Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

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PURPOSE We report the long-term findings and final analysis of a pivotal multicenter trial of ibrutinib monotherapy in previously treated patients with Waldenström macroglobulinemia (WM).

PATIENTS AND METHODS Sixty-three symptomatic patients with median prior therapies of two (range, one to nine therapies), of whom 40% were refractory to their previous therapy, received ibrutinib at 420 mg/d. Dose reduction was permitted for toxicity.

RESULTS The median follow-up was 59 months, and overall and major response rates were 90.5% and 79.4%, respectively. At best response, median serum immunoglobulin M declined from 3,520 to 821 mg/dL (P = .001 for all comparisons). Responses were impacted by mutated (Mut) MYD88 and CXCR4 status. Patients with MYD88Mut, wild-type (WT) CXCR4 showed higher major (97.2% v 68.2%; P < .0001) and very good partial (47.2% v 9.1%; P < .01) response rates and a shorter time to major response (1.8 v 4.7 months; P = .02) versus patients with MYD88WT/CXCR4Mut. Conversely, four patients who had MYD88WT disease showed no major responses. The median 5-year progression-free survival (PFS) rate for all patients was not reached, and was 70% and 38% for those with MYD88Mut/CXCR4WT and MYD88Mut/CXCR4Mut WM, respectively (P = .02). In patients with MYD88WT, the median PFS was 0.4 years (P < .01 for three-way comparisons). The 5-year overall survival rate for all patients was 87%. Grade ≥ 3 adverse events in more than one patient at least possibly related included neutropenia (15.9%), thrombocytopenia (11.1%), and pneumonia (3.2%). Eight patients (12.7%) experienced atrial arrhythmia, and seven of the eight continued therapy with medical management.

CONCLUSION Ibrutinib is highly active and produces long-term disease control in previously treated patients with WM. Treatment is tolerable. Response depth, time to major response, and PFS are impacted by MYD88 and CXCR4 mutation status.

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INTRODUCTION Whole-genome sequencing has revealed activating mutations in MYD88 and CXCR4 in patients with Waldenström macroglobulinemia (WM).1,2 MYD88 mutations are present in 93%-97% of patients with WM and trigger Bruton tyrosine kinase (BTK) activation through hematopoietic cell kinase (HCK), a SRC family member.3,4 Activating mutations in CXCR4 that include nonsense and frameshift variants are found in 30%-40% of patients with WM.2,5,6 WM cells that express either nonsense or frameshift CXCR4 mutations show enhanced and prolonged AKT and ERK activation in response to CXCL12 and resistance to ibrutinib.7,9 Ibrutinib is a small-molecule inhibitor of BTK and HCK, which triggers apoptosis of MYD88-mutated (Mut) WM cells.3,4 Given the role of BTK and HCK in pro-survival signaling of MYD88Mut WM, we initiated an investigator-sponsored study of ibrutinib monotherapy in previously treated, symptomatic patients with WM. The initial findings showed that ibrutinib was well tolerated, with overall and major response rates of 90% and 73%, respectively.10 These findings supported the regulatory approval of ibrutinib for the treatment of symptomatic WM. Herein, we report the long-term safety and efficacy of this pivotal trial and the impact of MYD88 and CXCR4 mutation status on long-term treatment response.

PATIENTS AND METHODS A flow diagram for patient enrollment and disposition is shown in Figure 1. Sixty-three patients with an independent review committee–confirmed clinicopatho-logical
**CONTEXT**

**Key Objective**
Does ibrutinib produce long-term responses in previously treated Waldenström macroglobulinemia (WM), and does MYD88 and CXCR4 mutation status impact clinical outcome?

**Knowledge Generated**
The median progression-free survival in previously treated patients with WM exceeded 5 years and was affected by both MYD88 and CXCR4 mutation status. With a median follow-up of 59 months, no unexpected toxicities were encountered, and the incidence of atrial fibrillation increased to 12.7%, though most of these patients continued therapy with medical management.

**Relevance**
Considering that patients in this study were heavily pretreated and that 40% were refractory to their previous therapy, the findings establish ibrutinib as a highly active and tolerable therapy for symptomatic, relapsed, or refractory patients with WM, with long-term sustained responses in most patients. Compared with other available therapies, the efficacy and long-term safety of ibrutinib make ibrutinib a preferable option for use in previously treated WM.

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Diagnosis of WM were enrolled and treated. Bone marrow (BM) disease burden was based on intertrabecular disease estimation. All patients provided written informed consent after institutional review board study approval. Eligibility included a need for treatment according to consensus guidelines, one or more prior treatments, platelets of $50 \times 10^9/L$, hemoglobin of $8 \text{ g/dL}$, absolute neutrophil count (ANC) of $1.0 \times 10^9/L$, serum creatinine level of $\leq 2 \text{ mg/dL}$, total bilirubin $\leq 1.5 \text{ mg/dL}$ (or $\leq 2.0 \text{ mg/dL}$ if attributable to tumor), serum AST and ALT levels $\leq 2.5$ times the upper limit of normal, and Eastern Cooperative Oncology Group performance status $\leq 2$. Patients with CNS disease involvement, with clinically significant cardiovascular disease, or on warfarin or medications that could prolong QT interval were excluded.

Enrollment began May 23, 2012, and closed June 13, 2013. Patients received ibrutinib on study for 40 months and thereafter, could opt for an extension study with commercial drug supply for response determination. The last patient evaluation and survival update was September 14, 2018. The primary objective was to determine the overall and major response rates using modified criteria from the 6th International Workshop on WM as before. A decrease of 25%-49%, 50%-89%, and $\geq 90\%$ in serum immunoglobulin M (IgM) levels denoted minor response (MR), partial response (PR), and very good partial response (VGPR). Normalization of serum IgM level, no monoclonal IgM spike, BM disease involvement, or pathological adenopathy or splenomegaly was required for complete response (CR). The overall response rate included MR or better, and major response rate included PR or better. Secondary objectives included determination of progression-free survival (PFS) and drug safety. Serum IgM and CBC counts were obtained at the beginning of each cycle for three cycles and every three cycles thereafter. BM biopsies and computed tomography (CT) scans.

**FIG 1.** Flow diagram for patient enrollment and disposition. MDS, myelodysplastic syndrome.
Intended therapy consisted of oral ibrutinib (420 mg/d) until disease progression or intolerance. Ibrutinib was held for ANC < 0.5 x 10^9/L, platelets < 25 x 10^9/L or < 50 x 10^9/L with bleeding, grade ≥ 3 nausea, vomiting or diarrhea, and grade ≥ 3 nonhematological toxicities. Filgrastim or transfusion support was permitted. Full-dose retreatment was permitted after toxicity recovery from first drug hold, but thereafter, reduction to 280 mg, then 140 mg, then discontinuation was required with subsequent events. Drug hold was recommended for 3-7 days before and after invasive procedures to minimize bleeding risk.

### Statistical Analysis

A Simon’s two-stage design was used, with α-level set at 0.05 and β-level set at 0.20; this assumed a null response rate of 20% and successful overall response rate of 40% on the basis of comparisons with other monotherapies used in previously treated WM. The Protocol (online only) was amended according to regulatory guidance to require enrollment of additional participants on the assumption that if the response rate for ibrutinib was 50%, the study would have > 80% power to show a lower boundary of the two-sided 95% CI for response rate > 32%. PFS was defined as the time between therapy initiation and disease progression, death, or last follow-up. The Kaplan-Meier (KM) method was used to estimate survival curves, which were compared by log-rank test. Univariable and multivariable logistic regression analyses were performed for attainment of major response and VGPR and Cox proportional hazards regression analyses for PFS. Pairwise comparisons were made using Wilcoxon signed rank test. One-way analysis of variance (ANOVA) with Tukey’s honestly significant difference (HSD) was used for three-way data comparisons for genomic cohorts. Fisher’s 3 x 4 exact probability test was used for categorical response comparisons by genotype. Cochran-Mantel-Haenszel test was used in the analysis of matched categorical data. $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC). The PFS graph was created with STATA 15 software (StataCorp, College Station, TX). Pharmacycics (Sunnyvale, CA) supported this investigator-initiated study and provided research funding and study drug.

### MYD88 and CXCR4 Mutation Genotyping

An allele-specific polymerase chain reaction (AS-PCR) assay was used to detect MYD88^L265P mutation in CD19-selected BM lymphoplasmacytic cells. Sanger sequencing was also performed for non-L265P MYD88 mutations.14 CXCR4 mutation status was determined by Sanger sequencing and AS-PCR for CXCR4^FSH140X mutations as before.15

### Results

#### Patients and Disease Characteristics

The baseline characteristics for the 63 patients with WM are listed in Table 1. Sanger sequencing for non-L265P MYD88 mutations and use of serial CD19-selected BM tissue revealed additional MYD88 and CXCR4 mutations, which
are updated herein from the original report. All 63 patients were genotyped for MYD88 mutations. Fifty-nine (93.6%) had activating MYD88 mutations, of whom 57 expressed CXCR4 mutations, of whom 22 had C-terminal domain mutations. Among the 22 patients with CXCR4 Mut disease (97.2% vs 33.3%; \( P = .01 \)), a finding consistent with previous observations.

Responses
The median study follow-up was 59 months (95% CI, 40 to 60 months). After ibrutinib, median serum IgM levels declined from 3,520 mg/dL (range, 724-8,390 mg/dL) to 4,000 mg/dL (range, 27-5,820 mg/dL) at best response (\( P < .001 \)). At pretherapy, 26 (41.0%) of 63 patients had a serum IgM \( \geq 4,000 \) mg/dL; after treatment at best response, one (1.6%) of 63 patients had a serum IgM \( > 4,000 \) mg/dL; after treatment at best response, one (1.6%) of 63 patients had a serum IgM \( > 4,000 \) mg/dL (\( P < .001 \)). Median BM involvement decreased from 60% (range, 3%-95%) to 20% (range, 0%-65%; \( P < .001 \)), and hemoglobin increased from a median of 10.3 g/dL to 14.2 g/dL (range, 8.2-13.8 g/dL) at best response (\( P < .001 \)). Responses included VGPR (n = 19; 30.2%), PR (n = 31; 49.2%), and MR (n = 7; 11.1%) for overall and major response rates of 90.5% and 79.4%, respectively (Table 2). VGPR attainment increased over time as follows: 6 (6.4%), 12 (12.7%), 18 (15.9%), 24 (19.1%), 36 (22.2%), \( > 36 \) (30.2%) months. There were no CRs. The median time to at least an MR, major response, and VGPR were 0.9 months (range, 0.9-21 months), 2 months (range, 0.9-51 months), and 15.5 months (range, 2-57 months), respectively. The median time to best response was 7.5 months (range, 1-57 months).

The findings from logistic regression analyses for determinants of major response and VGPR to ibrutinib are listed in Appendix Tables A1 and A2 (online only). Both major response and VGPR were not impacted by many of the traditional adverse predictors of response in WM. By univariable analysis, those with higher BM disease involvement (\( \geq 50 \)) and presence of extramedullary disease showed significantly greater major response and VGPR (Appendix Tables A1 and A2). Patients with higher serum \( \beta_2 \)-microglobulin levels (\( > 3.0 \) mg/L) also had greater VGPR by univariable analysis (Appendix Table A2). By multivariable analysis, only higher BM disease involvement (\( \geq 50 \)) at baseline remained significant for major response and trended toward significance for VGPR attainment (Appendix Table A2). The presence of MYD88\textsuperscript{Mut}/CXCR4\textsuperscript{Mut} disease was associated with significantly lower major response and VGPR by univariable analyses and remained significant by multivariable analysis for major response attainment (Appendix Tables A1 and A2).

Overall and major response rates were impacted by MYD88 and CXCR4 mutation status (Table 2). Those with MYD88\textsuperscript{Mut}/CXCR4\textsuperscript{Wild} showed more major responses versus those with MYD88\textsuperscript{Wild}/CXCR4\textsuperscript{Mut} disease (97.2% vs 68.2%; \( P < .0001 \)). The VGPR in patients with MYD88\textsuperscript{Mut}/CXCR4\textsuperscript{Wild} disease (47.2%) was greater versus those with MYD88\textsuperscript{Wild}/CXCR4\textsuperscript{Mut} disease (9.1%; Table 2). Conversely,

### Table 2. Response Rates and Kinetics of Response of Previously Treated Patients With WM Who Received Ibrutinib Monotherapy (n = 63)

| Variable                  | All          | MYD88\textsuperscript{Mut} | MYD88\textsuperscript{Wild} | MYD88\textsuperscript{Mut} | MYD88\textsuperscript{Wild} | \( P \)  |
|--------------------------|--------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--------|
| No. of patients          | 63           | 36                          | 22                          | 4                           |                             |        |
| Overall response rate    | 57 (90.5%)   | 36 (100.0)                  | 19 (86.4)                   | 2 (50.0)                    | \( < .0100 \)                |        |
| Major response rate      | 50 (79.4%)   | 35 (97.2)                   | 15 (68.2)                   | 0 (0.0)                     | \( < .0001 \)                |        |
| Categorical responses    |              |                             |                             |                             |                             |        |
| No response              | 6 (9.5%)     | 0 (0.0)                     | 3 (13.6)                    | 2 (50.0)                    | \( < .0001 \)                |        |
| Minor response           | 7 (11.1%)    | 1 (2.8)                     | 4 (18.2)                    | 2 (50.0)                    |                             |        |
| Partial response         | 31 (49.2%)   | 18 (50.0)                   | 13 (59.1)                   | 0 (0.0)                     |                             |        |
| Very good partial response| 19 (30.2%)  | 17 (47.2)                   | 2 (9.1)                     | 0 (0.0)                     |                             |        |
| Median time to response  |              |                             |                             |                             |                             |        |
| (> partial response)     | 1.8          | 1.8                         | 4.7                         | NA                          | \( .0200 \)                  |        |

NOTE. Data presented as No. (%). Response rates, including categorical responses and median time to attainment of least a minor and a major response for all patients and those stratified by MYD88 and CXCR4 mutation status, are provided. \( P \) values denote three-way comparisons among genomic cohorts.

Abbreviations: Mut, mutant; NA, not applicable; WM, Waldenström macroglobulinemia; WT, wild type.
four patients with MYD88<sup>WT</sup> disease showed no major responses (P < .0001 for differences in categorical responses for the three genomic groups). Improvements in serum IgM and hemoglobin levels at best response were also greater in patients who were MYD88<sup>Mut</sup>CXCR4<sup>WT</sup> versus the other two genotypes (P < .001 and P = .002, respectively, by one-way ANOVA and Tukey’s HSD; Appendix Fig A1, online only).

Among patients with MYD88<sup>Mut</sup>, CXCR4 mutation status did not impact the median time to an MR, which was 0.9 months for both groups (P = .38). For patients with MYD88<sup>Mut</sup> who were CXCR4<sup>WT</sup>, the median time to attaining at least a major response was shorter versus those with CXCR4<sup>Mut</sup> disease (1.8 vs 4.7 months, respectively; P = .02). There were no significant differences in overall response, major response, or VGPR among patients with CXCR4<sup>Mut</sup> with either nonsense or frameshift mutations.

Because MYD88 and CXCR4 mutation status can impact extramedullary and BM disease burden, a Cochran-Mantel-Haenszel test was performed. BM (≥ 50%) involvement remained a positive independent predictor of overall response, major response, and VGPR (P ≤ .05 for all categorical responses).

No significant changes in serum IgA and IgG levels occurred during the study course. The median serum IgA at baseline and at last assessments were 26 and 26 mg/dL, respectively (P = .98). For serum IgG, median values at baseline and at last assessments were 363 and 344 mg/dL, respectively (P = .39). Forty patients (64%) had extramedullary disease at baseline, including 37 with adenopathy (> 1.5 cm) and/or seven with splenomegaly (> 15 cm). Two patients experienced disease progression before

**FIG 2.** Progression-free survival (PFS) and overall survival (OS) for previously treated patients with Waldenström macroglobulinemia (WM) after ibrutinib monotherapy. Kaplan-Meier curves shown for all 63 patients with WM for (A) PFS and (C) OS. (B) PFS and (D) OS are shown for 62 patients with WM by MYD88 and CXCR4 mutation status. One patient with MYD88 mutation did not have CXCR4 mutation status determined. Log-rank P < .01 for PFS and P = .42 for OS comparisons by MYD88 and CXCR4 mutation status. Mut, mutated; WT, wild type.
serial imaging could be performed. At last CT scan, improvements or resolution of extramedullary disease were observed in 24 (63%) of 38 patients with serial imaging. Eleven (28.9%) of 38 patients had stable disease, and three (7.9%) experienced progressive extramedullary disease at last CT scan.

**PFS and Overall Survival**

Figure 2A shows the KM curves for PFS for all study participants. The 5-year PFS rate for all patients was 54% (95% CI, 39% to 67%). Notable baseline clinical features that were significantly associated with earlier PFS included treatment with three or more versus one to two prior lines of therapy (5-year PFS rate, 38% vs 68%; \( P = .01 \)) and BM disease burden ≥ 50% vs < 50% (5-year PFS rate, 69% vs 34%; \( P = .007 \)). Having a high versus low/intermediate International Prognostic Scoring System for Waldenström Macroglobulinemia score \(^{16,16} \) (5-year PFS rate, 38% vs 63%; \( P = .06 \)) and age > 65 vs ≤ 65 years (5-year PFS rate, 40% vs 65%; \( P = .07 \)) showed a trend toward significance for earlier PFS. Relapsed versus refractory disease, presence or absence of extramedullary disease, and serum IgM levels > 4,000 mg/dL at study entry did not impact PFS.

As shown in Figure 2B, MYD88 and CXCR4 mutation status impacted PFS. The median PFS was not reached for patients with MYD88\(^{Mut}\)/CXCR4\(^{WT}\) (5-year PFS rate, 70%; 95% CI, 50% to 84%). For patients with MYD88\(^{Mut}\)/CXCR4\(^{Mut}\), the median PFS was 4.5 years (5-year PFS rate, 38%; 95% CI, 16% to 60%; \( P = 0.02 \) vs MYD88\(^{Mut}\)/CXCR4\(^{WT}\)). Among patients with CXCR4\(^{Mut}\), the 5-year PFS rate was 50% (95% CI, 6% to 84%) and 36% (95% CI, 12% to 60%) for those with frameshift and nonsense variants, respectively. Compared with patients with MYD88\(^{Mut}\)/CXCR4\(^{WT}\) disease, those with frameshift CXCR4 mutations showed no significant difference \( (P = .57) \), whereas those with nonsense CXCR4 mutations had significantly shorter PFS \( (P = .04) \); Appendix Fig A2). For those with MYD88\(^{WT}\) disease, the median PFS was 0.4 years (95% CI, 0.01 to not reached; log-rank \( P < .01 \) for three-way comparison). All 4 patients with MYD88\(^{WT}\)/CXCR4\(^{WT}\) experienced disease progression within 2 years of treatment. Cox proportional hazards regression analysis for PFS is listed in Table 3. By multivariable analysis, BM involvement < 50%, prior treatment with three or more lines of therapy, presence of MYD88\(^{WT}\), and CXCR4\(^{Mut}\) disease were significant predictors for shorter PFS. The 5-year overall survival (OS) rate for all patients was 87% (Fig 2C). The 5-year OS rate was 93% (95% CI, 74% to 98%) and 80% (95% CI, 49% to 93%) for patients with MYD88\(^{Mut}\)/CXCR4\(^{Mut}\) and MYD88\(^{Mut}\)/CXCR4\(^{WT}\), respectively (log-rank \( P = .42 \); Fig 2D).

Thirty-six patients completed the study as planned. Reasons for coming off study included nonresponse (n = 1) or progressive disease (n = 14) that included two patients who transformed to diffuse large B-cell lymphoma that likely was a consequence of pre-ibrutinib nucleoside analog

**TABLE 3.** Cox Proportional Hazard Regression Analysis for Progression-Free Survival With Ibrutinib

| Variable | HR (95% CI) | \( P \) | HR (95% CI) | \( P \) |
|----------|------------|---|------------|---|
| Age > 65 years | 2.08 (0.92 to 4.70) | .08 | 1.25 (0.51 to 3.06) | .620 |
| Hemoglobin ≤ 11.5 g/dL | 1.09 (0.45 to 1.64) | .84 |
| β2-Microglobulin > 3 mg/L | 0.67 (0.28 to 1.57) | .35 |
| Serum IgM ≥ 4,000 mg/dL | 0.98 (0.43 to 2.20) | .96 |
| BM involvement ≥ 50% | 0.34 (0.15 to 0.78) | .01 | 0.25 (0.10 to 0.65) | .005 |
| Platelet count ≤ 100,000/μL | 2.52 (0.73 to 8.59) | .14 |
| Extramedullary disease | 0.75 (0.33 to 1.69) | .49 |
| Refractory disease | 0.82 (0.36 to 1.88) | .64 |
| > 2 lines of therapy | 2.82 (1.23 to 6.45) | .01 | 6.46 (2.32 to 18.0) | <.001 |
| Low IPSSWM | Reference* |
| Intermediate IPSSWM | 0.90 (0.28 to 2.83) | .85 |
| High IPSSWM | 2.00 (0.70 to 5.71) | .19 |
| MYD88\(^{Mut}\)/CXCR4\(^{WT}\) | Reference* |
| MYD88\(^{Mut}\)/CXCR4\(^{Mut}\) | 2.62 (1.09 to 6.34) | .03 | 4.39 (1.63 to 11.9) | .004 |
| MYD88\(^{WT}\)/CXCR4\(^{WT}\) | 14.9 (1.66 to 60.3) | <.001 | 37.0 (6.19 to 220.9) | <.001 |

Note. Univariable and multivariable analyses of baseline characteristics are shown. Abbreviations: BM, bone marrow; HR, hazard ratio; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; Mut, mutated; WM, Waldenström macroglobulinemia; WT, wild type.

*Reference standard for comparisons.
**TABLE 4.** Adverse Events Associated With Ibrutinib Therapy in Previously Treated Patients With Waldenström Macroglobulinemia (N = 63)

| Adverse Event                                | Grade 2 | Grade 3 | Grade 4 | Total Grades 2-4 |
|----------------------------------------------|---------|---------|---------|------------------|
| Blood and lymphatic system disorders         |         |         |         |                  |
| Anemia                                       | 2       | 1       | 0       | 3                |
| Thrombocytopenia                             | 1       | 5       | 2       | 8                |
| Neutropenia                                  | 5       | 6       | 4       | 15               |
| Febrile neutropenia                          | 0       | 0       | 1       | 1                |
| Cardiac disorders                            |         |         |         |                  |
| Atrial fibrillation                          | 5       | 1       | 0       | 6                |
| GI disorders                                 |         |         |         |                  |
| Bloating                                     | 1       | 0       | 0       | 1                |
| Constipation                                 | 2       | 0       | 0       | 2                |
| Diarrhea                                     | 2       | 0       | 0       | 2                |
| Duodenal ulcer                               | 1       | 0       | 0       | 1                |
| Gastric ulcer                                | 1       | 0       | 0       | 1                |
| Gastroesophageal reflux disease              | 5       | 0       | 0       | 5                |
| Mucositis oral                               | 3       | 0       | 0       | 3                |
| Other                                        | 1       | 0       | 0       | 1                |
| General disorders                            |         |         |         |                  |
| Edema in limbs                               | 1       | 0       | 0       | 1                |
| Infections and infestations                  |         |         |         |                  |
| Bronchial                                    | 2       | 0       | 0       | 2                |
| Endocarditis                                 | 0       | 1       | 0       | 1                |
| Eye                                          | 1       | 0       | 0       | 1                |
| Lung                                         | 3       | 2       | 0       | 5                |
| Sinusitis                                    | 1       | 0       | 0       | 1                |
| Skin                                         | 3       | 1       | 0       | 4                |
| Upper respiratory                            | 1       | 0       | 0       | 1                |
| Urinary tract                                | 2       | 0       | 0       | 2                |
| Procedural complications                     |         |         |         |                  |
| Postprocedure hemorrhage                      | 1       | 0       | 0       | 1                |
| Metabolism and nutrition disorders           |         |         |         |                  |
| Dehydration                                  | 2       | 0       | 0       | 2                |
| Other                                        | 1       | 0       | 0       | 1                |
| Musculoskeletal and connective tissue disorders |         |         |         |                  |
| Arthralgia                                   | 2       | 0       | 0       | 2                |
| Myalgia                                      | 2       | 0       | 0       | 2                |
| Other                                        | 2       | 0       | 0       | 2                |
| Nervous system disorders                     |         |         |         |                  |
| Headache                                     | 1       | 0       | 0       | 1                |
| Presyncope                                   | 1       | 0       | 0       | 1                |
| Syncope                                      | 0       | 1       | 0       | 1                |
| Respiratory, thoracic, and mediastinal disorders |         |         |         |                  |
| Cough                                        | 1       | 0       | 0       | 1                |

(continued on following page)
exposure, amyloid progression while in hematologic remission (n = 1), and progression that occurred during drug hold (ie, pseudoprogression; n = 3). All these events were counted as disease progression per protocol. Other reasons included withdrawal of consent for required protocol follow-up (n = 6); adverse events, as summarized in the next section (n = 4); change in therapy as a result of unrelated myelodysplasia (n = 1); and rectal carcinoma (n = 1).

Toxicities

Grade ≥ 2 toxicities that were at least possibly related to protocol therapy are listed in Table 4. Grade ≥ 3 adverse events in more than one patient deemed at least possibly related included neutropenia (15.9%), thrombocytopenia (11.1%), and pneumonia (3.2%). Neutropenia and thrombocytopenia were more common in heavily pre-treated patients. Eight (80%) of 10 and six (86%) of seven neutropenic and thrombocytopenic events, respectively, occurred in patients with three or more prior therapies (P < .05 for comparisons among patients with three or more vs fewer than three prior therapies). Eight patients (12.7%) had atrial arrhythmia (grade 1, n = 2; grade 2, n = 5; grade 3, n = 1) at a median of 15 months (range, 3-38 months) of starting ibrutinib, and seven of eight continued ibrutinib with medical management for the arrhythmia. Five patients came off study for adverse events, including procedure-related hemoptasia (n = 1), thrombocytopenia (n = 1), influenza-related pneumonia (n = 1), streptococcal endocarditis (n = 1), and atrial fibrillation (n = 1). Twelve patients experienced dose reductions to 280 mg/d (n = 9) and 140 mg/d (n = 3). Reasons for dose reductions included cytopenias (n = 5), dermatitis or rash (n = 2), stomatitis (n = 2), leg edema (n = 1), myalgias (n = 1), and atrial fibrillation (n = 1).

**DISCUSSION**

We present the long-term follow-up of the pivotal study for ibrutinib monotherapy in patients with symptomatic, relapsed, or refractory WM. The current report greatly extends the median follow-up to 59 months from 19.1 months at the initial report.10 We observed a high overall (90.5%) and major (79.4%) response rate, with deepening of responses during the follow-up period. The attainment of VGPR increased from 15.9% to 30.2%, which establishes ibrutinib as one of the most active monotherapies in WM. However, no CR was observed consistent with other BTK inhibitor studies in WM.18-23 While ibrutinib bLOCKs BTK and HCK signaling, other pathways, such as IRAK1/IRAK4 or SYK, that are triggered by MYD88Mut could provide ongoing prosurvival signaling.3,24

Response to ibrutinib was not impacted by many traditional adverse predictors of response. Patients with high BM involvement (≥ 50%) and extramedullary disease showed even higher major response and VGPR rates by univariable analysis. Because extramedullary disease is more typical of patients with MYD88Mut without concurrent CXCR4Mut, this comes as no surprise.5 However, high BM involvement is a feature of CXCR4Mut WM disease and remained significant for major response attainment, even by multivariable analysis.5,29 Consistent with these findings, patients with high BM involvement had also significantly longer PFS. In previous work, we observed that high BM involvement is associated with elevated CXCL13, a major prognostic factor for ibrutinib response.26 The disruption of BM microenvironmental support by ibrutinib that facilitates WM expansion could underpin these findings.

As in our initial report, both MYD88 and CXCR4 mutation status impacted responses.10,27 Although only four patients with MYD88wt were treated, none attained a major response, even with longer follow-up. Patients with MYD88Mut
have nuclear factor-κB–activating mutations that are distal to BTK, which likely explains these findings. Among patients with MYD88Mut, concurrent CXCR4Mut impacted response depth and time to major response. VGPRs were fewer, and time to major response was longer in patients with MYD88Mut/CXCR4Mut. Fewer VGPRs were also reported by Dimopoulos et al.18 in rituximab-refractory patients on ibrutinib alone and by Buske et al29 in patients treated with ibrutinib and rituximab. The use of CXCR4 inhibitors (ClinicalTrials.gov identifiers: NCT03225716 and NCT04274738) with ibrutinib is currently under investigation in patients with CXCR4Mut WM and may provide insights into overcoming the adverse effects of CXCR4Mut in patients with WM on BTK inhibitors.

Anemia is the most common morbidity affecting patients with WM. A rapid increase in hemoglobin levels was observed, with hemoglobin levels rising from 10.5 g/dL at baseline to 11.4 and 12.1 g/dL at 4 and 8 weeks, respectively. At best response, the median hemoglobin level was 14.2 g/dL, only marginally better than 13.8 g/dL noted in our original report and signifying the upfront benefits of anemia recovery with ibrutinib. Similarly, rapid decreases in serum IgM followed ibrutinib, with decreases of 35% and 50% at 4 and 8 weeks, respectively. At best response, median serum IgM levels declined by 77%. The decrease in serum IgM levels permitted discontinuation of plasmapheresis in all three patients with symptomatic hyperviscosity and bleeding related to acquired factor VIII deficiency in one patient. All nine patients treated for IgM-related demyelinating neuropathy who experienced disease progression or were refractory to rituximab showed stabilization or improvement of their sensory neuropathy. Progressive neuropathy occurred in only two of these patients during follow-up, which signified an important role for ibrutinib in the control of IgM demyelinating neuropathy in patients with WM.

A key finding was the long durability for ibrutinib response, with the median PFS > 5 years. By comparison with other agents and combinations used in relapsed or refractory WM, the median PFS observed with ibrutinib is superior.30,31 Moreover, the observed PFS was on par with autologous transplantation, which unlike ibrutinib, is affected by the number of prior lines of therapy, chemotherapeutic agents, and a high incidence of secondary malignancies. The findings provide a cogent case for the preferred use of ibrutinib in most previously treated patients who are BTK inhibitor naïve. Finally, the sustained long-term control of disease in the absence of a CR supports the notion that attainment of CR need not be the primary goal of therapy in WM.31,33

Overall, ibrutinib was tolerable in this previously treated WM population, and no unexpected toxicities were encountered. Grade ≥ 3 neutropenia and thrombocytopenia were more common in more heavily pretreated patients, a finding echoed in treatment-naïve patients in whom grade ≥ 3 cytopenias were rare. These findings would suggest that prior drug exposure is likely to account for these findings versus ibrutinib per se. Atrial arrhythmias occurred in eight patients (12.7%) after ibrutinib treatment, a rate similar to that observed in previous studies by us and others.34-37 Of note, all but one of these patients continued therapy with medical management. Our experience, and those of others, continues to reflect that the occurrence of atrial arrhythmias while on ibrutinib is not practice altering, and most patients can be managed with pharmacological rate control (eg, β-blockers), anti-arrhythmic agents, cardiac ablation, and/or anticoagulation without the need for ibrutinib dose reduction.34-37

In summary, our findings show that ibrutinib is highly active with long-term disease control in previously treated patients with WM. While ibrutinib responses were affected by both MYD88 and CXCR4 mutation status, long-term disease control was attained in patients with MYD88Mut disease, regardless of CXCR4 mutation status. Overall, treatment was tolerable, with no unexpected toxicities. The findings establish ibrutinib as one of the most active agents in symptomatic, relapsed, or refractory WM. Prospective, randomized studies against other commonly used treatment options, such as bendamustine and rituximab, other BTK-inhibitors, and combinations that include CXCR4 or BCL2 inhibitors, are needed to further define the optimal use of ibrutinib in WM management.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

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FIG A1. Changes in serum immunoglobulin M (IgM) and hemoglobin levels by MYD88 and CXCR4 mutation status. Changes in mean (A) serum IgM and (B) hemoglobin levels (± SEM) at best response are shown for patients by MYD88 and CXCR4 mutation status after ibrutinib treatment. $P < .001$ and $P = .002$, respectively, for serum IgM and hemoglobin differences between cohorts by one-way analysis of variance and Tukey’s honestly significant difference. MYD88 mutated (Mut), CXCR4 wild type (WT; $n = 36$), MYD88Mut CXCR4Mut ($n = 22$), and MYD88WT CXCR4WT ($n = 4$). One patient with MYD88Mut disease but whose CXCR4 mutation status was not determined was not included in this analysis.
FIG A2. Progression-free survival (PFS) by baseline characteristics for previously treated patients with Waldenström macroglobulinemia (WM) after ibrutinib monotherapy. Kaplan-Meier curves are shown for patients on the basis of (A) International Prognostic Scoring System WM (IPSSWM) score, (B) age, (C) number of prior lines of therapy, (D) relapsed or refractory status, (E) bone marrow (BM) burden, (F) presence or absence of extramedullary disease, (G) serum immunoglobulin M (IgM) level, and (H) MYD88 and CXCR status stratified by nonsense (NS) or frameshift (FS) mutations. Log-rank P values indicated for relevant comparisons. Mut, mutated; WT, wild type.
**TABLE A1.** Logistic Regression Analyses for Attainment of Major Response to Ibrutinib

| Variable                  | Univariable |          |          | Multivariable |          |          |
|---------------------------|-------------|----------|----------|---------------|----------|----------|
|                           | OR (95% CI) | P        | OR (95% CI) | P        |
| Age > 65 years            | 0.45 (0.13 to 1.58) | .21      |            |            |
| Hemoglobin ≤ 11.5 g/dL    | 1.61 (0.45 to 5.76) | .47      |            |            |
| β2-Microglobulin > 3 mg/L| 1.88 (0.51 to 6.84) | .34      |            |            |
| Serum IgM ≥ 4,000 mg/dL   | 0.84 (0.25 to 2.88) | .79      |            |            |
| BM involvement ≥ 50%      | 8.57 (2.05 to 35.8) | .003     | 11.10 (1.49 to 82.0) | .02  |
| Platelet count ≤ 100,000/µL | 1.64 (0.18 to 14.9) | .66      |            |            |
| Extramedullary disease    | 3.73 (1.05 to 13.3) | .04      | 2.51 (0.32 to 20.0) | .38  |
| Refractory disease        | 1.07 (0.30 to 3.73) | .92      |            |            |
| ≥ 3 lines of therapy      | 1.92 (0.52 to 7.05) | .33      |            |            |
| Low IPSSWM                | Referencea  |          |            |            |
| Intermediate IPSSWM       | 1.36 (0.26 to 7.23) | .72      |            |            |
| High IPSSWM               | 0.86 (0.18 to 4.16) | .86      |            |            |
| MYD88MUT-CXCR4WT          | Referenceb  |          |            |            |
| MYD88MUT-CXCR4Mut         | 0.06 (0.01 to 0.54) | .01      | 0.06 (0.01 to 0.72) | .03  |
| MYD88WT-CXCR4WT           | UTCc        |          |            |            |

NOTE. Univariable and multivariable analyses of baseline characteristics are shown. Abbreviations: BM, bone marrow; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; Mut, mutated; OR, odds ratio; UTC, unable to calculate; WT, wild type.

*aReference standard for comparison.
bNone of the patients with MYD88MUT attained a major response.

**TABLE A2.** Logistic Regression Analyses for Attainment of Very Good Partial Response to Ibrutinib

| Variable                  | Univariable |          |          | Multivariable |          |          |
|---------------------------|-------------|----------|----------|---------------|----------|----------|
|                           | OR (95% CI) | P        | OR (95% CI) | P        |
| Age > 65 years            | 0.80 (0.27 to 2.36) | .68      |            |            |
| Hemoglobin ≤ 11.5 g/dL    | 1.94 (0.55 to 6.89) | .31      |            |            |
| β2-Microglobulin > 3 mg/L| 11.10 (1.35 to 91.2) | .03      | 5.38 (0.53 to 54.2) | .15  |
| Serum IgM ≥ 4,000 mg/dL   | 0.51 (0.16 to 1.57) | .24      |            |            |
| BM involvement ≥ 50%      | 4.87 (1.24 to 19.1) | .02      | 3.91 (0.84 to 18.1) | .08  |
| Platelet count ≤ 100,000/µL | UTCa     |          |            |            |
| Extramedullary disease    | 7.76 (1.60 to 37.7) | .01      | 4.19 (0.72 to 24.3) | .11  |
| Refractory disease        | 2.15 (0.72 to 6.42) | .17      |            |            |
| ≥ 2 lines of therapy      | 1.30 (0.44 to 3.84) | .64      |            |            |
| Low IPSSWM                | Referencea  |          |            |            |
| Intermediate IPSSWM       | 1.03 (0.24 to 4.41) | .97      |            |            |
| High IPSSWM               | 1.18 (0.28 to 4.93) | .82      |            |            |
| MYD88MUT-CXCR4WT          | Referenceb  |          |            |            |
| MYD88MUT-CXCR4Mut         | 0.11 (0.03 to 0.55) | .007     | 0.28 (0.05 to 1.75) | .18  |
| MYD88WT-CXCR4WT           | UTCc        |          |            |            |

Abbreviations: BM, bone marrow; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; Mut, mutant; OR, odds ratio; UTC, unable to calculate; WT, wild type.

*aReference standard for comparison.

None of the patients with platelet count < 100,000/µL attained a very good partial response.

bReference standard for comparisons.

cNone of the patients with MYD88WT attained a very good partial response.