

Venetoclax in Previously Treated Waldenström Macroglobulinemia

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PURPOSE BCL2 is overexpressed and confers prosurvival signaling in malignant lymphoplasmacytic cells in Waldenström macroglobulinemia (WM). Venetoclax is a potent BCL2 antagonist and triggers in vitro apoptosis of WM cells. The activity of venetoclax in WM remains to be clarified.

PATIENTS AND METHODS We performed a multicenter, prospective phase II study of venetoclax in patients with previously treated WM (NCT02677324). Venetoclax was dose-escalated from 200 mg to a maximum dose of 800 mg daily for up to 2 years.

RESULTS Thirty-two patients were evaluable, including 16 previously exposed to Bruton tyrosine kinase inhibitors (BTKis). All patients were *MYD88 L265P*-mutated, and 17 carried *CXCR4* mutations. The median time to minor and major responses was 1.9 and 5.1 months, respectively. Previous exposure to BTKis was associated with a longer time to response (4.5 v 1.4 months; $P < .001$). The overall, major, and very good partial response rates were 84%, 81%, and 19%, respectively. The major response rate was lower in those with refractory versus relapsed disease (50% v 95%; $P = .007$). The median follow-up time was 33 months, and the median progression-free survival was 30 months. *CXCR4* mutations did not affect treatment response or progression-free survival. The only recurring grade ≥ 3 treatment-related adverse event was neutropenia ($n = 14$; 45%), including one episode of febrile neutropenia. Laboratory tumor lysis without clinical sequelae occurred in one patient. No deaths have occurred.

CONCLUSION Venetoclax is safe and highly active in patients with previously treated WM, including those who previously received BTKis. *CXCR4* mutation status did not affect treatment response.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is characterized by the malignant accumulation of immunoglobulin M (IgM)-secreting lymphoplasmacytic cells in the bone marrow (BM) and other organs.¹ Treatment options for WM include alkylating agents, anti-CD20 monoclonal antibodies, proteasome inhibitors, and Bruton tyrosine kinase inhibitors (BTKis).² Highly recurring somatic mutations in *MYD88* and *CXCR4* are found in patients with WM, and can affect disease presentation, prognosis, and treatment response to BTKis.³⁻⁵ WM remains incurable, and new treatment options are needed.

BCL2 is an essential regulator of the intrinsic pathway of apoptosis in normal and malignant cells. BCL2 is overexpressed in WM lymphoplasmacytic cells, particularly in patients with WM with *MYD88* mutations with similar levels of BCL2 expression regardless of *CXCR4* mutational status.⁶ Venetoclax is an oral BCL2 antagonist approved for the treatment of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia. In vitro treatment of *MYD88*-mutated WM cells engineered to

express either wild-type or mutated *CXCR4* with venetoclax triggered apoptosis and sensitized cells to various chemotherapeutics including BTKis.⁶ In a prospective phase I study, all four patients with WM attained a major response to venetoclax.⁷

Herein, we report the safety and efficacy of this first, prospective, multicenter study of venetoclax in relapsed or refractory WM.

PATIENTS AND METHODS

Study Design and Oversight

This study was an investigator-initiated, multicenter, prospective trial of single-agent venetoclax in patients with previously treated WM. The study enrolled patients at the Dana-Farber Cancer Institute, Weill Cornell Medical Center, City of Hope National Medical Center, and Stanford University Medical Center. Enrollment began in June 2016 and closed in February 2018. The date of data cutoff was December 31, 2020. The study was approved by the institutional review

ASSOCIATED CONTENT

Appendix

Protocol

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

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CONTEXT

Key Objective

Is venetoclax monotherapy a safe and effective therapy in patients with previously treated Waldenström macroglobulinemia (WM)?

Knowledge Generated

Venetoclax monotherapy, up to a dose of 800 mg by mouth once daily for 2 years, induced a high response rate in patients with WM, including 50% of patients previously exposed to Bruton tyrosine kinase inhibitors (BTKis) and 38% refractory to the preceding line of therapy. Venetoclax was well tolerated with only one episode of laboratory (not clinical) tumor lysis syndrome and manageable neutropenia. There were no episodes of immunoglobulin M flare, neuropathy, secondary myeloid neoplasms, or arrhythmia associated with venetoclax therapy.

Relevance

The findings of our study establish venetoclax as an active and tolerable therapy in patients with previously treated WM, regardless of previous exposure to BTKis. Given the manageable safety profile, future studies evaluating venetoclax in combination with anti-CD20 monoclonal antibodies or BTKis are warranted.

board at all study sites. All patients provided written informed consent for participation. AbbVie provided research funding and study drug. The trial was registered under ClinicalTrials.gov identifier [NCT02677324](https://clinicaltrials.gov/ct2/show/study/NCT02677324).

Study Patients

Adults with a diagnosis of WM were eligible if they were previously treated, had an Eastern Cooperative Oncology Group performance of ≤ 2 , adequate BM function (ie, neutrophil count ≥ 1.0 K/uL, platelet count ≥ 50 K/uL, and hemoglobin ≥ 8 g/dL), creatinine clearance ≥ 50 mL/min, adequate hepatic function, and met criteria to receive therapy.⁸ Relapsed disease was defined as attaining a response to previous therapy and meeting criteria for disease progression beyond 6 months after completing such therapy.⁹ Refractory disease was defined as not attaining a minor response (MR) or progressing while on or within 6 months of completing previous therapy. Exclusion criteria included CNS involvement, active HIV, hepatitis B or hepatitis C infection, concurrent therapy for other cancer, and current pregnancy or breastfeeding. A flow diagram is shown in [Figure 1](#).

Study Treatment

All treatments were provided in the outpatient setting. For the first six patients, venetoclax was administered orally once daily at 200 mg for 1 week, followed by 400 mg for 1 week, and then 800 mg for 2 years. Starting with the seventh patient, venetoclax was administered orally once daily at 400 mg for 1 week, followed by 800 mg for 2 years. Dose reductions were allowed for toxicity (Appendix [Table A1](#), online only). Three days before venetoclax, all patients started on allopurinol 300 mg once daily and 2-liter-per-day oral hydration for tumor lysis prophylaxis. Allopurinol was continued for 4 weeks. If oral hydration was not optimal, 2 L of normal saline was administered intravenously before the first dose of venetoclax. Granulocyte colony-stimulating factor (G-CSF) support was permitted for neutrophil count < 0.5 K/uL.

Assessments

Complete blood counts, comprehensive metabolic panel, and serum immunoglobulin levels were measured at baseline, once monthly for the first 3 months, and quarterly thereafter for the study duration. Tumor lysis monitoring with comprehensive metabolic panel, lactate dehydrogenase, phosphorus, and uric acid levels took place at 0, 8, and 24 hours on day 1 of each dose increase. BM aspiration and biopsies were obtained at baseline and 6, 12, and 24 months, and were evaluated at each participating institution. Computerized tomography scans with intravenous contrast were obtained at baseline and repeated at 6, 12, and 24 months if there was evidence of extramedullary disease at screening.

The primary objective was to determine the overall response rate (ORR), which included MR, partial response (PR), very good partial response (VGPR), and complete response. Secondary objectives included determining major response rate (PR or better), time to response, duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), and drug safety. The responses were defined according to modified criteria from the Sixth International Workshop on WM.^{9,10} Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

An allele-specific polymerase chain reaction assay was used to detect *MYD88 L265P* mutations in CD19-selected BM cells.¹¹ *CXCR4* mutational status was determined by Sanger sequencing and allele-specific polymerase chain reaction in CD19-selected BM cells.¹²

Statistical Analysis

A sample size of 32 participants was estimated using an alpha level of .05 and a power of 90%, assuming a null ORR $\leq 40\%$ and an alternative ORR $\geq 70\%$, on the basis

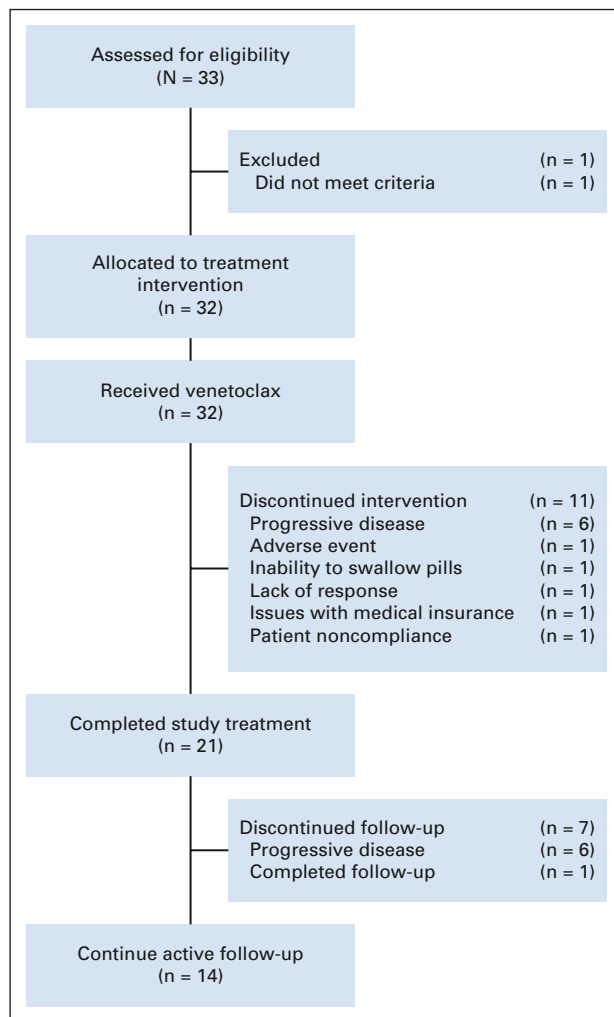


FIG 1. Flow diagram.

of response rates to other monotherapies in previously treated patients with WM. Data were categorized to facilitate analysis (Appendix Table A2, online only), and factors evaluated in response and survival analyses. Descriptive statistics, including proportions, medians, and ranges, were calculated. Differences between group categories were assessed using the Fisher exact test. The Kaplan-Meier method was used for time-to-event analyses with censoring, and the log-rank test to assess differences between group categories. *P* values < .05 indicate statistical significance. Statistical analyses and graphs were performed using STATA 17.0 (College Station, TX).

RESULTS

Patients and Disease Characteristics

A total of 33 patients were enrolled. One patient received venetoclax but was excluded from the analysis because further workup indicated this patient had IgM myeloma. The malignant cells expressed cyclin D1 and harbored the

t(11;14) translocation. This patient attained an MR and progressed after 8 months of therapy.

The baseline characteristics of all participants are shown in Table 1. The median time from the previous therapy to venetoclax initiation was 9 months (range, 1-115 months). Seven patients were treated in first relapse, and previous treatment included bortezomib, dexamethasone and rituximab (*n* = 4), bendamustine and ofatumumab (*n* = 1), BTKi (*n* = 1), and ofatumumab (*n* = 1). Of the 11 refractory patients, four were refractory to proteasome inhibitor–based regimens, three to BTKi, two to single agent anti-CD20 monoclonal antibodies, one to bendamustine and rituximab, and one to a phosphatidylinositol-3 kinase inhibitor.

Sixteen patients (50%) were previously treated with a BTKi. BTKis were the last therapy before venetoclax in 11 patients with a median time from BTKi cessation to venetoclax initiation of 3 months (range, 1-15 months), of whom eight were intolerant and three had progressed on BTKis. In the remaining five patients, one was intolerant and four had progressed on BTKis. The median time of BTKi exposure was 10 months (range, 2-83 months).

The *MYD88 L265P* mutation was detected in all patients. *CXCR4* mutations were detected in 17 patients, including 12 nonsense and five frameshift variants. Patients with *CXCR4* mutations were less likely to have adenopathy ≥ 1.5 cm (12% v 53%; *P* = .01) and had a lower median serum beta-2-microglobulin level (2.6 v 4.9 mg/dL; *P* = .002) versus those without *CXCR4* mutations.

Response to Therapy

Categorical responses included VGPR (*n* = 6; 19%), PR (*n* = 19; 61%), and MR (*n* = 1; 3%), for an ORR of 84% (95% CI, 66 to 95) and major response rate of 81% (95% CI, 63 to 93; Fig 2A). No patient attained a complete response. The ORR was lower in those with refractory versus relapsed disease (60% v 95%; *P* = .03; Fig 2B), and those who received ≥ 3 versus < 3 prior lines of therapy (63% v 95%; *P* = .04; Fig 2C). No other clinical or genomic factor, including prior BTKi exposure (Fig 2D), *CXCR4* mutational status (Fig 2E), and International Prognostic Scoring System for Waldenström Macroglobulinemia (Fig 2F), was associated with a lower ORR. The major response rate was also significantly lower in those with refractory versus relapsed disease (50% v 95%; *P* = .007). No other clinical or genomic factor was associated with a lower major response rate. No baseline characteristic was associated with VGPR attainment. The kinetics of response to venetoclax are shown in Appendix Fig A1 (online only).

The median times to minor and major response were 1.9 months (95% CI, 1.1 to 2.1) and 5.1 months (95% CI, 4.7 to 8.2), respectively. The median time to MR was longer in patients previously treated with BTKis (4.5 and 1.4 months; *P* < .001). The median time to MR for the 11 patients in whom BTKis were the last line before venetoclax was 4.5 months, and 4.7 months for the five who were

TABLE 1. Baseline Characteristics of the Participants

Characteristic	Participants (n = 32)
Age	
At WM diagnosis, years (range)	58 (38-72)
At venetoclax initiation, years (range)	66 (39-80)
> 65 years at venetoclax initiation, No. (%)	18 (56)
Sex, No. (%)	
Male	18 (56)
Female	14 (44)
Serum IgM level	
Median, mg/dL (range)	3,512 (642-7,970)
≥ 4,000 mg/dL, No. (%)	14 (44)
Hemoglobin level	
Median, g/dL (range)	10.6 (6.4-13.5)
≤ 11.5 g/dL, No. (%)	23 (72)
Platelet count	
Median, K/uL (range)	216 (60-445)
≤ 100 K/uL, No. (%)	3 (9)
Serum beta-2-microglobulin level	
Median, g/dL (range)	3.6 (1.9-9.8)
> 3 g/dL, No. (%)	19 (59)
IPSSWM score, No. (%)	
Low risk	12 (38)
Intermediate risk	8 (25)
High risk	12 (38)
BM involvement, No. (%)	
Median (range)	35 (4-90)
≥ 50%	13 (41)
Extramedullary disease, No. (%)	
Adenopathy ≥ 1.5 cm	9 (28)
Splenomegaly ≥ 15 cm	8 (25)
Genomic profiling, No. (%)	
<i>MYD88 L265P</i> mutation	32 (100)
<i>CXCR4</i> mutation	17 (53)
Prior therapies	
Median No. of prior therapies (range)	2 (1-10)
≥ 3 prior therapies, No. (%)	12 (38)
Previous anti-CD20 monoclonal antibodies, No. (%)	28 (88)
Previous proteasome inhibitors, No. (%)	21 (66)
Previous BTKi, No. (%)	16 (50)
Previous chemotherapy, No. (%)	15 (47)
Refractory to most recent therapy, No. (%)	11 (34)
Indications to treat	
Constitutional symptoms	17 (53)
Symptomatic anemia	14 (44)
Extramedullary disease ^a	4 (13)
Hyperviscosity	1 (3)

Abbreviations: BM, bone marrow; BTKi, Bruton tyrosine kinase inhibitor; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; WM, Waldenström macroglobulinemia.

^aIncluded mediastinal lymphadenopathy of 8 cm, splenomegaly of 22 cm, pleural effusion, and renal involvement (n = 1 each).

treated with BTKis at a previous time point. A serum IgM rebound, defined by a ≥ 25% increase in serum IgM between baseline and cycle 2, was observed in only two of the 11 patients in whom BTKis were the last line of therapy before venetoclax. The median time to major response was longer in those with previous BTKi exposure (8.5 and 4.4 months; $P < .001$); those with ≥ 3 prior lines of therapy (10.8 v 4.8 months; $P = .03$); and those with refractory versus relapsed disease (8.2 v 4.7 months; $P = .007$).

Serum IgM levels correlated with decrease in BM disease burden. At 6, 12, and 24 months, the median decrease in serum IgM level was 55%, 69%, and 72% and in BM involvement was 65%, 70%, and 75%, respectively (correlation $r = 0.94$). Of the nine patients with baseline lymphadenopathy (≥ 1.5 cm), eight (89%) showed decreased adenopathy with follow-up scans, and one was unevaluable. Of the eight patients with baseline splenomegaly (≥ 15 cm), four (50%) showed reduction in spleen size and one (13%) showed stability. Three patients were unevaluable for extramedullary disease response, as venetoclax was discontinued before assessments were performed.

PFS, TTNT, and Overall Survival

With a median follow-up of 33 months (range, 24-38 months), 19 patients have progressed. The median PFS was 30 months (95% CI, 27 to 38; Fig 3A). The 12- and 24-month PFS rates were 83% (95% CI, 64 to 93) and 80% (95% CI, 60 to 90), respectively. A trend for shorter PFS was observed for those with refractory disease (Fig 3B) and ≥ 3 lines of prior therapy (Fig 3C), but there was no difference in PFS on the basis of prior BTK inhibition (Fig 3D), *CXCR4* mutational status (Fig 3E), or International Prognostic Scoring System for Waldenström Macroglobulinemia (Fig 3F). No other factor was associated with a worse PFS.

Six patients progressed within the first 24 months, and 13 after completion of venetoclax therapy, including 10 between 24 and 36 months, and three after 36 months. Among patients who progressed after completion of 24 months of venetoclax therapy, 10 were in PR and three in VGPR. Attainment of VGPR was not associated with progression after 24 months of treatment completion ($P = .65$). The median DOR for the 19 patients who attained PR was 34 months (95% CI, 29 to 37) and for the six patients who attained VGPR was 37 months (95% CI, 10 to not evaluable). The DOR for the one patient who attained MR was 9 months.

Twelve patients have started a new therapy after venetoclax. The median TTNT has not been reached. The 30-month rate without subsequent therapy was 76% (57%-88%). The 30-month rate without subsequent therapy was lower for refractory patients than those with relapsed disease at 60% (95% CI, 25 to 83) and 85% (95% CI, 60 to 95), respectively ($P = .006$). All 32 patients were alive at

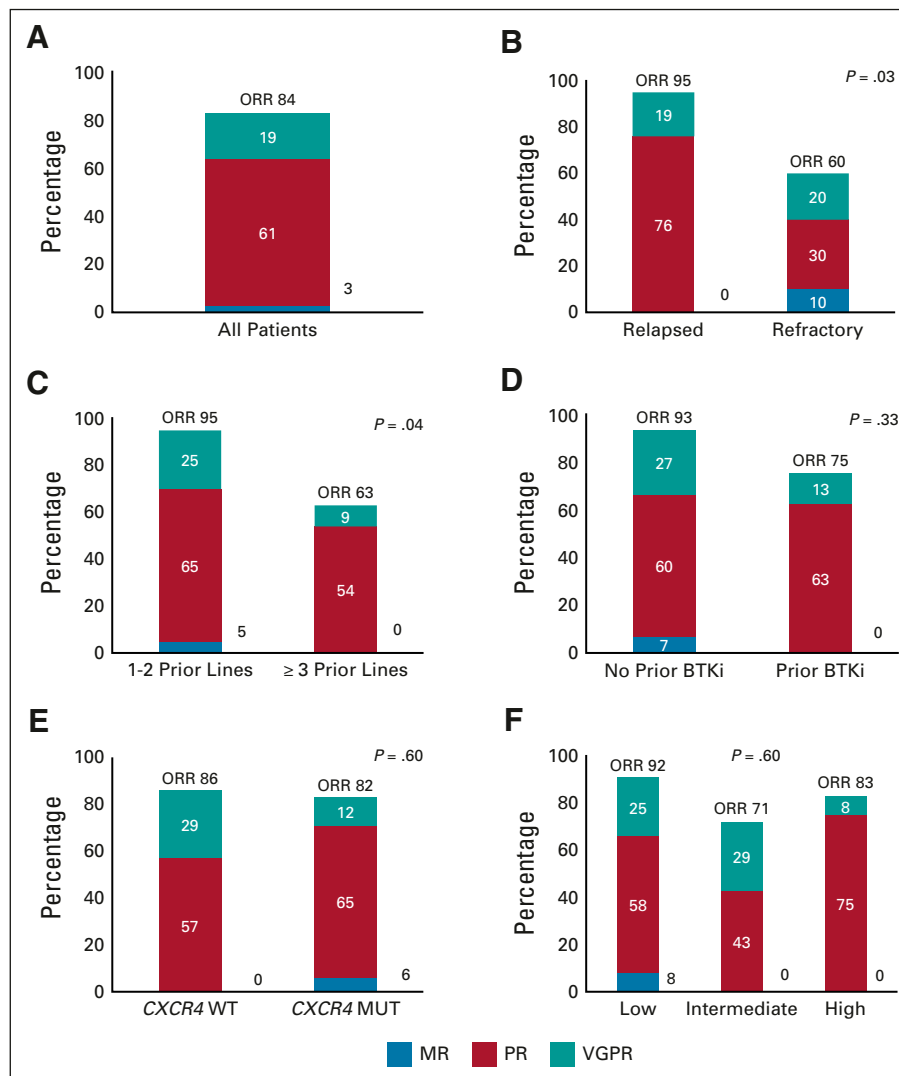


FIG 2. Categorical response rates to venetoclax for (A) all patients, and according to (B) relapsed or refractory disease, (C) number of previous lines of therapy, (D) prior BTKi exposure, (E) *CXCR4* mutational status, and (F) IPSSWM. BTKi, Bruton tyrosine kinase inhibitor; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; MR, minor response; MUT, mutated; ORR, overall response rate; PR, partial response; VGPR, very good partial response; WT, wild-type.

time of data cutoff, for a 30-month overall survival rate of 100% (95% CI, 89 to 100).

Patient Disposition

Twenty-one patients (66%) completed all scheduled therapy cycles and received a median number of 25.5 cycles (range, 1-26 cycles) of treatment. Eleven patients (34%) did not complete study therapy because of disease progression and initiation of new treatment (n = 6); inability to swallow pills (n = 1); Protocol (online only) noncompliance (n = 1); nonresponse (n = 1); related to medical insurance coverage (n = 1); and persistent pancytopenia (n = 1). Of the 21 patients who completed therapy, 15 continue in active follow-up; five had disease progression during follow-up and new treatment initiated; and one patient completed all follow-

ups. Of the 12 patients who started a new therapy during the study course, successor therapies included BTKi (n = 4); alkylators (n = 3), proteasome inhibitor (n = 1), and investigational agent (n = 4). Of the 13 patients who relapsed after 24 months, six required treatment at a median time from progression to next therapy of 6 months (range, 1-15 months). Seven patients have not yet required therapy. All the patients exposed to BTKis have responded.

Drug Administration and Safety

Seven patients (22%) had venetoclax dose reduction related to neutropenia (n = 2), pancytopenia (n = 1), fatigue not otherwise attributable (n = 1), diarrhea (n = 1), multiple grade 2 events (n = 1), and dosing noncompliance, that is, self-reduced (n = 1). Among these patients, four were

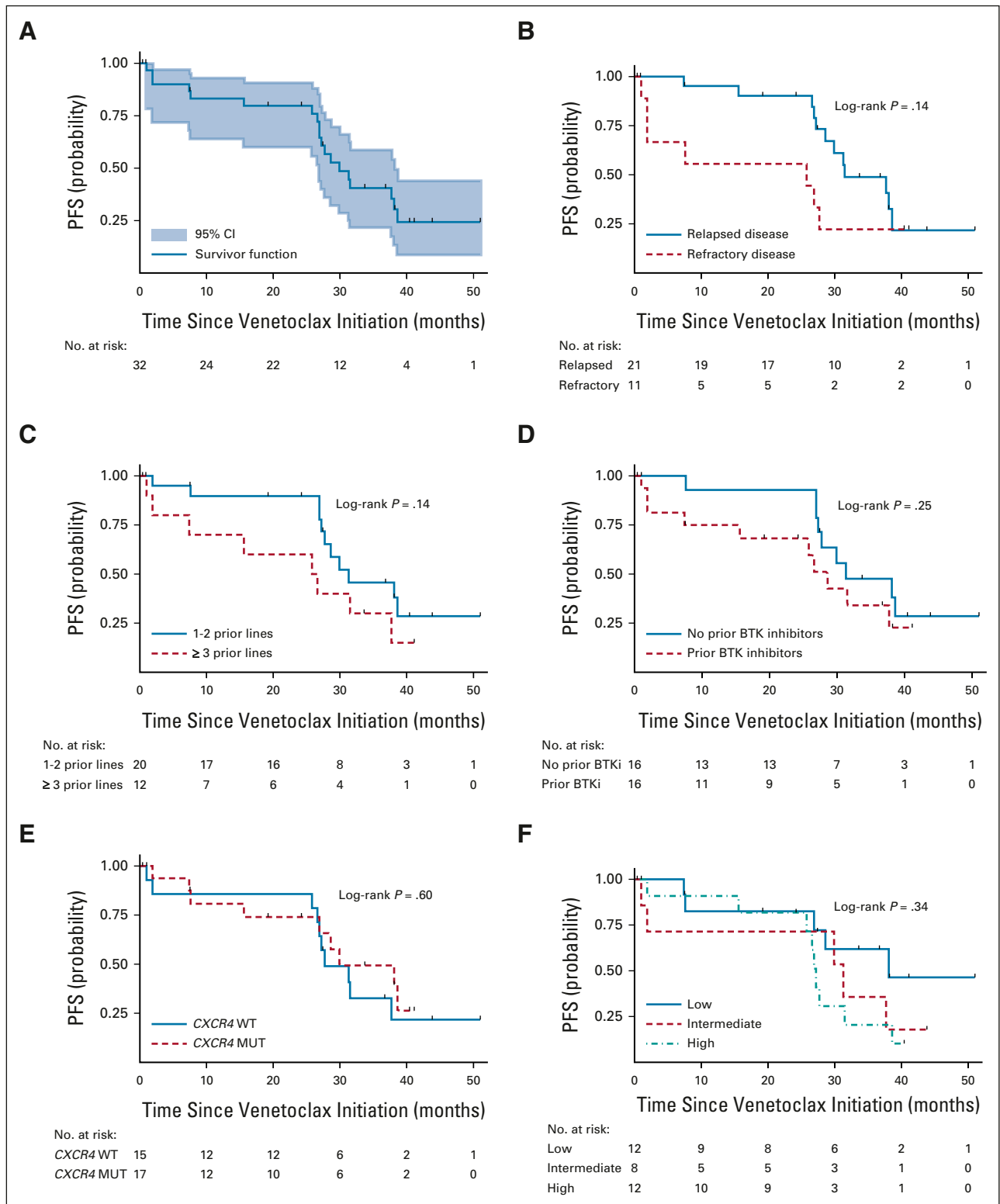


FIG 3. Kaplan-Meier curves for PFS for (A) the entire cohort, and according to (B) relapsed or refractory disease, (C) number of previous lines of therapy, (D) prior BTKi exposure, (E) *CXCR4* mutational status, and (F) IPSSWM. BTKi, Bruton tyrosine kinase inhibitor; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; MUT, mutated; PFS, progression-free survival; WT, wild-type.

reduced to 600; two to 400; and one to 300 mg daily. The only factor associated with dose reduction was female sex (70% v 14% in males). Dose reductions were not associated

with worse ORR, major response rate, VGPR rate, or PFS ($P > .05$ in all instances). Venetoclax was discontinued early in one patient because of pancytopenia.

TABLE 2. Grade 2 or Higher Adverse Events Associated With Venetoclax Therapy

Adverse Event	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Blood and lymphatic system disorders				
Neutropenia	3	8	6	17
Anemia	7	1	0	8
Lymphopenia	5	1	0	6
Thrombocytopenia	2	0	0	2
Febrile neutropenia	0	0	1	1
Ear and labyrinth disorders				
Tinnitus	0	1	0	1
GI disorders				
Nausea	4	0	0	4
Diarrhea	2	1	0	3
Constipation	0	1	0	1
Dyspepsia	0	1	0	1
Gastroesophageal reflux	1	0	0	1
General disorders				
Chills	1	0	0	1
Myalgia	1	0	0	1
Rash	1	0	0	1
Infections and infestations				
Upper respiratory infection	2	1	0	3
Sinusitis	2	0	0	2
Tooth infection	1	0	0	1
Urinary tract infection	1	0	0	1
Investigations				
Alkaline phosphatase increased	0	1	0	1
INR increased	1	0	0	1
Metabolism and nutrition disorder				
Hyperglycemia	0	1	0	1
TLS	0	1	0	1
Musculoskeletal and connective tissue disorders				
Back pain	1	0	0	1
Nervous system disorder				
Headache	1	1	0	2

Abbreviations: INR, international normalized ratio; TLS, tumor lysis syndrome.

Thirty-one patients (94%) experienced a grade ≥ 2 adverse event (Table 2). The only grade 4 adverse events were neutropenia ($n = 6$) and febrile neutropenia ($n = 1$). All seven participants received G-CSF, and all events resolved with a median of 4 days (range, 0-17 days). One participant was dose-reduced twice for neutropenia. One patient, who had generalized lymphadenopathy (3.7 cm), splenomegaly (27 cm), and leukocytosis (59 K/uL), experienced a laboratory tumor lysis syndrome (TLS) that was managed as an

inpatient and responded to intravenous fluids and one dose of rasburicase. No paradoxical IgM flare, secondary myeloid neoplasms, aggressive transformation, peripheral neuropathy, cardiac arrhythmia, or clinical TLS were observed on venetoclax therapy. No serum IgM rebound was documented after stopping venetoclax therapy.

There were 21 temporary venetoclax holds in 14 participants. Reasons for drug holds included neutropenia ($n = 6$), infections ($n = 4$), diarrhea ($n = 3$), and mouth sores, appendicitis, hip fracture, fatigue, stem-cell collection, laboratory TLS, jaw injury, and nausea ($n = 1$ each). The median duration of the drug hold was 6 days (range, 2-35 days). There was no difference in median serum IgM levels at the start and the end of the drug hold ($P = .25$).

There was no difference in median serum IgG and immunoglobulin A levels between baseline and end of treatment ($P > .05$ in both instances).

DISCUSSION

Herein, we present the results of, to our knowledge, this first, prospective phase II study evaluating the oral BCL2 antagonist venetoclax in previously treated WM. We found that venetoclax monotherapy was highly effective in patients with previously treated WM with an ORR of 84%, on the basis of which our study met its end point. Responders included those with refractory disease and those who received ≥ 3 prior therapies, although lower response rates were observed in these patients. Prior BTK exposure affected time to minor and major response attainment but did not affect depth of response or PFS. The delay in response for this patient cohort is unlikely to be fully explained by an IgM rebound following cessation of BTKis,¹³ as this was observed in only two patients. Conversely, BTKi-promoted selection of malignant clones overexpressing BCL2 family members (eg, BCLXL) has been postulated to contribute to relative resistance associated with venetoclax in patients with CLL and could be etiologic for this observation in patients with WM.¹⁴

Important secondary findings were a major response of 81% and the relatively long PFS of 30 months in this population of patients whose median prior therapies was two, and of whom 34% were refractory to previous therapy, including 50% previously exposed to BTKis. These efficacy outcomes compare favorably with non-BTKi regimens in previously treated WM, wherein PFS durations of 8-20 months have been observed.² Importantly, a rapid decline in PFS between months 24 and 36 was observed in 10 patients who completed the 2-year course of Protocol therapy, suggesting that indefinite continuation of venetoclax may be necessary in patients with WM. Importantly, *CXCR4* mutation status did not affect response or PFS to venetoclax, in contrast to experiences with BTKis.^{10,15} Since *MYD88* mutations were detected in all the participants, we were unable to assess the impact of venetoclax on *MYD88*

wild-type WM patients. Other markers of clinical benefit included improvement in hemoglobin levels and decrease in lymphadenopathy and splenomegaly. Notably, venetoclax led to impressive decreases in BM disease involvement. In comparison to BTKis, venetoclax offers a more robust clearance of BM disease burden.^{13,16,17}

The precise sequencing of BTKis and BCL2 inhibitors in WM remains to be clarified, and further study will be required to address this point. In CLL, resistance to venetoclax post-BTKi exposure has been observed, whereas BTKis appeared effective after venetoclax.^{18,19} Our results suggested similar levels of efficacy for venetoclax for either BTKi-naïve or previously exposed patients, thereby offering a meaningful, active treatment option for those previously exposed to a BTKi.

Neutropenia was the only grade 4 adverse event and was effectively managed with G-CSF. TLS, a major concern in patients with CLL receiving venetoclax,²⁰ was only observed as a laboratory anomaly without clinical manifestations in one patient in this study. A previous study also reported low rates of tumor lysis events in patients with indolent lymphomas treated with venetoclax, comparable with our findings.⁷ The favorable safety profile of venetoclax provides a platform to

study combination regimens in patients with WM. It would be of interest to investigate venetoclax in combination with anti-CD20 monoclonal antibodies in WM, given encouraging experience with this combination in CLL.²¹

Another promising combination is concurrent use of venetoclax with BTKis as suggested by in vitro WM studies, and ongoing findings from clinical trials examining the combination of ibrutinib and venetoclax in CLL and mantle cell lymphoma.^{6,22-25} As suggested by these combination studies, concurrent inhibition of BTK and BCL2 could potentially lead to more robust tumor killing and deeper responses including minimal residual disease achievement, a finding that remains elusive for most patients with WM with current pharmacotherapy. Given these observations, a prospective study evaluating ibrutinib and venetoclax in treatment-naïve patients with WM has been initiated (NCT04273139).

In conclusion, venetoclax is safe and highly active in patients with previously treated WM, including those previously treated with BTKis. *CXCR4* mutation status did not affect treatment response. The optimal duration of venetoclax therapy in WM is yet to be determined.

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PRIOR PRESENTATION

Presented at the 23rd Congress of the European Hematology Association, Stockholm, Sweden, June 14-17, 2018; at the 10th International Workshop for Waldenström Macroglobulinemia, New York, NY, October 11-13, 2018; at the 60th Annual Meeting of the American Society of Hematology, San Diego, CA, December 1-4, 2018; and at the 17th International Myeloma Workshop, Boston, MA, September 12-15, 2019.

SUPPORT

AbbVie provided drug and funds for this study.

CLINICAL TRIAL INFORMATION

NCT02677324

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.21.01194>.

DATA SHARING STATEMENT

Deidentified data, study protocol, and informed consent form will be available immediately and up to 3 years from publication. Requests should be made via e-mail to jorgej_castillo@dfci.harvard.edu.

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REFERENCES

- Owen RG, Treon SP, Al-Katib A, et al: Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol* 30:110-115, 2003
- Castillo JJ, Advani RH, Branagan AR, et al: Consensus treatment recommendations from the tenth International Workshop for Waldenstrom Macroglobulinaemia. *Lancet Haematol* 7:e827-e837, 2020
- Hunter ZR, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood* 123:1637-1646, 2014
- Treon SP, Xu L, Yang G, et al: MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med* 367:826-833, 2012
- Treon SP, Xu L, Guerrero ML, et al: Genomic landscape of Waldenstrom macroglobulinemia and its impact on treatment strategies. *J Clin Oncol* 38:1198-1208, 2020
- Cao Y, Yang G, Hunter ZR, et al: The BCL2 antagonist ABT-199 triggers apoptosis, and augments ibrutinib and idelalisib mediated cytotoxicity in CXCR4 Wild-type and CXCR4 WHIM mutated Waldenstrom macroglobulinaemia cells. *Br J Haematol* 170:134-138, 2015
- Davids MS, Roberts AW, Seymour JF, et al: Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol* 35:826-833, 2017
- Kyle RA, Treon SP, Alexanian R, et al: Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second international Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol* 30:116-120, 2003
- Owen RG, Kyle RA, Stone MJ, et al: Response assessment in Waldenstrom macroglobulinaemia: Update from the VIth International Workshop. *Br J Haematol* 160:171-176, 2013
- Treon SP, Meid K, Gustine J, et al: Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenstrom macroglobulinemia. *J Clin Oncol* 39:565-575, 2021
- Xu L, Hunter ZR, Yang G, et al: MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood* 121:2051-2058, 2013
- Xu L, Hunter ZR, Tsakmaklis N, et al: Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom macroglobulinaemia. *Br J Haematol* 172:735-744, 2016
- Treon SP, Tripsas CK, Meid K, et al: Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med* 372:1430-1440, 2015
- Haselager MV, Kielbassa K, Ter Burg J, et al: Changes in Bcl-2 members after ibrutinib or venetoclax uncover functional hierarchy in determining resistance to venetoclax in CLL. *Blood* 136:2918-2926, 2020
- Castillo JJ, Xu L, Gustine JN, et al: CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. *Br J Haematol* 187:356-363, 2019
- Dimopoulos MA, Trotman J, Tedeschi A, et al: Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): An open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol* 18:241-250, 2017
- Treon SP, Gustine J, Meid K, et al: Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenstrom macroglobulinemia. *J Clin Oncol* 36:2755-2761, 2018
- Roberts AW, Ma S, Kipps TJ, et al: Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. *Blood* 134:111-122, 2019
- Mato AR, Roeker LE, Jacobs R, et al: Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clin Cancer Res* 26:3589-3596, 2020
- Davids MS, Hallek M, Wierda W, et al: Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res* 24:4371-4379, 2018
- Seymour JF, Kipps TJ, Eichhorst B, et al: Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* 378:1107-1120, 2018
- Kuo HP, Ezell SA, Schweighofer KJ, et al: Combination of ibrutinib and ABT-199 in diffuse large B-cell lymphoma and follicular lymphoma. *Mol Cancer Ther* 16:1246-1256, 2017
- Zhao X, Bodo J, Sun D, et al: Combination of ibrutinib with ABT-199: Synergistic effects on proliferation inhibition and apoptosis in mantle cell lymphoma cells through perturbation of BTK, AKT and BCL2 pathways. *Br J Haematol* 168:765-768, 2015
- Jain N, Keating M, Thompson P, et al: Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med* 380:2095-2103, 2019
- Tam CS, Anderson MA, Pott C, et al: Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N Engl J Med* 378:1211-1223, 2018



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Venetoclax in Previously Treated Waldenström Macroglobulinemia**

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APPENDIX

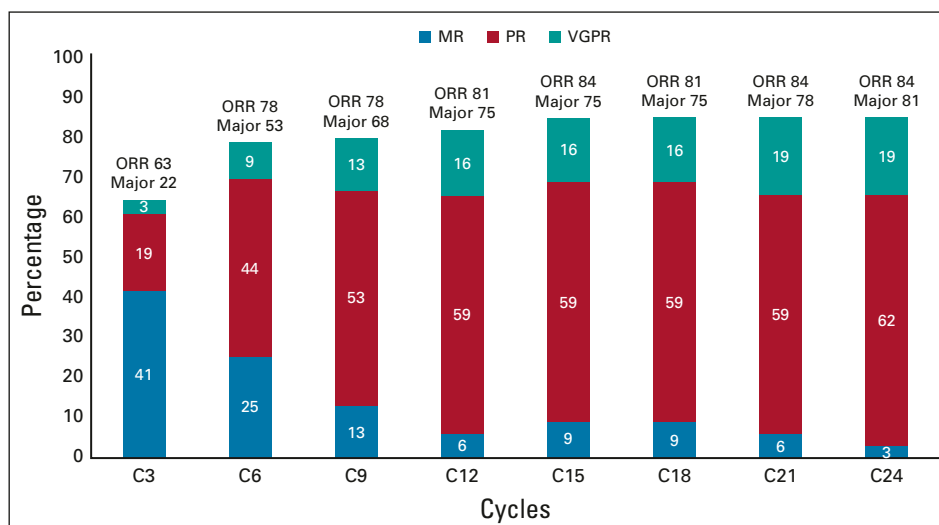


FIG A1. Response kinetics to venetoclax in patients with previously treated WM. MR, minor response; ORR, overall response rate; PR, partial response; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

TABLE A1. Venetoclax Dose Modification Guidelines

Cohort 1					
	Dose Level 1 (mg)	Dose Level –1 (mg)	Dose Level –2 (mg)	Dose Level –3 (mg)	Dose Level –4 (mg)
Week 1 starting dose	200	100	100	—	—
Week 2 first dose escalation	400	200	200	—	—
Week ≥ 3	800	600	600	200	100
Escalation to target dose and all cycles thereafter					
Cohort 2					
	Dose Level 1 (mg)	Dose Level –1 (mg)	Dose Level –2 (mg)	Dose Level –3 (mg)	Dose Level –4 (mg)
Week 1 starting dose	400	200	100	—	—
Week ≥ 2	800	600	400	200	100
Escalation to target dose and all cycles thereafter					

Dosing will be held for any of the following conditions: Grade 4 absolute neutrophil count ($< 500/\mu\text{L}$) for > 7 days (neutrophil growth factors are permitted). Grade 4 platelets ($< 25,000/\mu\text{L}$) or in subjects with baseline thrombocytopenia, decrease of $> 75\%$ from baseline or $< 20,000/\mu\text{L}$, whichever is higher. Hold until grade 3 unless active bleeding. Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy). Any other related grade 4 toxicities and any unmanageable nonhematologic grade 3 toxicities.

Drug modification or discontinuation actions for ABT-199–related events: First hold: ABT-199 until recovery from criteria to hold; may restart at original dose level. Second hold: ABT-199 until recovery from criteria to hold; restart at –1 dose level. Third hold: ABT-199 until recovery from criteria to hold; restart at –2 dose level (if applicable, see Tables 6-1 and 6-2). Fourth hold: ABT-199 until recovery from criteria to hold; restart at –3 dose level (if applicable, see Tables 6-1 and 6-2). Fifth hold: ABT-199 until recovery from criteria to hold; restart at –4 dose level (if applicable, see Tables 6-1 and 6-2). Sixth hold: discontinue ABT-199.

If a participant has a drug hold, the schedule of assessments will not change. If participants do not meet treatment criteria on day 1 of the cycle, the cycle will not be delayed.

TABLE A2. Data Categorization for Analysis

Variable	Categories
Age, years	≤ 65 > 65
Sex	Male Female
Hemoglobin level, g/dL	≤ 11.5 > 11.5
Platelet count, K/uL	≤ 100 > 100
Serum beta-2-microglobulin level, mg/dL	≤ 3 > 3
Serum IgM level, mg/dL	< 4,000 ≥ 4,000
BM involvement, %	< 50 ≥ 50
IPSSWM risk	Low Intermediate High
Lymphadenopathy ≥ 1.5 cm	Yes No
Splenomegaly ≥ 15 cm	Yes No
<i>CXCR4</i> mutational status	Wild-type Mutated
Previous BTKi exposure	Yes No
Disease status	Relapsed Refractory
No. of previous lines of therapy	< 3 ≥ 3

Abbreviations: BM, bone marrow; BTK, Bruton tyrosine kinase inhibitor; IgM, immunoglobulin M; IPPSSWM: International Prognostic Scoring System for Waldenström Macroglobulinemia.