# Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenström Macroglobulinemia

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**This study aimed to determine the activity and safety of weekly bortezomib and rituximab in patients with untreated Waldenström Macroglobulinemia (WM). Patients with no prior therapy and symptomatic disease were eligible. Patients received bortezomib IV weekly at 1.6 mg/m$^2$ on days 1, 8, 15, q 28 days × 6 cycles, and rituximab 375 mg/m$^2$ weekly on cycles 1 and 4. Primary endpoint was the percent of patients with at least a minor response (MR). Twenty-six patients were treated. At least MR was observed in 23/26 patients (88%) (95% CI: 70–98%) with 1 complete response (4%), 1 near-complete response (4%), 15 partial remission (58%), and 6 MR (23%). Using IgM response evaluated by nephlometry, all 26 patients (100%) achieved at least MR or better. The median time to progression has not been reached, with an estimated 1-year event free rate of 79% (95% CI: 53, 91%). Common grade 3 and 4 therapy related adverse events included reversible neutropenia in 12%, anemia in 8%, and thrombocytopenia in 8%. No grade 3 or 4 neuropathy occurred. The combination of weekly bortezomib and rituximab exhibited significant activity and minimal neurological toxicity in patients with untreated WM. Am. J. Hematol. 85:670–674, 2010.** © 2010 Wiley-Liss, Inc.

## Introduction

Waldenström Macroglobulinemia (WM) is a low grade lymphoma characterized by the presence of lymphoplasmacytic cells in the bone marrow and an increase in the IgM monoclonal protein in the serum [1–4]. Although indolent, it remains incurable with a median overall survival (OS) of 5 years, with a 36% 5-year survival in patients with high risk WM based on the ISS-WM scoring system [2,3,5,6].

Prior studies in newly diagnosed untreated patients with WM have focused on the use of alkylating agents or nucleoside analogs. Rituximab alone, or in combination, has become one of the most widely used therapeutic agents in WM, with an overall response rate that includes minor response (MR) or better of about 55%. However, rituximab may initially increase the IgM level leading to an IgM flare in about 50% of patients [7,8]. It may also lead to delayed responses. Therefore, novel combinations of agents that improve on the response rate observed with single agent rituximab are needed.

Rituximab regulates several signaling pathways that promote cell survival and proliferation, including the PI3K, nuclear-factor κ-B (NF-kB), as well as the ERK signaling pathways [9]. We have previously shown that the proteasome inhibitor bortezomib specifically targets NF-kB in WM cells [10], and enhances the cytotoxic activity of rituximab in antibody-dependent cellular cytotoxicity assays [11]. Therefore, the combination of bortezomib and rituximab may lead to synergistic responses in vivo in patients with this disease.

Prior studies have examined the activity of bortezomib in combination with rituximab and dexamethasone (BDR regimen) in untreated patients with WM. In a recent study using BDR, the overall response rate was 96% with 3 CR, 2 near CR (nCR), 3 very good partial responses VGPR, 11 PR, and 3 MR. However, grade 3 peripheral neuropathy occurred in over 30% of patients and grade 2 in 39% of patients, indicating that studies evaluating different schedules of bortezomib are needed for patients with WM. In addition, the role of high dose dexamethasone in the treatment of WM is not well defined. Therefore, we designed this phase II clinical trial to examine the response rate, toxicity, and survival in patients with untreated WM using weekly bortezomiib at 1.6 mg/m$^2$ in combination with rituximab without the addition of dexamethasone.



## Methods

*Eligibility.* Study participants were at least 18 years of age with untreated symptomatic WM. Patients must have had no prior therapy. Patients must have had symptomatic disease requiring therapy for WM according to the consensus recommendations for WM [12]. Patients had measurable monoclonal IgM immunoglobulin concentration on serum electrophoresis and IgM immunoglobulin protein twice the upper limit of normal by nephlometry and evidence of lymphoplasmacytic cells in the bone marrow. CD20 positive disease must be present on bone marrow biopsy. Eligibility criteria also included a serum concentration of AST or ALT $<3$ times the upper limit of the normal range, a serum total bilirubin $<2$ mg/dL, a measured creatinine $<2.5$ times the upper limit of the normal range, a platelet count of $\geq$75,000/mm$^2$, and an absolute neutrophil count of at least 1,000/mm$^2$. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki; approval was obtained from the institutional review board at each of the participating centers, (clinical trials.gov, NCT00422799).

*Study design and treatment.* Patients received bortezomib IV weekly at 1.6 mg/m$^2$ on days 1, 8, 15, q 28 days × 6 cycles, and rituximab 375 mg/m$^2$ at days 1, 8, 15, 22, on cycles 1 and 4. Patients with progressive disease after two cycles were taken off therapy. Patients with stable or responsive disease continued on therapy for a total of six cycles, (See Consort diagram). There was no maintenance therapy. Antiviral prophylaxis was recommended in all patients prior to initiation of therapy and for 3 months after completion of the six cycles.

Dose modifications for attributable toxicities were allowed. Bortezomib could be reduced from 1.6 mg/m$^2$ to 1.3 mg/m$^2$ to 1.0 mg/m$^2$. No

Additional Supporting Information may be found in the online version of this article.

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dose reductions were allowed for rituximab, however, the rate of infusion of rituximab could be modified for hypersensitivity or infusion-related events. No dose re-escalation was allowed.

*Efficacy and safety assessments.* Tumor assessment was performed using the consensus panel recommendations [13]. Patients were assessed every 28 days during the six cycles of therapy and every 3 months thereafter. Patients who came off therapy were monitored every 3 months until they progressed, were treated with another therapy, or died.

Response was calculated from the M spike measurement (or IgM measurement) of cycle 1 day 1 prior to therapy. In six (23%) cases, screening M spikes were used for calculation of response instead of cycle 1 day 1 values, because these patients received plasmapheresis between screening and initiation of therapy.

Adverse events were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) from the first dose until 30 days after the last dose of therapy.

*Statistical analysis.* The primary endpoint was the percent of patients with at least a MR and secondary endpoints included safety, time to progression (TTP), progression-free survival (PFS), OS, and time to next therapy (TTNT). TTNT is an important endpoint for patients with WM because often these patients meet criteria for progression (>25% increase in IgM protein), but remain asymptomatic and clinically are not treated until they become symptomatic based on the consensus recommendations for treatment of WM patients [12,13]. Therefore, we wanted to capture both the TTP and the TTNT because they both provide information that is important in clinical practice.

This study used a two-stage design (22 eligible on the first stage and 13 eligible on the second stage). In first stage, 12 responses were required and overall 22 were required to achieve 0.86 probability of concluding effectiveness assuming 70% promising rate and 0.09 assuming 50% promising rate. After 22 eligible patients had been entered, 18 patients achieved a MR or better (82% [90% CI: 63, 94%]). At this time, four patients were waiting to be treated. Since the lower limit of the 90% confidence interval (CI) excluded the nonpromising rate (even if the remaining four patients did not achieve a MR), the study accrual was modified to 26 eligible patients. Patient characteristics were summarized and compared between responders and nonresponders using Fisher's exact test for binary endpoints and Wilcoxon Rank Sum test for continuous endpoints. Estimated response proportions were reported along with exact two-stage binomial 95% CIs. Median time to response, defined as the time to first response and duration of response were reported among responding patients. The time to event endpoints were estimated using Kaplan-Meier methodology. TTP, PFS, and OS are measured from the time of therapy initiation to the time of first event (PD for TTP, PD or death for PFS, and death for OS). Patients without the event are censored at the date they were last known to be in remission for TTP, in remission and alive for PFS, and alive for OS. TTNT is measured from the end of treatment to the initiation of next therapy, censored at date last known alive without initiation of next therapy. Cox proportional hazard model was used to evaluate the impact of multiple factors on time to event endpoints. All *P*-values are two-sided. Statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute).

## Results

### *Patients and treatment*

From December 2007 to April 2009, 26 patients were enrolled in four centers. Table I shows selected characteristics of all 26 patients. The median age at enrollment was 63 years (range, 43–85). The median IgM level at enrollment was 4,277 mg/dL (range, 428–7,940), and the median M spike by serum protein electrophoresis was 2.3 g/dL (range, 0.4–4.5). The median hemoglobin at enrollment was 11.1 g/dL (range, 6.9–15.5) with 50% ($n$ = 13) of the patients with anemia (<11 g/dL). Median β-2 microglobulin at enrollment was 3.5 mg/dL (range,1.4–5.4) with 42% ($n$ = 11) of the patients with β-2 microglobulin >3.5 mg/dL. One (4%) of the patients had platelets <100,000. The median percent of bone marrow involvement was 60% (range, 15–90). There was evidence of disease in soft tissue assessment, including organomegaly or lymphadenopathy, in 13 patients (50%). Fifty-four percent of the patients were intermediate or high risk by the ISS-WM staging system at the time of enrollment.

**TABLE I. Baseline Characteristics**

| Patient characteristic | $N$ = 26 | % |
|---|---|---|
| Median age, years (range) | 62.5 | (43–85) |
| Gender, Male | 15 | 58 |
| Race: White | 24 | 92 |
| Race: African American | 1 | 4 |
| Race: Other | 1 | 4 |
| Ethinicity: Hispanic or latino | 1 | 4 |
| ECOG PS | | |
| 0 | 19 | 73 |
| 1 | 6 | 23 |
| 2 | 1 | 4 |
| Median IgM at screening (mg/dL) | 4,277 | Range (428–7,940) |
| Median M spike at screening (g/dL) | 2.3 | Range (0.4–4.5) |
| Median hemoglobin (g/dL) | 11.1 | Range (6.9–15.5) |
| Median platelets count | 242 | 74–388 |
| Median β 2 microglobulin | 3.5 | Range (1.4–5.4) |
| % bone marrow involvement | 60 | Range (15–90) |
| Lymph nodes and HSM assessment by CT scan | | |
| Evidence of disease | 13 | 50 |
| No evidence of disease | 11 | 42 |
| Not done | 2 | 8 |
| ISS-WM (at enrollment) | | |
| High risk | 3 | 12 |
| Intermediate risk | 11 | 42 |
| Low risk | 10 | 38 |
| Unknown[a] | 2 | 8 |

[a] Serum B2 was not measured in two patients at screening.

All patients had symptomatic disease requiring initiation of therapy based on consensus recommendations for WM. As indicated above, 50% of the patients were treated for anemia (<11 g/dL). Of the other 13 patients, 6 had an IgM level >4,000 mg/dL with hyperviscosity symptoms. The other seven patients had either significant tumor burden on bone marrow biopsy (70–90% involvement of the bone marrow), or evidence of bulky lymphadenopathy with constitutional B symptoms of disease.

Among the 26 patients, 20 (77%) received six cycles of bortezomib treatment per protocol and 25 (96%) completed rituximab treatment per protocol. Five (19%) completed only five cycles of bortezomib and one (4%) completed only three cycles. One patient (4%) completed only one cycle of rituximab (four doses). Unplanned dose delays occurred in two (8%) of patients. Dose modifications of bortezomib occurred in seven (27%) of patients. Treatment was completed in 19 (73%) of patients, and 7 (28%) patients did not complete all 6 cycles of therapy: of which, 3 (12%) due to toxicity and 4 (15%) due to withdrawal of consent.

### *Efficacy*

Of the 26 patients, 1 achieved complete response (CR) (4%), 1 achieved a near complete response (nCR) (4%), 15 achieved partial remission (PR) (58%), and 6 achieved MR (23%) (Table II). At least MR or better was observed in 23/26 patients (88%), (95% CI: 70–98%). At least PR or better was observed in 65% of the patients (95% CI: 44–83%). The rest of the patients ($N$ = 3, 12%) had stable disease. There were no cases of progression during therapy. The median time to best overall response was 3.7 months (range, 0.9–14.8).

Per the consensus recommendations, responses that include PR or better included measurement of nodal response on CT scans. PR was assessed as patients having 50% reduction in pathological lymph nodes. Similarly, CR was assessed as having complete resolution of lymph nodes involved. In this study, 13/26 (50%) patients had measurable

**TABLE II. Response Measured by M-Spike or Using IgM Measured by Nephlometry**

| Response | M-spike *N* (%) | IgM by Nephlometry *N* (%) |
|---|---|---|
| CR | 1 (4) | 2 (8) |
| nCR | 1 (4) | N/A |
| PR | 15 (58) | 15 (58) |
| MR | 6 (23) | 9 (35) |
| SD | 3 (12) | 0 |
| PD | 0 (0) | 0 |
| CR + nCR + PR + MR[a] | 23 (88) | 26 (100) |
| CR + nCR + PR[b] | 17 (65) | 17 (65) |

[a] 95% exact two-stage CIs for proportion of patients with CR + nCR + PR + MR by M-spike is (70,98) and with a CR + PR + MR by nephlometry is (87,99).

[b] 95% exact two-stage CIs for proportion of patients with a CR + nCR + PR by M-spike is (44,83) and with a CR + PR by nephlometry is (44,83).

disease by CT scan measurements. Of these, one achieved a complete remission and six patients achieved partial response by monoclonal protein and confirmed by CT scan measurements. Of the other six patients, five achieved MR and one achieved stable disease by monoclonal protein and confirmed by CT scan measurements.

Using IgM response evaluated by nephlometry, all 26 patients (100%) achieved at least MR or better (95% CI: 87–99%), with 2 CR, 15 PR, and 9 MR (Table II). Improvement in responses occurred in follow-up after completion of the six cycles of therapy in three patients.

Figure 1A shows the maximum percent change from baseline in IgM over all cycles among responding patients ($n = 26$). Figure 1B,C show the median and interquartile range for IgM and hemoglobin values, respectively in response to therapy per each cycle. The increase in hemoglobin shown in Fig. 1C is indicative of the clinical response in these patients.

Previous studies have shown that rituximab can cause a transient increase in the IgM (IgM flare) in up to 50% of patients. In this study, eight patients (31%) developed a transient increase in the IgM during therapy, with a median of 40% (absolute increase of 1,097 mg/dL) increase in IgM (range, 16–150%, absolute values of 330–1,713 mg/dL). These flares occurred after cycle 1 or cycle 4 of therapy (post rituximab). All of these patients had a response to therapy.

### *Time to event analysis*

After a median follow-up of 14 months, six patients have progressed and three have subsequently started another therapy, two patients started subsequent therapy without documented 25% progression in the paraprotein, and one patient died due to disease without documented 25% progression by the paraprotein. Seventeen patients remain alive without evidence of disease progression.

The median duration of response (MR or better) has not been reached; response has remained >12 months in 59% (95% CI: 31, 78%) of patients, Fig. 2A. The median PFS has not been reached, with an estimated 1-year event free rate of 75% (95% CI: 50, 89%). (Fig. 2B). The median TTP has not been reached, with an estimated 1-year event free rate of 79% (95% CI: 53, 91%). The median OS has not been reached with estimated 1-year OS of 96% (95% CI: 74, 99%). The median TTNT has not been reached, with an estimated 1-year new-therapy free after the end of protocol therapy was 68% (95% CI: 39, 86%), Fig. 2C.

### *Safety*

Adverse events that were related to therapy (possible, probable, or definite) included 6 (23%) grade 1 toxicities, 10 (38%) grade 2 toxicities, 7 (27%) grade 3 toxicities, and 3 (12%) grade 4 toxicities. A summary of all toxicities related to therapy is shown in Table III. The most common grade 3 and 4 therapy related adverse events included neutropenia in 12%, anemia in 8%, thrombocytopenia in 8%, and leucopenia in 4%, Fever without neutropenia occurred in 8% of patients. Other grade 3 and 4 toxicities included nausea, vomiting, lymphopenia, allergic reactions, dizziness, and syncope in 4% of patients. There were no grade 3 or 4 peripheral neuropathy; however, grade 1 and 2 occurred in 14 (54%) patients. Of these, only four (15%) had grade 2 neu-

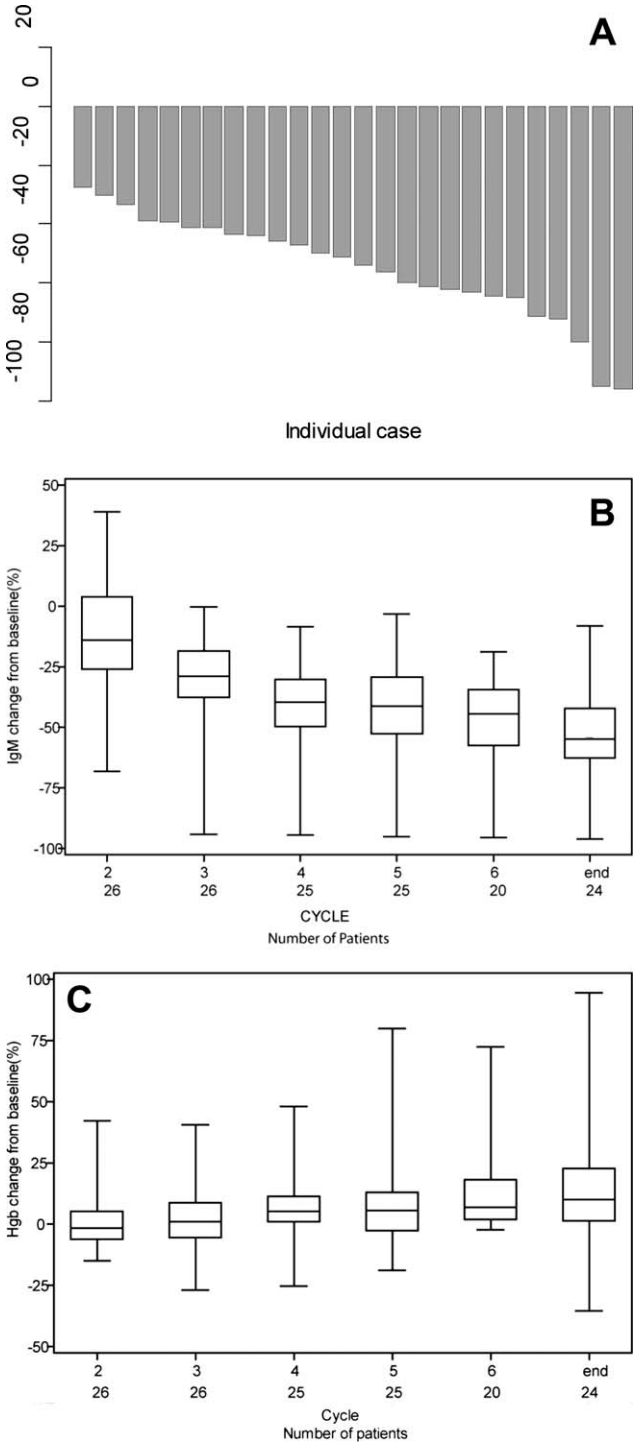


Figure 1. (A) Maximum decrease in IgM in responding patients. (B) Median and interquartile range (with 10th–90th percentile) for IgM values in response to therapy per each cycle. (C) The median and interquartile range (with 10th–90th percentile) for hemoglobin values in response to therapy per each cycle.

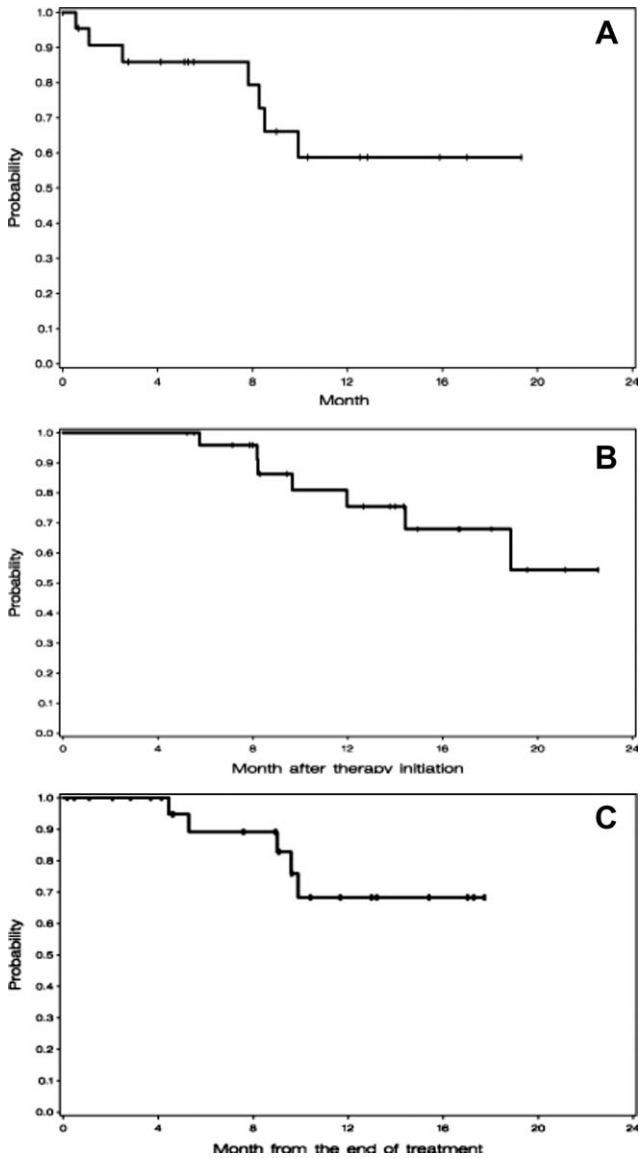


Figure 2. (A) Duration of response (MR or better). (B) Progression-free survival. (C) Time to next therapy.

**TABLE III. Summary of Treatment-Related Adverse Events >10% of Patients, *N* = 26**

| Toxicity type | Grd 1–2 | Percent | Grd 3–4 | Percent |
|---|---|---|---|---|
| Hematological | | | | |
| Hemoglobin | 19 | 73 | 2 | 8 |
| Leukocytes | 12 | 46 | 1 | 4 |
| Neutrophils | 12 | 46 | 3 | 12 |
| Thrombocytopenia | 8 | 31 | 2 | 8 |
| Gastronintestinal | | | | |
| Diarrhea | 10 | 38 | | |
| Constipation | 5 | 19 | | |
| Nausea | 12 | 46 | 1 | 4 |
| Vomiting | 4 | 15 | 1 | 4 |
| Taste disturbance | 3 | 12 | | |
| Infections | | | | |
| Infection-respiratory | 1 | 4 | | |
| Infection eye (conjunctivitis) | 1 | 4 | | |
| Herpes Zoster reactivation | 1 | 4 | | |
| Infection other | 1 | 4 | | |
| Electrolytes and liver function studies | | | | |
| Hyperglycemia | 11 | 42 | | |
| ALT, SGPT | 3 | 12 | | |
| AST, SGOT | 5 | 19 | | |
| Neurological/pain/others | | | | |
| Sensory neuropathy | 14 | 54 | | |
| Fatigue | 16 | 62 | 2 | 8 |
| Dizziness | 2 | 8 | 1 | 4 |
| Allergic reaction | 7 | 27 | 1 | 4 |
| Fever with no neutropenia | 4 | 15 | | |
| Lower ext edema | 4 | 15 | | |
| Joint pain | 3 | 12 | | |
| Dyspnea | 3 | 12 | | |

ropathy. Baseline grade 1 neuropathy before the start of therapy was present in five (19%) of patients. Herpes zoster reactivation grade 1 occurred in one patient despite being on valcyclovir prophylaxis therapy.

## Discussion

Current recommendations for frontline therapy of patients with WM include the use of alkylating agents (e.g: chlorambucil or cyclophosphamide), nucleoside analogs, (e.g fludarabine), rituximab alone, and combinations of these agents [12,14–18]. Long-term exposure to chlorambucil or nucleoside analogs in patients who are eligible for stem cell transplant is not recommended [17]. In addition, recent studies have shown that nucleoside analogs can increase the risk of malignant transformation and myelodysplasia [19]. Therefore, there is a critical need for the development of combinations using novel therapeutic agents that have less side effects and long-term toxicities. Bortezomib has emerged as a targeted agent that has significant activity in patients with WM, alone or in combination [20–22]. A recent study conducted by Treon et al. has demonstrated significant clinical activity of the combination of bortezomib, dexamethasone, and rituximab (BDR) as upfront therapy for WM [20]. However, there was significant neurological toxicity in this trial [20]. Therefore, we designed this protocol to examine the use of weekly bortezomib (at 1.6 mg/$m^2$) along with rituximab in patients with newly diagnosed WM. In addition, this trial was designed without the addition of dexamethasone to assess whether there is a need for dexamethasone in these patients and to avoid the toxicity of high dose dexamethasone.

In this study, at least MR or better was observed in 23/26 patients (88%), with 1 CR, 1 nCR, 15 PR, and 6 MR. Using IgM evaluated by nephlometry, all 26 patients (100%) achieved at least MR or better, with 2 CR, 19 PR, and 9 MR. These responses are highly significant and comparable to other regimens using combinations of rituximab with alkylating agents or nucleoside analogs [18]. Therefore, the combination of bortezomib and rituximab should be considered as one of the recommended options of treatment for patients with newly diagnosed WM. The responses were also comparable to the study using twice a week bortezomib, dexamethasone, and rituximab (BDR) [20].

The median time to best overall response was 3.7 months (range, 0.9–14.8). Some patients continued to respond after completing the six cycles of therapy. Therefore, future studies in WM should continue long-term follow-up as some patients achieve their best response after 1 year of initiation of therapy.

Unlike the BDR study where rituximab and bortezomib maintenance was used every 3 months for 2 years [20], this study did not require maintenance therapy. To date, these patients have not reached median duration of response, TTP, progression-free survival, or TTNT; with a median follow-up of 14 months. Longer follow-up of this study, as well as other studies may help determine whether

maintenance therapy improves TTP and progression-free survival in patients with WM.

The most common grade 3 and 4 therapy related adverse events included reversible neutropenia in 12%, anemia in 8%, and thrombocytopenia in 8%. No grade 3 or 4 neuropathy occurred in these patients. Therefore, the use of weekly bortezomib has significantly less neurotoxicity compared to the use of twice a week bortezomib in patients with WM.

In summary, we recommend the use of weekly bortezomib in combination with rituximab as an effective and safe regimen for upfront therapy in WM. Other ongoing studies using weekly bortezomib will help consolidate these results. Combinations using other novel agents with bortezomib and rituximab may improve the depth of response in these patients.

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