

# BORTEZOMIB: PROTEASOME INHIBITION AS AN EFFECTIVE ANTICANCER THERAPY

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■ **Abstract** VELCADE® (bortezomib, Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ) is a first-in-class proteasome inhibitor developed specifically for use as an antineoplastic agent. Inhibition of the proteasome results in disruption of homeostatic mechanisms within the cell that can lead to cell death. Bortezomib's first indication, for the treatment of relapsed myeloma in patients who have received at least two prior treatments and progressed on their previous treatment, was based in part on the magnitude of activity demonstrated in phase II trials. Bortezomib is currently indicated for patients who have received at least one prior therapy in the United States and European Union, although patients in the European Union must have already undergone bone marrow transplantation or be unsuitable for the procedure. A phase III trial demonstrated the superiority of bortezomib over high-dose dexamethasone in response rate, time to progression, and survival in patients with myeloma who had relapsed after 1–3 prior therapies. Clinical development is ongoing to investigate its activity as monotherapy and in combination regimens for the treatment of non-Hodgkin's lymphoma, solid tumors, and earlier presentations of myeloma.

## INTRODUCTION

VELCADE® (bortezomib, Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ) is the first of a new class of pharmacologic agents—proteasome inhibitors—to be approved for clinical use. Proteasome inhibition represents a unique approach to anticancer therapy by targeting the proteasome, the key regulator of intracellular protein degradation. Its first indication, for the treatment of patients with multiple myeloma who have received at least two prior therapies and progressed on their most recent therapy, was based on robust preclinical data demonstrating growth inhibition and apoptosis of myeloma cells following exposure to bortezomib (1–6) and on phase I and II data that defined an optimal dosing schedule, a manageable toxicity profile, and evidence of remarkable activity in patients with relapsed,

refractory myeloma (7–10). Its current indication in the United States and European Union, as a treatment for patients with multiple myeloma who have received one prior therapy, was based on the efficacy and safety demonstrated in a randomized, phase III trial (47).

In vitro studies have shown that bortezomib demonstrates cytotoxicity against a broad range of other cancer cell types, including prostate, lung, breast, colon, and non-Hodgkin's lymphoma (11–15). Moreover, it induces additive or synergistic activity when combined with several other antineoplastic agents and overcomes drug resistance (1, 6, 15, 16).

## Overview

Multiple myeloma is an incurable malignancy that is diagnosed in more than 15,000 people annually in the United States (17). The most aggressive first-line treatment involves the delivery of intensified chemotherapy followed by myeloablation and autologous stem cell transplantation for patients who are appropriate candidates, yet median survival with this treatment is generally 5 years or less (18–20). Relapse is virtually inevitable, and historically, response duration decreases with each additional salvage regimen (21). Thus, an urgent need exists for new types of effective treatments.

Aggressive high-dose chemotherapeutic approaches with myeloablation followed by stem cell transplantation are a viable therapeutic option only for patients who can tolerate the associated toxicities. The combination of vincristine, doxorubicin, and dexamethasone (VAD) has been the induction regimen of choice for the treatment of multiple myeloma. In general, transplantation-eligible patients need to be in reasonably good health and younger than 65 years old (18, 19). However, because at least one half of patients are older than 65 (21), many patients are high-risk candidates for peripheral blood stem cell transplantation. Standard chemotherapeutic approaches have lower rates of response and median survival than transplantation (22). Standard-dose melphalan combined with prednisone has been the conventional first-line treatment for decades and is still used for the treatment of transplantation-ineligible patients. VAD is used as a first-line or salvage regimen, as is high-dose dexamethasone.

Relapse in myeloma is typically attributed to a combination of factors, but acquired resistance to chemotherapy and increased speed of tumor cell proliferation are two important factors (21, 23). Thus, an important characteristic of new compounds is the ability to circumvent or overcome drug resistance, coupled with potent antitumor activity that slows or aborts proliferation.

At the time of this writing, bortezomib is the only antineoplastic agent approved for the treatment of relapsed, refractory myeloma in the past decade in the United States and the European Union, but the phase III clinical development of compounds for the treatment of myeloma is active (Table 1) (23a). Indeed, it is likely that other agents, possibly THALOMID® (thalidomide, Celgene Corp., Warren, NJ) and REVLIMID® (CC-5013, Celgene Corp., Warren, NJ), will be approved in the United States and the European Union in the near future. Trials that

**TABLE 1** Recently approved and investigational phase III compounds for the treatment of multiple myeloma (23a)

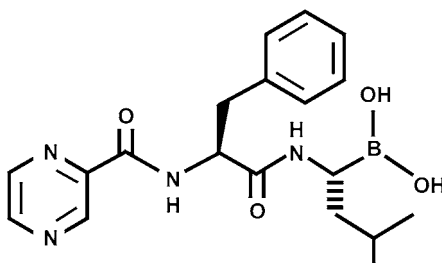
Agent	Clinical trials
Newly approved	
VELCADE® (bortezomib, Millennium Pharmaceuticals, Inc.)	For the treatment of myeloma in patients who have received at least one prior therapy
Phase III	
DOXIL® (doxorubicin HCl liposome injection, Ortho Biotech, Johnson & Johnson)	In combination with bortezomib and dexamethasone as a substitute for doxorubicin in the VAD regimen
GENASENSE® (oblimersen, Bcl-2 antisense, G3139, Genta, Inc. and Aventis)	For relapsed multiple myeloma in combination with dexamethasone
REVLIMID® (Celgene Corp.)	For previously treated patients with myeloma
THALOMID® (thalidomide, Celgene Corp.)	For front-line treatment and early-stage disease

combine the use of established compounds with new or investigational agents in an attempt to maximize antitumor activity and avoid or retard the development of chemoresistance are in progress.

## INTRODUCTION TO THE COMPOUND

### Chemistry and Mechanism of Action

Bortezomib is a modified boronic dipeptide with a molecular weight of 384.24 and a formula of  $C_{19}H_{25}BN_4O_4$  (Figure 1). Although provided as the mannitol boronic ester in a lyophilized powder, when the compound is reconstituted in water it exists in equilibrium with monomeric boronic acid, its hydrolysis product.

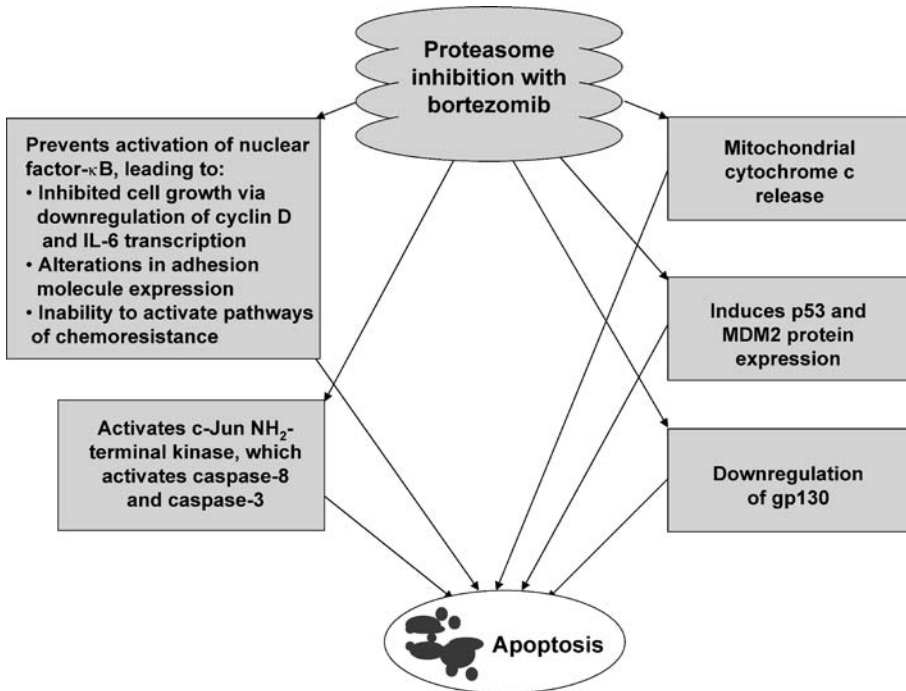


**Figure 1** Chemical structure of bortezomib.

Bortezomib functions as an inhibitor of the 26S proteasome, the principal regulator of intracellular protein degradation. The proteasome consists of a multisubunit protein complex that cleaves proteins via the coordinated catalytic activities of three distinct proteolytic sites, with chymotryptic, tryptic, and post-glutamyl peptide hydrolytic-like activities. Bortezomib selectively and reversibly inhibits the chymotryptic site, and this function allows it to inhibit the degradation of proteins critically involved in regulation of cell proliferation and survival, with mechanisms most thoroughly investigated in myeloma cells (Figure 2) (3–5). The disruption of these pathways also deregulates signaling molecules critical to interactions between the myeloma cell and the bone marrow microenvironment, ultimately leading to growth inhibition and apoptosis.

## Pharmacodynamics

Proteasome inhibition with bortezomib has been studied in lysates of whole blood samples in patients with various malignancies (7, 9, 24). The dose-response curve is approximately linear for doses up to  $1.3 \text{ mg/m}^2$ , when it shows a tendency to plateau at approximately 65%–70% inhibition (9, 24). Thus, doses greater than



**Figure 2** Mechanisms by which proteasome inhibition with bortezomib leads to apoptosis in myeloma cells (3–5).

1.3 mg/m<sup>2</sup> would be unlikely to demonstrate any significantly greater pharmacodynamic effect (7). Maximal percent inhibition of proteasome activity is observed within 1 h after dosing, followed by a return toward baseline, which is most rapid in the first 24 h (7, 24). With sequential dosing, proteasome activity shows a decreased rate of recovery. This phenomenon may in part explain the observed temporal profile of certain toxicities (24). Recovery of normal function occurs as long as at least 72 h separates the doses (9).

Proteasome activity in human tumor samples has been measured in parallel with its activity in blood. Proteasome inhibition in prostate and lymph node samples was similar to that in blood. Inhibition of activity in the bone marrow was approximately one half that observed in blood (24).

Proteasome activity is not impaired or accentuated in patients with renal impairment who are not dialysis dependent. Proteasome activity was found to be similar regardless of renal function in a subgroup analysis of patients enrolled in phase II trials (25).

## Pharmacokinetics and Metabolism

Pharmacokinetic studies have been reported in patients with advanced malignancies after administration of bortezomib in combination with either gemcitabine or irinotecan (26, 27). Bortezomib rapidly cleared from plasma and distributed into the cellular compartment. Exposure, as measured by the area under the concentration-time curve, was dose proportionate at the recommended dose levels of 1.0 and 1.3 mg/m<sup>2</sup>. The peak plasma concentration was very similar when bortezomib was administered as a single dose on days 1 and 8, but total body clearance markedly decreased and was accompanied by a prolongation of the terminal-phase half-life. The terminal elimination half-life is very long, estimated to be greater than 10 h (26, 27).

Several studies have explored a possible pharmacokinetic interaction when bortezomib is administered along with either gemcitabine or irinotecan. In each of these studies, the pharmacokinetic profile of bortezomib did not differ from that expected with monotherapy, and the profile of the concomitant antineoplastic agent did not differ from those of historical controls (26, 27).

The primary mechanism of inactivation is intracellular oxidative deboronation via cytochrome p450 enzymes 3A4, 2D6, 2C19, 2C9, and 1A2 (27a). No pharmacokinetic studies have been completed with bortezomib in patients with renal or hepatic impairment, but the National Cancer Institute has reported that there are studies ongoing (27b, 27c).

## CLINICAL EFFICACY

### Phase I Studies

Among four phase I studies fully published to date, two recruited patients with hematologic malignancies (9, 28) and two recruited patients with solid tumors

(7, 24); two additional trials of bortezomib in combination with other antineoplastic agents in patients with hematologic malignancies have been recently completed (Table 2) (29, 30). Dosing with bortezomib on a twice-weekly schedule enabled recovery of proteasome activity toward baseline and resulted in a manageable toxicity profile. The most consistently reported dose-limiting toxicities in these trials were diarrhea, electrolyte imbalances, and neurotoxicity. Twice-weekly dosing for 4 weeks followed by a 2-week rest resulted in a maximal tolerated dose of 1.04 mg/m<sup>2</sup>, whereas twice-weekly dosing for 2 weeks followed by a 1-week rest resulted in a higher tolerated dose. Thus, the latter schedule, which yielded the same dose intensity, was chosen for further phase II testing. The remarkable activity observed in multiple myeloma in phase I studies led to phase II studies in this patient population.

Two phase I trials of bortezomib, one in combination with melphalan and the other in combination with doxorubicin, have shown activity in patients with relapsed or refractory hematologic malignancies (29, 30). The rationale for these studies emanated from preclinical studies that demonstrated that bortezomib has chemosensitizing properties. Activity reported in these trials has been extremely promising (complete response + partial response of 50%–73%), and importantly, ~50% of patients with prior resistance to melphalan or doxorubicin responded to the original agent combined with bortezomib.

## Phase II Studies

**MULTIPLE MYELOMA** Two phase II trials were conducted in patients with advanced multiple myeloma, and patients in each trial who had benefited from treatment or who had the potential to benefit were allowed continued treatment or retreatment for enrollment in an extension trial (Table 3) (8, 10, 31). The response criteria in multiple myeloma in each of the bortezomib trials were based on the criteria of the European Group for Blood and Marrow Transplantation (32). Using these criteria, a complete response required a 6-week confirmation of complete disappearance of serum and urinary paraprotein and a negative immunofixation test, as well as resolution of established plasmacytomas, stable bone disease, and normalization of corrected serum calcium. A near-complete response required the same criteria, except that the immunofixation test could be positive.

In the SUMMIT (Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy) trial, 202 heavily pretreated patients with relapsed and refractory myeloma were treated with bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 of a 3-week cycle for up to eight cycles (10). An independent review committee assessed all final responses in the phase II bortezomib trials, providing an additional measure of validity to the data. The overall response rate (complete response + partial response + minimal response) was 35% for bortezomib alone. Among patients with a complete response, 89% had disease that had been refractory to the last treatment. Response to bortezomib was independent of most prognostic factors, including chromosome 13 deletion. The only factors predictive of a lower

**TABLE 2** Summary of phase I dose-escalation studies with bortezomib as monotherapy in patients with any malignancies and in combination in patients with hematologic malignancies\*

Therapy	Patients (n)	Regimen	MTD, mg/m <sup>2</sup>	Major dose-limiting toxicities	Activity	Reference
Mono	Hematologic tumors (27)	Twice weekly for 4 weeks every 6 weeks	1.04	Fatigue, hyponatremia, hypokalemia, malaise (thrombocytopenia was not a dose-limiting toxicity but its occurrence did influence dosing)	Activity in 9 of 9 patients with myeloma and in 2 of 10 with non-Hodgkin's lymphoma	9
Mono	Acute leukemia (15)	Twice weekly for 4 weeks every 6 weeks	1.25	Orthostatic hypotension, nausea, diarrhea, fluid retention	Decrease in blast count in 4 of 15 patients	28
Mono	Solid tumors (43)	Days 1, 4, 8, and 11 of a 3-week cycle	1.56	Diarrhea, sensory neurotoxicity	1 PR in a patient with non-small-cell (bronchioloalveolar) lung cancer	7
Mono	Solid tumors (53)	Once weekly for 4 weeks of a 5-week cycle	1.6	Diarrhea, hypotension	2 patients with ≥50% decrease in serum PSA and 2 patients with a partial response in lymphadenopathy	24
+ melphalan	Multiple myeloma (22)	B: days 1, 4, 8, and 11 of a 4-week cycle Melphalan: days 1-4	Not yet reached for either agent	Anemia	Ongoing; PR or better in >50% of patients	29
+ peg-LD	Hematologic tumors (42)	B: days 1, 4, 8, and 11 of a 3-week cycle; peg-LD: day 4	B: 1.5 peg-LD: 30	Diarrhea, syncope, neutropenia, thrombocytopenia, constipation, neuropathy, palmar-plantar erythrodysesthesia, hypotension, hyponatremia	PR or better in 73% of patients with myeloma; encouraging activity in other hematologic tumors	30

\* Abbreviations: B, bortezomib; MTD, maximal tolerated dose; peg-LD, pegylated liposomal doxorubicin; PR, partial response; PSA, prostate-specific antigen.

**TABLE 3** Summary of results of two phase II studies in relapsed and/or refractory multiple myeloma (8, 10, 31)

Trial	SUMMIT		CREST
No. treated	202	28	26
No. evaluable	193	27	26
Median no. of prior treatment regimens	6	3	3
Bortezomib dose, mg/m <sup>2</sup>	1.3	1.0	1.3
Response to bortezomib alone, %			
Any response (complete, partial, or minimal)	35	33	50
Complete or near complete	10	11	4
Partial	18	19	35
Median time to progression, mo.	7 <sup>a</sup>	7.0 <sup>b</sup>	11.0 <sup>b</sup>
Median duration of response, mo. <sup>c</sup>	12.7 <sup>a</sup>	9.5 <sup>b</sup>	13.7 <sup>b</sup>
Median time to response, mo.	1.3	1.3	1.5

<sup>a</sup>Bortezomib alone.<sup>b</sup>Bortezomib ± dexamethasone.<sup>c</sup>Complete, partial, or minimal response.

rate of response were age 65 years or older and >50% infiltration of the bone marrow by plasma cells.

In the CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) trial (8), 67 patients with relapsed or refractory myeloma following front-line therapy were randomized to receive bortezomib 1.0 or 1.3 mg/m<sup>2</sup> on the same schedule as used in SUMMIT. This exploratory study was not powered to compare dose levels. Activity was observed in patients on either dose, providing reassurance that dose reduction to 1.0 mg/m<sup>2</sup> would remain therapeutic for patients prescribed the lower dose because of dose-associated toxicity.

In SUMMIT and CREST, patients with progressive disease after two cycles or stable disease after four cycles could receive oral dexamethasone 20 mg on the day of and day after bortezomib. Additional responses were observed in both trials with combination therapy (33).

Patients who had a calculated creatinine clearance as low as 14 ml/min but who were not on dialysis were enrolled in phase II trials. Although the number of patients with severely impaired renal function (creatinine clearance 30 ml/min or less) was limited to 10, toxicities were manageable in this subgroup, and the response rate was similar regardless of baseline renal function (25). Importantly, renal function as assessed by mean serum creatinine over time did not worsen during the course of the study.

The encouraging activity of bortezomib in relapsed, refractory disease and its demonstrated activity in combination with dexamethasone spurred the investigation of its use as first-line treatment in patients with myeloma. Two trials evaluating the combination of bortezomib with dexamethasone or dexamethasone and



doxorubicin have recently been completed (34, 35). Results from both studies indicate very promising response rates (complete response + partial response of 88%–95% pretransplant) and that bortezomib-based regimens are feasible as induction regimens prior to stem cell transplantation.

**NON-HODGKIN'S LYMPHOMA AND OTHER MALIGNANCIES** In the treatment of patients with relapsed indolent or aggressive non-Hodgkin's lymphoma, results from three phase II trials have shown encouraging results, with several partial and complete responses (36–38). In two of these trials, bortezomib was administered at a higher dose (1.5 mg/m<sup>2</sup>) but at the same schedule (twice weekly for the first 2 weeks of a 3-week cycle for up to eight cycles) as used in phase II trials for the treatment of myeloma (36, 37). Numerous phase II trials in patients with other advanced solid malignancies are ongoing, or the results have been published (Table 4) (39–46). Many of the trials are exploring the chemosensitizing properties of bortezomib by combining it with other antineoplastic agents.

### Phase III Studies

The pivotal phase III trial, APEX (Assessment of Proteasome Inhibition for Extending Remissions), was a large international randomized study comparing bortezomib with high-dose dexamethasone in 669 patients with myeloma who had relapsed after 1–3 prior therapies (47). Patients who were refractory to dexamethasone were excluded. Bortezomib was administered for the first eight cycles using the phase II schedule, and thereafter, the patients received bortezomib 1.3 mg/m<sup>2</sup> on day 1 of the first 4 weeks of a 5-week cycle for an additional three cycles.

**TABLE 4** Phase II trials of bortezomib ± other antineoplastic agents in patients with advanced solid malignancies

Tumor type	Therapy	Best response	Reference
Renal cell	Monotherapy	Partial response in 4 of 37 assessable patients	39
Renal cell	Monotherapy	Partial response in 1 of 21 assessable patients	40
Colon	+ Irinotecan	Final results not yet fully reported	41
Lung	+ Docetaxel	Final results not yet fully reported, but encouraging responses observed at an interim analysis	42
Lung	Monotherapy	Final results not fully reported	43
Prostate	+ Docetaxel	Final results not yet fully reported, but encouraging activity indicated by decreases in serum prostate-specific antigen; partial responses observed at an interim analysis	44
Neuroendocrine carcinoma	Monotherapy	Stable disease in 8 of 10 evaluable patients	45
Hepatocellular carcinoma	Monotherapy	Final results not fully reported	46

Bortezomib demonstrated superiority over dexamethasone in terms of response rate, time to progression, and survival.

## POSTMARKETING SURVEILLANCE

Since approval for bortezomib was granted by the U.S. Food and Drug Administration in May 2003, the product label has been revised at the initiative of the sponsor based on an ongoing global pharmacovigilance review. The revisions include the description of the occurrence or exacerbation of congestive heart failure in patients with cardiac risk factors, and the risk of tumor lysis syndrome in patients treated with bortezomib. Also added were more details on the risk of thrombocytopenia in patients with low platelet counts prior to treatment and recommendations for dose reduction in the event of thrombocytopenia (47a).

## SAFETY AND TOLERABILITY

The toxicity profile of bortezomib is predictable and generally manageable with routine interventional measures. Nausea, fatigue, and diarrhea are the most frequently reported treatment-emergent adverse events (8, 10, 48). The most frequently reported drug-related grade 3/4 events in phase II clinical trials of bortezomib were thrombocytopenia, fatigue, peripheral neuropathy, neutropenia, lymphopenia, and hyponatremia (Table 5). Thrombocytopenia with bortezomib is cyclical, decreasing during the administration of treatment in the first two weeks and recovering toward baseline during the third week—the rest phase of the cycle. Patients with low baseline counts are at greatest risk of developing clinically significant thrombocytopenia (10, 49).

Peripheral neuropathy was the adverse event that led to the highest proportion of discontinuations in phase II trials: 9% in CREST and 4% in SUMMIT (8, 10). Baseline symptoms of peripheral neuropathy were present in many of the patients enrolled in these trials and were attributed to previous treatment with neurotoxic agents. Importantly, follow-up after completing or stopping bortezomib revealed that peripheral neuropathy improved or resolved in the majority of patients enrolled in the SUMMIT trial (10).

Continuation of or retreatment with bortezomib was available to patients in SUMMIT or CREST who had the potential to benefit from prolonged therapy. In a preliminary analysis of the data, patients received bortezomib for a median of 45.1 weeks or 14 cycles (range 7–32) in both the parent and extension trials with no evidence of cumulative or permanent long-term toxicity (48).

In the randomized, phase III APEX trial, the rates of grade 3 adverse events were higher in the bortezomib group; however, the rates of grade 4 and serious adverse events, as well as treatment discontinuation owing to adverse events, were similar in the bortezomib and dexamethasone arms (47). The most common grade 3 adverse events with bortezomib included transient thrombocytopenia (26%), neutropenia

**TABLE 5** Grade 3/4 adverse events reported in  $\geq 10\%$  of patients in phase II trials of patients with relapsed and/or refractory multiple myeloma (8, 10)

<b>Trial</b>	<b>SUMMIT</b>		<b>CREST</b>
No. treated	202	28	26
Bortezomib dose, mg/m <sup>2</sup>	1.3	1.0	1.3
Event, % of patients			
Thrombocytopenia	31	29	23
Neutropenia	14	11	23
Peripheral neuropathy	12	7	15
Fatigue	12	BT*	BT
Pneumonia	BT	0	15
Pain in limb	BT	11	8
Lymphopenia	BT	11	12
Hyponatremia	BT	11	8
Weakness	BT	4	12

\* BT, below 10% threshold.

(12%), anemia (9%), peripheral neuropathy (7%), and diarrhea (7%). Despite the increased rate of thrombocytopenia with bortezomib, the rate of clinically significant bleeding events was similar in the two arms. Furthermore, symptoms of grade  $\geq 2$  peripheral neuropathy resolved or improved in more than half of the patients, with a median time to resolution of 107 days.

## REGULATORY AFFAIRS

As of July 2005, bortezomib has been approved in the United States and the European Union for the treatment of patients with multiple myeloma who have received at least one prior therapy. Patients in the European Union must have already undergone bone marrow transplantation or be unsuitable for the procedure. Bortezomib is also approved in  $>50$  countries for the treatment of patients with multiple myeloma who have received at least two prior therapies and who have progressed on their most recent treatment.

## CONCLUSION

Inhibition of the proteasome represents a novel approach to the treatment of malignancy, and bortezomib is the first proteasome inhibitor to become available for clinical use. In vitro work demonstrated that proteasome inhibition disrupts multiple signaling pathways within the myeloma cell and those that regulate its interaction with its microenvironment, resulting in growth inhibition and apoptosis. These investigations spawned intensive clinical development in multiple

myeloma that ultimately led to the approval of bortezomib as monotherapy in patients with relapsed, refractory disease. A phase III trial comparing bortezomib with high-dose dexamethasone demonstrated the superiority of bortezomib in terms of median time to progression, response rate, and survival in patients with relapsed myeloma. The toxicity profile of bortezomib is predictable and manageable, with peripheral neuropathy and cyclical thrombocytopenia reported as the most clinically significant adverse events.

Clinical trials of bortezomib in combination regimens with dexamethasone or dexamethasone and doxorubicin have also demonstrated promising activity in the first-line treatment of myeloma. Bortezomib is also being investigated for the treatment of other types of malignancies, including non-Hodgkin's lymphoma and solid tumors such as non-small-cell lung carcinoma. Because bortezomib also acts as a chemosensitizer, its use in combination regimens is being actively explored.

## FUTURE PERSPECTIVE

The clinical development of bortezomib proceeded at a rapid pace: Less than five years elapsed from the first report of its potent in vitro antitumor activity (11) to its approval for clinical use in the United States. Given that it represents the first in a novel class of therapeutics, its evolution was remarkable. Its antitumor activity as monotherapy and its chemosensitizing properties are only beginning to be investigated in tumor types other than myeloma. Formal pharmacokinetic studies with bortezomib are also ongoing, as are evaluations to determine whether important interactions occur between bortezomib and other compounds. Indeed, the large number of clinical trials that are ongoing at many centers indicates that the therapeutic potential of this agent is considered profound.

## INFORMATION RESOURCES

The literature cited provides detailed information on preclinical investigations and clinical trials of bortezomib. Recent excellent reviews describing the function of proteasomes and the potential of proteasome inhibition as an antineoplastic strategy include References 50–52.

**The *Annual Review of Medicine* is online at <http://med.annualreviews.org>**

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