix Figs A3B and A3C, online only), including patients with baseline thrombocytopenia and anemia, as a result of continued treatment and responses. These outcomes in hematologic parameters are notable considering the extent of disease in this patient population and the lack of blood count limits for trial enrollment.

Ofatumumab demonstrates significant activity and a favorable safety profile, providing meaningful clinical improvements in poor-risk patients with heavily pretreated FA-ref and BF-ref CLL. Results are especially encouraging for a single-agent mAb used in such heavily pretreated patients as in this salvage setting. Importantly, similar response rates were seen irrespective of prior exposure to rituximab-containing treatments and irrespective of refractoriness to fludarabine combined with cyclophosphamide and rituximab, a standard regimen in earlier lines of CLL therapy. Phase III trials are needed to confirm therapeutic efficacy in patients with CLL. Further investigation of ofatumumab is warranted in earlier disease settings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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