

# Ibrutinib discontinuation in Waldenström macroglobulinemia: Etiologies, outcomes, and IgM rebound

Joshua N. Gustine<sup>1</sup> | Kirsten Meid<sup>1</sup> | Toni Dubeau<sup>1</sup> | Patricia Severns<sup>1</sup> |  
Zachary R. Hunter<sup>1,2</sup> | Yang Guang<sup>1,2</sup> | Lian Xu<sup>1</sup> | Steven P. Treon<sup>1,2</sup> |  
Jorge J. Castillo<sup>1,2</sup> 

<sup>1</sup>Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, Massachusetts;  
<sup>2</sup>Department of Medicine, Harvard Medical School, Boston, Massachusetts

## Correspondence

Jorge J. Castillo, Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, 450 Brookline Ave, Mayer 221, Boston, MA 02115.  
Email: jorgej\_castillo@dfci.harvard.edu

## Abstract

Ibrutinib is the first approved therapy for symptomatic patients with Waldenström macroglobulinemia (WM). The reasons for discontinuing ibrutinib and subsequent outcomes have not been previously evaluated in WM patients. We therefore conducted a retrospective review of 189 WM patients seen at our institution who received treatment with ibrutinib, of whom 51 (27%) have discontinued therapy. Reasons for discontinuation include: disease progression ( $n = 27$ ; 14%), toxicity ( $n = 15$ ; 8%), nonresponse ( $n = 5$ ; 3%), and other unrelated reasons ( $n = 4$ ; 2%). The cumulative incidence of ibrutinib discontinuation at 12, 24, 36, and 48 months from treatment initiation was 22%, 26%, 35%, and 43%, respectively. A baseline platelet count  $\leq 100$  K/ $\mu$ L and presence of tumor CXCR4 mutations were independently associated with 4-fold increased odds of ibrutinib discontinuation. An IgM rebound ( $\geq 25\%$  increase in serum IgM) was observed in 37 patients (73%) following ibrutinib discontinuation and occurred within 4 weeks for nearly half of patients. The response rate to salvage therapy was 71%; responses were higher in patients without an IgM rebound and when salvage therapy was initiated within 2 weeks of stopping ibrutinib. Patients who discontinued ibrutinib due to disease progression versus nonprogression events had significantly shorter overall survival (21 versus 32 months;  $P = .046$ ). Response to salvage therapy was associated with an 82% reduction in the risk of death following ibrutinib discontinuation. WM patients who discontinue ibrutinib require close monitoring, and continuation of ibrutinib until the next therapy should be considered to maintain disease control.

## 1 | INTRODUCTION

Waldenström macroglobulinemia (WM) is a B-cell malignancy characterized by bone marrow infiltration with IgM-secreting lymphoplasmacytic lymphoma.<sup>1</sup> Activating somatic mutations in MYD88 and CXCR4 are present in 90%-95% and 30%-40% of WM patients, respectively.<sup>2-5</sup> Preclinical studies demonstrated the MYD88 L265P mutation triggers pro-survival nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling in WM cells through Bruton tyrosine kinase (BTK), whereas CXCR4 mutations confer in vitro drug resistance, including the BTK inhibitor ibrutinib.<sup>6-8</sup> These findings prompted a pivotal phase II study evaluating ibrutinib in 63 previously treated WM patients.<sup>9</sup> Ibrutinib therapy was associated with both a high overall response rate (91%) and major response rate (73%), and an estimated 24-month progression-free and overall survival of 69% and 95%,

respectively. An important finding was the role of MYD88 and CXCR4 mutation status as determinants of ibrutinib response. Patients with wild-type (WT) MYD88 had no major responses, while mutated MYD88 patients with a CXCR4 mutation had fewer major responses versus those with WT CXCR4 (62% versus 92%).<sup>10</sup> Delayed major response attainment ( $>6$  months) was also observed for CXCR4 mutated patients. Treatment was generally well tolerated; neutropenia (22%) and thrombocytopenia (14%) were the only related grade  $\geq 2$  adverse events occurring in  $>10\%$  of patients. On the basis of these results, ibrutinib became the first approved therapy for WM by the United States (US) Food and Drug Administration and the European Medicines Agency. Similar findings have since been reported in a multicenter study with 31 WM patients who were refractory to rituximab, and in a phase II study evaluating ibrutinib as primary therapy for WM patients.<sup>11,12</sup>

Despite the durable activity and tolerability of ibrutinib in WM, treatment discontinuation will be required for some patients due to unacceptable toxicity or disease progression. Discontinuation of ibrutinib has been associated with an adverse prognosis in patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL).<sup>13–16</sup> However, outcomes following ibrutinib discontinuation in patients with WM have not been previously evaluated. We therefore reviewed our experience with WM patients treated with ibrutinib who subsequently stopped therapy to determine their clinicopathological characteristics, prognostic factors, and outcomes.

## 2 | METHODS

### 2.1 | Patient selection and variable identification

We performed a retrospective review of patients seen at our institution between May 2012 and April 2017 who met clinicopathological criteria for WM and received ibrutinib therapy.<sup>1</sup> Patient charts were manually reviewed to identify patients who discontinued ibrutinib for any reason. Pertinent clinical and pathological data were collected from the time of ibrutinib initiation to last follow-up or death. Response assessment to ibrutinib therapy was defined according to international guidelines.<sup>17</sup> The presence of MYD88 and CXCR4 mutations were determined by allele-specific polymerase chain reaction and Sanger sequencing methods, as previously described.<sup>4,18</sup>

### 2.2 | Statistical considerations

Patient characteristics are presented using descriptive characteristics. Continuous variables were categorized to facilitate analysis, and comparisons were made using the Chi-square and Fischer exact test. Univariate and multivariate logistic regression models were fit to evaluate the association between clinicopathological variables, and the risk of ibrutinib discontinuation and an IgM rebound; the outcome measure was odds ratio (OR) with 95% confidence interval (CI). An IgM rebound was defined as a  $\geq 25\%$  increase in serum IgM level, with an absolute increase of at least 500 mg/dL, following discontinuation of ibrutinib. The time to events was estimated using the Kaplan–Meier method for incomplete observations, and comparisons between groups were made using the log-rank test. The Cox-proportional hazard regression method was used to fit univariate and multivariate models for overall survival; the outcome measure was hazard ratio (HR) with 95% CI. *P*-values  $< .10$  were included in the multivariate analysis. *P*-values were two-sided and considered statistically significant if  $< .05$ . All calculations and graphs were obtained using the STATA/SE 13.1 (StataCorp, College Station, Texas).

## 3 | RESULTS

### 3.1 | Patient characteristics

A total of 189 patients with WM who received treatment with ibrutinib were identified. After a median treatment duration of 13 months (range 0.3–60), 51 patients (27%) have discontinued ibrutinib, and 138

patients (73%) remain on therapy. Ibrutinib was initiated at 420 mg PO daily for all except two patients with Bing-Neel syndrome (560 mg). The median time from WM diagnosis to ibrutinib initiation was 45 months (range 0.6–302); 138 patients (73%) received ibrutinib in the relapsed/refractory setting, and 51 (27%) in the frontline setting. Previously treated patients had a median of 2 (range 1–8) prior therapies, including an anti-CD20 monoclonal antibody ( $n = 129$ ; 93%), proteasome inhibitor ( $n = 74$ ; 54%), alkylator ( $n = 73$ ; 53%), and nucleoside analogue ( $n = 33$ ; 24%). MYD88 and CXCR4 mutations were detected in 98% (171/174) and 37% (59/159) of genotyped patients, respectively. The clinical characteristics of these patients at the time of ibrutinib initiation are shown in Table 1. WM patients who discontinued ibrutinib were more likely to have a baseline platelet count  $\leq 100$  K/ $\mu$ L (22% versus 7%;  $P = .006$ ) and harbor a CXCR4 mutation (60% versus 27%;  $P < .001$ ) compared to patients who did not discontinue ibrutinib.

### 3.2 | Risk of ibrutinib discontinuation

The cumulative incidence of ibrutinib discontinuation at 12, 24, 36, and 48 months from treatment initiation was 22%, 26%, 35%, and 43%, respectively (Figure 1A). The median time to ibrutinib discontinuation was 7 months (95% CI 6–9). By univariate analysis, a baseline serum IgM level  $> 4000$  mg/dL, serum  $\beta_2$ -microglobulin level  $> 3.0$  mg/l, and treatment for extramedullary disease were associated with lower odds of ibrutinib discontinuation, whereas a baseline platelet count  $\leq 100$  K/ $\mu$ L and CXCR4 mutation were associated with higher odds of ibrutinib discontinuation. Age, sex, hemoglobin level, bone marrow involvement, International Prognostic Scoring System for WM (IPSSWM) score, treatment indication, prior treatment status, or MYD88 mutation status were not associated with higher or lower odds of ibrutinib discontinuation. In the multivariate analysis, a baseline platelet count  $\leq 100$  K/ $\mu$ L (OR 3.85, 95% CI 1.20–12.3;  $P = .02$ ) and CXCR4 mutation (OR 3.89, 95% CI 1.74–8.69;  $P = .001$ ) were independently associated with higher odds of ibrutinib discontinuation. A baseline serum IgM level  $> 4000$  mg/dL (OR 0.38, 95% CI 0.17–0.86;  $P = .02$ ) also remained associated with lower odds of ibrutinib discontinuation. The univariate and multivariate models for ibrutinib discontinuation are shown in Table 2.

Ibrutinib was discontinued in 27 patients (14%) due to progressive disease (PD). The cumulative incidence of ibrutinib discontinuation at 12, 24, 36, and 48 months was 13%, 13%, 15%, and 15%, respectively (Figure 1B). Sixteen patients (59%) with disease progression harbored a CXCR4 mutation. An increase in serum IgM level was not observed for 15 patients (55%) at the time of disease progression. The presentation among these patients included malignant pleural effusions ( $n = 5$ ), progressive anemia ( $n = 4$ ), amyloidosis ( $n = 2$ ), histological transformation to diffuse large B-cell lymphoma ( $n = 2$ ), Bing-Neel syndrome ( $n = 1$ ), and renal involvement ( $n = 1$ ). Both patients with histological transformation had prior treatment with nucleoside analogues.

Non-PD events caused ibrutinib discontinuation in 24 patients (13%) including toxicity ( $n = 15$ ; 8%), nonresponse ( $n = 5$ ; 3%), and unrelated miscellaneous reasons ( $n = 4$ ; 2%). Four patients deemed to be nonresponders all harbored a CXCR4 mutation, and the decision to stop

TABLE 1 Clinical characteristics at the time of ibrutinib initiation

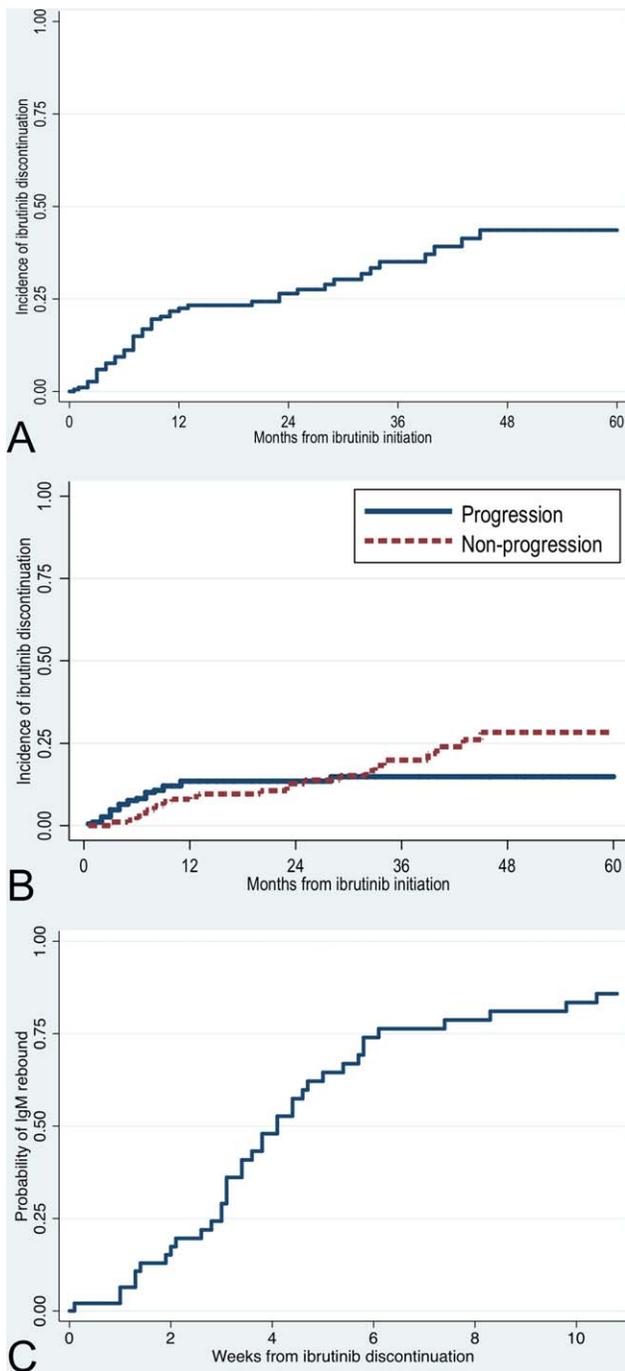
Characteristic	All patients (n = 189)	Discontinued ibrutinib		P-value <sup>a</sup>
		Yes (n = 51)	No (n = 138)	
Age				
>65 years	114 (60%)	29 (57%)	85 (62%)	.56
≤65 years	75 (40%)	22 (43%)	53 (38%)	
Sex				
Male	128 (68%)	32 (63%)	96 (70%)	.37
Female	61 (32%)	19 (37%)	42 (30%)	
Serum IgM level				
>4000 mg/dL	80 (42%)	16 (31%)	64 (46%)	.06
>7000 mg/dL	12 (6%)	5 (10%)	7 (5%)	
Hemoglobin level				
>11.5 g/dl	59 (31%)	17 (33%)	42 (30%)	.70
≤11.5 g/dl	130 (69%)	34 (67%)	96 (70%)	
Platelet count				
>100 K/ $\mu$ L	169 (89%)	40 (78%)	129 (93%)	.006
≤100 K/ $\mu$ L	20 (11%)	11 (22%)	9 (7%)	
Serum $\beta_2$ -microglobulin level				
>3.0 mg/L	140 (74%)	33 (64%)	107 (78%)	.07
≤3.0 mg/L	49 (26%)	18 (35%)	31 (22%)	
Bone marrow involvement				
<50%	82 (43%)	25 (49%)	57 (41%)	.21
≥50%	107 (57%)	26 (51%)	81 (59%)	
IPSSWM score				
Low	47 (25%)	15 (29%)	32 (23%)	.18
Intermediate	56 (30%)	10 (20%)	46 (33%)	
High	86 (46%)	26 (51%)	60 (43%)	
Prior treatment status				
Untreated	51 (27%)	11 (22%)	40 (29%)	.31
Treated	138 (73%)	40 (78%)	98 (71%)	
Treatment indication				
Anemia	104 (56%)	28 (56%)	76 (55%)	.95
Hyperviscosity	31 (17%)	7 (14%)	24 (18%)	.57
Constitutional symptoms	64 (34%)	18 (36%)	46 (34%)	.76
Peripheral neuropathy	15 (8%)	6 (12%)	9 (7%)	.23
Extramedullary disease	20 (11%)	2 (4%)	18 (13%)	.11
Tumor genotype				
MYD88 mutated	172 (98%)	48 (98%)	124 (99%)	.85
CXCR4 mutated	59 (37%)	29 (60%)	30 (27%)	<.001

<sup>a</sup>P-value denotes comparison between patients who did and did not discontinue ibrutinib.

ibrutinib was made after a median treatment duration of 3.4 months (range 2.0–5.3). One patient with WT MYD88 did not respond to ibrutinib. The unrelated miscellaneous events include: patient choice, splenic rupture, cardiac arrest, and acute myeloid leukemia (prior therapy with cladribine, cyclophosphamide, bendamustine). The 12-, 24-, 36-, and 48-month cumulative incidence of ibrutinib discontinuation was 8%, 12%, 20%, and 28%, respectively (Figure 1B). Therapy-limiting adverse events included: atrial fibrillation ( $n = 2$ ), bleeding ( $n = 2$ ), fatigue ( $n = 2$ ), headache ( $n = 2$ ), elevated aspartate and alanine aminotransferase levels ( $n = 2$ ), arthralgias ( $n = 2$ ), thrombocytopenia ( $n = 1$ ), recurrent mouth sores ( $n = 1$ ), and painful subcutaneous nodules ( $n = 1$ ).

### 3.3 | Serum IgM rebound

An IgM rebound was observed in 37 patients (73%) following the discontinuation of ibrutinib. Median serum IgM levels for patients with an IgM rebound increased from 1669 mg/dL (range 351–6248) to a peak of 3419 mg/dL (range 955–8530) ( $P = .0002$ ) with a median increase of 70% (range 25–1702%). Seventeen patients (46%) had an increase in serum IgM level back to preibrutinib baseline. The cumulative incidence of an IgM rebound at 4 and 8 weeks after stopping ibrutinib was 48% and 79%, respectively (Figure 1C). An increased risk of an IgM rebound at 4 weeks (72% versus 29%) and 8 weeks (95% versus 66%)



**FIGURE 1** Estimated cumulative incidence of ibrutinib discontinuation from treatment initiation (A), time to ibrutinib discontinuation according to the reason for cessation of therapy (B), and estimated cumulative incidence of an IgM rebound following discontinuation of ibrutinib (C) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

was observed for patients with PD versus non-PD ibrutinib discontinuation ( $P = .002$ ). Six patients (16%) with an IgM rebound developed symptomatic hyperviscosity and required emergent plasmapheresis; 4 (67%) of these patients had a serum IgM level  $>4000$  mg/dL at the time of ibrutinib discontinuation. The median time from ibrutinib discontinuation to hyperviscosity syndrome was 25 days (range 18–37).

One patient with anti-MAG antibody peripheral neuropathy experienced worsening neurological symptoms associated with an IgM rebound causing the serum IgM level to increase from 351 to 955 mg/dL. Among the 14 patients without an IgM rebound, 8 patients initiated salvage therapy within two weeks of ibrutinib discontinuation, 4 patients with non-PD discontinuation have not yet required salvage therapy, one patient developed acute myeloid leukemia, and one patient who developed hyperviscosity syndrome while on active therapy received prophylactic plasmapheresis prior to discontinuation of ibrutinib. By univariate analysis, male sex was associated with lower odds of an IgM rebound following ibrutinib discontinuation (OR 0.18, 95% CI 0.03–0.90;  $P = .04$ ). Age, hemoglobin level, serum IgM, ibrutinib dose, time on ibrutinib, prior treatment status, and MYD88 and CXCR4 mutation status were not associated with higher or lower odds of an IgM rebound ( $P > .05$  for all comparisons).

### 3.4 | Salvage therapy

Thirty-eight patients (75%) received salvage therapy following ibrutinib discontinuation. The median time to salvage therapy was 5 weeks (95% CI 3.6–8.1). The cumulative incidence of salvage therapy at 4, 8, and 12 weeks following ibrutinib discontinuation was 37%, 62%, and 72%, respectively. Patients discontinuing ibrutinib due to PD versus non-PD events had a shorter time to the initiation of salvage therapy (3.4 versus 11 weeks;  $P < .001$ ). Twenty-seven patients (71%) responded to salvage therapy with the following regimens: combination therapy with an anti-CD20 monoclonal antibody and alkylator (16/22; 73%), proteasome inhibitor (4/5; 80%), or nucleoside analogue (2/2; 100%); BCL2 inhibitor (3/5; 60%); and miscellaneous (2/4; 50%). Patients without an IgM rebound were more likely to respond to salvage therapy versus those with an IgM rebound (100% versus 62%;  $P = .04$ ). Moreover, response rates were higher among PD patients who began salvage therapy  $\leq 2$  versus  $> 2$  weeks from ibrutinib discontinuation (100% versus 57%;  $P = .02$ ), whereas no difference was observed for patients with non-PD ibrutinib discontinuation ( $P = .58$ ). Thirteen patients (24%) have not received salvage therapy, of whom 9 discontinued ibrutinib due to a non-PD event. Reasons for not receiving salvage therapy include: treatment not required ( $n = 6$ ; 46%), patient choice ( $n = 4$ ; 31%), death due to progressive disease ( $n = 2$ ; 15%), and acute myeloid leukemia ( $n = 1$ ; 8%).

### 3.5 | Survival analysis

With a median follow-up of 17 months (range 1.1–60), 16 patients (31%) have died following ibrutinib discontinuation. The median OS from ibrutinib discontinuation was 32 months (95% CI 19–not reached) with an estimated 1-, 2-, and 3-year OS of 72%, 56%, and 45%, respectively (Figure 2A). Patients who discontinued ibrutinib due to PD versus non-PD events had significantly shorter OS (21 versus 32 months;  $P = .046$ ; Figure 2B). All deaths occurred in patients who received ibrutinib in the relapsed/refractory setting after a median of 4 (range 2–8) prior therapies. Causes of death include: progressive disease ( $n = 14$ ; 88%), acute myeloid leukemia ( $n = 1$ ; 6%), and congestive heart failure

TABLE 2 Univariate and multivariate models for ibrutinib discontinuation

Variable	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age >65 years	0.82 (0.43-1.57)	.56		
Male sex	0.74 (0.38-1.45)	.37		
Serum IgM level >4000 mg/dL	0.53 (0.27-1.04)	.07	0.38 (0.17-0.86)	.02
Serum IgM level >7000 mg/dL	2.03 (0.25-6.73)	.24		
Hemoglobin level $\leq$ 11.5 g/dL	0.88 (0.44-1.74)	.70		
Platelet count $\leq$ 100 K/ $\mu$ L	3.94 (1.52-10.2)	.005	3.85 (1.20-12.3)	.02
Serum $\beta_2$ -microglobulin >3.0 mg/L	0.53 (0.26-1.07)	.08	0.50 (0.21-1.19)	.12
Bone marrow involvement $\geq$ 50%	0.66 (0.34-1.28)	.22		
IPSSWM Score				
Low	Reference			
Intermediate	0.46 (0.19-1.16)	.10		
High	0.92 (0.43-1.99)	.84		
Treatment Indication				
Anemia	1.02 (0.53-1.96)	.95		
Hyperviscosity	0.77 (0.31-1.91)	.57		
Constitutional symptoms	1.11 (0.57-2.19)	.76		
Peripheral neuropathy	1.94 (0.65-5.76)	.23		
Extramedullary disease	0.28 (0.06-1.23)	.09	0.23 (0.03-2.10)	.19
Previously treated	1.48 (0.69-3.18)	.31		
MYD88 mutated	1.62 (0.12-22.8)	.72		
CXCR4 mutated	4.12 (2.02-8.42)	<.001	3.89 (1.74-8.69)	.001

OR: odds ratio; CI: confidence interval.

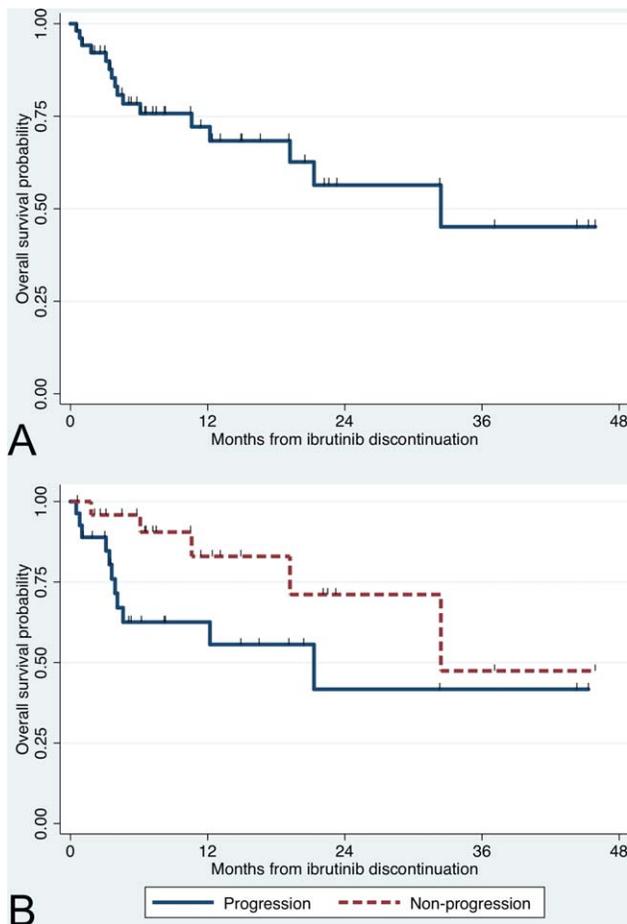
( $n = 1$ ; 6%). By univariate analysis, response to salvage therapy was associated with a decreased risk of death following ibrutinib discontinuation (HR 0.18, 95% CI 0.04-0.71;  $P = .02$ ). Age, sex, hemoglobin level, serum IgM, ibrutinib dose, time on ibrutinib, IgM rebound, and MYD88 and CXCR4 mutation status were not associated with an increased or decreased risk of death ( $P > .05$  for all comparisons).

## 4 | DISCUSSION

Ibrutinib is the first approved therapy for symptomatic patients with WM. Understanding the factors responsible for ibrutinib discontinuation and subsequent outcomes may help direct management strategies to optimize patient care, and was the focus of this retrospective study. Our most salient results can be summarized as follows: (i) 22% of WM patients discontinue ibrutinib within one year of initiation; (ii) discontinuation due to toxicity or nonresponse is more common early in therapy and becomes progressively infrequent; (iii) disease progression on active therapy is uncommon with an estimated 4-year rate of 15%; (iv) a baseline platelet count  $\leq$ 100 K/ $\mu$ L and CXCR4 mutations are independently associated with 4-fold increased odds of discontinuation; (v) nearly half of WM patients experience an IgM rebound within 4 weeks of stopping ibrutinib; and (vi) response to salvage therapy is associated with an 82% reduction in the risk of death following ibrutinib discontinuation.

Our data show WM patients with CXCR4 mutations are more likely to discontinue ibrutinib therapy. This expands upon prior studies demonstrating CXCR4 mutations confer both in vitro and clinical resistance to ibrutinib.<sup>7-9,11</sup> Acquired BTK C481S mutations are also strongly associated with CXCR4 mutations in the development of ibrutinib resistance.<sup>19</sup> Importantly, 80% of patients deemed to be ibrutinib nonresponders in our cohort harbored a CXCR4 mutation, and all discontinued ibrutinib within 6 months of treatment initiation. It is possible the decision to stop ibrutinib in these patients may have been premature given the limited treatment duration. In the pivotal phase II trial, objective responses to ibrutinib were less likely at 6 months in WM patients with mutated versus WT CXCR4 (62% versus 91%); however, higher response rates were seen in CXCR4 mutated patients with prolonged ibrutinib exposure.<sup>9</sup> Alternative therapies should therefore be considered in CXCR4 mutated patients requiring immediate disease control.<sup>20</sup> Only three MYD88 WT patients in our study cohort were exposed to ibrutinib. These were patients enrolled in our initial clinical trial. Treatment with ibrutinib is generally not recommended in MYD88 WT patients given the limited activity in this population.<sup>9,10,20</sup> These findings emphasize how MYD88 and CXCR4 mutation status can be useful in the therapeutic management of WM patients.

An important observation was the occurrence of an IgM rebound in most patients following ibrutinib discontinuation. Abrupt increases in serum IgM levels can potentiate IgM-related morbidity in WM patients,



**FIGURE 2** Overall survival curve following ibrutinib discontinuation (A), and overall survival following according to the cause of ibrutinib discontinuation (B) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

such as hyperviscosity, cryoglobulinemia, cold agglutininemia, peripheral neuropathy, and acquired von Willebrand disease.<sup>21</sup> In this study, we observed the acute onset of symptomatic hyperviscosity in 16% of patients with an IgM rebound. Most patients who developed symptomatic hyperviscosity had high serum IgM levels (ie, >4000 mg/dL) at the time of ibrutinib discontinuation. A recent study showed the risk for symptomatic hyperviscosity increased exponentially with increasing serum IgM levels above 3000 mg/dL.<sup>22</sup> Taken together, these findings highlight the importance of monitoring serum IgM levels in WM patients immediately following discontinuation of ibrutinib. In as well, plasmapheresis should be performed prior to discontinuing ibrutinib in patients with symptomatic hyperviscosity as an IgM rebound could precipitate hyperviscosity-related injury, ie, retinal or central nervous bleeding. Plasmapheresis may also be reasonable as hyperviscosity prophylaxis when stopping ibrutinib in patients with high serum IgM levels. A similar approach is recommended for WM patients undergoing rituximab-based therapy with a serum IgM level >4000 mg/dL given the risk of an IgM flare.<sup>23,24</sup>

Many patients did not have an increase in serum IgM level at the time of disease progression on ibrutinib. The BTK substrate STAT5A regulates IgM secretion in WM cells, and its selective inhibition by ibrutinib may contribute to this discordant finding.<sup>25,26</sup> Discordance between

serum IgM level and marrow disease burden reduction have been previously reported with ibrutinib.<sup>9</sup> Response assessment can be complicated by IgM discordance since consensus criteria for response in WM rely primarily on changes in serum IgM levels, although the development of clinically significant disease-related symptoms can also indicate disease progression.<sup>17</sup> Moreover, cessation of STAT5A inhibition likely contributes to the IgM rebound described herein, as well as the transient increases in serum IgM level observed when ibrutinib is temporarily withheld due to toxicity or procedures.<sup>9,27</sup> It is noteworthy that these serum IgM increases may persist for more than six months following ibrutinib reinstatement, and do not necessarily indicate treatment failure.<sup>28</sup>

Akin to CLL and MCL, outcomes were less favorable for WM patients with disease progression versus those discontinuing ibrutinib for other reasons.<sup>13-16</sup> We identified response to salvage therapy as an important predictor of outcome in WM patients following ibrutinib discontinuation, and should herald efforts to maximize response rates in the salvage setting. Ahn et al. proposed the seamless transition between ibrutinib and subsequent treatment may forestall disease acceleration in CLL.<sup>29</sup> Consistent with this hypothesis, we observed higher response rates in patients without an IgM rebound, as well as in those who initiated salvage therapy within two weeks of stopping ibrutinib. Continuation of ibrutinib until the next therapy may therefore be a reasonable approach to maintain disease control and increase the likelihood of salvage response, particularly for patients progressing on ibrutinib. Such an approach may also mitigate the risk of an IgM rebound after stopping ibrutinib. Additional studies are needed to further clarify the management of WM patients with acquired ibrutinib resistance.

In summary, discontinuation of ibrutinib therapy is associated with CXCR4 mutations in WM patients. Rapid rebounds in serum IgM level often occur after stopping ibrutinib and may cause symptomatic hyperviscosity. Patients who discontinue ibrutinib require close monitoring, and continuation of ibrutinib until the next therapy should be considered to maintain disease control.

## ACKNOWLEDGMENTS

Parts of this research was presented at the 59<sup>th</sup> American Society of Hematology Annual Meeting in Atlanta, GA, in December 2017. Dr. Castillo would like to acknowledge the support of the WMR Fund.

## DISCLOSURES

SPT has received honoraria and/or research funds from Pharmacylics. JJC has received honoraria and/or research funds from Abbvie, Gilead, Janssen, Millennium and Pharmacylics.

## AUTHOR CONTRIBUTIONS

JNG and JJC designed the study. JNG drafted the manuscript. JJC performed the analysis. All the authors took care of patients, gathered data, and critically reviewed and approved the final manuscript.

## ORCID

Jorge J. Castillo  <http://orcid.org/0000-0001-9490-7532>

## REFERENCES

- [1] Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol*. 2003;30(2):110–115.
- [2] Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med*. 2012;367(9):826–833.
- [3] Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood*. 2014;123(11):1637–1646.
- [4] Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood*. 2013;121(11):2051–2058.
- [5] Xu L, Hunter ZR, Tsakmaklis N, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenström Macroglobulinaemia. *Br J Haematol*. 2016;172(5):735–744.
- [6] Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. *Blood*. 2013;122(7):1222–1232.
- [7] Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenström's Macroglobulinemia. *Leukemia*. 2015;29(1):169–176.
- [8] Cao Y, Hunter ZR, Liu X, et al. CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P)-directed survival signalling in Waldenström macroglobulinaemia cells. *Br J Haematol*. 2015;168(5):701–707.
- [9] Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430–1440.
- [10] Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. *N Engl J Med*. 2015;373(6):584–586.
- [11] Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (INNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol*. 2017;18(2):241–250.
- [12] Treon SP, Gustine JN, Meid K, et al. Ibrutinib is highly active as first line therapy in symptomatic Waldenström's Macroglobulinemia. *Blood*. 2017;130:2767.
- [13] Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood*. 2015;125(13):2062–2067.
- [14] Cheah CY, Chihara D, Romaguera JE, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. *Ann Oncol*. 2015;26(6):1175–1179.
- [15] Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1(1):80–87.
- [16] Jain P, Thompson PA, Keating M, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. *Cancer*. 2017;123(12):2268–2273.
- [17] Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinaemia: update from the Vth International Workshop. *Br J Haematol*. 2013;160(2):171–176.
- [18] Xu L, Hunter ZR, Tsakmaklis N, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenström Macroglobulinaemia. *Br J Haematol*. 2015;172:735–744.
- [19] Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. *Blood*. 2017;129(18):2519–2525.
- [20] Hunter ZR, Yang G, Xu L, et al. Genomics, signaling, and treatment of Waldenström macroglobulinemia. *J Clin Oncol*. 2017; JCO2016710814.
- [21] Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721–732.
- [22] Gustine JN, Meid K, Dubeau T, et al. Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia. *Br J Haematol*. 2017;177(5):717–725.
- [23] Treon SP, Branagan AR, Hunter Z, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol*. 2004;15(10):1481–1483.
- [24] Ghobrial IM, Fonseca R, Greipp PR, et al. Initial immunoglobulin M "flare" after rituximab therapy in patients diagnosed with Waldenström macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*. 2004;101(11):2593–2598.
- [25] Hodge LS, Ziesmer SC, Yang Z-Z, et al. Constitutive activation of STAT5A and STAT5B regulates IgM secretion in Waldenström's macroglobulinemia. *Blood*. 2014;123(7):1055–1058.
- [26] Mahajan S, Vassilev A, Sun N, et al. Transcription factor STAT5A is a substrate of Bruton's tyrosine kinase in B cells. *J Biol Chem*. 2001;276(33):31216–31228.
- [27] Castillo JJ, Palomba ML, Advani R, Treon SP. Ibrutinib in Waldenström macroglobulinemia: latest evidence and clinical experience. *Ther Adv Hematol*. 2016;7(4):179–186.
- [28] Gustine JN, Meid K, Dubeau T, et al. Impact of ibrutinib dose intensity on patient outcomes in previously treated Waldenström macroglobulinemia. *Blood*. 2017;130:4051.
- [29] Ahn IE, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. *Blood*. 2017; 129(11):1469–1479.

**How to cite this article:** Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenström macroglobulinemia: Etiologies, outcomes, and IgM rebound. *Am J Hematol*. 2018;93:511–517. <https://doi.org/10.1002/ajh.25023>