

## Phase I-II Trial of Bortezomib Plus Oral Cyclophosphamide and Prednisone in Relapsed and Refractory Multiple Myeloma

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### ABSTRACT

#### Purpose

The combination of oral weekly cyclophosphamide and alternate day prednisone is a convenient regimen for relapsed/refractory multiple myeloma (MM), and we sought to improve its efficacy by adding bortezomib, a proteasome inhibitor with proven antimyeloma activity.

#### Patients and Methods

We conducted a phase I-II trial evaluating six dose levels to define the maximum tolerated dose (MTD) of this combination in relapsed/refractory MM. An additional 10 patients were evaluated at the highest dose level reached.

#### Results

Thirty-seven patients were treated on this study. The MTD was not defined. Both of the highest dose levels of bortezomib tested (1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 and 1.5 mg/m<sup>2</sup> on days 1, 8, and 15, each on a 28-day cycle) could be safely given with cyclophosphamide 300 mg/m<sup>2</sup> per week and prednisone. At these dose levels, the overall response rate was 95% (complete responses [CR] plus partial response plus minimal response), with CR observed in more than 50% of patients. The weekly bortezomib regimen resulted in fewer instances of grade 3 thrombocytopenia and grade 1 to 2 peripheral neuropathy; the 1-year progression-free and overall survival probabilities with this dose level were 83% (95% CI, 73% to 96%) and 100%, respectively.

#### Conclusion

Weekly bortezomib 1.5 mg/m<sup>2</sup> plus oral cyclophosphamide and prednisone produces an unprecedented response rate and encouraging 1-year survival in relapsed/refractory patients with MM. Further evaluation of this promising regimen is warranted both in relapsed and newly diagnosed disease.

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### INTRODUCTION

Multiple myeloma (MM) can be controlled but remains largely incurable with current drug therapy. The introduction of new drugs with unique mechanisms of action has increased the number of treatment options beyond our previous armamentarium of high-dose corticosteroids, alkylating agents, and autologous stem cell transplantation (ASCT), and has substantially improved the survival of patients with relapsed/refractory disease.<sup>1-4</sup> Novel agents produce higher response rates when given with other cytotoxic drugs, and many promising combination regimens have been reported, although the superiority of any one combination over another remains to be established.<sup>5-8</sup>

Bortezomib, a first-in-class proteasome inhibitor with impressive single-agent activity in relapsed/refractory myeloma, is an ideal drug to use in

combination with other agents, as myelosuppression is usually mild, noncumulative, and readily reversible between cycles.<sup>2,3</sup> Increased risk of venous thromboembolism, noted with many thalidomide- and lenalidomide-based combinations, has not been observed with bortezomib-based therapy. However, disadvantages have included the need for frequent intravenous doses and the potential for peripheral neuropathy.

Oral cyclophosphamide regimens have been used more commonly for MM in Canada and Europe than in the United States. A 1987 National Cancer Institute of Canada trial reported that cyclophosphamide 150 to 250 mg/m<sup>2</sup> (maximum 500 mg) per week, initially given intravenously, and prednisone 100 mg every second day produced a response rate of 30% in patients refractory to melphalan.<sup>9</sup> Others have described variations of this regimen using oral cyclophosphamide,<sup>10,11</sup> and our

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**Table 1.** Dose Escalation Schedule

Dose Level	Bortezomib		Cyclophosphamide Dose Per Week (mg/m <sup>2</sup> )*	Prednisone Dose Every 2 Days (mg)
	Dose (mg/m <sup>2</sup> )	Day		
1	0.7	1, 8, 15	150	100
2	0.7	1, 8, 15	300	100
3	1.0	1, 8, 15	300	100
4	1.0	1, 4, 8, 11	300	100
5	1.3	1, 4, 8, 11	300	100
6	1.5	1, 8, 15	300	100

\*Cyclophosphamide given orally as a single morning dose on days 1, 8, 15, and 22 (before bortezomib if due on same day). Cycle length was 28 days.

group has previously published a retrospective analysis of oral weekly cyclophosphamide at a fixed dose of 500 mg, plus 50 or 100 mg of prednisone on alternate days, in MM progressive after ASCT. Partial responses (PR) were seen in 41% and minimal responses (MR) in 20%; stable disease was noted in 20%.<sup>12</sup> Despite the infrequency of complete response (CR), the progression-free survival (PFS) was 19 months, and median overall survival 28 months.<sup>12</sup> This regimen was well tolerated; significant myelosuppression was uncommon, in contrast to the cumulative stem cell damage that often accompanies oral melphalan administration.<sup>13</sup> The results of oral cyclophosphamide-containing regimens compare favorably with different salvage regimens. We sought to optimize a combination of oral cyclophosphamide and prednisone with bortezomib in a phase I-II trial in relapsed/refractory myeloma. In addition to identifying the maximum tolerated dose (MTD) of this regimen, we wished to evaluate schedules in which bortezomib was given once as well as twice per week.

## PATIENTS AND METHODS

### Eligibility

This was an open-label, dose-finding study. The eligibility criteria included: confirmed diagnosis of relapsed/refractory MM; age  $\geq$  18 years;  $\geq$  one prior chemotherapy regimen; Eastern Cooperative Oncology Group performance status 0 to 2; serum creatinine level  $\leq$  186  $\mu$ mol/L; hemoglobin  $\geq$  80 g/L, absolute neutrophil count (ANC)  $\geq$  1.0  $\times$  10<sup>9</sup>/L, and the ability to maintain a platelet count  $\geq$  50  $\times$  10<sup>9</sup>/L; no serious comorbid illness or other malignancy within 3 years (excluding skin cancer or cervical cancer in situ); and informed consent. After one patient who was given granulocyte colony-stimulating factor (G-CSF) to bring up his ANC to be eligible for the trial developed grade 3 neutropenia during cycle 1, the protocol was modified to exclude the use of G-CSF within 2 weeks of study entry.

### Phase I Dose Escalation Schedule

Three patients were entered at each dose level; if no dose limiting toxicity (DLT) was observed, three patients were entered onto the next dose level. If two or three patients experienced DLT, the escalation was stopped and the previous dose level was defined as the MTD. If one patient experienced DLT, three more were entered at the same dose level. If  $\geq$  one of the six patients experienced DLT, the escalation was stopped and the previous level was defined as the MTD. Once the MTD was identified, 10 more patients were entered at that level to further define the response rate and toxicities as well as to better estimate the CIs.

Toxicity was assessed after cycle 1 using the National Cancer Institute Common Toxicity Criteria version 3. DLT was defined as  $\geq$  grade 3 nonhematologic toxicity or grade 4 hematologic toxicity with platelets  $\leq$  10  $\times$  10<sup>9</sup>/L on more than one occasion despite transfusion support or neutropenia lasting

longer than 5 days and/or with neutropenic fever defined as an elevated temperature confirmed on at least two occasions.

A total of six dose levels were planned (Table 1). Prednisone was given every second morning while cyclophosphamide was given orally as a single morning dose, before bortezomib, on days 1, 8, 15, and 22 with granisetron or prochlorperazine as an antiemetic. Bortezomib was either given on days 1, 4, 8, and 11 or days 1, 8, and 15 depending on the dose level. The cycle length was 28 days. One half of the usual weekly dose of cyclophosphamide was utilized in dose level 1, while the full dose of 300 mg/m<sup>2</sup> was given thereafter.

All patients received antacid therapy with either an H<sub>2</sub>-blocker or proton pump inhibitor. After several patients experienced respiratory infections with cycle 1, the protocol was amended to require oral levofloxacin 500 mg per day in cycle 1. Hematopoietic growth factors were allowed after cycle 1, while transfusions were permitted to maintain the hemoglobin over 80 g/L and platelet count higher than 50  $\times$  10<sup>9</sup>/L.

### Assessment of Response

Antitumor responses were evaluated after two cycles using the European Bone Marrow Transplant criteria of Blade et al<sup>14</sup> with the addition of near complete response (nCR) referring to patients in whom all criteria for CR were met except for persistent immunofixation positivity, as described by Richardson et al.<sup>2</sup> For patients without a measurable monoclonal protein by serum/urine electrophoresis, serum free light chain levels were followed using the Freelite assay (The Binding Site, Birmingham, United Kingdom); responses were assessed using the International Myeloma Working Group criteria.<sup>15</sup>

### Statistical Considerations

Progression-free survival and overall survival were calculated from the time of study entry until the date of progression or death without progression, and death from any cause, respectively, using the Kaplan-Meier method.<sup>16</sup> Patients were censored at the date of last follow-up if alive free of progression or date of last follow-up known to be alive, respectively.

## RESULTS

### Patient Characteristics

Table 2 summarizes the characteristics of the 37 patients entered into this trial. The median age was 60 years (range, 38 to 74 years). Two of nine patients with conventional bone marrow cytogenetics had abnormal metaphases. Fluorescence in situ hybridization studies were available for deletion 13q, t(4;14), t(11;14), and/or p53 deletion in 46% of patients. All but three patients had received induction with high-dose dexamethasone alone or vincristine, doxorubicin, and dexamethasone and ASCT. Thirty-four patients had received prior intravenous cyclophosphamide (2.5 g/m<sup>2</sup>) for stem cell mobilization. The median number of prior regimens was two (range, one to six). Eleven had been previously exposed to oral cyclophosphamide, and seven had progressed on oral alkylating agents.

**Table 2.** Patient Characteristics

Characteristic	Value
Median age, years	60
Range	38-74
Male:female	21:16
Immunoglobulin subtype, No.	
IgG	24
IgA	5
Light chain only	8
Median $\beta$ 2-microglobulin level, nmol/L	267
Range	114-874
Median albumin, g/L	39
Range	30-45
Prior VAD or Dex + ASCT	34
No. of ASCTs	
One	29
Two	5
Median No. of prior regimens	2
Range	1-6
Marrow cytogenetics by conventional G banding	
Normal	7
Abnormal	
Hyperdiploidy of odd numbered chromosomes	1
t(11;14)	1
Marrow cytogenetics by FISH	
Deletion 13q	
Present	2
Absent	9
t(4;14)	
Present	1
Absent	8
t(11;14)	
Present	2
Absent	3
Abnormal <i>CCD1</i> gene on chromosome 11	2
<i>p53</i> deletion	
Present	0
Absent	6
Other prior agents	
Melphalan and prednisone	7
Thalidomide	14
Lenalidomide	1
Other chemotherapy	2
Cyclophosphamide	
For stem cell mobilization	34
Oral weekly	11
Bortezomib	1

Abbreviations: IgG, immunoglobulin G; IgA, immunoglobulin A; VAD, vincristine, doxorubicin, and dexamethasone; Dex, dexamethasone; ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization.

### Toxicity With Cycle 1

Table 3 lists the toxicities seen with the first cycle. The most frequent grade 3 and 4 toxicities were nausea with or without vomiting in three patients (8%), thrombocytopenia in five (13%) and neutropenia in three (8%). However, the criteria for DLT were not met and the MTD was not reached.

Several toxicities warrant further description, however. First, two patients developed community-acquired pneumonia at dose level 1; these infections occurred during the winter months, when many other patients in our center experienced similar respiratory infections. The

data safety and monitoring board allowed the trial to continue with the subsequent use of prophylactic levafloxacin during cycle 1; no further episodes of pneumonia occurred during the initial cycle. Second, the patient given G-CSF to raise his ANC for the trial developed grade 3 neutropenia during the first cycle at dose level 4; this patient went on to receive a total of three cycles with further growth factor and platelet transfusion support before myeloma progression. Finally, one patient experienced grade 3 increases in AST and ALT during cycle 1 on day 4 at dose level 4; subsequent doses of cyclophosphamide were reduced and the studies rapidly normalized. The patient's myeloma progressed on day 28. This individual had a history of fluctuating liver tests with prior therapy, including ASCT.

### Toxicities During Cycle 2 to 8

Subsequent cycles were generally well tolerated, and only 11% of patients discontinued the trial due to toxicity (Appendix Table A1, online only). Of note, there were 20 episodes of grade 3 or 4 thrombocytopenia with bortezomib 1.3 mg/m<sup>2</sup> twice weekly (dose level 5; 43% of cycles) compared with no such episodes with the weekly dose of 1.5 mg/m<sup>2</sup> (dose level 6). The typical, reversible decrease in platelet counts described with single agent bortezomib was seen at these dose levels.<sup>17</sup>

### Infections

Six episodes of pneumonia occurred, including two patients with multiple episodes. Other infections included one urinary tract infection, one sinusitis, and one episode of febrile neutropenia. There were two instances of herpes simplex while 11 episodes of varicella zoster occurred for an incidence of 30%. Notably, antiviral prophylaxis was strongly recommended, but not mandated, during this trial.

### Dose Reductions After Cycle 1

One patient who received dose level 2 experienced recurrent neutropenia; the bortezomib dose was reduced in cycle 3 and the cyclophosphamide dose in cycles 3 and 4. The patient with pre-existing low blood counts treated at dose level 4, described above, underwent a reduction in cyclophosphamide dose in cycle 2 due to thrombocytopenia and again in cycle 3, with a concomitant decrease in bortezomib, after experiencing febrile neutropenia. At dose level 5, two patients had the dose of bortezomib reduced to 1.0 mg/m<sup>2</sup> twice weekly, one in cycle 4 due to peripheral neuropathy and the other in cycle 2 due to neutropenia which also necessitated a decrease in the cyclophosphamide dose.

At dose level 6, the weekly dose of bortezomib was reduced from 1.5 mg/m<sup>2</sup> to 1.3 mg/m<sup>2</sup> in two patients, one in cycle 3 due to hypokalemia in part associated with persistent nausea and vomiting requiring two reductions in cyclophosphamide dose; this patient had a long-standing history of gastrointestinal symptoms that antedated the trial; the other patient had the bortezomib dose reduced in cycle 5 after an episode of varicella zoster.

The dose of prednisone was reduced to 50 mg on alternate days due to poor steroid tolerance in cycle 3 in two and cycle 4 in one patient.

### Protocol Therapy Delivered

Twenty-four patients (65%) completed all eight planned cycles. Thirteen discontinued treatment early, due to progression in eight patients, physician preference (one patient with stable disease after five

**Table 3.** Grade 3-4 Toxicities With Cycle 1 by Dose Level Based on National Cancer Institute Common Toxicity Criteria Version 3

Dose Level	No.	Grade 3		Grade 4		Dose-Limiting Toxicity
		Hematologic	Nonhematologic	Hematologic	Nonhematologic	
1	6	2 community-acquired pneumonia				No
2	3					No
3	3					No
4	6	1 neutropenia	1 ↑ AST/ALT	1 thrombocytopenia		No
5	6	1 nausea	1 thrombocytopenia; 1 hypophosphatemia; 1 varicella zoster*	1 neutropenia		No
6	3	1 nausea/vomiting	1 thrombocytopenia	1 neutropenia		No
6 (phase II)	10	1 nausea/vomiting/diarrhea	1 thrombocytopenia; 1 hypokalemia; 1 hypophosphatemia	1 thrombocytopenia		No

\*Grade 2.

cycles), and toxicity in four patients. One patient treated at dose level 2 stopped therapy after cycle 7 due to neutropenia and grade 2 peripheral neuropathy while two treated at dose level 5 discontinued after cycle 7 due to grade 2 peripheral neuropathy and dizziness in one and pneumonia in another. The former patient remains in unmaintained nCR for 1 year after stopping the protocol. One other patient treated at dose level 6 was taken off study after cycle 4 due to grade 1 peripheral neuropathy, euphoria, and dizziness.

#### Treatment After Protocol Completion

After completion of the protocol, one patient in CR elected to continue all three drugs at dose level 4 until disease progression was documented after eight more cycles; no toxicity was observed. Twenty-two patients continued oral cyclophosphamide and prednisone alone for a median of 5 months (range, 1 to 18 months).

Of the 18 patients who have not progressed, eight are off all therapy, eight continued on cyclophosphamide and prednisone for a median of 9 months (range, 1 to 15 months) after finishing protocol therapy, one was on prednisone alone, and one in continuous PR had cyclophosphamide changed to thalidomide, with prednisone, at the discretion of the referring physician 15 months after completing dose level 1.

#### Response Rates

Table 4 describes the response rates by dose level. At dose level 5, which included the full recommended doses of all three drugs (although bortezomib was given on a 28-day schedule), the overall re-

sponse rate was 100% (50% CR/nCR and 50% PR). At dose level 6, utilizing weekly bortezomib at a dose of 1.5 mg/m<sup>2</sup>, including the expanded cohort, the CR rate was 54% (95% CI, 25% to 81%), PR rate was 31% (95% CI, 9% to 61%), and the MR rate was 7.5% (95% CI, 0% to 32%), for an overall response rate of 91.5% (95% CI, 68% to 100%).

#### Disease Progression

The median follow-up of all patients was 14 months (range, 14 to 30 months). Nineteen patients progressed or died; the actuarial 1-year PFS was 56% (95% CI, 38% to 71%) for all 37 patients, with a median PFS of 15 months (95% CI, 10.6 to 15.9 months; Fig 1A). Importantly, the 1-year PFS was 83% (95% CI, 47% to 96%) and the median PFS has not yet been reached in the group of patients treated at dose level 6—the dose selected for phase II study. Only two patients in this cohort progressed, at 3.5 and 7 months (Fig 1B).

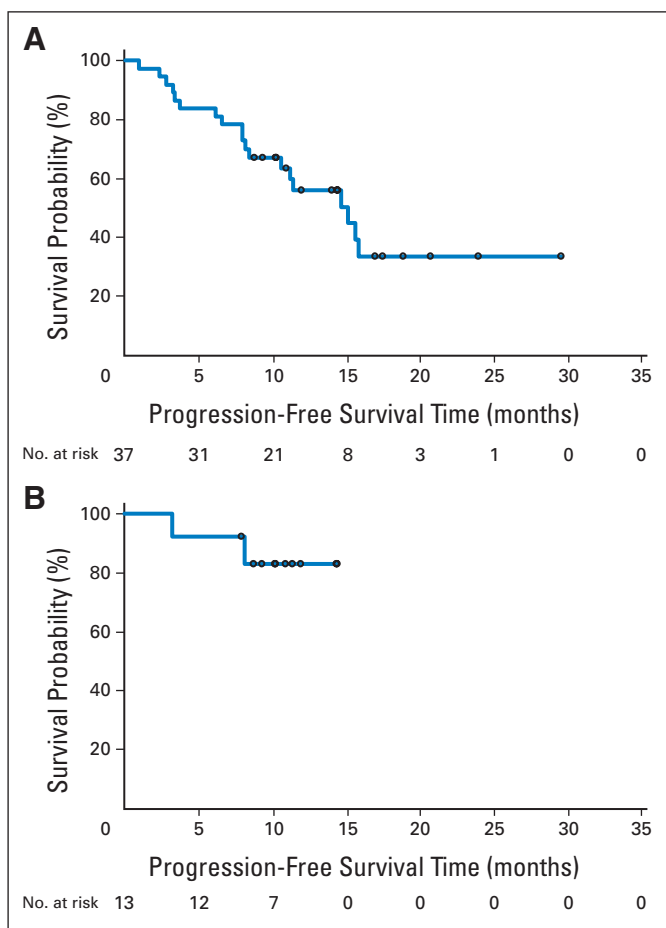
Of the 18 patients who have not yet progressed, one was treated at dose level 1, two at dose level 4, four at dose level 5, and 11 at dose level 6. Eight are off all antimyeloma therapy, including one in PR at 1 month and seven in CR/nCR at a median of 6 months (range, 1 to 12 months) after stopping cyclophosphamide and prednisone alone. These patients remain free of progression at a median of 17 months (range, 11 to 24 months) after starting the trial.

#### Overall Survival

The actuarial overall survival at 1 year is 89% (95% CI, 73% to 96%). Twelve patients have died, all from multiple myeloma (Fig 2).

**Table 4.** Best Response Rate by Dose Level

Dose Level	No.	Response									
		Complete/Near Complete		Partial		Minimal		Stable Disease		Progression	
		No.	%	No.	%	No.	%	No.	%	No.	%
1	6	—	—	1	16	2	33	1	16	2	33
2	3	—	—	2	67	1	33	—	—	—	—
3	3	—	—	1	33	—	—	2	67	—	—
4	6	2	33	2	33	—	—	1	17	1	17
5	6	3	50	3	50	—	—	—	—	—	—
6	13	7	54	4	31	1	7.5	1	7.5	—	—



**Fig 1.** Progression-free survival. (A) Of the 37 patients treated at all dose levels, 19 have progressed or died. The 1-year progression-free survival probability was 56% (95% CI, 38% to 71%). (B) Of the 13 patients treated at dose level 6, two have progressed. The 1-year progression-free survival probability was 83% (95% CI, 47% to 96%).

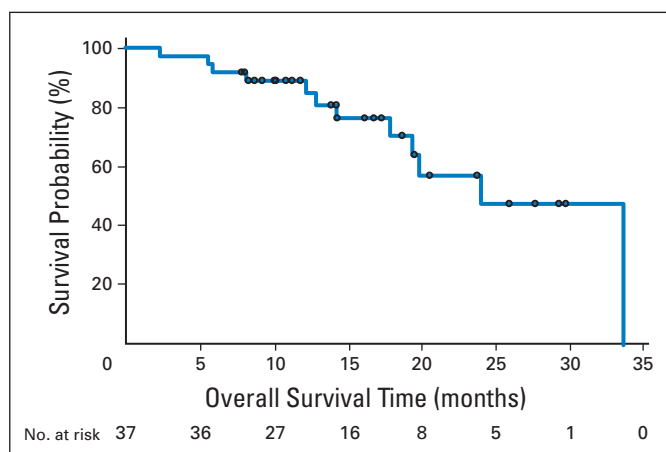
The median overall survival for all patients is 24.3 months (95% CI, 19.6 to 34.6 months). None of the patients in dose level 6 has died at a median follow-up of 12 months.

### Influence of Cytogenetics

The single patient with t(4;14) remained in continuous CR 17 months after protocol entry (dose level 5) and 8 months after stopping cyclophosphamide and prednisone. The two patients with deletion 13q were treated at dose level 6 and remained in nCR and PR for 8 and 11 months, respectively. One of the three patients with t(11;14) remained in PR at 15.5 months after treatment with dose level 4, while the other two, one of whom also had deletion 13q, remained in PR at 4 months and CR at 8 months, respectively, after commencing dose level 6.

## DISCUSSION

This study demonstrates that full doses of bortezomib, 1.3 mg/m<sup>2</sup> twice per week, can be combined with oral cyclophosphamide 300 mg/m<sup>2</sup> per week and alternate day prednisone, at least using a 28-day cycle length, with acceptable toxicity and an excellent response rate.



**Fig 2.** Overall survival. Among the 37 patients treated at all dose levels, 12 have died. The 1-year overall survival probability was 89% (95% CI, 73% to 96%).

Although peripheral neuropathy, usually grade 1, and grade 3 thrombocytopenia occurred relatively frequently at this dose level, they were manageable, reversible, and not dose-limiting. However, two of six patients at this dose level completed only seven of eight planned cycles due to toxicity. Moreover, the antitumor effect appeared to be preserved when a somewhat higher dose of bortezomib—1.5 mg/m<sup>2</sup>—was given only once per week for three doses with the same oral combination. Myelosuppression was milder with less thrombocytopenia, and no significant peripheral neuropathy or neuropathic pain was observed with this dosing schedule. The use of prednisone, rather than dexamethasone, in our regimen also likely contributed to the excellent tolerance. Recently, prolonged use of high-dose dexamethasone therapy has been associated with more toxicity, at least when used as part of first-line therapy.<sup>18</sup>

Infectious complications were also manageable in this population of relapsed/refractory patients. As described in other bortezomib series, varicella zoster occurred in a significant proportion (30%) in the absence of routine antiviral prophylaxis.<sup>19</sup> Such prophylaxis should be used with this regimen and will be incorporated into our future trials.

There has been concern that myeloma may progress when the interval between bortezomib doses increases, as in certain maintenance schedules. Weekly bortezomib in our regimen was active, with a low rate of early progression, suggesting the need for twice weekly administration may be less when an alkylating agent and corticosteroid are used during the 2-week period without bortezomib.

Responses were achieved rapidly and were observed after the first cycle, with the best response achieved after two cycles in the majority of patients treated at the higher dose levels. The CR/nCR rate with dose levels 5 and 6, using the 1.3 and 1.5 mg/m<sup>2</sup> doses of bortezomib, was ≥ 50%, and the overall response rate was 85% to 100% in this relatively small group of patients. This response rate compares favorably with other potentially more myelosuppressive combination regimens that utilize novel agents. High-grade and durable responses were observed in patients known to have unfavorable cytogenetics, although these studies were not available in all patients.<sup>20,21</sup>

Response duration is another critical factor in evaluating newer therapies for relapsed/refractory myeloma. In the initial trials of single-agent bortezomib, therapy could be continued on an extension

program,<sup>22</sup> particularly if CR had not been achieved. Despite this, the median time to progression was approximately 6 months. Moreover, some patients do not achieve the maximal response until many cycles have been given. Although the optimum duration of bortezomib therapy is uncertain, the ability to administer a regimen for prolonged periods without marked toxicity would likely be advantageous. One of our patients elected to continue all three drugs, at dose level 4, until disease progression was documented after a total of 16 cycles, without toxicity. The favorable toxicity profile of this regimen suggests that long-term therapy may be feasible.

Although most of our patients received cyclophosphamide and prednisone alone, albeit for a relatively short period, after completing the eight cycles of protocol therapy, seven patients remain in unmaintained CR/nCR for periods of up to 1 year off all therapy. The absence of a formal bortezomib-based maintenance schedule over and above the oral combination does not allow us, in the context of this study, to adequately address the issue of prolonged therapy, however, and it should be evaluated as part of future studies.

In summary, this pilot study found that a triple drug regimen incorporating weekly bortezomib with cyclophosphamide and prednisone was convenient, well tolerated, and effective. The efficacy of this regimen needs to be evaluated in a larger, controlled, comparative study, but our preliminary observations indicated that overall response rates were notable in terms of both quality and duration. Evaluation of this combination is warranted in studies involving newly diagnosed as well as relapsed/refractory patients. A Canadian trial comparing our weekly and twice weekly bortezomib combination is planned.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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■ ■ ■  
**Appendix**

**Table A1.** Major Toxicities of Cycles 2 to 8 by Dose Level Based on National Cancer Institute Common Toxicity Criteria Version 3

Toxicity by Grade	Level			
	All	4	5	6
Total No. of cycles given	251	35	46	96
Neutropenia				
3	4	1 (fever)		
4	1	1		
Thrombocytopenia				
3	23	4	19	1
4	3	2	1	
Nausea and vomiting, grade 3				1
Diarrhea, grade 3				1
Varicella zoster				
2	8	1	1	5
3	2			1
Peripheral neuropathy				
1	18	3	4	9
2	2		1	