original reports abstract

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, bone marrow disease involvement declined from 60% to 20%, and hemoglobin rose from 10.3 to 14.2 g/dL ($P < .001$ for all comparisons). Responses were impacted by mutated (Mut) *MYD88* and *CXCR4* status. Patients with *MYD88*^{Mut}, 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 *MYD88*^{Mut}*CXCR4*^{Mut}. Conversely, four patients who had *MYD88*^{WT} 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 *MYD88*^{Mut}*CXCR4*^{WT} and *MYD88*^{Mut}*CXCR4*^{Mut} WM, respectively ($P = .02$). In patients with *MYD88*^{WT}, 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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ASSOCIATED CONTENT

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Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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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 prosurvival signaling of *MYD88*^{Mut} 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.

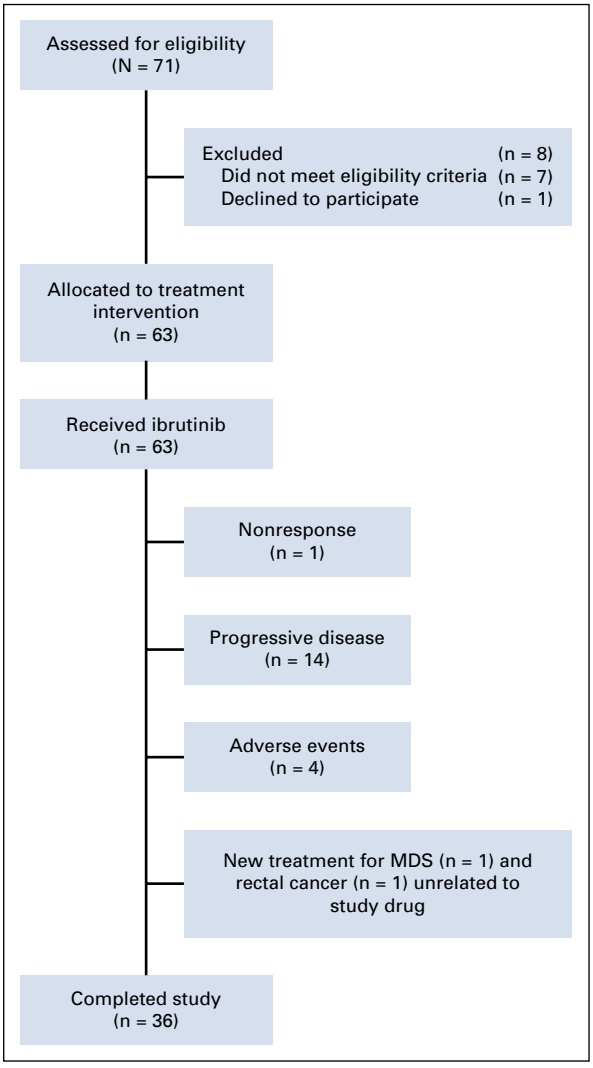

FIG 1. Flow diagram for patient enrollment and disposition. MDS, myelodysplastic syndrome.

diagnosis of WM were enrolled and treated.[11] 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,[12] one or more prior treatments, platelets of $\geq 50 \times 10^9$/L, hemoglobin of ≥ 8 g/dL, absolute neutrophil count (ANC) of $\geq 1.0 \times 10^9$/L, serum creatinine level of ≤ 2 mg/dL, total bilirubin ≤ 1.5 mg/dL (or < 2.0 mg/dL if attributable to tumor), serum AST and ALT levels ≤ 2.5 times the upper limit of normal, and Eastern Cooperative Oncology Group performance status ≤ 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.[10,13] 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

(if extramedullary disease was present at baseline) were repeated at cycles 6, 12, 24, and as needed thereafter for CR or progressive disease assessment.

Intended therapy consisted of oral ibrutinib (420 mg/d) until disease progression or intolerance. Ibrutinib was held for ANC $< 0.5 \times 10^9$/L, platelets $< 25 \times 10^9$/L or $< 50 \times 10^9$/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 discontinuance was required with subsequent events. Drug hold was recommended for 3-7 days before and after invasive procedures to minimize bleeding risk.

TABLE 1. Baseline Characteristics of Previously Treated Patients With WM Who Received Ibrutinib Monotherapy (N = 63)

Characteristic	All Patients With WM
No. of patients	63
Median age, years (range)	63 (44-86)
Sex	
Male	48 (76)
Female	15 (24)
IPSSWM score	
Low	14 (22)
Intermediate	27 (43)
High	22 (35)
Serum Igs, mg/dL	
Median IgM (range)	3,520 (724-8,390)
IgM > 4,000	26 (41)
Median IgA (range)	26 (0-125)
Median IgG (range)	381 (49-2,770)
Median ANC, μL (range)	3,180 (1,140-10,970)
Hemoglobin level, g/dL	
Median (range)	10.5 (8.2-13.8)
< 11	37 (59)
< 10	25 (40)
Platelet count, μ/L	
Median (range)	214,000 (24,000-459,000)
< 100,000/μL	7 (11)
Serum β_2-microglobulin, mg/L	
Median (range)	3.9 (1.3-14.2)
> 3	45 (71)
> 3.5	35 (56)
Median BM disease involvement	60 (3–95)
Extramedullary disease, cm	
Adenopathy > 1.5	37 (59)
Splenomegaly > 15	7 (11)
Prior treatment status	
Median prior therapies (range)	2 (1-9)
≥ 3 therapies	27 (43)
Refractory to previous therapy	25 (40)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia[17]; WM, Waldenström macroglobulinemia.

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 3×4 exact probability test was used for categorical response comparisons by genotype. Cochran-Mantel-Haenszel test was used in the analysis of matched categorical data. $P \leq .05$ 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). Pharmacyclics (Sunnyvale, CA) supported this investigator-initiated study and provided research funding and study drug.

MYD88 and *CXCR* 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 $CXCR4^{S338X}$ 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.[10] All 63 patients were genotyped for *MYD88* mutations. Fifty-nine (93.6%) had activating *MYD88* mutations, of whom 57 expressed a T→C transversion and one a TG→CT transversion at 38182641 on chromosome 3p22.2 that predicted for $MYD88^{L265P}$, and one had an $MYD88^{S243N}$ mutation. Sixty-two patients were genotyped for *CXCR4* mutations, of whom 22 had C-terminal domain mutations. Among the 22 patients with $CXCR4^{Mut}$, 18 had nonsense and four had frameshift variants. All patients with $CXCR4^{Mut}$ were $MYD88^{Mut}$. Germline sequencing confirmed the somatic nature of *MYD88* and *CXCR4* variants. There were four patients who were wild type (WT) for *MYD88*, none of whom had *CXCR4* mutations. No significant differences in baseline characteristics for *MYD88* and *CXCR4* mutation status were observed, except for a greater incidence of adenopathy among patients with $CXCR4^{WT}$ versus $CXCR4^{Mut}$ (68.3% *v* 33.3%; $P = .01$), a finding consistent with previous observations.[5]

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 821 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 > 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 (range, 8.2-13.8 g/dL) to 14.2 g/dL (range, 8.6-17.5 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 (≥ 50%) and presence of extramedullary disease showed significantly greater major response and VGPR (Appendix Tables A1 and A2). Patients with higher serum β_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 (≥ 50%) at baseline remained significant for major response and trended toward significance for VGPR attainment (Appendix Table A2). The presence of $MYD88^{Mut}CXCR4^{Mut}$ 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 $MYD88^{Mut}CXCR4^{WT}$ showed more major responses versus those with $MYD88^{Mut}CXCR4^{Mut}$ disease (97.2% *v* 68.2%; $P < .0001$). The VGPR in patients with $MYD88^{Mut}CXCR4^{WT}$ disease (47.2%) was greater versus those with $MYD88^{Mut}CXCR4^{Mut}$ 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	$MYD88^{Mut}$ $CXCR4^{WT}$	$MYD88^{Mut}$ $CXCR4^{Mut}$	$MYD88^{WT}$ $CXCR4^{WT}$	*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, months					
Major 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*^{WT} 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*^{Mut}*CXCR4*^{WT} 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*^{Mut}, *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*^{Mut} who were *CXCR4*^{WT}, the median time to attaining at least a major response was shorter versus those with *CXCR4*^{Mut} disease (1.8 *v* 4.7 months, respectively; $P = .02$). There were no significant differences in overall response, major response, or VGPR among patients with *CXCR4*^{Mut} 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 ($P \leq .05$ 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

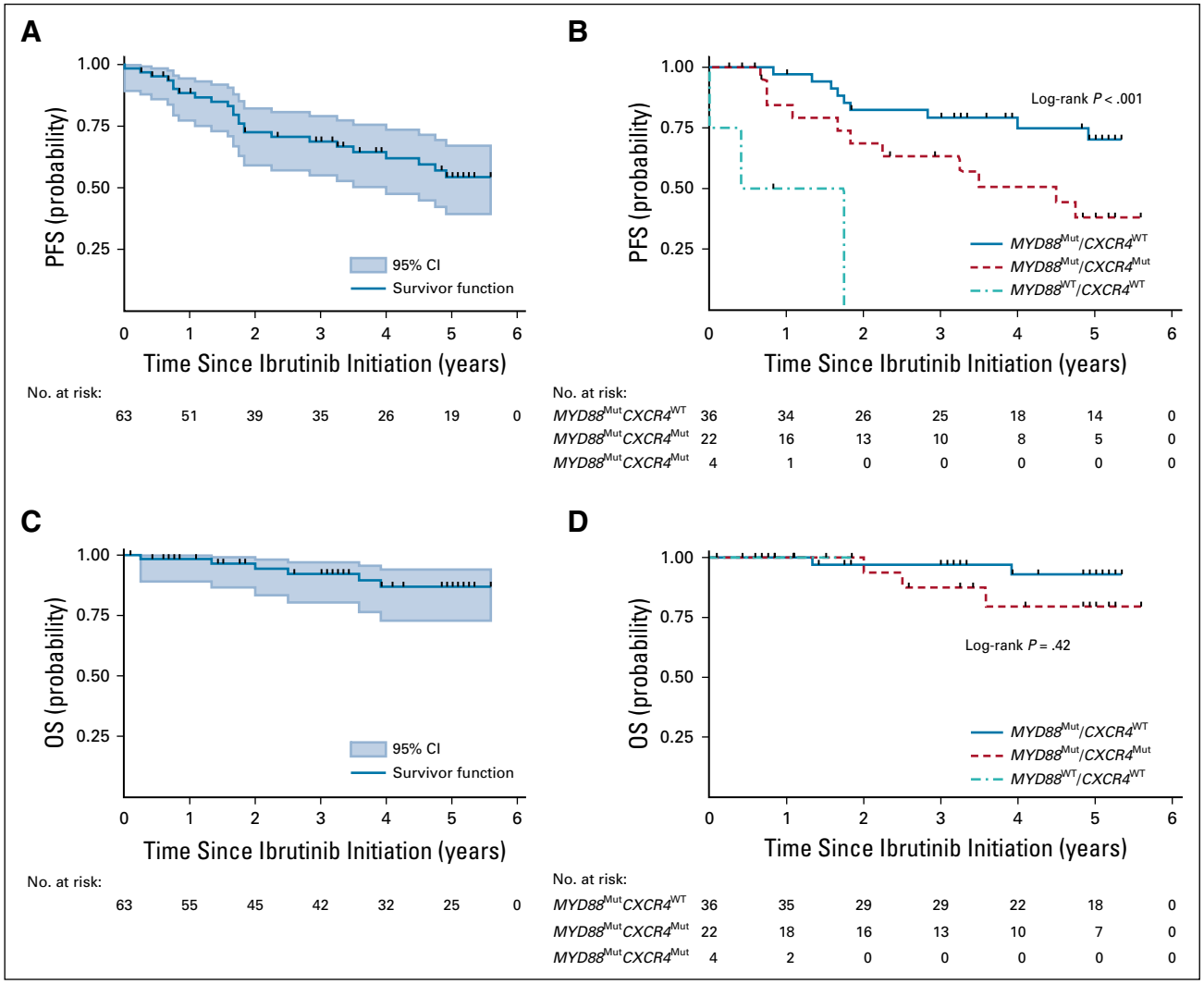

FIG 2. Progression-free survival (PFS) and overall survival (OS) for previously treated patients with Waldenström macroglobulinemia (WM) after ibrutinib monotherapy. Kaplan-Meier curves shown for all 63 patients with WM for (A) PFS and (C) OS. (B) PFS and (D) OS are shown for 62 patients with WM by *MYD88* 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%). Baseline clinical features and their association with PFS are shown in Appendix Figure A2 (online only). 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% *v* 68%; $P = .01$) and BM disease burden ≥ 50% *v* < 50% (5-year PFS rate, 69% *v* 34%; $P = .007$). Having a high versus low/intermediate International Prognostic Scoring System for Waldenström Macroglobulinemia score[16] (5-year PFS rate, 38% *v* 63%; $P = .06$) and age > 65 *v* ≤ 65 years (5-year PFS rate, 40% *v* 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 or ≤ 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%; $P = 0.02$ *v* *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}*CXCR*^{WT} and *MYD88*^{Mut}*CXCR*^{Mut}, 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

	Univariable		Multivariable	
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		
β_2-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 IPPSWM	Reference[a]			
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[a]			
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.

[a]Reference standard for comparisons.

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

	No.			
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)

TABLE 4. Adverse Events Associated With Ibrutinib Therapy in Previously Treated Patients With Waldenström Macroglobulinemia (N = 63) (continued)

Adverse Event	No.			
	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Epistaxis	2	0	0	2
Other	1	0	0	1
Skin and subcutaneous tissue disorders				
Pruritus	1	0	0	1
Other	2	0	0	2
Vascular disorders				
Hypertension	4	0	0	4
Hypotension	1	0	0	1

NOTE. Grade ≥ 2 adverse events deemed by investigators to be possibly, probably, or definitely associated with protocol therapy are shown. The No. of individual patients with the indicated toxicity are listed, with the highest grade toxicity shown for an individual patient. Eight patients had atrial fibrillation, including two with grade 1 events (not shown in table).

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 pretreated patients. Eight (80%) of 10 and six (86%) of seven grade ≥ 3 neutropenic and thrombocytopenic events, respectively, occurred in patients with three or more prior therapies ($P < .05$ for comparisons among patients with three or more *v* 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 arrythmia. Five patients came off study for adverse events, including procedure-related hematoma (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 *MYD88*^{Mut} 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 *MYD88*^{Mut} without concurrent *CXCR4*^{Mut}, this comes as no surprise.[5] However, high BM involvement is a feature of *CXCR4*^{Mut} WM disease and remained significant for major response attainment, even by multivariable analysis.[5,25] Consistent with these findings, patients with high BM involvement also had 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 *MYD88*^{WT} were treated, none attained a major response, even with longer follow-up. Patients with *MYD88*^{WT}

have nuclear factor-κB–activating mutations that are distal to BTK, which likely explains these findings.[28] Among patients with *MYD88*^{Mut}, concurrent *CXCR4*^{Mut} impacted response depth and time to major response.[10,27] VGPRs were fewer, and time to major response was longer in patients with *MYD88*^{Mut}*CXCR4*^{Mut}. Fewer VGPRs were also reported by Dimopoulos et al[18] in rituximab-refractory patients on ibrutinib alone and by Buske et al[29] 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 *CXCR4*^{Mut} WM and may provide insights into overcoming the adverse effects of *CXCR4*^{Mut} 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, chemorefractory state, and a high incidence of secondary malignancies.[32] 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 $\geq$ 3 neutropenia and thrombocytopenia were more common in more heavily pretreated patients, a finding echoed in treatment-naïve patients in whom grade $\geq$ 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 *MYD88*^{Mut} 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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APPENDIX

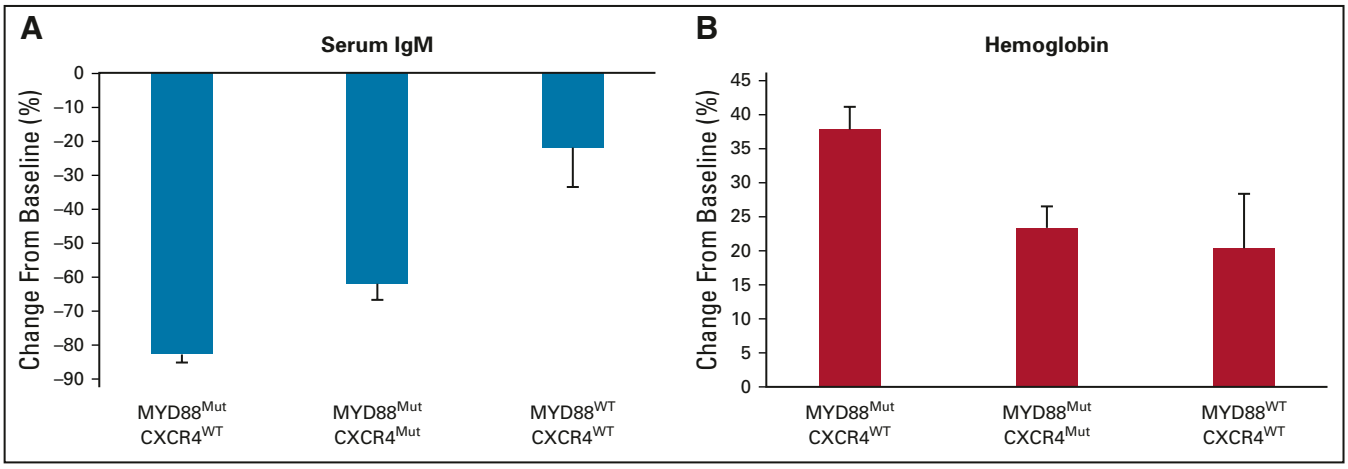

FIG A1. Changes in serum immunoglobulin M (IgM) and hemoglobin levels by *MYD88* and *CXCR4* mutation status. Changes in mean (A) serum IgM and (B) hemoglobin levels (± SEM) at best response are shown for patients by *MYD88* and *CXCR4* mutation status after ibrutinib treatment. $P < .001$ and $P = .002$, 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), $MYD88^{Mut}CXCR4^{Mut}$ (n = 22), and $MYD88^{WT}CXCR4^{WT}$ (n = 4). One patient with $MYD88^{Mut}$ disease but whose *CXCR4* mutation status was not determined was not included in this analysis.

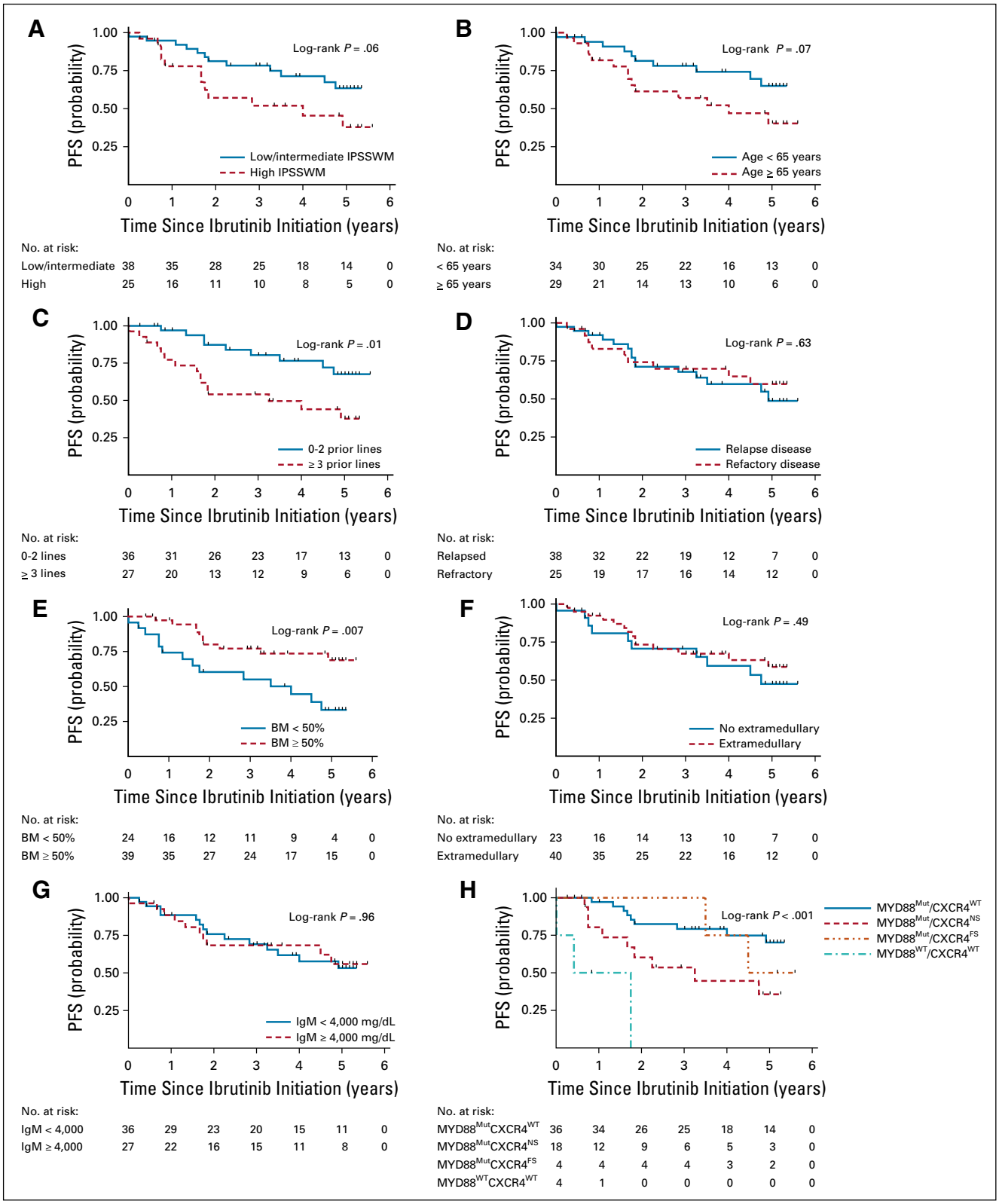

FIG A2. Progression-free survival (PFS) by baseline characteristics for previously treated patients with Waldenström macroglobulinemia (WM) after ibrutinib monotherapy. Kaplan-Meier curves are shown for patients on the basis of (A) International Prognostic Scoring System WM (IPSSWM) score, (B) age, (C) 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

	Univariable		Multivariable	
Variable	**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		
β_2-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	Reference[a]			
Intermediate IPSSWM	1.36 (0.26 to 7.23)	.72		
High IPSSWM	0.86 (0.18 to 4.16)	.86		
MYD88^{Mut}*CXCR4*^{WT}	Reference[a]			
MYD88^{Mut}*CXCR4*^{Mut}	0.06 (0.01 to 0.54)	.01	0.06 (0.01 to 0.72)	.03
MYD88^{WT}*CXCR4*^{WT}	UTC[b]			

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.

[a]Reference standard for comparison.

[b]None of the patients with *MYD88*^{WT} attained a major response.

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

	Univariable		Multivariable	
Variable	**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		
β_2-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	UTC[a]			
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 IPPSWM	Reference[b]			
Intermediate IPSSWM	1.03 (0.24 to 4.41)	.97		
High IPSSWM	1.18 (0.28 to 4.93)	.82		
MYD88^{Mut}*CXCR4*^{WT}	Reference[b]			
MYD88^{Mut}*CXCR4*^{Mut}	0.11 (0.03 to 0.55)	.007	0.28 (0.05 to 1.75)	.18
MYD88^{WT}*CXCR4*^{WT}	UTC[c]			

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.

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

[b]Reference standard for comparisons.

[c]None of the patients with *MYD88*^{WT} attained a very good partial response.