JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

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

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Published at jco.org on July 25, 2018.

Processed as a Rapid Communication manuscript.

Clinical trial information: NCT02604511.

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0732-183X/18/3699-1/$20.00

ABSTRACT

Purpose
Ibrutinib is active in previously treated Waldenström macroglobulinemia (WM). *MYD88* mutations (*MYD88*^{MUT}) and *CXCR4* mutations (*CXCR4*^{MUT}) affect ibrutinib response. We report on a prospective study of ibrutinib monotherapy in symptomatic, untreated patients with WM, and the effect of *CXCR4*^{MUT} 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 *MYD88*^{MUT} and *CXCR4*^{MUT}.

Results
A total of 30 patients with WM received ibrutinib. All carried *MYD88*^{MUT}, and 14 (47%) carried a *CXCR4*^{MUT}. 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% *v* 71%) and very good partial (31 *v* 7%) responses were higher and time to major responses more rapid (1.8 *v* 7.3 months; $P = 0.01$) in patients with wild-type *CXCR4* versus those with *CXCR4*^{MUT}, respectively. With a median follow-up of 14.6 months, disease in two patients (both with *CXCR4*^{MUT}) 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. *CXCR4*^{MUT} status affects responses to ibrutinib.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is an IgM-secreting lymphoplasmacytic lymphoma.[1] 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.[2,3] *MYD88* mutations (*MYD88*^{MUT}) trigger NF-κB activation via divergent pathways involving Bruton's tyrosine kinase (BTK) and IRAK1/IRAK4.[4] 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 *MYD88*^{MUT} cells.[5] At least 40 different *CXCR4* somatic mutations have been identified in patients with WM.[6,7] Patients with *CXCR4* mutations (*CXCR4*^{MUT}) have higher serum IgM levels and greater incidence of symptomatic hyperviscosity.[6] WM cells expressing *CXCR4*^{MUT} also show enhanced AKT and ERK activation, and resistance to ibrutinib.[8-10]

Ibrutinib is an orally administered, small-molecule inhibitor of BTK and HCK that triggers apoptosis of *MYD88*^{MUT} WM cells.[4,5] Among

DOI: https://doi.org/10.1200/JCO.2018.78.6426

previously treated patients with WM, results of a prospective, investigator-sponsored study of ibrutinib monotherapy[11] showed an overall response rate (ORR) of 90%, a major response rate (MRR) of 77.7%, and a median progression-free survival (PFS) > 5 years. That study supported the first regulatory approval of an agent for treating WM (Clinicaltrial.gov identifier NCT01614821).[11] An important finding of that study was the effect of *MYD88*^{MUT} and *CXCR4*^{MUT} status on response outcome. Previously treated patients with WM with wild-type *MYD88* (*MYD88*^{WT}) disease showed no major responses to ibrutinib. The presence of *CXCR4*^{MUT} in patients with *MYD88*^{MUT} adversely affected time to major response; overall, major, and very good partial response (VGPR) rates; as well as the median time to progression.[12]

Among patients with rituximab-refractory disease (Clinicaltrial.gov identifier: NCT02165397; arm C of the iNNOVATE [Ibrutinib for Patients With Rituximab-Refractory Waldenström Macroglobulinemia] trial), Dimopoulos et al[13] 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 *MYD88*^{WT} disease did not respond, whereas patients with *MYD88*^{MUT} or *CXCR4*^{MUT} had slower improvements in serum IgM and hemoglobin levels versus their counterparts with wild-type *CXCR4* (*CXCR4*^{WT}) 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 *CXCR4*^{MUT} 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 Clinicaltrial.gov (Clinicaltrial.gov identifier: NCT02604511). Enrollment began on January 26, 2016, and closed December 28, 2016. The last patient evaluation and survival update were done on January 22, 2018. The primary end point was determination of the MRR, consisting of partial response (PR), VGPR, and complete response (CR), and ORR, which included minor responses by International Workshop for Waldenström Macroglobulinemia-6 criteria.[14] For response purposes, pathologic adenopathy and splenomegaly was defined as any node > 1.5 cm and > 15 cm in the longest axis. A ≥ 10% reduction by computed tomography (CT) scans in the bidimensional measurements of target lymph nodes and/or long axis of the spleen supported extramedullary disease response for PR and VGPR assessment.[11] Resolution of pathologic adenopathy or splenomegaly, no evidence of bone marrow (BM) disease involvement, normalization of serum IgM level, and no monoclonal IgM spike were required for CR attainment. Secondary end points included safety and tolerability assessments, PFS and OS determination, and effect of *MYD88*^{MUT} and *CXCR4*^{MUT} on ibrutinib response. Serum IgM measurement and complete blood cell counts were obtained at the beginning of each cycle for three cycles, and then every three cycles thereafter. BM biopsies and CT scans (if extramedullary disease was present at baseline) were repeated at cycles 6, 12, and 24, and annually thereafter.

Treatment-naïve patients were eligible if they met International Workshop for Waldenström Macroglobulinemia -2 diagnostic criteria, and criteria to treat.[1,15] Measurable disease was required (ie, serum IgM twice of more the upper limit of normal [ie, ≥ 480 mg/dL]); platelet count ≥ 50×10^9/L; absolute neutrophil count ≥ 1.0×10^9/L; creatinine clearance of ≥ 30 mL/min; total bilirubin ≤ 2.0 mg/dL, or < 2.5 mg/dL if attributable to hepatic infiltration by WM or Gilbert syndrome; serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase levels ≤ 2.5 times the upper limit of normal; and Eastern Cooperative Oncology Group performance status ≤ 2. Patients with CNS involvement or who were taking warfarin were excluded.

Intended therapy consisted of daily oral ibrutinib (420 mg) for 48 4-week cycles until disease progression or treatment intolerance. For hematologic toxicities, ibrutinib was held for absolute neutrophil count < 0.5×10^9/L; platelet count < 25×10^9/L or < 50×10^9/L with bleeding; grade ≥ 3 nausea, vomiting, or diarrhea; and grade ≥ 3 nonhematologic toxicities. Filgrastim or transfusional support was permitted. Full-dose retreatment was permitted after toxicity recovery from the first drug hold; thereafter, reductions to 280 mg, then 140 mg, then discontinuance, were required with subsequent events. Drug hold was recommended for 3 to 7 days before and after invasive procedures to minimize bleeding risk.

MYD88^{MUT} *and CXCR*^{MUT} *Genotyping*

An allele-specific polymerase chain reaction assay was used to detect *MYD88*^{L265P} mutation in CD19-selected BM lymphoplasmacytic cells. Sanger sequencing was also performed for non-L265P *MYD88*^{MUT}. *CXCR4*^{MUT} status was determined by Sanger sequencing and allele-specific polymerase chain reaction for *CXCR4*^{S338X} mutations, as reported.[16-18]

Statistical Analysis

The null hypothesis assumed that the MRR would be ≤ 40%. The MRR and its exact 95% CIs would be calculated and the null hypothesis rejected if the lower boundary of the 95% CI exceeded 40%. On the basis of the assumption that the MRR for ibrutinib is 70%, for 30 evaluable patients, the study would have a slightly > 90% power to declare that the lower boundary of the two-sided 95% CI for MRR would exceed 40%. A major response in 18 of 30 patients or more would be required to declare that the trial met its primary end point. The evaluable population was defined as all enrolled patients with WM who received at least one cycle of ibrutinib and had at least one postbaseline disease assessment. Kaplan-Meier estimation was used for time-to-response assessments, and the log-rank test was used to compare the time to response by *CXCR4* status.

PFS was defined as time between initiation of therapy and date of progression, death, or last follow-up. For time-to-event analyses with censoring, the Kaplan-Meier method was used. Pairwise comparisons were made using the Wilcoxon signed-rank test. The Holm-Bonferroni correction was used for multiple hypothesis testing of baseline characteristics on the basis of *CXCR4*^{MUT} status. Pearson correlation coefficient was used for linear comparisons. $P \leq .05$ were considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC). The PFS graph was created with Stata, version 13 (StataCorp, College Station, TX). The study drug was provided by Pharmacyclics (Sunnyvale, CA).

RESULTS

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 *MYD88*^{L265P}, and 14 (47%) had *CXCR4*^{MUT}. The clinical characteristics by *CXCR4*^{MUT} status are listed in Table 1. A higher incidence of adenopathy (50% *v* 14%; $P = .04$) was observed among patients with *CXCR4*^{WT} disease, as previously observed.[6] Patients with *CXCR4*^{WT} disease also had lower median serum IgM levels (3,928 *v* 5,295 mg/dL) versus those with

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

Characteristic	All Patients With WM (N = 30)	*MYD88*^{MUT} *CXCR4*^{WT} (n = 16)	*MYD88*^{MUT} *CXCR4*^{MUT} (n = 14)	*P**
Age, median (range), years	67 (43-83)	67 (43-83)	67 (43-75)	.94
Sex, No. (%)				
Male	23 (77)	12 (75)	11 (79)	.99
Female	7 (23)	4 (25)	3 (21)	
IPSSWM score, No. (%)				
Low	5 (17)	3 (19)	2 (14)	.36
Intermediate	11 (37)	4 (25)	7 (50)	
High	14 (47)	9 (56)	5 (36)	
Serum immunoglobulin				
IgM, median (range), mg/dL	4,370 (844-10,321)	3,928 (858-10,321)	5,295 (844-7,450)	.31
IgM > 3,000 mg/dL, No. (%)	18 (60)	9 (56)	9 (64)	.65
IgA, median (range), mg/dL	62 (11-576)	62 (15-576)	60 (11-132)	.96
IgG, median (range), mg/dL	563 (191-3,251)	606 (278-3,251)	470 (191-1,108)	.38
ANC, median (range), μL	3,370 (1,680-9,900)	3,450 (1,750-9,900)	3,220 (1,680-6,270)	.38
Hemoglobin, median (range), g/dL	10.3 (7.5-14.4)	10.1 (8.6-14.4)	10.6 (7.5-13.5)	.23
< 11 g/dL, No. (%)	20 (67)	12 (75)	8 (57)	.30
< 10 g/dL, No. (%)	10 (33)	7 (44)	3 (21)	.20
Platelet count, median (range), μL	247,000 (59,000-491,000)	288,000 (129,000-418,000)	199,000 (59,000-491,000)	.12
< 100,000/μL, No. (%)	2 (7)	0 (0)	2 (14)	.12
Serum β_2-microglobulin, median (range), mg/L	3.8 (2.0-7.6)	4.2 (2.3-6.9)	3.4 (2.0-7.6)	.07
> 3 mg/L, No. (%)	22 (73)	13 (81)	9 (64)	.29
BM disease involvement, median (range), %	65 (5-95)	60 (5-95)	70 (10-90)	.60
Extramedullary disease, No. (%)				
Adenopathy (> 1.5 cm)	10 (33)	8 (50)	2 (14)	.04
Splenomegaly (> 15 cm)	5 (17)	4 (25)	1 (7)	.19

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

CXCR4^{MUT} WM, but the difference did not reach statistical significance.[6] After Holm-Bonferroni correction for multiple hypothesis testing, baseline characteristics were not significantly different on the basis of *CXCR4*^{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, 57 to 5,280 mg/dL) at best response ($P < .001$). Pretherapy, 18 of the 30 patients (60.0%) had a serum IgM level ≥ 3,000 mg/dL; after treatment, at best response, two of 30 patients (6.7%) had a serum IgM level ≥ 3,000 mg/dL ($P < .001$). Median BM involvement decreased from 65% to 20% ($P < .001$), whereas hemoglobin concentration increased from a median of 10.3 g/dL to 13.9 g/dL at best response ($P < .001$). Responses included VGPR (n = 6; 20%), PR (n = 19; 63%), and minor response (n = 5; 17%) for ORR and MRR of 100% and 83.0%, respectively (Table 2). There were no CRs. The 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 baseline age (< 65 *v* ≥ 65 years), Eastern Cooperative Oncology Group status (0 *v* ≥ 1), WM International Prognostic Scoring System score,[19] serum β_2-microglobulin levels (< 3.0 *v* > 3.0 mg/L), hemoglobin level (< 11 *v* > 11 g/dL), serum IgM level (< 4,000 *v* ≥ 4,000 mg/dL), and BM disease involvement

Table 2. Response Rates and Kinetics of Response for Treatment-Naïve, Symptomatic Patients With Waldenström Macroglobulinemia Who Received Ibrutinib Monotherapy (N = 30)

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

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

(< 50% *v* ≥ 50%). MRRs (94% *v* 71.0%) and VGPR rates (31% *v* 7%) were higher in patients with *CXCR4*^{WT} versus those with *CXCR4*^{MUT} 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 *CXCR4*^{WT} versus *CXCR4*^{MUT} disease, respectively. ORR (Fig 1A) and MRR (Fig 1B) were delayed in patients with *CXCR4*^{MUT} disease and showed improvement after 3 and 6 cycles of therapy, respectively, when compared with patients with *CXCR4*^{WT} disease. Whereas deeper responses (as assessed by serial IgM changes) lagged for patients with *CXCR4*^{MUT} WM, improvements in hemoglobin concentration had similar kinetics over time for patients with *CXCR4*^{WT} disease and those with *CXCR4*^{MUT} 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.

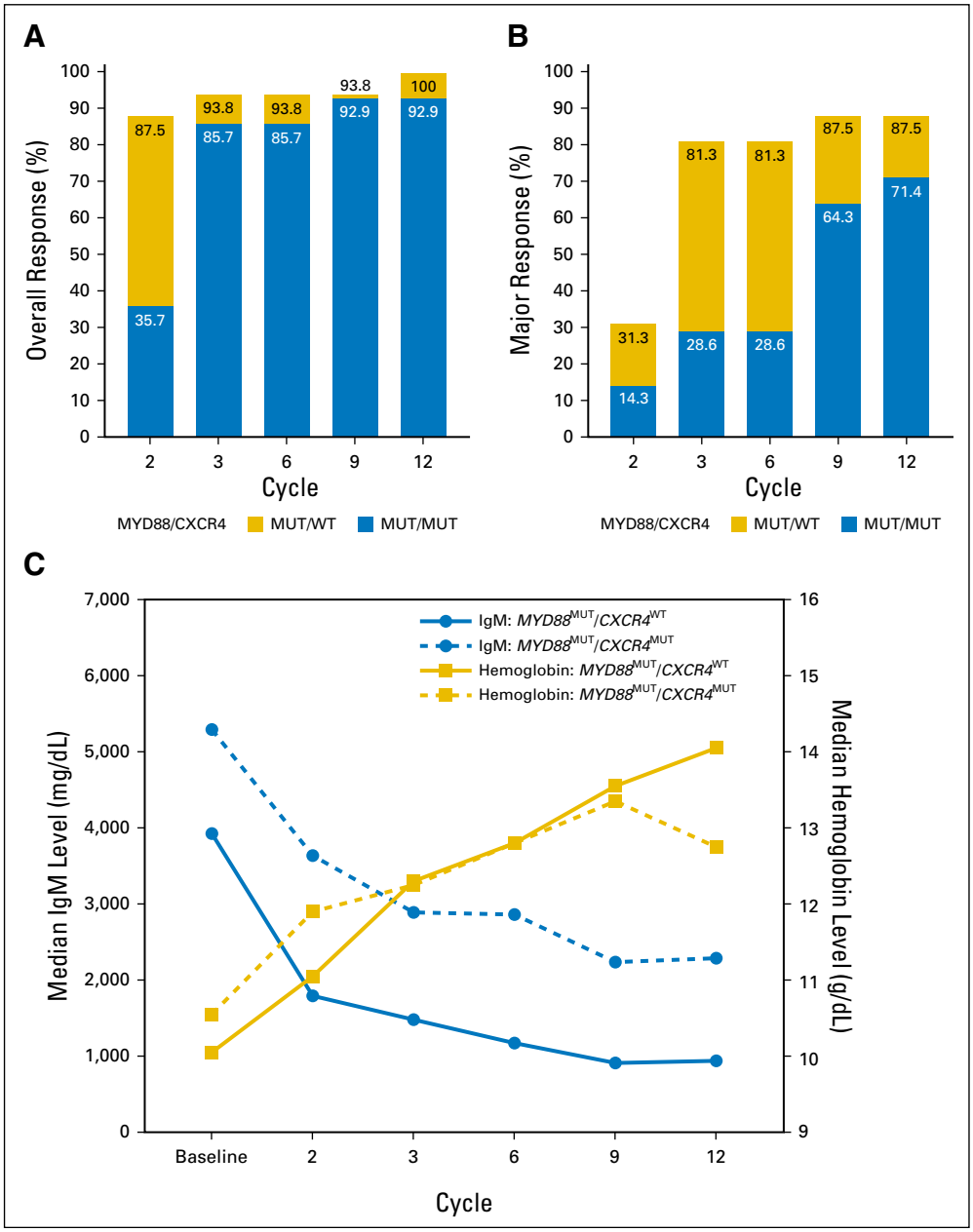

Fig 1. Cumulative overall and major response rates, and changes in serum IgM and hemoglobin levels by treatment cycles stratified by *CXCR4*^{MUT} status. (A) Overall and (B) major responses, and (C) serial changes in serum IgM and hemoglobin levels by ibrutinib treatment cycles by *CXCR4*^{MUT} status are shown at the denoted cycle. All patients had *MYD88*^{MUT} 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*^{MUT} 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 experienced atrial flutter while receiving ibrutinib and underwent cardiac ablation. After ablation, this patient developed sustained atrial fibrillation while not receiving ibrutinib, followed by ventricular arrhythmia 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-naïve patients with WM. We observed

Table 3. Adverse Events Associated With Ibrutinib Therapy in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia

Event or Abnormality	Grade, No. (%)			Total Grades 2-4*, No. (%)
	2	3	4	
Alanine transaminase elevation	0 (0)	1 (3)	0 (0)	1 (3)
Arthralgia	2 (7)	0 (0)	0 (0)	2 (7)
Aspartate transaminase elevation	0 (0)	1 (3)	0 (0)	1 (3)
Atrial fibrillation	3 (10)	0 (0)	0 (0)	2 (7)
Bruising	2 (7)	0 (0)	0 (0)	2 (7)
Cellulitis	1 (3)	0 (0)	0 (0)	1 (3)
Diarrhea	1 (3)	0 (0)	0 (0)	1 (3)
Drug-induced hepatitis	0 (0)	1 (3)	0 (0)	1 (3)
Foot pain	0 (0)	1 (3)	0 (0)	1 (3)
Hematoma	1 (3)	0 (0)	0 (0)	1 (3)
Hypertension	2 (7)	2 (7)	0 (0)	4 (13)
Mucosal infection	1 (3)	0 (0)	0 (0)	1 (3)
Neck abscess	1 (3)	0 (0)	0 (0)	1 (3)
Neutropenia	2 (7)	0 (0)	0 (0)	2 (7)
Palpitations	1 (3)	0 (0)	0 (0)	1 (3)
Pneumonia	1 (3)	0 (0)	0 (0)	1 (3)
Procedural hemorrhage	1 (3)	0 (0)	0 (0)	1 (3)
Rash, maculopapular	1 (3)	0 (0)	0 (0)	1 (3)
Rash, vasculitic	1 (3)	0 (0)	0 (0)	1 (3)
Rectal bleeding	0 (0)	1 (3)	0 (0)	1 (3)
Thrombocytopenia	0 (0)	1 (3)	0 (0)	1 (3)
Upper respiratory infection	2 (7)	0 (0)	0 (0)	2 (7)
Urinary tract infection	2 (7)	0 (0)	0 (0)	2 (7)

*Grade 2-4 adverse events deemed by investigators to be possibly, probably, or definitively associated with protocol therapy are shown.

a high ORR (100%) and MRR (83%), and responses were durable, with 18-month PFS and OS rates of 92% and 100%, respectively. Similar response rates were also observed in previously treated patients with WM receiving ibrutinib.[12,13] Responses exceeded 5 years in previously treated patients in the pivotal trial, whereas among patients with rituximab-refractory disease, the 18-month PFS was 86% with shorter follow-up, demonstrating durable benefit for ibrutinib in WM.[12,13]

By comparison, ORRs of 40% to 90% have been reported in treatment-naïve patients with WM with rituximab alone or in combination.[20-28] In the United States, rituximab monotherapy is the option most used for treatment-naïve patients with WM, according to SEER-linked Medicare data.[29] 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.[20-22] 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.[23-28,30,31] IgM flare due to rituximab is common in patients with WM and can lead to symptomatic hyperviscosity and aggravation of symptoms related to the IgM paraprotein.[32,33] 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.[34] 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.[11,13]

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.[11,13] 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.[20,21,23-25]

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.[35-37] One patient who developed an atrial arrhythmia had a potential predisposition (ie, a mildly enlarged left atrium related to valvular disease).[36] 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.[35-37]

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.[11] 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.[11,12]

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 *CXCR4*^{WT} versus *CXCR4*^{MUT} disease, respectively. As well, the time to attaining a major response was more rapid (1.8 *v* 7.3 months) in those with *CXCR4*^{WT} disease. Similar response kinetics were also observed in our ibrutinib monotherapy trial in previously treated patients with WM.[11] More rapid IgM response kinetics were also observed by Dimopoulos et al[13] for patients with rituximab-refractory *CXCR4*^{WT} disease who received ibrutinib monotherapy. In response to these findings, a clinical study of ibrutinib plus the anti-CXCR4 monoclonal antibody ulocuplumab has been initiated for patients with WM with *CXCR4*^{MUT} disease (Clinicaltrial.gov identifier: NCT03225716). It is interesting that both patients whose disease progressed while in this study in the follow-up period had *CXCR4*^{MUT} disease. In the pivotal study, patients with *CXCR4*^{MUT} disease also had a shorter median PFS compared with those with *CXCR4*^{WT} 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 *CXCR4*^{MUT} status. Overall, treatment was well tolerated, with no unexpected toxicities. Ibrutinib is safe and effective in treatment-naïve patients with symptomatic WM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Pharmacyclics (grant funding and ibrutinib) and by Peter Bing, a Translational Research Grant from the Leukemia and Lymphoma Society, the Linda and Edward Nelson Fund for Waldenström Macroglobulinemia Research, the Bauman Fund for Waldenström Macroglobulinemia Research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Research Funding: Janssen, Pharmacyclics
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Research Funding: Millennium (Inst), AbbVie (Inst), Janssen Pharmaceuticals (Inst), Pharmacyclics (Inst)