United States Food and Drug Administration Approval Summary: Bortezomib for the Treatment of Progressive Multiple Myeloma after One Prior Therapy

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Abstract

Purpose: On March 25, 2005, bortezomib (Velcade for Injection; Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) received regular approval from the U.S. Food and Drug Administration (U.S. FDA) for the treatment of multiple myeloma (MM) progressing after at least one prior therapy. This approval was based on bortezomib's efficacy and safety which was shown in a single, large, comparative international open-label phase 3 trial that randomized 669 patients with MM previously treated with at least one systemic regimen to receive single-agent bortezomib or high-dose dexamethasone. The FDA analysis of the trial data and bortezomib's regulatory development are summarized here.

Experimental Design and Results: Following a preplanned interim analysis of time to disease progression (the primary end point), an independent data-monitoring committee advised the sponsor to halt the study and offer bortezomib to all dexamethasone-treated study patients. Time to progression was significantly prolonged in the bortezomib treatment arm (median, 6.2 months) compared with the dexamethasone arm (median, 3.5 months; log-rank test, $P < 0.0001$; hazard ratio, 0.55; 95% confidence interval, 0.44-0.69). Analysis of overall survival done on the interim database (with 20% of events) showed the superiority of bortezomib for patients (log-rank test, $P < 0.05$; hazard ratio, 0.57; 95% confidence interval, 0.40-0.81). Using criteria from the European Group for Blood and Marrow Transplantation, the response rate (complete plus partial response) with bortezomib was also superior to dexamethasone (38% versus 18%; $P < 0.0001$). Adverse events on the bortezomib arm were similar to those previously observed in phase 2 studies; some notable adverse events included asthenia, peripheral neuropathy, thrombocytopenia, and neutropenia.

Conclusions: The U.S. FDA had earlier (May 2003) granted bortezomib accelerated approval for the treatment of patients with MM progressing after two prior therapies. The results of the phase 3 trial and the FDA analysis of the data, along with the sponsor's completion of other post-marketing commitments, confirm bortezomib's benefit and support regular approval.

On March 25, 2005, the U.S. Food and Drug Administration (U.S. FDA) granted regular approval to bortezomib (Velcade for Injection; Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceutical Research and Development, L.L.C.) for the treatment of progressive multiple myeloma (MM) in patients who have received at least one prior therapy. Regular marketing approval of a drug is based on the demonstration of a clinical benefit or an effect on an established surrogate for clinical benefit (1, 2).

Regulatory Background

The initial New Drug Application for bortezomib was filed in January 2003. In May 2003, bortezomib received accelerated approval from the U.S. FDA for the treatment of progressive MM in patients who had received at least two prior therapies.[1] That approval was based on FDA analysis of evidence of durable responses, including complete responses, in heavily

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[1] Velcade label (package insert) and approval letter. Available online at http://www.fda.gov/cder/approval/index/htm.

pretreated patients in two phase 2 studies (3). These early findings were considered likely to predict clinical benefit.

The Accelerated Approval (subpart H) regulations[2] allow an "accelerated" marketing approval for a new drug provided that it shows a meaningful therapeutic benefit over existing treatments under certain conditions, including:

- use in serious or life-threatening illnesses and
- an effect on a surrogate end point which is reasonably likely to predict clinical benefit or an effect on a clinical end point other than survival or irreversible morbidity.

This form of approval is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit; fulfilling this commitment allows the drug to receive regular (full) approval.[3] In considering the distinctions between regular and accelerated approval, the standard of "substantial evidence" is the same in each approval process, but the end point on which the results are based is different, i.e., for accelerated approval, the end point may be a "surrogate, reasonably likely" to predict clinical benefit.

Thus, in January 2003, when the initial New Drug Application for marketing approval of bortezomib was submitted, the sponsor had already met with the FDA and had initiated a phase 3 study to evaluate that drug's role in a less heavily pretreated patient population (patients with progressive MM following at least one prior systemic therapy). This protocol had reached ~50% of its planned patient accrual at the time of bortezomib's accelerated approval in May 2003.

In conjunction with the 2003 accelerated approval, Millennium Pharmaceuticals committed to (*a*) complete a study characterizing the frequency, severity, and reversibility of bortezomib-associated peripheral neuropathy noted in phase 2 and 3 studies, (*b*) complete an ongoing extension study of bortezomib use beyond eight cycles, and (*c*) complete and report the results of a phase 3 controlled study in a less heavily pretreated myeloma patient population. Millennium Pharmaceuticals and the FDA agreed that these additional studies would advance the safe use of bortezomib. This report reviews the FDA analysis of the phase 3 trial supporting the regular approval of bortezomib.

Phase III Study Design

The regular approval of bortezomib was based on findings of its efficacy and safety in a large, international, multicenter phase 3 prospective study. This randomized, open-label trial compared single-agent bortezomib with single-agent, "high-dose" dexamethasone in patients with MM progressing after at least one prior therapy. Eligible patients had previously been diagnosed with MM by standard criteria and had progressive disease following one, two, or three prior systemic therapies. Other patient eligibility requirements included measurable disease (determined either by serum or urine myeloma protein assay or plasmacytoma measurements), baseline creatinine clearance ≥20 mL/min, platelet count ≥50 × 10^9/L, hemoglobin ≥7.5 g/dL, absolute neutrophil count ≥0.75 × 10^9/L, and serum calcium, corrected <14 mg/dL. Additional eligibility requirements included adequate functional status and dexamethasone sensitivity.

Criteria for study ineligibility were baseline peripheral neuropathy interfering with function (≥grade 2 according to the Common Terminology Criteria for Adverse Events), cardiac amyloidosis, or other cardiac or unstable medical conditions. Also, because the control treatment was dexamethasone, the study protocol specified that patients deemed to be resistant to high-dose dexamethasone were ineligible. Previous high-dose dexamethasone therapy was defined as >500 mg dexamethasone or its equivalent over a 10-week period, whether administered alone or as part of the vincristine-doxorubicin-dexamethasone regimen or other regimen. Dexamethasone resistance was defined as showing less than a partial response to dexamethasone, progressive disease within 6 months after discontinuing dexamethasone, or discontinuation of dexamethasone because of grade ≥3 dexamethasone-related toxic effects. Use of dexamethasone as the control arm and the dexamethasone dose used were considered appropriate based on expert opinion and literature review (4–6).

The primary end point of the study was time to progression of disease (TTP), defined as the time from randomization until evidence of progressive disease was satisfied. Criteria for MM progression (or relapse from complete response) and for MM response were those defined by the European Group for Blood and Marrow Transplantation (EBMT; ref. 7) using clinical and laboratory findings. Secondary end points in this study were overall survival, rate and duration of response, frequency of infections ≥grade 3, time to skeletal-related events, and safety. Response and progression were assessed by a validated computer program algorithm based on the EBMT criteria. All patients had clinical and laboratory evaluations every 3 weeks for the first 39 weeks. Serum and urine protein measurements were done in a central laboratory and results were entered directly into the study database.

The sample size was estimated to provide 80% power to detect a 30% improvement in TTP over the control arm with an overall two-sided α of 0.05. The statistical plan included an interim analysis of TTP, with appropriate allocation of type 1 error rate, when approximately half the total expected TTP events had occurred. Randomization was centralized and stratified by three factors: (*a*) the number of prior regimens received (one only or more than one), (*b*) TTP after prior treatment (progression during or within 6 months of the most recent therapy versus >6 months after the most recent therapy), and (*c*) baseline β_2-microglobulin levels (≤2.5 versus >2.5 mg/L).

Patients in the single-agent bortezomib arm were to receive a dose of 1.3 mg/m^2 by rapid i.v. bolus on days 1, 4, 8, and 11 (four doses) every 3 weeks for up to eight cycles, followed by up to three additional 5-week cycles of once weekly dosing (four doses). The dose was to be recalculated on day 1 of each cycle based on the patient's actual body surface area. Patients in the high-dose dexamethasone group were to receive up to four 5-week treatment cycles followed by up to five 4-week treatment cycles. During each 5-week treatment cycle, dexamethasone-treated patients were to receive 40 mg/d dexamethasone orally once daily on days 1 to 4, 9 to 12, and 17 to 20

[2] 21 Code of Federal Regulations part 314, subpart H. Available online at http://www.fda.gov/cder/guidance/append4.pdf.

[3] 21 Code of Federal Regulations part 314.510 Available online at http://www.fda.gov/cder/guidance/append4.pdf.

of a 35-day cycle. A complete 5-week treatment cycle consisted of 12 days of dexamethasone every 35 days for up to four cycles. During each subsequent 4-week treatment cycle, patients were to receive 40 mg/d dexamethasone orally once daily on days 1 to 4 every 28 days for up to five cycles. The maximum duration of protocol therapy was 39 weeks in the bortezomib group and 40 weeks in the dexamethasone group, after which patients who had not experienced progressive disease were to be observed until progressive disease. Patients progressing on dexamethasone could subsequently receive bortezomib.

All patients were to receive i.v. bisphosphonates every 3 to 4 weeks unless contraindicated and were to receive other supportive care in accordance with local standards. For bortezomib-related neuropathy, dose adjustments followed the bortezomib label (package insert; see footnote 1, above). Patients in the dexamethasone treatment arm who showed progressive disease were then eligible to crossover to the bortezomib arm.

Study Results

This multinational trial enrolled 669 patients with MM between May 2002 and October 2003. The patient characteristics and disease at baseline, presented in Table 1, were similar in the two study arms. Of all 669 patients randomized, 40% of bortezomib-treated patients versus 35% of dexamethasone-treated patients had received only one prior systemic therapy. For both groups, the median number of prior therapies was two. About 40% of patients in each study arm had previously received dexamethasone, and 98% of patients had at least some previous exposure to steroids. For both groups, the myeloma protein types were similar. A total of 38% of the study patients were from sites in the U.S.

Protocol violations were uncommon and seemed balanced between both arms. A review of the eligibility records determined two types of eligibility violations: 9% of all patients met the protocol-specified criteria for refractoriness to dexamethasone on entry into the study, and 3% of patients did not have measurable disease. Exclusion of these patients did not alter the results.

Drug exposure seemed to be similar in the two study arms, although the treatment schedules were different. During the first 15 weeks on each treatment arm, 55% of dexamethasone-treated patients and 56% of bortezomib-treated patients remained on the assigned therapy. For the dexamethasone arm, 40% of patients received at least one dose in all four of the 5-week treatment cycles of therapy, and 6% received at least one dose in all nine cycles. For bortezomib, 34% of patients received at least one dose in all eight of the 3-week cycles of

Table 1. Baseline disease and patient characteristics in 669 patients with progressive MM enrolled in the phase 3 study of bortezomib versus dexamethasone

	Bortezomib (%)	Dexamethasone (%)	Total (%)
	333 (49.8)	336 (50.2)	669
Age (y)	62 (48-74)	61 (47-73)	61 (47-74)
Karnofsky performance status (*n*)	322	325	647
≤50	1 (<1)	1 (<1)	2 (<1)
60	17 (5)	12 (4)	29 (4)
70	24 (7)	41 (13)	65 (10)
80	98 (30)	100 (31)	198 (31)
90 or 100	182 (57)	171 (53)	353 (55)
β2-Microglobulin, median (mg/L)	3.7	3.6	3.6
Serum creatinine (≥1.5 mg/dL)	52 (16)	57 (17)	109 (16)
Creatinine clearance (*n*)	330	323	653
>60 mL/min	220 (67)	212 (66)	432 (66)
31-60 mL/min	93 (28)	100 (31)	193 (30)
21-30 mL/min	9 (3)	6 (2)	15 (2)
≤20 mL/min	8 (2)	5 (2)	13 (2)
Hypercalcemia (any grade)	23 (7)	24 (7)	47 (7)
Prior therapy			
Only one prior regimen	132 (40)	119 (35)	251 (37.5)
Corticosteroid use	325 (98)	332 (99)	657 (98)
Prior high-dose dexamethasone	124 (37)	145 (43)	269 (40)
Prior stem cell transplant	222 (67)	229 (68)	451 (67)
Prior alkylating agent	302 (91)	310 (92)	612 (91)
Hemoglobin, median (g/dL)	10.8	10.9	10.8
Platelet count, median ($\times 10^9$/L)	192	188	189
Platelet count, % (<75 $\times 10^9$/L)	6	4	5
Serum albumin, median (g/dL)	3.9	3.9	3.9
Time since diagnosis, median (y)	3.5	3.1	3.3
Plasmacytomas (%)	10	7	8

therapy, and 13% received at least one dose in all 11 cycles. The average number of bortezomib doses during the study was 22 (range, 1-44; median, 20).

For the TTP end point, disease progression was first indicated by laboratory measurement (increasing serum or urine protein or incident hypercalcemia) in 84% of the bortezomib-treated patients and 81% of the dexamethasone-treated patients. The other instances of disease progressions on both treatment arms were based on investigator-determined outcomes such as plasmacytoma measurements and changes in bone or bone marrow.

Efficacy. The study Data Monitoring Committee met in December 2003, as planned by the protocol, to review bortezomib's safety and the results of a single interim analysis of TTP done after 55% (254 of 460) of progression events were observed. As a result of the interim analysis and the recommendation of the Committee, all patients on the dexamethasone arm were offered bortezomib treatment as of December 15, 2003. The data and results that follow reflect the early termination of the study. Analyses were done using the intention-to-treat populations for each study arm.

TTP, response rates, and overall survival for patients receiving bortezomib were significantly superior statistically to those in dexamethasone-treated patients (see Table 2). The median TTP on the bortezomib arm was 6.2 months compared with 3.5 months for dexamethasone (log-rank test, $P < 0.0001$). Figure 1 shows the Kaplan-Meier TTP curves available for each treatment arm at the time the study was terminated. Because of the early termination, the median duration of follow-up for surviving patients ($n = 534$) was limited to 8.3 months, and the survival analysis was considered preliminary, with 20% of the events (deaths) observed up to the time of study termination.

An additional exploratory analysis of progression-free survival was done by the FDA to examine the correlation between TTP and progression-free survival in this study. For the TTP analysis, patients who died prior to a progression event were censored. Progression-free survival events include progressions as well as deaths (without prior progression) on each study arm. Over the same time interval as the TTP analysis, there were a total of 42 deaths without progression: 14 on the bortezomib arm and 28 on the dexamethasone arm. The median progression-free survival for the bortezomib-treated patients was 5.7 months versus 3.1 months for the dexamethasone-treated patients; log rank, $P < 0.0001$; hazard ratio, 0.55 (95% confidence interval, 0.45-0.67). Thus, the progression-free survival results are concordant with the TTP analysis.

Table 2. Efficacy results in a phase 3 study of bortezomib versus dexamethasone in 669 patients with progressive MM after one prior therapy

	All patients		
	Velcade		Dexamethasone
Efficacy endpoint	$n = 333$		$n = 336$
TTP			
Events, n (%)	147 (44)		196 (58)
Median (95% confidence interval)*	6.2 mo (4.9-6.9)		3.5 mo (2.8-4.2)
Hazard ratio (95% confidence interval) †		0.55 (0.44-0.69)	
P ‡		<0.0001	
Overall survival			
Events (deaths) n (%)	51 (15)		84 (25)
Hazard ratio (95% confidence interval) †		0.57 (0.40-0.81)	
P ‡§		<0.05	
Response rate ($n = 627$)‖	$n = 315$		$n = 312$
Complete response, n (%)¶	20 (6)		2 (<1)
Partial response, n (%)¶	101 (32)		54 (17)
Near-complete response, n (%)¶**	21 (7)		3 (<1)
Complete response + partial response, n (%)¶	121 (38)		56 (18)
P ††		<0.0001	
Response duration (mo)			
Complete response (median)¶	9.9		Not estimable
Near-complete response (median)¶	11.5		9.2
Complete response + partial response (median)¶	8.0		5.6

*Kaplan-Meier estimate.
†Hazard ratio is based on Cox proportional-hazard model with treatment as the single independent variable. A hazard ratio <1 indicates an advantage for bortezomib.
‡P value based on the stratified log-rank test.
§Precise P value cannot be rendered (see text).
‖Response population includes patients who had measurable disease at baseline and received at least one dose of the study drug.
¶EBMT criteria (7).
**Near-complete response meets all EBMT criteria for complete response but has positive immunofixation; grouped with the partial responses by EBMT.
††P value for response rate (complete response + partial response) from the Cochran-Mantel-Haenszel χ^2 test adjusted for the stratification factors.

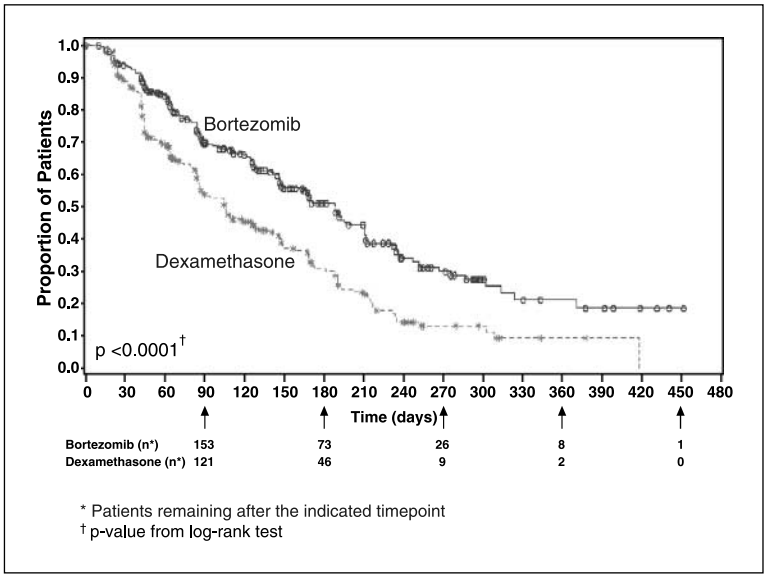

Fig. 1. Kaplan-Meier TTP for the ITT population, bortezomib versus dexamethasone for patients with progressive MM after one prior therapy.

Survival and safety analysis data were censored as of January 15, 2004. In the bortezomib-treated group, the survival improvement is regarded as statistically significant ($P < 0.05$); however, the precise estimate of the effect size and the corresponding nominal P value could not be evaluated with the available survival information. No significant differences between study arms were observed in the secondary end points of grade ≥3 infections, blood transfusions, or time to skeletal events. Bisphosphonates were administered to 92% of all study patients, and use of prophylactic antibiotics was more common on the dexamethasone arm.

Safety. Adverse events (AE) occurring at a frequency of 15% or greater are listed in Table 3. Among the 331 bortezomib-treated patients, the most commonly reported AEs were asthenic conditions (61%), diarrhea (57%), nausea (57%), constipation (42%), peripheral neuropathy (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric disorders (each 35%), anorexia and decreased appetite (34%), paresthesia and dysesthesia (27%), anemia and headache (each 26%), and cough (21%). The most commonly reported AEs among the 332 patients in the dexamethasone-treated group were psychiatric disorders (49%), asthenic conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung infections (each 21%).

Fourteen percent of patients in the bortezomib-treated arm experienced a grade 4 AE; the most common grade 4 toxic effects were thrombocytopenia (4%), neutropenia (2%), and hypercalcemia (2%). Sixteen percent of dexamethasone-treated patients experienced a grade 4 AE, and the most common grade 4 toxicity was hyperglycemia (2%). AEs observed in this phase 3 study did not differ materially from those identified in previous phase 2 studies of bortezomib.

Deaths within 30 days of the last dose of study drug were reported for 14 bortezomib-treated patients and 25 dexamethasone-treated patients. Of the deaths in this phase 3 study, four were considered to be bortezomib associated: one case each of cardiogenic shock, respiratory insufficiency, congestive heart failure, and cardiac arrest. Four deaths were considered dexamethasone associated: two cases of sepsis, one case of bacterial meningitis, and one case of sudden death at home.

Discussion

The study population was broadly representative of patients with MM (whose disease had relapsed after at least one prior therapy), albeit slightly younger. The stratified randomization seemed to balance the relevant prognostic factors between the two treatment groups (see Table 1). Although the study was open-label in design, the determination of progression was based primarily on the quantitative laboratory assessment of myeloma protein changes as defined by the EBMT criteria. This laboratory-based method of ascertaining progression helps reduce possible ascertainment bias in an open-label study.

In myeloma, disease progression and response end points could often be determined by the laboratory measurement of monoclonal myeloma proteins (in this study, determinations of progressive disease were laboratory based in 84% of progressions). The end point criteria and laboratory assessments in this study, intended for drug registration, were prespecified in the protocol and done per protocol, with symmetry of assessment timing and minimal missing data. For usual clinical care, there are various criteria for assessing disease response and progression, as discussed elsewhere (8).

In the U.S., over the last 20 years, no other chemotherapy agents have shown efficacy and safety sufficient to receive approval as MM therapy; thus, there are no recent regulatory precedents. Prior agents approved for use in MM have included: melphalan for the palliative treatment of MM, cyclophosphamide for the palliative treatment of MM, carmustine for the palliative treatment of MM, pamidronate for the adjunctive treatment of osteolytic lesions of MM, and zoledronate for the adjunctive treatment of MM.

The correlation between TTP or response results and an overall survival benefit in myeloma remains poorly defined, at least in part because of the modest antitumor effects of earlier treatment options. In an evaluation of end points following the initial therapy of myeloma, TTP, but not magnitude of response, has been reported to correlate with survival (9). A benefit in TTP encompasses the effects of treatment in patients whose disease is stabilized as well as in patients with responsive disease. In this large study, the magnitude of the difference in

Table 3. Common AEs in a phase 3 study of bortezomib versus dexamethasone in 669 patients with progressive MM after one prior therapy

	Bortezomib (n = 331), n (%)			Dexamethasone (n = 332), n (%)		
	All events	Grade 3 events	Grade 4 events	All events	Grade 3 events	Grade 4 events
Adverse event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	26 (8)	3 (<1)
Anemia	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Headache	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Anorexia and appetite decreased	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Paresthesia and dysesthesia	91 (27)	6 (2)	0	38 (11)	1 (<1)	
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Lower respiratory/lung infections	48 (15)	12 (4)	2 (<1)	69 (21)	24 (7)	1 (<1)

TTP between treatment arms (favoring bortezomib; hazard ratio, 0.55; stratified log-rank test, $P < 0.0001$) is substantial and is associated with a survival benefit as well. It should be noted that smaller magnitudes of difference in TTP, by themselves, in a myeloma study may not necessarily provide convincing evidence of clinical benefit.

For bortezomib-treated patients, the improvement in TTP observed in this study was also supported by an improved response rate, including complete responses. Complete responses of sufficient magnitude and duration may represent a clinical benefit in hematologic diseases because those patients may be spared infections, transfusions, and other supportive interventions with their associated toxicities. In this study, 20 patients (6%) receiving bortezomib were reported to have achieved a complete response according to EBMT criteria (7), which are quite stringent and were developed to describe results following stem cell transplantation. Another 7% of bortezomib-treated patients achieved a near-complete response as described by EBMT criteria (persisting myeloma protein only detectable by immunofixation). In an earlier phase 2 study of bortezomib in heavily pretreated patients with MM, a complete response rate of 2.7% was reported and was verified during FDA review (3). The achievement of complete responses (using stringent criteria) outside the transplant setting represents an important advance in myeloma therapy.

Conclusion

Bortezomib has shown efficacy with safety in a large phase 3 randomized study in patients with MM that has progressed following at least one prior therapy. Millennium Pharmaceuticals planned and implemented bortezomib's development efficiently and satisfied U.S. regulatory requirements. The FDA review of the trial data corroborated the study findings. The regular marketing approval and the drug's revised labeling reflect the evidence of benefit.

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