Report from the FDA

Approval Summary for Bortezomib for Injection in the Treatment of Multiple Myeloma

Peter F. Bross, Robert Kane, Ann T. Farrell, Sophia Abraham, Kimberly Benson, Margaret E. Brower, Sean Bradley, Jogarao V. Gobburu, Anwar Goheer, Shwu-Luan Lee, John Leighton, Cheng Yi Liang, Richard T. Lostritto, William D. McGuinn, David E. Morse, Atiqur Rahman, Lilliam A. Rosario, S. Leigh Verbois, Grant Williams, Yong-Cheng Wang, and Richard Pazdur

Division of Oncology Drug Products, Center for Drug Evaluation and Research, United States Food and Drug Administration, Rockville, Maryland

ABSTRACT

Purpose: **Multiple myeloma is a malignant plasma cell disorder accounting for about 10% of hematological malignancies. Despite treatment advances, including hematopoietic stem-cell transplantation to facilitate administration of high-dose cytotoxic chemotherapy, the median survival remains approximately 3 years and long-term remissions are rare. Bortezomib (Velcade, formerly known as PS-341; Millennium Pharmaceuticals, Cambridge MA) is a dipeptide boronic acid that inhibits the 20S proteasome involved in the degradation of intracellular proteins, including those affecting cell cycle regulation in mammalian cells. Described herein are the analyses by the United States Food and Drug Administration (FDA) of clinical and nonclinical data submitted in the New Drug Application. Chemistry manufacturing and controls, animal toxicology, and biopharmaceutical data are described. The results of Phase I and Phase II clinical studies in patients with multiple myeloma are summarized. The marketing approval and postmarketing commitments are discussed.**

Results: **Toxicology studies in the rat and monkey identified hematological, lymphoid, cardiac, renal, gastrointestinal, and neurological toxicities of bortezomib. A steep dose-toxicity effect was noted at doses ≥0.9 mg/m^2. Administration of doses ≥3.0 mg/m^2 to monkeys resulted in cardiovascular collapse and death 12–14 h postdose. Histopathological evidence of axonal and myelin degeneration of dorsal root ganglia, peripheral nerves, and spinal cord were observed in monkeys and rodents; concurrent clinical observations included tremors and decreased activity.**

Pharmacokinetic studies in patients with advanced malignancies demonstrated that the mean elimination half-life after the first bortezomib dose varied from 9 to 15 h at doses ranging from 1.45 to 2.00 mg/m^2. The drug is metabolized by cytochrome P450–3A4, -2D6, -2C19, -2C9, and -1A2. Three Phase I studies were performed in a total of 123 patients with advanced malignancies. Dose-limiting toxicity included diarrhea and sensory neurotoxicity. No dose-limiting hematological toxicity was reported.

Safety and efficacy were evaluated in an open-label, Phase II study of 202 patients with multiple myeloma who had received at least two prior therapies and had demonstrated disease progression on their most recent therapy. A smaller dose finding study of 54 patients provided additional supportive information. Bortezomib was administered by i.v. bolus on days 1, 4, 8, and 11 in a 21-day cycle for up to eight cycles. The initial dose was 1.3 mg/m^2 except for 28 patients in the dose-finding study who received a 1.0 mg/m^2 dose. The primary study end point in this single-arm trial was response rate, easily measured and thought to correlate with clinical benefit in patients with myeloma. One hundred eighty-eight patients who met the inclusion criteria were included in the FDA efficacy analysis population. Complete responses (CRs) were observed in 5 patients and partial responses (PRs) in 47 patients for an overall response (OR) rate (OR = CR + PR) of 28%. The dose finding study of 54 patients showed a higher response rate for patients given 1.3 mg/m^2 compared with 1.0 mg/m^2 twice weekly for two of the 3-week schedule, but the study was too small for statistical dose-response comparisons. The most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) in 65%, nausea (64%), diarrhea (51%), appetite decreased (including anorexia; 43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%, including peripheral sensory neuropathy and peripheral neuropathy aggravated), pyrexia (36%), vomiting (36%), and anemia (32%).

Conclusions: **The FDA granted marketing approval to Millennium Pharmaceuticals on May 13, 2003 for bortezomib for use as a single agent for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. Accelerated approval was based on a surrogate end point of response rate rather than clinical benefit, such as an improvement in survival. The recommended dose of bortezomib is 1.3 mg/m^2 administered twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12–21). Accelerated approval was based on the results of two Phase II studies in a total of 256 patients and additional Phase I safety information. Mandated Phase IV study commitments to characterize clinical efficacy and safety more precisely are discussed.**

Received 12/22/03; revised 3/3/04; accepted 3/8/04.
Requests for reprints: Peter F. Bross, United States Food and Drug Administration, HFM 755, 1401 Rockville Pike, Rockville, MD 20852. E-mail: bross@cber.fda.gov.

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder accounting for ~10% of hematological malignancies. There are approximately 45,000 people in the United States living with multiple myeloma and an estimated 14,600 new cases of multiple myeloma are diagnosed each year.[1] The reported incidence is 5 per 100,000 with a peak at age ~70 years; rates are higher in African Americans and in men (1). Multiple myeloma was first described in 1844; and in 1962, Bergsagel *et al.* (2) reported that melphalan, the phenylalanine derivative of nitrogen mustard, could induce remissions in about one-third of patients. Many cytotoxic regimens induce remissions, but effects on survival have been difficult to demonstrate despite increasing doses of conventional cytotoxic chemotherapy (3). Median overall survival does not exceed 3 years with conventional chemotherapy (4).

High-dose chemotherapy followed by hematopoietic stem cell rescue has been shown to increase the percentage of complete remissions to almost 50% in selected patients (*versus* 1–13% with conventional dose therapy), but the disease commonly recurs (5, 6). High-dose chemotherapy may increase the CR rate and time-to-progression; however, myeloablative therapy has not consistently shown a survival improvement (7). Double autologous (tandem) transplantation has recently been shown to improve long-term survival in eligible patients less than 60 years old, but the majority of patients eventually relapsed even after the double transplant (8). Subsequent treatment responses occur less frequently and are of shorter duration (9).

Salmon *et al.* (10) first reported the efficacy of high-dose prednisone in this disease in 1967, and glucocorticoids are still a mainstay of myeloma therapy. Recent research has focused on other alternatives to cytotoxic chemotherapy. In 1999, Singhal *et al.* (11) reported durable responses with thalidomide in multiple myeloma, and subsequent studies have confirmed its activity (12–13). In 2003, Richardson *et al.* (14) reported on the efficacy results of bortezomib, an inhibitor of the 20S proteasome, in advanced multiple myeloma. This article describes the analysis of clinical and nonclinical data that led to accelerated marketing approval of bortezomib for the treatment of multiple myeloma.

RESPONSE CRITERIA IN MULTIPLE MYELOMA

Multiple myeloma is characterized by the clonal proliferation of plasma cells. Except in 1–2% of patients with nonsecretory myeloma, an abnormal monoclonal immunoglobulin heavy- and/or light-chain paraprotein, known as M protein or M component, is readily quantifiable in the serum and/or urine of patients with multiple myeloma and has been used to measure the response to therapy and progression. In 1968 and 1973, the Chronic Leukemia and Myeloma Task Force of the National Cancer Institute published guidelines for the determination of response in multiple myeloma, specifying a response parameter of 50% reduction in paraprotein measured by protein electrophoresis (PEP) of serum (SPEP) or urine (UPEP; Ref. 15). The Southwest Oncology Group (SWOG) subsequently refined the remission criteria to require a 75% reduction in serum and a 90% reduction in urine paraprotein (16, 17).

CRs were rarely reported with earlier treatment options; however, the development of newer combination and dose-intensive therapy led to new proposals for assessing treatment response. In 1989, Gore *et al.* reported their response evaluation in a series of patients with myeloma treated with combination chemotherapy followed by high dose-melphalan and stem cell rescue (18). The Gore study reported a complete remission rate of 50% based on disappearance of M protein by PEP with the additional requirement of a confirmatory repeat electrophoresis finding 3 months later. Complete resolution of myeloma protein by PEP subsequently became a criterion for complete remission in the era of high-dose chemotherapy and stem-cell transplantation (7, 19–21).

In 1998, the European Group for Blood and Marrow Transplant (EBMT) proposed even stricter criteria for the assessment of CR in myeloma patients after high-dose therapy (22). These criteria include the complete absence of myeloma protein by immunofixation (IF) techniques as well as by PEP, and results must be confirmed at least 6 weeks later. In addition, bone marrow plasmacytosis must be reduced to less than 5%. Absence of serum and urine paraprotein measured by IF has recently been used to define CRs for both conventional and high-dose regimens (23, 24, 12). Lahuerta *et al.* (25) published a retrospective study suggesting that complete remission by immunofixation electrophoresis status is a more sensitive predictor of survival and time to progression than complete remission by PEP. Differences among response categories are summarized in Table 1.

THE PROTEASOME PATHWAY

The ubiquitin-proteasome pathway is thought to play a critical role in the degradation of proteins involved in cell cycle control and tumor growth. A complex enzyme cascade first marks proteins destined for degradation by the covalent addition

Table 1 Response criteria used in the efficacy analysis

Response category	IF[a]	Reduction of M protein required	
		SPEP	UPEP
EBMT			
CR[b]	Negative	100%	100%
PR	NR	50%	90%
MR	NR	25%	50%
SWOG remission[c]	NR	75%	90%

[a] IF, immunofixation; M protein, myeloma protein; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; EBMT, European Group for Blood and Marrow Transplant; CR, complete response; PR, partial response; NR, not required; MR, minimum response; SWOG, Southwest Oncology Group.

[b] EBMT CR also required <5% plasma cells in bone marrow, after Blade *et al.* (22).

[c] SWOG remission, after Alexanian *et al.* (16) and Salmon *et al.* (17).

[1] Source of information, national program of cancer registries. Internet address: http://www.cdc.gov/cancer/npcr/uscs/report/

of multiple molecules of ubiquitin (26). The proteasome hydrolyzes only those proteins that have been marked for destruction by this ubiquitin enzyme cascade (27, 28). The 20S proteasome, the core component of the proteasome complex, is composed of four subunits forming a hollow cylinder that has multiple proteolytic sites on the interior wall (29). The proteasome-complex degrades proteins as it moves them through this cylinder. This 20S proteasome must first bind to various other large proteins known as activators (PA700 and PA28 are examples) to form proteasome-activator complexes before it can hydrolyze the ubiquitin-bound protein substrates. These activators can bind to form different complexes, each with different protein substrate specificity. The most frequently studied proteasome complex is the 26S proteasome, a large molecule heterotrimer formed by the 20S proteasome and two PA700 activators (30–33). The proteasome can affect cell division through ubiquination and degradation of inhibitory proteins through the regulation of nuclear transcription factors (34–38). Evidence suggests that the inhibition of the proteasome can act through multiple mechanisms leading to an arrest of cell growth. Inhibition of the proteasome may also have other consequences. Limited *in vitro* research suggests that the inhibition of the proteasome pathway might lead to the accumulation of abnormal proteins, including prion-related protein (PrP), as demonstrated in transfected neuronal cell lines (39). The clinical consequences of this protein accumulation are unknown.

BORTEZOMIB (PS-341, VELCADE)

The search for molecules that could inhibit the 20S proteasome *in vitro* led to the discovery of bortezomib (Velcade, PS-341; Millennium Pharmaceuticals, Inc., Cambridge, MA), a small, dipeptide boronic acid that reversibly inhibits the chymotrypsin-like proteolytic activity site of the 20S proteasome of mammalian cells (40). Bortezomib exhibits cytotoxic, growth-inhibitory, and antitumor activities in several *in vitro* and *in vivo* assay systems and binds to the proteasome at lower concentrations than it does to other tested proteases. In replicating cells *in vitro*, bortezomib appears to cause cell cycle arrest at the transition of G_2-M, and the inhibited cells then initiate apoptosis (41). In the standard National Cancer Institute panel of 60 human cell lines, bortezomib inhibited cell growth and, in some cases, was cytotoxic for human tumor cells. The average IC_{50} of bortezomib across the 60 cell lines was 3.8 nM. In athymic mice implanted with both the HT-29 human colon and the PC-3 human prostate-tumor xenograft models, bortezomib given i.v. weekly for 4 weeks (3 mg/m^2) decreased tumor volume by up to 50 and 65%, respectively. Resistance to bortezomib cytotoxicity has been noted over time *in vitro*. This resistance is probably not mediated by overexpression of transmembrane molecular pumps, such as the multidrug resistance protein.

After *in vivo* dosing, inhibition of proteasome activity, measured in lysate from whole blood from animals or humans, recovers to normal in about 48–72 h (42). Repeat dosing causes greater inhibition compared with a single dose at the same level (about 30% after a single dose compared with almost 99% after seven daily doses). Inhibition could be detected in tissue from colon, muscle, prostate, and liver but not in the testes or brain of rodents. The inhibition in the liver was significantly greater than in WBCs. Thus far, there is no evidence of a relationship between *ex vivo* measurements of proteasome inhibition and clinical efficacy.

Bortezomib inhibited the degradation of cytochrome P450–2E1 by proteasomes after ethanol induction, thus preventing the return of intracellular expression of the enzyme to constitutive levels (43). Other cytochromes P450 may also be degraded by proteasomes after induction (44). Bortezomib has the potential to modify the metabolism of a broad range of chemicals by changing the intracellular concentration of cytochrome P-450 (45). Thus, proteasome inhibition by bortezomib may modify a patient's exposure to drugs that are metabolized by cytochrome P-450.

CHEMISTRY

Bortezomib is a modified dipeptide boronic acid. The drug substance exists in its cyclic anhydride form in the solid state as a trimeric boroxine. The product is provided as a mannitol boronic ester that, in reconstituted form, exists in equilibrium with its hydrolysis product, the monomeric boronic acid. The chemical name for the monomeric form is [(1*R*)-3-methyl-1-{[(2*S*)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]-amino}butyl]boronic acid. The molecular weight is 384.24, and the molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3–3.8 mg/ml in a pH range of 2–6.5. Bortezomib is available for i.v. injection as a sterile lyophilized powder in single-dose vials containing 3.5 mg bortezomib and 35 mg mannitol, USP. In this form, the drug product is stable and can be stored at controlled room temperature. The lyophilized powder drug product is reconstituted with 0.9% NaCl to a final concentration of 1 mg/1 ml before injection. The chemical structure is shown in Fig. 1.

TOXICOLOGY

Traditional toxicological and toxicokinetic parameters, neuropathological evaluations, and proteasome activity determinations were examined. Bortezomib was administered to rats as a single dose and twice weekly for 2 weeks and for 26 weeks. Bortezomib was poorly tolerated when administrated daily, even at very low doses. Nonclinical tolerability studies suggested that intermittent dosing permitted more prolonged dosing regimens by allowing a return toward baseline of 20S proteasome activity before the subsequent dose. In the 9-cycle 26-week rat study,

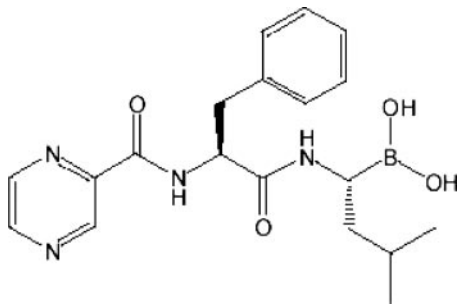

Fig. 1 Bortezomib structure. Bortezomib is a modified dipeptide boronic acid derived from leucine and phenylalanine.

drug-related mortality was observed at ≥0.9 mg/m^2 (days 23–180) and was due primarily to hematopoietic and lymphoid system depletion, along with gastrointestinal hyperplasia and necrosis. Histopathological changes were observed in the heart, liver, lung, kidney, sciatic nerve (necrosis), and spinal cord; in general, similar findings albeit with less severity were observed in scheduled-death animals. Animals who were dosed at ≥0.9 mg/m^2 and who survived to week 26 (end of treatment) exhibited various forms of neurotoxicity including degeneration of dorsal root ganglia, peripheral nerves, and spinal cord. Nephrotoxicity, including eosinophilic casts, inflammation, hypertrophy, tubular dilation, and glomerulonephritis was observed at 26 weeks of treatment at doses ≥0.6 mg/m^2; a comparable incidence of tubular dilation was observed after 8 weeks of recovery in males. Cardiac histopathological changes included increased incidence of perivascular necrosis, myocardial degeneration, hemorrhage, and inflammation. Thrombocytopenia was observed at all dose levels. After the 8-week recovery interval, myocardial inflammation, cardiac necrosis, and tubular dilation of the kidney (males only) persisted. There appeared to be some indication of reversibility of other findings at this time.

Bortezomib was administered to monkeys as a single dose, a daily dose for 13 days, twice-weekly for 2 weeks, and twice-weekly for 4- and 13-three week cycles. In the 13-cycle monkey study, bortezomib-related mortality was observed at dosages ≥0.9 mg/m^2. Findings included severe anemia, dehydration, gastrointestinal diffuse mucosal hyperplasia, thrombocytopenia, neurotoxicity, and cardiotoxicity. There was an increased incidence of clinically observable findings, typically associated with neurotoxicity, in treated animals when compared with controls during bortezomib administration. The frequency of histopathological findings demonstrating neurotoxicity was reduced after 8 weeks of recovery.

Clinical neurotoxicity was reported in monkeys, rats, and mice; findings included nerve degeneration of dorsal root ganglia, peripheral nerves, dorsal spinal roots and dorsal tracts of the spinal cord at ≥0.6 mg/m^2 (one-half of the recommended clinical dose of 1.3 mg/m^2). Histopathological incidence of neurotoxic effects in monkeys appeared greater compared with that in rodents. Clinical observations included tremors and reduced activity in monkeys; rats also exhibited reduced activity. Nephrotoxicity was observed at doses ≥0.9 g/m^2 in monkeys; males appeared to be more susceptible. Lymphoid atrophy and/or necrosis occurred in thymus, spleen, lymph nodes, and gut-associated lymphoid tissue. In addition, necrosis, atrophy, and hyperplasia of the gastrointestinal tract were observed in monkeys surviving to 38 weeks.

Dose- and schedule-dependent changes in *AUC* (area under the curve) and C_{max} (maximum concentration) occurred in both species. Drug exposure with increasing dose was more linear in monkeys compared with rodents; the explanation for this difference is unknown. After multiple doses, a decrease in clearance resulted in an increase in the terminal elimination half-life ($t_{1/2}$) and *AUC* (3–4-fold) in rats and cynomolgus monkeys, suggesting drug accumulation. Even though there were no gender differences in systemic exposure, it appears that female decedent rats exhibited a greater degree of toxicity compared with males based on the number and types of lesions, as well as on the total number of unscheduled deaths. Using an *ex vivo* 20S proteasome assay to measure inhibition of the chymotrypsin-like proteolytic activity in whole blood cells, proteasome inhibition increased with dose and returned to baseline by about 72 h in rats and monkeys. After a single dose of [^{14}C]bortezomib, bortezomib-related radioactivity was eliminated slowly from tissues (with highest concentrations in liver and kidneys); incomplete recovery of administered radioactivity in rats and monkeys suggests extensive tissue distribution and retention of bortezomib and its metabolites. Radioactivity was detected in the brain of monkeys but not of rats.

Cardiovascular safety pharmacology studies conducted in cynomolgus monkeys showed that the administration of dosages ≥3.0 mg/m^2 resulted initially in physiologically significant heart rate elevations, then profound progressive hypotension, bradycardia, and death 12–14 h postdose. Additional studies in monkeys showed bortezomib increased heart rate (≥1.2 mg/m^2), decreased mean arterial pressure (≥2.4 mg/m^2), increased ventricular contractility (≥3.6 mg/m^2), and increased cardiac output (≥3.6 mg/m^2). Mortality was not reported in this study; however, this study is inadequate to address drug-associated mortality observed in the previous studies because these monkeys were sacrificed before signs of terminal hypotension and imminent mortality occurred. Bortezomib-related radioactivity was distributed to the myocardium. Histopathological findings in repeat-dose monkey studies showed cardiac necrosis at doses ≥0.9 mg/m^2. Whether the observed cardiac effects are dependent on local drug disposition and/or direct drug-myocardial toxicity is unknown.

Bortezomib exhibited clastogenic activity in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells but was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) or the *in vivo* micronucleus assay. Teratological effects were examined in the rat and the rabbit. No formal evaluation of fertility or peri- and postnatal development (Segments I and III, respectively) were conducted. Pregnant rabbits given bortezomib during organogenesis at a dose of 0.6 mg/m^2 experienced significant postimplantation loss and a decreased number of live fetuses at minimally maternally toxic doses. Live fetuses also showed significant decreases in fetal weight. This dose is approximately one-half the clinical dose (1.3 mg/m^2). On the basis of embryo lethality findings in rats and rabbits, and the effects on primary and secondary sex organs observed in the 6-month rat study and the 9-month monkey toxicity studies, bortezomib is likely to have an adverse effect on pregnancy. However, bortezomib was not teratogenic in rats and rabbits at the highest dose tested, 0.5 mg/m^2 in the rat and 0.6 mg/m^2 in the rabbit, when administered during organogenesis. These dosages also are approximately one-half of the human clinical dose. Bortezomib is labeled "Pregnancy category D;" because of the potential of significant adverse effects on the developing fetus, women are strongly advised not to become pregnant while taking bortezomib.

CLINICAL STUDIES SUPPORTING APPROVAL

Three Phase I dose finding trials of bortezomib as monotherapy were performed in a total of 123 patients with a variety of advanced malignancies. Two Phase II studies were performed in 256 patients with multiple myeloma who had not achieved a

response to, or who had relapsed after, initial therapy. If patients progressed after two cycles or experienced no improvement after four cycles, dexamethasone 20 mg daily p.o. for 2 days was added to each bortezomib dose. An extension studies allowed continued therapy in those patients who appeared to benefit. The extension study provided safety information on longer-term therapy and efficacy information on response duration.

PHASE I STUDIES

The Phase I studies were performed in patients with advanced malignancies using weekly and twice-weekly dosing schedules. Weekly dosing was associated with dose-limiting toxicities of diarrhea, hypotension, tachycardia, and syncope with doses >1.6 mg/m^2. The maximum tolerated dose was found to be 1.3 mg/m^2 when given twice-weekly in the first 2 weeks of a 3-week cycle. This compares with a maximum tolerated dose of 1.04 mg/m^2 when given twice-weekly for the first 4 weeks in a 6-week cycle. At the 1.3 mg/m^2 dose, the 1-h mean percentage proteasome inhibition measured in patients' WBCs on day 1, cycle 1, is higher than the corresponding value at cycle 7 (70.5 *versus* 55%). The relationship between proteasome inhibition and dose suggests that the optimal bortezomib dose may be between 1.0 mg/m^2 and 1.3 mg/m^2. The twice-weekly dosing each 21-day cycle was selected because ~25% more drug could be tolerated.

PHASE II CLINICAL STUDIES

Two Phase II studies assessed the safety and efficacy of bortezomib. A small, open-label, randomized Phase II dose-finding study, Clinical Response and Efficacy Study of bortezomib in the Treatment of relapsing multiple myeloma (CREST) was performed in 54 patients with relapsed multiple myeloma to provide some dose-response data (46). The 1.3-mg/m^2 dose was compared with the 1.0-mg/m^2 dose using a 21-day cycle with treatment given during the first 2 weeks. The sponsor chose the higher dose because of a somewhat higher overall response rate that included minimal responders. The larger Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy (SUMMIT) was an open-label, single-arm, multicenter study of patients who had received at least two prior therapies and demonstrated disease progression on their most recent therapy (15). Patients were eligible if they had relapsed after a response to standard first-line chemotherapy (*e.g.,* vincristine-doxorubicin-dexamethasone or melphalan-prednisone) or high-dose chemotherapy, and were refractory (*i.e.*, failure to achieve at least CR, PR, or stable disease) to their most recent chemotherapy. Primary refractory patients were not enrolled.

Bortezomib 1.3 mg/m^2 was administered by i.v. bolus over 3–5 s on days 1, 4, 8, and 11 in a 21-day cycle. A maximum of eight cycles (24 weeks) was planned, but treatment could be continued for responding patients in a continuation study. Treatment was withheld in patients experiencing $\geq$ grade 3 nonhematological or grade 4 hematological toxicities until resolution or grade 1 was attained, and treatment was then resumed at the next lower dose level, either 1.0 or 0.7 mg/m^2. Patients with progressive disease after completing two cycles or who experienced no response after four cycles could be treated with the addition of dexamethasone, 20 mg p.o. (each day of, and the day after, bortezomib administration, *i.e.,* 40 mg with each dose). These patients were analyzed separately for efficacy and were not included in the primary analysis. Safety assessments performed during treatment included monitoring for adverse events, a directed questionnaire for neurological toxicities, specialized neurological testing, and clinical examinations.

The SUMMIT trial enrolled 202 patients. Eighty-four % had IgG or IgA myeloma and advanced disease at diagnosis, and 80% had a Karnofsky performance-status score $\geq$80. The mean age was 59 years; 81% were white, 10% were black, and 60% were male. Ninety-two % had been treated with three or more of the major classes of agents used to treat myeloma (steroids, alkylating agent, thalidomide, or anthracyclines). The median number of previous therapies was six (range, 2–15). Sixty-four % had received high-dose therapy and stem-cell transplantation. Five patients had not been treated with cytotoxic chemotherapy; these were excluded from the efficacy analysis. In comparison, the CREST study enrolled a less heavily pretreated population; the mean number of prior therapies was three, compared with six in the larger study. The mean Karnofsky performance-status score was also higher in the CREST study; otherwise, the trial characteristics were similar. Baseline patient and disease characteristics for both studies are summarized in Table 2.

RESULTS

The primary objective of the Phase II studies was the determination of overall response rate (CR + PR + minimal response). Responses were assigned by an Independent Review Committee based on the EBMT criteria described above (section "Response Criteria in Multiple Myeloma"). PRs required a 50% reduction in serum M protein and 90% reduction in urine M protein. Additional response analyses including remission by SWOG criteria and rate of complete resolution of M protein by PEP were performed to facilitate comparison with other reports of available therapy (see Table 1.) Minimal responses were not included in the United States Food and Drug Administration (FDA) analysis because these responses were deemed less likely to predict clinical benefit. All of the responses required confirmation at 6 weeks by protein electrophoresis (CRs required repeat IF also.)

Fifty-four patients were enrolled in the CREST study. The response rate (CR+PR) was 38% in the 1.3-mg/m^2 group compared with 30% in the 1.0-mg/m^2 group. One patient in each group experienced a CR by EBMT criteria, and two additional patients in the 1.0-mg/m^2 group experienced complete resolution of myeloma M protein by PEP. If minimal responses were included, the (CR + PR + minimal response) rate was 50% in the 1.3-mg/m^2 group compared with 33% in the 1.0-mg/m^2 group. This observation of a higher response rate led the sponsor to recommend the higher dose for further study, although the numbers were too small for statistical dose-response comparisons.

In the SUMMIT study, the FDA analysis identified 188 patients of the 202 enrolled who had evaluable disease and who fulfilled all eligibility criteria. The study population included patients with numerous adverse prognostic features including β_2 microglobulin levels above 4 mg/liter, cytogenetic abnormali-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.