Ibrutinib Monotherapy in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia

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ABSTRACT

Purpose
Ibrutinib is active in previously treated Waldenström macroglobulinemia (WM). MYD88 mutations (MYD88MUT) and CXCR4 mutations (CXCR4MUT) affect ibrutinib response. We report on a prospective study of ibrutinib monotherapy in symptomatic, untreated patients with WM, and the effect of CXCR4MUT status on outcome.

Patients and Methods
Symptomatic, treatment-naïve patients with WM were eligible. Ibrutinib (420 mg) was administered daily until progression or unacceptable toxicity. All tumors were genotyped for MYD88MUT and CXCR4MUT.

Results
A total of 30 patients with WM received ibrutinib. All carried MYD88MUT, and 14 (47%) carried a CXCR4MUT. After ibrutinib treatment, median serum IgM levels declined from 4,370 to 1,513 mg/dL, bone marrow involvement declined from 65% to 20%, and hemoglobin level rose from 10.3 to 13.9 g/dL (P < .001 for all comparisons). Overall (minor or more than minor) and major (partial or greater than partial) responses for all patients were 100% and 83%, respectively. Rates of major (94% vs 71%) and very good partial (31 vs 7%) responses were higher and time to major responses more rapid (1.8 vs 7.3 months; P = 0.01) in patients with wild-type CXCR4 versus those with CXCR4MUT, respectively. With a median follow-up of 14.6 months, disease in two patients (both with CXCR4MUT) progressed. The 18-month, estimated progression-free survival is 92% (95% CI, 73% to 98%). All patients are alive. Grade 2/3 treatment-related toxicities in 5% of patients included arthralgia (7%), bruising (7%), neutropenia (7%), upper respiratory tract infection (7%), urinary tract infection (7%), atrial fibrillation (10%), and hypertension (13%). There were no grade 4 or unexpected toxicities.

Conclusion
Ibrutinib is highly active, produces durable responses, and is safe as primary therapy in patients with symptomatic WM. CXCR4MUT status affects responses to ibrutinib.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is an IgM-secreting lymphoplasmacytic lymphoma. Despite treatment advances, disease in most patients eventually progresses and new treatment options are needed. Whole-genome sequencing has revealed activating mutations in MYD88 and CXCR4 in patients with WM. MYD88 mutations (MYD88MUT) trigger NF-kB activation via divergent pathways involving Bruton’s tyrosine kinase (BTK) and IRAK1/IRAK4. Hematopoietic cell kinase (HCK), an SRC family member, is also transcriptionally upregulated and activated by mutated MYD88. HCK transactivates BTK, AKT, and ERK, and promotes their prosurvival signaling in MYD88MUT cells. At least 40 different CXCR4 somatic mutations have been identified in patients with WM. Patients with CXCR4 mutations (CXCR4MUT) have higher serum IgM levels and greater incidence of symptomatic hyperviscosity. WM cells expressing CXCR4MUT also show enhanced AKT and ERK activation, and resistance to ibrutinib.

Ibrutinib is an orally administered, small-molecule inhibitor of BTK and HCK that triggers apoptosis of MYD88MUT WM cells.
That study supported the iNNOVATE [ibrutinib for Patients With Rituximab-Refractory Waldenström Macroglobulinemia] trial, Dimopoulos et al reported an ORR of 90% and an MRR of 71% with ibrutinib monotherapy. The 18-month PFS and overall survival (OS) rates were 86% and 97%, respectively. One patient with MYD88WT disease did not respond, whereas patients with MYD88MUT or CXCR4MUT had slower improvements in serum IgM and hemoglobin levels versus their counterparts with wild-type CXCR4 (CXCR4WT) WM.

Herein, we report on the safety and efficacy of a prospective study of ibrutinib monotherapy in symptomatic, treatment-naïve patients with WM and the effect of CXCR4MUT status on response outcome.

Patients and Methods

All patients provided written informed consent after institutional review board approval was given. The study was registered at Clinicaltrials.gov (Clinical trial identifier: NCT02165397; arm C of the iNNOVATE [ibrutinib for Patients With Rituximab-Refractory Waldenström Macroglobulinemia] trial). Dimopoulos et al reported an ORR of 90% and an MRR of 71% with ibrutinib monotherapy. The 18-month PFS and overall survival (OS) rates were 86% and 97%, respectively. One patient with MYD88WT disease did not respond, whereas patients with MYD88MUT or CXCR4MUT had slower improvements in serum IgM and hemoglobin levels versus their counterparts with wild-type CXCR4 (CXCR4WT) WM.

Among patients with rituximab-refractory disease (Clinicaltrials.gov identifier: NCT02165397; arm C of the iNNOVATE [ibrutinib for Patients With Rituximab-Refractory Waldenström Macroglobulinemia] trial), Dimopoulos et al reported an ORR of 90% and an MRR of 71% with ibrutinib monotherapy. The 18-month PFS and overall survival (OS) rates were 86% and 97%, respectively. One patient with MYD88WT disease did not respond, whereas patients with MYD88MUT or CXCR4MUT had slower improvements in serum IgM and hemoglobin levels versus their counterparts with wild-type CXCR4 (CXCR4WT) WM.

Herein, we report on the safety and efficacy of a prospective study of ibrutinib monotherapy in symptomatic, treatment-naïve patients with WM and the effect of CXCR4MUT status on response outcome.

Patients and Disease Characteristics

Thirty-one patients were enrolled after written consent. One patient was ineligible after pathologic review of a lymph node biopsy specimen showed transformation to diffuse large B-cell lymphoma before protocol therapy was started. The baseline characteristics for the 30 patients with WM are listed in Table 1. All patients expressed MYD88L265P, and 14 (47%) had CXCR4MUT. The clinical characteristics by CXCR4MUT status are listed in Table 1. A higher incidence of adenopathy (50% v 14%; P = .04) was observed among patients with CXCR4WT disease, as previously observed. Patients with CXCR4MUT disease also had lower median serum IgM levels (3,928 v 5,295 mg/dL) versus those with
CXCR4\textsuperscript{MUT} WM, but the difference did not reach statistical significance.\textsuperscript{6} After Holm-Bonferroni correction for multiple hypothesis testing, baseline characteristics were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

**Responses**

Median serum IgM levels for the 30 patients with WM declined from 4,370 mg/dL (range, 844 to 10,321 mg/dL) to 1,513 mg/dL (range, 1,513-13,900 mg/dL), respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

**Table 1.** Baseline Characteristics for Treatment-Naive Patients With WM Who Received Ibrutinib Monotherapy (N = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients With WM (N = 30)</th>
<th>MYD88\textsuperscript{WT}</th>
<th>CXCR4\textsuperscript{WT} (n = 16)</th>
<th>MYD88\textsuperscript{MUT}</th>
<th>CXCR4\textsuperscript{MUT} (n = 14)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>67 (43-83)</td>
<td>67 (43-83)</td>
<td>67 (43-75)</td>
<td>.94</td>
<td></td>
<td></td>
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<td>Sex, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>23 (77)</td>
<td>12 (75)</td>
<td>11 (79)</td>
<td>.99</td>
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<td>Female</td>
<td>7 (23)</td>
<td>4 (25)</td>
<td>3 (21)</td>
<td></td>
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<td>IPSSWM score, No. (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>5 (17)</td>
<td>3 (19)</td>
<td>2 (14)</td>
<td>.36</td>
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<tr>
<td>Intermediate</td>
<td>11 (37)</td>
<td>4 (25)</td>
<td>7 (50)</td>
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<td></td>
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<tr>
<td>High</td>
<td>14 (47)</td>
<td>9 (56)</td>
<td>5 (36)</td>
<td></td>
<td></td>
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<td>Serum immunoglobulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM, median (range), mg/dL</td>
<td>4,370 (844-10,321)</td>
<td>3,928 (858-10,321)</td>
<td>5,295 (844-7,450)</td>
<td>.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM &gt; 3,000 mg/dL, No. (%)</td>
<td>18 (60)</td>
<td>9 (56)</td>
<td>9 (64)</td>
<td>.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA, median (range), mg/dL</td>
<td>62 (11-576)</td>
<td>62 (15-576)</td>
<td>60 (1-132)</td>
<td>.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG, median (range), mg/dL</td>
<td>563 (191-3,251)</td>
<td>607 (278-3,251)</td>
<td>470 (191-1,108)</td>
<td>.38</td>
<td></td>
<td></td>
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<tr>
<td>ANC, median (range), µL</td>
<td>3,370 (1,680-9,900)</td>
<td>3,450 (1,750-9,900)</td>
<td>3,220 (1,680-6,270)</td>
<td>.38</td>
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<td>Hemoglobin, median (range), g/dL</td>
<td>10.3 (7.5-14.4)</td>
<td>10.1 (8.6-14.4)</td>
<td>10.6 (7.5-13.5)</td>
<td>.23</td>
<td></td>
<td></td>
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<tr>
<td>Platelet count, median (range), µL</td>
<td>247,000 (59,000-491,000)</td>
<td>288,000 (129,000-418,000)</td>
<td>199,000 (59,000-491,000)</td>
<td>.12</td>
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<td>Serum β2-microglobulin, median (range), mg/L</td>
<td>3.8 (2.0-7.6)</td>
<td>4.2 (2.3-6.9)</td>
<td>3.4 (2.0-7.6)</td>
<td>.07</td>
<td></td>
<td></td>
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<td>BM disease involvement, median (range), %</td>
<td>65 (5-95)</td>
<td>60 (5-95)</td>
<td>70 (10-90)</td>
<td>.60</td>
<td></td>
<td></td>
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<tr>
<td>Extramedullary disease, No. (%)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Adenopathy (&gt; 1.5 cm)</td>
<td>10 (33)</td>
<td>8 (50)</td>
<td>2 (14)</td>
<td>.04</td>
<td></td>
<td></td>
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<tr>
<td>Splenomegaly (&gt; 15 cm)</td>
<td>5 (17)</td>
<td>4 (25)</td>
<td>1 (7)</td>
<td>.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients with WM had MYD88\textsuperscript{WT} disease. Abbreviations: ANC, absolute neutrophil count; IPSSWM, International Prognostic Scoring System, Waldenström macroglobulinemia; MUT, mutation; WM, Waldenström macroglobulinemia. *P values denote differences between MYD88\textsuperscript{WT} CXCR4\textsuperscript{WT} and MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT} cohorts. After Holm-Bonferroni correction for multiple hypothesis testing, baseline characteristics were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All Patients (N = 30)</th>
<th>MYD88\textsuperscript{WT}</th>
<th>CXCR4\textsuperscript{WT} (n = 16)</th>
<th>MYD88\textsuperscript{MUT}</th>
<th>CXCR4\textsuperscript{MUT} (n = 14)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, No. (%)</td>
<td>30 (100)</td>
<td>16 (100)</td>
<td>14 (100)</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>Major response rate, No. (%)</td>
<td>25 (83)</td>
<td>15 (94)</td>
<td>10 (71)</td>
<td>.16</td>
<td></td>
<td></td>
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<tr>
<td>Categorical response, No. (%)</td>
<td>Minor</td>
<td>5 (17)</td>
<td>1 (6)</td>
<td>4 (29)</td>
<td>.16</td>
<td></td>
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<tr>
<td>Partial</td>
<td>19 (63)</td>
<td>10 (63)</td>
<td>9 (64)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good partial response</td>
<td>6 (20)</td>
<td>5 (31)</td>
<td>1 (7)</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to response, months</td>
<td>Minor response (≥ minor response)</td>
<td>1.0</td>
<td>0.9</td>
<td>1.7</td>
<td>.07</td>
<td></td>
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<tr>
<td>Major response (≥ partial response)</td>
<td>1.9</td>
<td>1.8</td>
<td>7.3</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients with Waldenström macroglobulinemia had MYD88\textsuperscript{WT} disease. Abbreviation: MUT, mutation. *P values denote differences between MYD88\textsuperscript{WT} CXCR4\textsuperscript{WT} and MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT} cohorts.

\textsuperscript{6} Median time to response, months

\textsuperscript{1} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{19} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{20} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{21} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{22} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{23} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{24} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{25} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{26} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{27} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{28} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.

\textsuperscript{29} Median time to at least minor and major responses was 1.0 and 1.9 months, respectively. ORR and MRR were not significantly different on the basis of CXCR4\textsuperscript{MUT} status.
(<50% v >50%), MRRs (94% v 71.0%) and VGPR rates (31% v 7%) were higher in patients with CXCR4WT versus those with CXCR4MUT disease (Table 2). Moreover, the median time to at least a minor (0.9 v 1.7 months; P = .07) and major response (1.8 v 7.3 months; P = .01) was shorter in those with CXCR4WT versus CXCR4MUT disease, respectively. ORR (Fig 1A) and MRR (Fig 1B) were delayed in patients with CXCR4MUT disease and showed improvement after 3 and 6 cycles of therapy, respectively, when compared with patients with CXCR4WT disease. Whereas deeper responses (as assessed by serial IgM changes) lagged for patients with CXCR4MUT WM, improvements in hemoglobin concentration had similar kinetics over time for patients with CXCR4WT disease and those with CXCR4MUT disease (Fig 1C).

Among subpopulations of interest, CT-defined adenopathy (≥1.5 cm) was present in 10 patients at baseline. Serial CT imaging for these patients showed adenopathy decreased or normalized (n = 9) or remained stable (n = 1) during therapy. Among five patients with CT-defined splenomegaly (≥15 cm), spleen size normalized in all five patients with serial CT imaging. Four of 29 patients tested (13.8%) had acquired Von Willebrand factor (VWF) deficiency; after treatment VWF antigen, VWF ristocetin cofactor, and FVIII procoagulant activity levels normalized in three (75%) of these patients. One patient had a Coombs test–positive (ie, IgG-positive, anti-K antibody-related) autoimmune hemolytic anemia with a baseline hemoglobin concentration of 9.5 g/dL; after treatment with ibrutinib, VGPR was achieved and the hemoglobin concentration increased to 14.9 g/dL at best response. No patient received treatment of paraprotein-related peripheral neuropathy.

Fig 1. Cumulative overall and major response rates, and changes in serum IgM and hemoglobin levels by treatment cycles stratified by CXCR4MUT status. (A) Overall and (B) major responses, and (C) serial changes in serum IgM and hemoglobin levels by ibrutinib treatment cycles by CXCR4MUT status are shown at the denoted cycle. All patients had MYD88MUT disease. MUT, mutation; WT, wild type.
**PFS**

With a median on treatment duration of 13.4 months (range, 1.8 to 21.1 months), 26 patients (87%) are receiving active protocol therapy. Two patients with CXCR4<sup>MUT</sup> disease met progression criteria, including one who self-withheld therapy while on vacation for 15 days. This patient continued to receive ibrutinib per protocol because of sustained clinical benefit (ie, improvement in hemoglobin). Three patients discontinued therapy because of ventricular fibrillation and asystole that followed cardiac ablation and was unrelated to study drug (n = 1); patient decision to use commercially sourced ibrutinib; and drug-induced hepatitis that resolved after ibrutinib cessation. With a median study follow-up of 14.6 months (range, 1.8 to 21.6 months), all patients are alive. The estimated PFS at 18 months is 92.0% (95% CI, 73.0% to 98.0%).

**Toxicities**

Grade ≥ 2 treatment-related toxicities are reported in Table 3. Grade 2/3 toxicities that were at least possibly related to protocol therapy and that occurred in > 5% of patients included arthralgia (7%), atrial fibrillation (10%), bruising (7%), hypertension (13%), neutropenia (7%), upper respiratory tract infection (7%), and urinary tract infection (7%). There were no grade 4 toxicities related to protocol therapy. Atrial arrhythmias related to ibrutinib occurred in three patients (all grade 2). Two patients had paroxysmal atrial fibrillation and continued full-dose ibrutinib after anticoagulation with a Factor Xa inhibitor. One patient with a history of left atrial enlargement after valvular disease underwent cardiac ablation. After ablation, this patient developed sustained atrial fibrillation and asystole. The patient was successfully resuscitated, and taken off the study. One patient discontinued the study for drug-induced hepatitis that resolved 2 months after ibrutinib discontinuance. Dose reduction to 140 mg/d occurred in one patient for grade 3 foot pain and grade 2 rash. Both toxicities improved at the lower dose and the patient’s disease continues to respond to treatment.

Infection events were uncommon and limited to grade 2 events (two upper respiratory tract infections; two urinary tract infections). Median serum IgA levels decreased from 62 mg/dL (range, 11 to 576 mg/dL) to 39 mg/dL (range, 13 to 30 mg/dL; P = .04); median serum IgG levels declined from 563 mg/dL (range, 191 to 3,251 mg/dL) to 462 mg/dL (range, 226 to 1,052 mg/dL; P = .003). No patient required intravenous immunoglobulin replacement. No episodes of IgM flare were observed, though rebound of serum IgM level (> 25% over nadir and > 500 mg/dL) occurred in six of 16 patients (37.5%) in whom ibrutinib was held for any reason. In five of these six patients, serum IgM returned to prehold levels or better after restarting therapy at a median of 4.6 months (range, 3.4 to 11.2 months). One patient’s serum IgM level remained elevated after self-holding the drug for 15 days; this patient’s disease met criteria for progression. Eight (50%) of the 16 patients in whom ibrutinib was held for any reason experienced a decline in hemoglobin concentration > 0.5 g/dL, including five patients with a decrease ≥ 1.0 g/dL. The median time to recovery of hemoglobin concentration for these patients was 3.7 months (range, 3.4 to 6.1 months).

**DISCUSSION**

We report herein a prospective study of ibrutinib monotherapy in symptomatic, treatment-naive patients with WM. We observed

<table>
<thead>
<tr>
<th>Event or Abnormality</th>
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<th>3</th>
<th>4</th>
<th>Total Grades 2-4*, No. (%)</th>
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<tr>
<td>Alanine transaminase elevation</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
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<tr>
<td>Arthralgia</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
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<tr>
<td>Aspartate transaminase elevation</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
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<tr>
<td>Bruising</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Cellulitis</td>
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<td>0 (0)</td>
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<td>1 (3)</td>
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<td>Diarrhea</td>
<td>1 (3)</td>
<td>0 (0)</td>
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<td>Drug-induced hepatitis</td>
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<td>1 (3)</td>
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<td>Procedural hemorrhage</td>
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<td>1 (3)</td>
<td>0 (0)</td>
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<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
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</table>

*Grade 2-4 adverse events deemed by investigators to be possibly, probably, or definitively associated with protocol therapy are shown.
Ibrutinib. One patient who developed an atrial arrhythmia had consistent with our previous experience and that of others with population of patients with WM, and no unexpected toxicities.

hemoglobin levels improve more slowly with rituximab-based 11.2 and 12.3 g/dL at 4 and 8 weeks, respectively. By comparison, versus rituximab monotherapy, more toxicities have also been higher ORRs (range, 80% to 95%) and MRRs (range, 70% to 85%) and 1.9 months, respectively.

PFS was 86% with shorter follow-up, demonstrating durable benefit for ibrutinib in WM. By comparison, ORRs of 40% to 90% have been reported in treatment-naïve patients with WM and with rituximab alone or in combination. In the United States, rituximab monotherapy is the option most used for treatment-naïve patients with WM, according to SEER-linked Medicare data. The use of standard and extended rituximab therapy results in ORRs and MRRs of 40% to 60% with time to response of 3 to 4 months, and time-to-best response > 1 year. By comparison, ibrutinib shows more rapid response kinetics, with time to minor and major responses of 1.0 and 1.9 months, respectively.

Although combinations with rituximab have resulted in higher ORRs (range, 80% to 95%) and MRRs (range, 70% to 85%) versus rituximab monotherapy, more toxicities have also been recognized, with many of these regimens including prolonged myelosuppression, immunosuppression, peripheral neuropathy, myelodysplasia, and secondary malignancies. Occasionally, rituximab is common in patients with WM and can lead to symptomatic hyperviscosity and aggravation of symptoms related to the IgM paraprotein. Often patients with WM with high serum IgM levels (ie, > 4,000 mg/dL) undergo empirical plasmapheresis to prevent symptomatic hyperviscosity as a result of an IgM flare. In contrast, no flare in serum IgM levels was observed with ibrutinib in this study of treatment-naïve patients, nor in previously treated patients with WM.

Rapid improvement in hemoglobin levels after ibrutinib were also recognized in this study of treatment-naïve patients with similar kinetics to those observed in previously treated patients with WM. Hemoglobin levels rose from 10.3 g/dL at baseline to 11.2 and 12.3 g/dL at 4 and 8 weeks, respectively. By comparison, hemoglobin levels improve more slowly with rituximab-based therapies and may even decline during active therapy with alkylator or nucleoside analog combinations, as a result of their myeloablative effects.

Overall, ibrutinib was well tolerated in this treatment-naïve population of patients with WM, and no unexpected toxicities were encountered. Atrial arrhythmias occurred in 10% of patients, consistent with our previous experience and that of others with ibrutinib. One patient who developed an atrial arrhythmia had a potential predisposition (ie, a mildly enlarged left atrium related to valvular disease). ibrutinib was discontinued in this patient due to complications related to cardiac ablation, whereas the other two patients continue to receive full-dose ibrutinib. Our previous experiences and those of others continue to reflect that the occurrence of atrial arrhythmias on ibrutinib is not practice altering, and most patients can be managed with pharmacologic rate control (eg, β blockers), antiarrhythmic agents, cardiac ablation, and/or anticoagulation without the need for ibrutinib dose reduction.

In our prior study of previously treated patients with WM, we observed a rapid rebound in serum IgM levels and declines in hemoglobin levels after ibrutinib drug hold, regardless of etiology. Similarly, a rebound in serum IgM level occurred in 37.5% of patients, and decline in hemoglobin level occurred in 50% of all patients after ibrutinib hold in treatment-naïve patients with WM. The time to recovery of serum IgM and hemoglobin levels after ibrutinib hold was approximately 4 months. These findings are unlikely to be due to rapid disease progression, because serial declines in BM disease burden were observed in most of these patients; the findings are likely due to nontumoricidal effects of ibrutinib. The BTK substrate STAT5A regulates IgM secretion in WM cells and its selective inhibition by ibrutinib; release upon ibrutinib discontinuance likely contributed to the IgM rebound.

As with our prior experience with ibrutinib monotherapy in previously treated patients with WM, the MRR (94% v 71%), including attainment of VGPR (31% v 7%), was higher in patients with CXCR4WT versus CXCR4MUT disease, respectively. As well, the time to attaining a major response was more rapid (1.8 v 7.3 months) in those with CXCR4WT disease. Similar response kinetics were also observed in our ibrutinib monotherapy trial in previously treated patients with WM. More rapid IgM response kinetics were also observed by Dimopoulos et al for patients with rituximab-refractory CXCR4WT disease who received ibrutinib monotherapy. In response to these findings, a clinical study of ibrutinib plus the anti-CXCR4 monoclonal antibody ulocumab has been initiated for patients with WM with CXCR4MUT disease (Clinicaltrial.gov identifier: NCT03225716). It is interesting that both patients whose disease progressed while in this study in the follow-up period had CXCR4MUT disease. In the pivotal study, patients with CXCR4MUT disease also had a shorter median PFS compared with those with CXCR4WT disease (42 v > 60 months).

In summary, ibrutinib is active in treatment-naïve patients with WM. An ORR of 100%, and 18-month PFS and OS rates of 92% and 100%, respectively, were achieved with ibrutinib monotherapy, including in patients with high tumor and serum IgM burden and those with intermediate- and high-risk disease. ibrutinib responses were affected by CXCR4WT disease status. Overall, treatment was well tolerated, with no unexpected toxicities. Ibrutinib is safe and effective in treatment-naïve patients with symptomatic WM.


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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ibrutinib Monotherapy in Symptomatic, Treatment-Na¨ıve Patients with Waldenstr¨öm Macroglobulinemia

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