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


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.

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/m²), but refractoriness to...
fludarabine was associated with a low response rate (20% in fludarabine-refractory patients vs 56% in fludarabine-sensitive patients; \( P = .02 \)).

Opatumumab (HuMax-CD20) is a human mAb that binds a distinct epitope composed of both small and large loops on the CD20 molecule. 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. 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. 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.

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 \( \geq 18 \) years) with active CLL (1996 National Cancer Institute Working Group [NCI-WG] criteria) indicated for treatment, tumor immunophenotype of CD5\(^+\) CD20\(^+\) CD23\(^-\), Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and life expectancy of \( \geq 6 \) 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). Bulk 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\(^{25,26} \)) 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 \( \geq 2 \) 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 hematologic and at screening, week 12, and months 9, 12, 18, and 24 for evaluation of human antihuman antibodies (HAHAs). Blood chemistry and hematologic samples were analyzed at central laboratories (Bio-Analytical Research Corporation, Lake Success, NY) in the United States and in Europe, and HAHAs were 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. 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\(^{27,28} \) 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...
Ofatumumab in Fludarabine-Refractory CLL

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. Among all characteristics evaluated, 17p deletion in the BF-ref group was the only factor associated with lower response rate (Table 2).

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

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>FA-ref (n = 59)</th>
<th>BF-ref (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>65</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>Prior response rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to FCR†</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Other†</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>Refractory to FC‡</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Other‡</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Palpable lymph node size, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>11</td>
<td>56</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai stage I or II</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Rai stage III or IV</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>46</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>FISH cytogenetic abnormalities§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p del</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>No 17p del</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>11q del</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>No 11q del</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>No 12q trisomy</td>
<td>54</td>
<td>70</td>
</tr>
</tbody>
</table>

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

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.

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.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FA-ref (n = 59)</th>
<th>BF-ref (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>Range</td>
<td>41-96</td>
<td>43-84</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>57</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>No. of prior treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>1-14</td>
<td>1-16</td>
</tr>
<tr>
<td>Duration of CLL, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Range</td>
<td>1-18.6</td>
<td>0.7-18.0</td>
</tr>
<tr>
<td>Largest lymph node size, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>≤ 5</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Palpable lymph node size, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>≤ 5</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Rai stage at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I or II</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>III or IV</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>Binet stage at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>51</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>1-2</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>Prior alkyting therapy</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>Prior rituximab-containing regimen</td>
<td>35</td>
<td>43</td>
</tr>
</tbody>
</table>

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.
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.

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

<table>
<thead>
<tr>
<th>Improvement in Clinical Parameters</th>
<th>FA-ref</th>
<th>BF-ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients With Abnormal Clinical Parameters at Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Patients With Improvement From Baseline to Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete resolution of constitutional symptoms</td>
<td>31</td>
<td>46</td>
</tr>
<tr>
<td>Complete resolution of lymphadenopathy (nodes &lt; 1 cm)</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>Complete resolution of splenomegaly</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>Complete resolution of hepatomegaly</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Normalization of neutrophil count (from &lt; 1.5 x 10^9/L to ≥ 1.5 x 10^9/L)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Improvement in hemoglobin level (from ≤ 11.0 g/dL to &gt; 11.0 g/dL)</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>Improvement in platelet count (from ≤ 100 x 10^9/L to &gt; 50% increase or &gt; 100 x 10^9/L)</td>
<td>29</td>
<td>44</td>
</tr>
</tbody>
</table>

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

![Fig 1](image-url)
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 predominately 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.

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); 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.

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. 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 re-
duction 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 sub-
groups 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 en-
couraging to appreciate responses in patients who may be considered
higher risk, such as those with advanced disease stage, age ≥ 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, re-
sponders 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
therapy; detailed pharmacokinetic and pharmacodynamic analyses
may provide further insights.

Ofatumumab was well tolerated, there were no unexpected tox-
icities, 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). 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 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 re-
sponse 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.

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