

Prospective Clinical Trial of Ixazomib, Dexamethasone, and Rituximab as Primary Therapy in Waldenström Macroglobulinemia



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Abstract

Purpose: Proteasome inhibition is of proven efficacy in patients with Waldenström macroglobulinemia (WM). However, WM remains incurable with standard treatments. Novel agents, safe and effective, are needed.

Patients and Methods: We designed a prospective phase II study evaluating the combination of ixazomib, dexamethasone, and rituximab (IDR) as primary therapy in symptomatic patients with WM. Protocol therapy consisted of oral ixazomib, 4 mg, with intravenous or oral dexamethasone, 20 mg, on days 1, 8, and 15 every 4 weeks for induction cycles 1 and 2, and in combination with intravenous rituximab, 375 mg/m², on day 1, every 4 weeks for cycles 3 to 6. Maintenance therapy followed 8 weeks later with IDR given every 8 weeks for 6 cycles.

Results: Twenty-six patients were enrolled. All patients had the MYD88 L265P mutation, and 15 patients (58%) had a CXCR4 mutation. The median time to response was 8 weeks, which was longer (12 weeks) in WM patients with CXCR4 mutations ($P = 0.03$). The overall response rate was 96%, and the major response rate was 77%. With a median follow-up of 22 months, the median progression-free survival was not reached. Grade ≥ 2 adverse events reported in >1 patient included infusion-related reactions (19%), rash (8%), and insomnia (8%).

Conclusions: IDR offers a highly effective and well tolerated, neuropathy-sparing regimen for primary therapy in patients with WM. This trial is registered at www.clinicaltrials.gov under ID NCT02400437. *Clin Cancer Res*; 24(14): 3247–52. ©2018 AACR.

Introduction

Waldenström macroglobulinemia (WM) is a rare lymphoma characterized by the accumulation of IgM-secreting lymphoplasmacytic cells in the bone marrow (BM) and other organs along with the presence of the MYD88 L265P mutation in over 90% of patients (1). As WM remains incurable with standard treatment regimens, there is an ongoing need for effective and safe agents for these patients.

Proteasome inhibitors are effective agents for the primary treatment of WM (2–5). However, toxicity remains of importance. Treatment-related neuropathy is common with bortezomib and has led to premature treatment discontinuation (2, 4). Carfilzomib has associated with hyperlipasemia, hypogammaglobulinemia, and cardiomyopathy (5). In addition, the frequent i.v. or subcutaneous administration of these agents might prove to be inconvenient when compared with an orally administered agent.

Ixazomib is an oral proteasome inhibitor with low incidence of neuropathy that is active in multiple myeloma, but has not been previously evaluated in WM. We hypothesized that the combination of ixazomib, dexamethasone, and rituximab

(IDR) would have a high efficacy rate and low toxicity as primary therapy in WM.

Patients and Methods

This was a prospective, investigator-initiated phase II study that enrolled patients at the Dana-Farber Cancer Institute. The study registered under Clinicaltrials.gov ID NCT02400437. The Institutional Review Board of the Harvard/Dana-Farber Cancer Center granted study approval. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained in all participants prior to treatment initiation. Ixazomib was supplied by Takeda Pharmaceuticals. Rituximab and dexamethasone were obtained commercially.

Eligible participants had a clinicopathologic diagnosis of WM (6), were previously untreated, and met criteria for treatment initiation according to second International Workshop for WM guidelines (7). Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0–2, neutrophil count ≥ 1.0 K/ μ L, platelet count ≥ 75 K/ μ L, total bilirubin ≤ 1.5 times the upper limit of normal (ULN), alanine and aspartate aminotransferase ≤ 3 times the ULN, and creatinine clearance ≥ 30 mL/min. Selected exclusion criteria were pregnant or lactating women, central nervous system involvement, HIV, hepatitis B or hepatitis C infection, or known gastrointestinal condition that could interfere with swallowing or absorption of ixazomib.

Treatment protocol consisted of ixazomib 4 mg orally on days 1, 8, and 15, dexamethasone 20 mg p.o. on days 1, 8, and 15, and rituximab 375 mg/m² i.v. on day 1 (IDR), which were administered for six 4-week cycles (induction) followed by six 8-week cycles (maintenance) for a total of 12 cycles. Patients received

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Translational Relevance

Based on the results of this prospective phase II study, the combination of ixazomib, dexamethasone, and rituximab (IDR) is safe and effective as primary therapy for patients with symptomatic Waldenström macroglobulinemia (WM). With regard to safety, the toxicity profile of IDR appears benign, in comparison with bortezomib or carfilzomib-based combinations, with a low rate of mild neuropathy. In addition, IDR provides the convenience of an orally administered medication, ixazomib, in addition to one of the most commonly used medications in WM, rituximab, improving the response rate in these patients. Of interest for future research is the potential adverse effect of CXCR4 mutations in time to response to IDR in WM patients. In conclusion, IDR is an easy-to-use and easy-to-tolerate regimen that has the potential to become a leading option in the primary treatment of patients with symptomatic WM.

maintenance if they had at least a minor response or derived clinical benefit from induction. Rituximab was held for the first two cycles of therapy to minimize risk of IgM flare. Rituximab was administered after ixazomib and dexamethasone. Herpes zoster prophylaxis and proton pump inhibitors or H2 blockers were administered throughout IDR therapy. Prophylactic use of plasmapheresis and hold on rituximab administration for patients with serum IgM level of >4,000 mg/dL prior to the administration of rituximab was recommended. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03 (8).

Baseline studies consisted of complete blood counts, comprehensive metabolic panel, serum IgM and beta-2-microglobulin levels, serum protein electrophoresis, BM biopsy and aspiration, and CT scans of the chest, abdomen, and pelvis. Efficacy and toxicity were assessed on the first day of each cycle starting at cycle 2, and thereafter off therapy every 12 weeks. At interphase and end of maintenance, BM biopsy and aspiration and CT scans of the chest, abdomen, and pelvis, if extramedullary disease was present at baseline, were required.

An allele-specific PCR assay was used for determination of MYD88 L265P using DNA isolated from CD19-selected BM cells as previously described (1, 9). CXCR4 mutation status was determined by Sanger sequencing of CD19-selected BM cells as previously described (10).

The primary objective of the study was determination of very good partial response (VGPR) or better. Secondary objectives were determination of overall response rate (ORR), progression-free survival (PFS), as well as safety and tolerability of IDR. Sample size was predicated on an expected VGPR or better of 40% and a minimal acceptable VGPR rate of 18% based on assumptions derived from previous published experience with proteasome inhibitors. Response determinations were made using consensus criteria adapted from the third International Workshop on WM (11). Time to progression was defined as time between initiation of therapy and date of progression, death, or last follow-up. The Kaplan–Meier method was used to estimate survival curves, which were compared using the log-rank test. The Wilcoxon rank-sum test was used for analysis of continuous variables. *P* values < 0.05 were considered statistically significant. All graphics and calculations were obtained using STATA (StataCorp LP).

Table 1. Baseline characteristics of 26 patients who received protocol therapy

| Characteristics | Median or number | Range or % |
|-----------------------------|------------------|------------|
| Age at WM diagnosis (years) | 62.5 | 46–81 |
| Age at enrollment (years) | 65 | 46–82 |
| Male sex | 21/26 | 81% |
| Serum IgM (mg/dL) | 4,528 | 653–7,650 |
| Serum IgA (mg/dL) | 61.5 | 8–140 |
| Serum IgG (mg/dL) | 609 | 160–4,677 |
| Hemoglobin (g/dL) | 10.2 | 6.9–13.2 |
| Platelet count (K/ μ L) | 211.5 | 77–420 |
| Beta-2-microglobulin (mg/L) | 4.0 | 1.8–10.8 |
| Low IPSSWM score | 5/26 | 19% |
| Intermediate IPSSWM score | 11/26 | 42% |
| High IPSSWM score | 10/26 | 38% |
| Adenopathy | 14/26 | 54% |
| Splenomegaly | 3/26 | 12% |
| BM involvement (%) | 55% | 5–95% |
| MYD88 L265P mutation | 26/26 | 100% |
| CXCR4 mutation | 15/26 | 58% |

Results

Between May 2015 and May 2016, 26 patients were enrolled and received protocol therapy. One patient was enrolled but did not receive protocol therapy, as the patient was diagnosed with transformation to diffuse large B-cell lymphoma during screening. Baseline characteristics of 26 participants are shown in Table 1. Reasons for treatment initiation included anemia (*n* = 13), hyperviscosity (*n* = 8), fatigue (*n* = 4), neuropathy (*n* = 2), splenomegaly (*n* = 1), pancytopenia (*n* = 1), and pleural effusions (*n* = 1). All patients have completed protocol therapy. Median number of cycles received was 12 (range, 4–12). Twenty-one patients (81%) completed the 12 planned cycles of therapy. All patients had the MYD88 L265P mutation, and 15 (58%) had a CXCR4 mutation.

At best response, median serum IgM level decreased from 4,528 to 1,188.5 mg/dL (range, 69–5,500 mg/dL), median hemoglobin increased from 10.2 to 13.7 g/dL (range, 9.8–16.5 g/dL), and median BM involvement decreased from 55% to 6% (range, 0%–70%). *P* value < 0.001 for all comparisons. Serum IgM and hemoglobin levels during active therapy are shown in Fig. 1A. At end of induction, serum IgM level was 2,279 mg/dL (range, 287–5,820 mg/dL; *P* < 0.001 compared with baseline), hemoglobin level was 12.7 g/dL (range, 10.4–14.6 g/dL; *P* < 0.001 compared with baseline), and BM involvement was 15% (range, 0–76%; *P* < 0.001 compared with baseline). At end of maintenance, serum IgM level was 1,010 mg/dL (76–5,715 mg/dL; *P* < 0.001 compared with baseline and with end of induction), hemoglobin level was 13.2 g/dL (range, 9.2–15.7 g/dL; *P* < 0.001 compared with baseline and with end of induction), and BM involvement was 5% (0%–70%; *P* < 0.001 compared with baseline and *P* = 0.1 compared with end of induction). Median time to response (TTR) was 8 weeks, which was longer in CXCR4-mutated (MUT) patients at 12 weeks versus 8 weeks in CXCR4 wild-type (WT) patients (log-rank *P* = 0.03). Using consensus response criteria, VGPR was 15%, partial response (PR) was 62%, and minor response (MR) was 19%, with major response rate (PR or better) of 77% and ORR (MR or better) of 96%. No complete responses were observed. Rates of VGPR, PR, and MR/stable disease (SD) in CXCR4 MUT and CXCR4 WT patients were 7%, 67%, and 27%, and 27%, 55%, and 18% (*P* = 0.35).

Fourteen patients (54%) had lymphadenopathy (at least 1 lymph node >1.5 cm in largest diameter per CT scans) at treatment

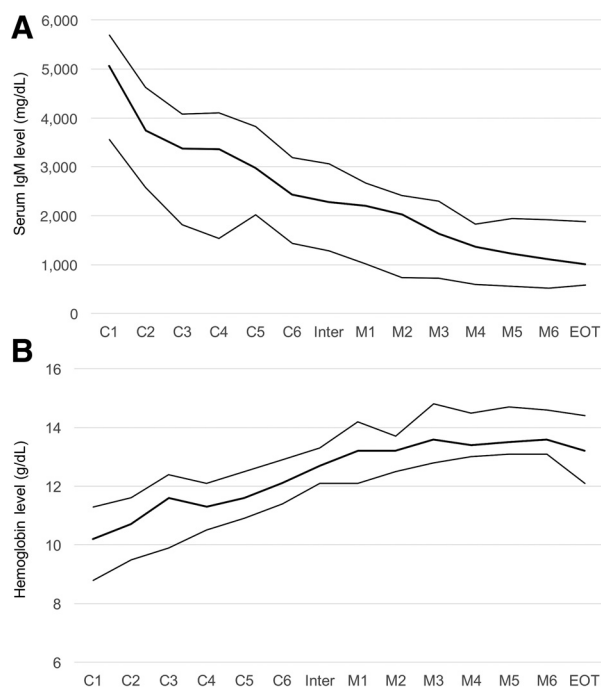


Figure 1. Impact of ixazomib, dexamethasone, and rituximab therapy on (A) serum IgM and (B) hemoglobin levels. The thick line represents the median, and the thin lines represent the interquartile range. C, induction cycle; Inter, interphase; M, maintenance cycle; EOT, end of treatment.

initiation. At end of induction, 8 patients had decreased and 3 had stable lymphadenopathy and 3 were not assessed. At end of treatment, 4 patients had resolved, 4 had decreased, 1 had stable, and 1 had increased lymphadenopathy and 4 were not assessed. Three patients presented with splenomegaly (spleen size at least 15 cm per CT scans). At end of induction, 2 had decrease and 1 had stable splenomegaly. At end of treatment, 1 had resolved, 1 had increase, and 1 had stable splenomegaly. Two patients had neuropathy at treatment initiation. At end of treatment, 1 had near resolution of neuropathic symptoms and 1 had stable neuropathy.

At time of this report, median follow-up time was 22 months [95% confidence interval (CI), 19–26 months], and 7 patients (27%) had progressed. Median PFS has not been reached (Fig. 2A). Age > 65 years, hemoglobin level < 11.5 g/dL, platelet count < 100 k/ μ L, B2M level > 3 g/L, serum IgM level > 7,000 mg/dL, presence of lymphadenopathy, BM involvement > 50%, CXCR4 mutational status, and International Prognostic Scoring System for WM (IPSSWM) score were not associated with better or worse PFS (data not shown). Categorical response assessment was associated with PFS. Patients achieving MR/SD had a median PFS of 22 months (95% CI, 14–not reached), whereas the median PFS was not reached in patients achieving PR and VGPR ($P = 0.02$; Fig. 2B). There was no progression on patients who achieved VGPR and no deaths during the follow-up period. From 7 patients who progressed, 3 had necessitated therapy. Two patients enrolled in a clinical trial and 1 patient received bendamustine and rituximab. All patients have responded to next therapy.

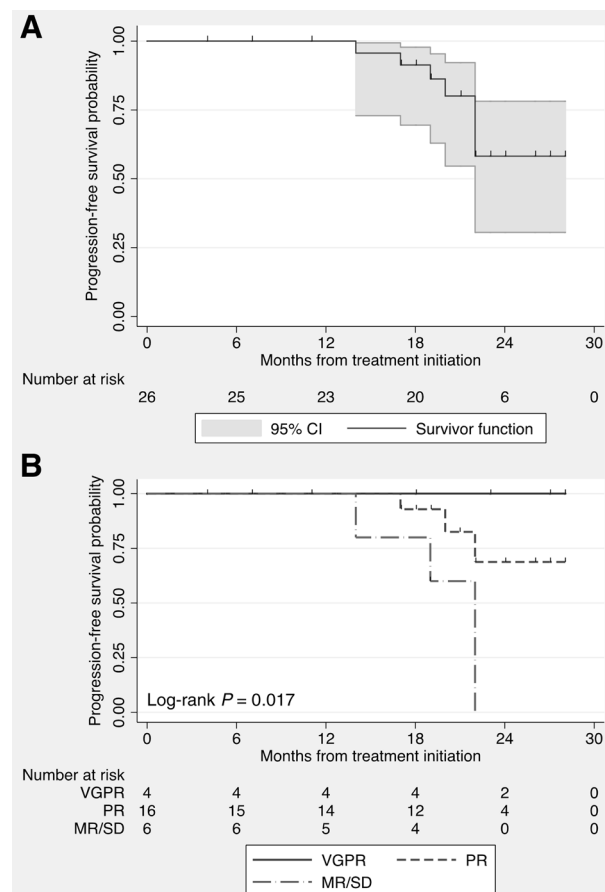


Figure 2. Impact of ixazomib, dexamethasone, and rituximab therapy on PFS for (A) the entire cohort, and (B) according to categorical response.

Two patients did not complete induction therapy. One due to grade 3 peripheral neuropathy (PN) due to worsening diabetic neuropathy, and one due to lack of clinical benefit, although the patient was in a minor response. At the end of study, 3 additional patients came off study. One due to grade 3 pneumonia and sepsis and 2 due to suboptimal response. A complete list of adverse events at least possibly related to study treatment is shown in Table 2. Most common adverse events (grades 1 and 2) included infusion reactions ($n = 10$), nausea ($n = 9$), insomnia ($n = 7$), and rash ($n = 7$). Grade 3 adverse events included neuropathy ($n = 1$), pneumonia ($n = 1$), and sepsis ($n = 1$). No grade 4 adverse events were reported.

Three patients developed rituximab intolerance (severe infusion reactions) while on treatment protocol at 3.5, 4, and 8 months, and rituximab had to be stopped but continued ixazomib and dexamethasone. All 3 patients had disease progression within 24 months of starting protocol therapy. An IgM flare (increase in serum IgM of at least 25%) was seen in 2 patients after receiving rituximab on cycle 3. Both patients were asymptomatic from the flare and did not need plasmapheresis. Serum IgM stabilized and later went back to baseline in both cases. The median IgG level decreased from 609 mg/dL (range, 160–4,677 mg/dL) to 409 mg/dL (range, 113–822 mg/dL;

Table 2. Adverse events possibly, probably, or definitely associated with protocol therapy; number of events (%)

| Toxicity type | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------------------------|------------|-----------|-----------|----------|---------|
| Bloating | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Blood in stool | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Chills | 4 (15.4%) | 4 (15.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Constipation | 2 (7.7%) | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Diarrhea | 5 (19.2%) | 5 (19.2%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Dizziness | 4 (15.4%) | 4 (15.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Dysgeusia | 4 (15.4%) | 4 (15.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Dyspepsia | 3 (11.5%) | 2 (7.7%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Edema | 5 (19.2%) | 4 (15.4%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Epistaxis | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fatigue | 2 (7.7%) | 2 (7.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fever | 4 (15.4%) | 3 (11.5%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Flushing | 2 (7.7%) | 2 (7.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hiccups | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hyperglycemia | 5 (19.2%) | 4 (15.4%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Infusion-related reaction | 10 (38.5%) | 5 (19.2%) | 5 (19.2%) | 0 (0%) | 0 (0%) |
| Insomnia | 7 (26.9%) | 5 (19.2%) | 2 (7.7%) | 0 (0%) | 0 (0%) |
| Joint pain | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Laryngitis | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Malaise | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Muscle cramps | 2 (7.7%) | 2 (7.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Muscle soreness | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Muscle weakness | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nausea | 9 (34.6%) | 9 (34.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Neuropathy | 6 (23.1%) | 5 (19.2%) | 0 (0%) | 1 (3.8%) | 0 (0%) |
| Palpitations | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pneumonia | 1 (3.8%) | 0 (0%) | 0 (0%) | 1 (3.8%) | 0 (0%) |
| Pruritus | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Rash | 7 (26.9%) | 5 (19.2%) | 2 (7.7%) | 0 (0%) | 0 (0%) |
| Restless legs | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Sepsis | 1 (3.8%) | 0 (0%) | 0 (0%) | 1 (3.8%) | 0 (0%) |
| Sinus tachycardia | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Sinusitis | 1 (3.8%) | 0 (0%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Sore throat | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Stomach pain | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Vomiting | 4 (15.4%) | 3 (11.5%) | 1 (3.8%) | 0 (0%) | 0 (0%) |
| Weight gain | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) |

$P = 0.02$). Two patients necessitated i.v. immunoglobulin replacement due to recurrent respiratory infections. Both patients had serum IgG level of less than 200 mg/dL. The median IgA level decreased from 62 mg/dL (range, 8–140 mg/dL) to 33 mg/dL (range, 7–109 mg/dL; $P < 0.001$).

Discussion

Ixazomib is an oral proteasome inhibitor, fully approved by the FDA for the treatment of patients with multiple myeloma. As a single agent, ixazomib has shown to be safe in patients with multiple myeloma. In a phase I study evaluating ixazomib administered twice weekly to patients with relapsed and/or refractory multiple myeloma, the rate of PN was 12% with manageable anemia, thrombocytopenia, nausea, and rash (12). A similar adverse event profile was reported in a phase I study evaluating weekly ixazomib as a single agent in patients with relapsed and/or refractory multiple myeloma, with a grade 1 neuropathy rate of 20% (13).

Proteasome inhibitors have previously shown high efficacy as primary therapy for patients with WM, however with toxicity. A prospective study on the combination of bortezomib, dexamethasone, and rituximab (BDR) in which bortezomib was administered intravenously twice a week reported a median TTR of 1.4 months, ORR of 96%, VGPR or better of 35%, and median

PFS of 5.5 years (4, 14). However, 60% of patients had to discontinue therapy due to PN. Another study evaluated BDR with bortezomib administered intravenously twice a week for the first cycle and weekly from cycles 2 to 5 (2, 15). ORR was 85%, VGPR or better was 10%, and median PFS was 3.6 years. PN occurred in 46% of patients with neuropathic pain in 20%. A study evaluating carfilzomib, rituximab, and dexamethasone reported median TTR of 2.1 months, ORR of 87%, VGPR of 36%, median PFS of 3.8 years, and PN rate of 20% (5, 16). Despite efficacy, grade 4 neutropenia, and grade 3 anemia, hyperglycemia, hyperlipasemia, and cardiomyopathy (in 1 patient) were reported.

Other treatment options for primary therapy in WM include bendamustine and rituximab and the recently approved oral Bruton tyrosine kinase inhibitor ibrutinib. Both treatment regimens are highly efficacious with fast responses, ORR of over 90%, and prolonged PFS (17–19). In terms of safety, however, bendamustine has been associated with a small risk of secondary myeloid malignancies and myelodysplasia (20), which should be taken into account, especially in younger patients with WM. Ibrutinib also carries a distinct toxicity profile with increased risk of bleeding and atrial fibrillation (17, 19). Furthermore, ibrutinib therapy is indefinite, and besides cost, which is on itself significant, also lack of compliance can affect efficacy, as recent studies have shown that dose intensity lower than 97% associates

with shorter PFS in WM patients (21). Finally, CXCR4 MUT patients have slower, more superficial and shorter responses to ibrutinib (22).

It is important to note that 3 patients treated with IDR developed intolerance to rituximab. Rituximab intolerance has previously been described in WM patients with an incidence of 7%, a rate that appears higher than the rates of rituximab intolerance reported in patients with chronic lymphocytic leukemia and follicular lymphoma treated with rituximab-containing regimens (23). In clinical practice, rituximab can be substituted by ofatumumab. However, in the present study, no substitutions were allowed and patients continued with therapy without rituximab. The three patients who developed rituximab intolerance had disease progression within 24 months of therapy initiation. Our study also shows that depth of response associates with PFS duration as patients who achieved MR/SD reached a median PFS of 22 months, but the median PFS was not reached in patients who achieved PR or VGPR to IDR. Furthermore, none of the patients who achieved VGPR have yet progressed.

Our study is not without limitations, which include a relatively small sample size, a follow-up time just short of 2 years, and an overrepresentation of patients with CXCR4 mutations. Given the rarity of the disease, study cohorts of a few dozens of patients are rather the norm in WM. It is important to note that the median PFS was not yet reached at 2 years, which compares favorably with published data in bortezomib- and carfilzomib-based regimens. The excess of patients with CXCR4 could be due to patient selection. CXCR4-mutated patients appeared more resistant to IDR, which could have negatively affected response outcomes; the VGPR rates in CXCR4 MUT and WT were 7% and 27%, respectively. This is the first study showing that CXCR4 mutations can have a negative impact in TTR and depth of response in WM patients. In addition, proteasome inhibitors have modest activity against extramedullary disease. Our results are consistent with previously reported data on bortezomib and carfilzomib (4, 5). Finally, of 5 patients that came off study, 3 were for lack of clinical benefit, 1 for grade 3 diabetic neuropathy, and 1 due to grade 3 infection. The latter two were considered at least possibly related to therapy, but there were other potential contributors.

With a VGPR rate of 15%, the study did not meet its primary objective of VGPR rate of 40% or better. However, the median

TTR was 2 months, ORR was 96%, and median PFS was not reached at 2 years of follow-up. Patients also had improvements in lymphadenopathy and splenomegaly. IDR also appears well tolerated with no reported grade 4 adverse events and a rate of grade 1 PN of 20%, which was similar to previously published studies in multiple myeloma. Additional benefits of ixazomib therapy include the convenience of oral intake and potential ease of combination with existing available agents. Considering the response rate and excellent toxicity profile of IDR, we believe IDR represents another treatment option for the primary therapy of patients with WM.

Disclosure of Potential Conflicts of Interest

J.J. Castillo reports receiving commercial research grants from Takeda. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: J.J. Castillo, S.P. Treon

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.J. Castillo, K. Meid, J.N. Gustine, S.P. Treon

Writing, review, and/or revision of the manuscript: J.J. Castillo, K. Meid, S.P. Treon

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.J. Castillo, K. Meid, J.N. Gustine, L. Xu

Study supervision: J.J. Castillo, K. Meid

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