National PBM Drug Monograph

Bortezomib (Velcade™)

December 2003

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

The purpose of this monograph is to review the clinical data associated with the 26S proteasome inhibitor bortezomib approved in May 2003 for relapsed and refractory multiple myeloma. The primary efficacy outcome is overall rate of response, including complete, partial, and minimal responses. Secondary outcomes of interest include time to progression on bortezomib alone and in combination with dexamethasone, survival, safety, and rate of response in combination with dexamethasone.

Synonyms: PS341; Velcade™ (Millenium Pharmaceuticals)

Pharmacology/Pharmacokinetics[1,2,3,4,5,6]

The proteasome is a large, multiprotein complex found in the nucleus and cytoplasm of all cells that destroys obsolete protein messages and short-lived proteins. Obsolete proteins are tagged for destruction by the proteasome with multiple ubiquitin molecules in a process termed polyubiquitination. Targeted proteins include those with critical functions such as cell cycle regulation, transcription, apoptosis, angiogenesis, and cell adhesion.

Of particular interest is regulation of NF-κB, a transcription factor. Inactive NF-κB is bound in the cytoplasm to its inhibitor IκB. When stimulated, IκB is phosphorylated, ubiquinated, and degraded by the proteasome releasing NF-κB and allowing it to locate to the nucleus. Activation of NF-κB is associated with chemoresistance, cell survival, and proliferation.

In multiple myeloma, NF-κB is constitutively active and promotes cell survival through expression of genes encoding for cytokines, cell adhesion molecules, and cell growth and survival factors. Inhibition of proteasome activity by bortezomib prevents activation of NF-κB, interferes with the destruction of anti-apoptotic pathways, and may sensitize cells to selective chemotherapy drugs; the end result is increased apoptosis.

	Bortezomib
Metabolism	Primarily CYP3A4, 2D6, 2C19, 2C9, 1A2
Elimination	Pathways not characterized in humans
Half-life	9-15 hours
Protein Binding	83%

The pharmacokinetics of bortezomib at the recommended dose have not been fully characterized.

FDA Approved Indication(s) and Off-label Uses

Treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

Off-label uses: first and second-line therapy in multiple myeloma, combination therapy with dexamethasone in multiple myeloma, breast cancer, pancreatic cancer, colon cancer, prostate cancer, head and neck cancer.

Dosage and Administration[7,8]

The recommended dose in multiple myeloma is bortezomib 1.3mg/m^2/dose given as a bolus intravenous injection twice weekly for 2 weeks (i.e. on days 1, 4, 8, and 11) followed by a 10-day rest; thus, each cycle is 21 days. Consecutive doses should be administered at least 72 hours apart.

Prior to use, reconstitute each 3.5mg vial with 3.5ml of 0.9% Sodium Chloride Injection, USP to make 1mg/ml. Once reconstituted, the solution may be stored at 25°C (77°) for up to 8 hours in the original vial (note: bortezomib contains no preservative). The solution may be stored in a syringe for up to 3 hours but total storage should not exceed 8 hours.

Dosing in Renal Failure: No pharmacokinetic information is available in patients with creatinine clearance less than 13ml/min or on hemodialysis. Limited data in patients with a serum creatinine ≤2.5mg/dL indicates no reduction in proteasome inhibition or increase in toxicity with mild to moderate renal impairment. Further studies are needed.

Dosing in Hepatic Impairment: Bortezomib clearance may decrease in patients with hepatic impairment. They should be closely monitored.

Dose Modifications:

Severity of symptom	Modification
Grade 3 Non-Hematologic toxicity Except peripheral neuropathies	Hold therapy until toxicity resolves. Reinitiate at a 25% dose reduction (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0mg/m^2 reduced to 0.7mg/m^2)
Grade 4 Hematologic toxicity	Hold therapy until toxicity resolves. Reinitiate at a 25% dose reduction (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0mg/m^2 reduced to 0.7mg/m^2)
Peripheral Neuropathy	
Grade 1 (paresthesias and/or lack of reflexes) Without pain or loss of function	No modification
Grade 1 with pain or Grade 2 (interferes with function but not ADL's)	Reduce to 1.0mg/m^2
Grade 2 with pain or Grade 3 (interferes with ADL's)	Hold bortezomib until toxicity resolves, then restart at a reduced dose of 0.7mg/m^2 once a week
Grade 4 (Permanent sensory loss)	Discontinue therapy

Patients with severe pre-existing peripheral neuropathy should be treated only after careful assessment of risks and benefits.

Adverse Effects (Safety Data)

Adverse Events Reported in ≥10% (N=228)

	All Patients (%)		
Adverse Event	All	Grade 3	Grade 4
Asthenia	65	18	<1
Nausea	64	6	0
Diarrhea	51	7	<1
Decreased appetite	43	3	0
Constipation	43	2	0
Thrombocytopenia	43	27	3
Peripheral neuropathy	37	14	0
Pyrexia	36	4	0
Vomiting	36	7	<1
Anemia	32	9	0

Headache	28	4	0
Arthralgia	26	5	0
Pain in limb	26	7	0
Edema	25	1	0
Neutropenia	24	13	3
Paresthesia/dysesthesia	23	3	0
Dyspnea	22	3	<1
Dizziness	21	1	0
Rash	21	<1	0
Dehydration	18	7	0
URT Infection	18	0	0
Cough	17	<1	0
Bone pain	14	2	0
Anxiety	14	0	0
Myalgia	14	2	0
Back pain	14	4	0
Muscle cramps	14	<1	0
Dyspepsia	13	0	0
Abd pain	13	2	0
Dysgeusia	13	<1	0
Hypotension	12	4	0
Rigors	12	<1	0
H. Zoster	11	<1	0
Pruritus	11	0	0
Blurred vision	11	<1	0
Pneumonia	10	5	0

Pregnancy Category: D
Nursing Mothers: It is unknown if bortezomib crosses into breast milk. Because of the potential of harm to nursing infants, advise mothers not to breastfeed while receiving bortezomib.

Precautions/Contraindications

Contraindications: Prior hypersensitivity to bortezomib, boron, or mannitol

Precautions:
Peripheral Neuropathy: Bortezomib causes a primarily peripheral neuropathy, although cases of sensori-motor neuropathy have been reported. Patients with new or worsening neuropathy may need a change in their dose and schedule (see Dose Modifications). Patients with pre-existing signs and symptoms of neuropathy may experience a worsening of symptoms. There is limited outcome data regarding neuropathy; in clinical trials 70% of patients previously received neurotoxic agents and 80% had pre-existing neuropathy.
Hypotension: Orthostatic hypotension occurs throughout therapy in about 12% of patients. Use with caution in patients with a history of syncope, when given concomitantly with other drugs known to be associated with hypotension, in patients with electrolyte disturbances (may exacerbate hypokalemia and hyponatremia) and in patients who are dehydrated. Management of orthostasis includes hydration, adjustment of antihypertensives, and mineralocorticoids.
Thrombocytopenia: Occurs in about 40% of patients, is maximal at day 11 and recovers by the start of the next cycle. The onset is more common in the first 1 or 2 cycles, but can occur anytime in therapy. Patients with low baseline counts are at increased risk. Temporary discontinuation in patients with Grade 4 thrombocytopenia may be warranted as cases of gastrointestinal and intracerebral hemorrhage have been reported during thrombocytopenia.
Gastrointestinal Events: Nausea, diarrhea, constipation, and vomiting may lead to dehydration and require treatment with fluids, electrolytes, antiemetics, and antidiarrheals.

Drug Interactions

No formal drug interaction studies have been conducted. Because bortezomib is a substrate for multiple cytochrome P450 isoenzymes, patients receiving inhibitors or inducers of CYP3A4 should be closely monitored for toxicity and potentially decreased efficacy.

Concomitant use with oral antihyperglycemic agents may require close monitoring as patients receiving both drugs in clinical trials experienced hyper or hypoglycemia.

Efficacy Measures

Primary Endpoint: Overall response rate (includes complete response, partial response, and minimal response) as defined by the European Group for Blood and Marrow Transplantation criteria.[9]

Secondary Endpoints:
Time to Progression with bortezomib alone or in combination with dexamethasone
Survival
Safety
Rate of response in combination with dexamethasone
Quality of Life

Clinical Trials (see Appendix)

Phase I:
Bortezomib was tested in several phase I dose escalation trials on a weekly and twice weekly IV bolus schedule. As weekly doses approached 2mg/m^2 hypotension and syncope became more frequent. On a twice weekly schedule for 2 weeks followed by 1 week of rest, diarrhea and neuropathy were dose limiting. Twice weekly doses for 4 weeks followed by 2 weeks of rest resulted in a lower maximum tolerated dose of 1.04mg/m^2.

Phase II:[10]
Two phase II studies tested a twice weekly for 2 weeks followed by 1 week of rest schedule. In the first, smaller, study 54 patients were randomized between two different bortezomib doses. Patients had relapsed following first-line therapy. The FDA CR + PR rate was 23% in the 1mg/m^2 group and 35% in the 1.3mg/^{2} group; the p value was not significant. Separate safety data was not available as this was published in abstract form and in the FDA Medical Review.

The larger study enrolled 202 patients in a single arm study to test the 1.3mg/m^2 dose. Patients were more heavily pretreated having relapsed following first-line therapy and were refractory to salvage therapy. The median number of previous treatments was 6 and included prior bone marrow/stem cell transplant therapy in about two-thirds. 188 patients were eligible for evaluation. Nine were excluded because of non-measurable disease; five were excluded because of minimal prior therapy.

Response rate was the primary endpoint. Durable complete response rates in hematologic disease may be evidence of clinical benefit. The Blade response criteria used in this study has not been validated outside of bone marrow transplant as a surrogate for clinical benefit. Based on literature support these criteria are reasonably likely to predict clinical benefit. Literature support and practitioner consultants to the FDA also recommend the partial response be considered for clinical benefit. The FDA utilized the Blade criteria as well as the Southwest Oncology Group (SWOG) criteria when evaluating response rates.

Results	N(%)	95% CI
Overall response (Blade)(CR+PR)	52(27.7)	(21,35)
CR	5(2.7)	(1,6)
PR	47(25)	(19,32)
SD	46(24)	
Clinical remission (SWOG)	33(17.6)	(12,24)
Kaplan-Meier Med Duration of Response	365 days	(224, NE)
Median Survival	16 months	

CR (Blade)= 100% disappearance of monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart and <5% plasma cells in bone marrow with stable bone disease and calcium
PR (Blade)= ≥50% reduction in serum myeloma protein and ≥90% reduction in urine myeloma protein on at least 2 occasions at least 6 weeks apart, stable bone disease and calcium
Clinical Remission (SWOG)= ≥75% reduction in serum myeloma protein and/or ≥90% reduction in urine myeloma protein on at least 2 occasions at least 6 weeks apart, stable bone disease and calcium

Response to bortezomib was independent of sex, type of myeloma, serum beta$_2$-microglobulin, or type or number of previous therapies. Patients ≥65 years old had a lower response rate (19% versus 32%, p=0.06). Patients with more than 50% plasma cells in the bone marrow at the start of therapy had a lower response (20% versus 35%, p=0.03).

Approximately 33% of patients required a dose reduction and 63% of patients had at least one dose held. The mean number of cycles administered was six.

Secondary Endpoints:
Hemoglobin response – in patients with a CR or PR, 89% had at least a 1g/dL increase and 72% had a maximum increase of 2g/dL.
Platelet counts, levels of normal immunoglobulins, Performance Status - increased in those with a CR or PR
QoL –Improvements in mean global QoL scores and symptom scores occurred in patients achieving a CR or PR
Response to adding dexamethasone – Per the protocol, patients with stable or progressive disease on bortezomib subsequently received dexamethasone in addition to bortezomib. In 74 evaluable patients receiving the combination, 18% (13/74) had a minimal or partial response, including 6 patients previously refractory to corticosteroids.

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Course/patient ($)
Bortezomib	1.3mg/m^2 Days 1, 4, 8, & 11	682.66	2,730.64

Utilization

TOTAL REPORTED PRIME VENDOR PURCHASES OF BORTEZOMIB FOR JULY 1,2003-NOVEMBER 30, 2003

VISN	Total NDC Units	Total Dollars Spent	COURSES
1	67	$44,366	16.75
2	13	$8,608	3.25
3	18	$11,919	4.5
4	4	$2,649	1
5	42	$27,812	10.5
6	20	$13,244	5
7	64	$42,598	16
8	40	$26,487	10
9	104	$69,058	26
10	57	$37,744	14.25
11	20	$13,244	5
12	38	$25,163	9.5
15	47	$31,122	11.75
16	76	$50,476	19
18	19	$12,581	4.75
19	16	$10,595	4
20	43	$28,474	10.75
21	49	$31,557	12.25
22	7	$4,635	1.75
23	23	$15,230	5.75
Grand Total	**767**	**$507,561**	

Conclusions

Clinical Efficacy

In phase I trials, bortezomib was administered weekly and twice weekly for 2, 3, or 4 weeks. Weekly doses produced hypotension and syncope as doses increased. At twice weekly dosing, diarrhea and neuropathy were dose limiting.

The phase II registration trial evaluated bortezomib at a twice weekly for 2 weeks followed by 1 week of rest schedule in patients who had relapsed following initial therapy and had relapsed on their current therapy. This was a heterogeneous population. Previous therapies included steroids in 99%, alkylating agents in 92%, anthracyclines in 81%, thalidomide in 83%, stem cell transplant/other high dose therapy in 64%, and experimental or other therapy in 44% making them a heavily pre-treated population with chemoresistance highly likely.

The sponsor reported an overall response rate of 35% according to the Blade criteria. The FDA excluded several patients because of non-measurable disease or minimal prior therapies, and calculated an overall response rate (CR+PR) of 27.7%. The median duration of response was 12 months. Some responders became transfusion independent and some showed recovery of normal immunoglobulin synthesis.

The relationship between durable complete responses and clinical benefits is unclear. The Blade criteria have not been validated outside of the transplant population as evidence of "likely to predict" a clinical benefit, although expert opinion found sufficient literature support to suggest using these criteria as a surrogate for clinical benefit.

Safety

The FDA reviewed safety data from the registration trial and from those patients in the smaller phase II trial who received 1.3mg/m^2 doses.

Most common AE's: asthenia (65%), nausea (64%), diarrhea (51%), anorexia (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%), pyrexia (36%), vomiting (36%), anemia (32%).

Most common Severe AE's (≥grade 3): thrombocytopenia (29%), peripheral neuropathy (14%), neutropenia (15%), asthenia (11%), anemia (9%), diarrhea (7%), nausea (7%), vomiting (7%).

Most common Serious AE's: pyrexia (7%), pneumonia (7%), diarrhea (5%), vomiting (5%), dehydration (5%), and nausea (4%).

Special cautions:
Peripheral neuropathy –Although improvement in peripheral neuropathy occurred after bortezomib was stopped, the degree and reversibility of peripheral neuropathy with prolonged drug exposure is uncertain
Cardiovascular events –Hypotension/syncope may be drug-related and/or influenced by hydration status and cardiovascular reserve. Hydration status should be monitored and treated, especially in the case of patients with diarrhea or vomiting. In monkeys, single doses of 3mg/m^2 caused acute cardiovascular mortality that has not been described in humans. Doses of up to 2mg/m^2 given weekly have been studied in humans.
Gastrointestinal events- Nausea and vomiting should be expected and prevented with antiemetics. Diarrhea should be closely monitored and treated to prevent dehydration.

Special populations:
There was no difference in the incidence of adverse effects in those <65 years old and those >65 years old.

Hepatic/renal impairment- There is inadequate information to assess the effects of hepatic or renal impairment on bortezomib pharmacokinetics.

Recommendations

Multiple myeloma is characterized by the clonal proliferation of plasma cells at multiple sites in the bone marrow. Although most patients respond to initial treatment (chemotherapy, steroids, radiation), most eventually relapse due to resistant tumor cells. These resistant cells are due to either inherent resistance or protective interactions within the bone marrow microenvironment. With conventional therapy the median overall survival is 3-4 years.

The mainstay of therapy has been melphalan plus prednisone, although CR's are rare with a median survival of just under 3 years. The deep dose-response curve for IV melphalan led to investigations into the use of stem cells to reduce the excessive morbidity and treatment-related mortality associated with treatment. Autotransplantation using peripheral blood stem cells and high-does melphalan is now considered standard therapy for patients <65 years old. In fact, autotransplants produce CR rates of 30-40% with median survival of 4-5 years. For patients <55 years old with low beta-2-microglobulin, a 10 year survival rate of 43% has been reported following transplant. Tandem transplants are being investigated to try and increase the CR rate and extend the duration of response and survival. Allogeneic transplants carry a high mortality rate in this population and minitransplants are being investigated for consolidation therapy following an autologous transplant. Typical first line therapies for patients who are

transplant candidates include high-dose dexamethasone plus/minus thalidomide or VAD (vincristine + doxoruibicin + dexamethasone) for cytoreduction prior to transplantation. Initial therapies for patients who are not transplant candidates include VAD, thalidomide plus/minus high dose dexamethasone, cyclophosphamide plus prednisone, melphalan plus prednisone, VBMCP (M2 protocol vincristine + carmustine + melphalan + cyclophosphamide + prednisone). Salvage therapy following relapse after first-line therapy includes combination chemotherapy, high dose dexamethasone, and newer agents like thalidomide and arsenic trioxide.[11]

Inhibition of the proteasome by bortezomib blocks the signal transduction pathways mediated by NF-κB, resulting in stimulation of apoptosis. In addition, multiple myeloma cells express many cell surface molecules that regulate cell adhesion (involved in tumor metastasis) and the angiogenic process. These molecules are regulated by the NF-κB signal pathway and may play a role in the mechanism of cell death caused by inhibition of NF-κB. Finally, many tumor cells, including myeloma cells, have higher than normal levels of NF-κB. The activity of NFκB is enhanced by chemotherapy and radiation thereby inducing chemotherapy resistance. Inhibition of NF-κB by bortezomib has overcome chemotherapy resistance in tumor cell lines when combined with chemotherapy drugs or steroids.[12,13,14]

In highly refractory disease, bortezomib produces a CR or PR with a median duration of response of 12 months in approximately 28% of patients who have received at least 2 prior therapies and have progressed on the last one. The effectiveness is based on response rates that may be likely to predict clinical benefit. Further follow-up and a comparison study are needed. Toxicities include peripheral neuropathy, thrombocytopenia, diarrhea, nausea, and neutropenia but severe toxicities are uncommon. The small percentage of patients who achieve a CR (3%) is considered an improvement over currently available therapy. The PR rate is similar to other salvage therapy PR rates, although the duration of response will need to be investigated in a comparative trial. Currently there are on-going trials evaluating bortezomib versus dexamethasone/bortezomib plus dexamethasone, bortezomib as first line therapy, bortezomib in combination with chemotherapy, and bortezomib in combination with chemotherapy for solid tumors. Due to the in vitro ability to overcome chemotherapy resistance, the main role of bortezomib in the future will likely be in combination therapy. It is a viable option for patients who have failed at least two prior therapies.

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Reviewed by:
Date: January 2004

Appendix

<table>
<tr><th>Study</th><th>Inclusion/Exclusion</th><th>Patient Characteristics</th><th>Results</th></tr>
<tr>
<td>Richardson et al 2003[15]
Phase II
MC, OL, NR

Bortezomib 1.3mg/m^2 IVB twice a week for 2 weeks on days 1,4,8,11 in a 21-day cycle for upt to 8 cycles. If PD or SD after 2 cycles add dexamethasone on the day of and day after bortezomib
At the end of 8 cycles patients could continue to receive drug in a separate extension trial.

Supported by Millennium</td>
<td>Relapsed or refractory myeloma
(relapsed following 1st line chemo or 1st line high dose therapy and refractory to salvage chemo)
Measurable disease (serum monoclonal immunoglobulin or urinary monoclonal light chain)</td>
<td>
<table>
<tr><th>Characteristic (n=202)</th><th>Value</th></tr>
<tr><td>Age-yr (mean)</td><td>60</td></tr>
<tr><td>Time since dx –yr (median)</td><td>4</td></tr>
<tr><td>Serum beta$_2$ microglobulin mg/L (median)</td><td>3.5</td></tr>
<tr><td>Hgb (median)</td><td>10.2</td></tr>
<tr><td>Platelets (median)</td><td>162,000</td></tr>
<tr><td>Previous therapy (%)
Any corticosteroid
Any alkylating agent
Any anthracycline
Thalidomide
Stem-cell transplant</td><td>
100
92
81
83
64</td></tr>
<tr><td></td><td></td></tr>
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</td>
<td>N=193 evaluable
<table>
<tr><th>Response (bortezomib alone)</th><th>Percent of patients</th></tr>
<tr><td>Any response</td><td>35</td></tr>
<tr><td>Complete or near complete
Partial response
Minimal response</td><td>10
18
7</td></tr>
<tr><td>No change</td><td>24</td></tr>
<tr><td>Response (bortezomib + dex)</td><td></td></tr>
<tr><td>Partial or minimal response</td><td>18</td></tr>
</table>
Median time to first response = 1.3 months
Median time to progression (bortezomib alone) = 7 mos
Median duration of response = 12 months
Median survival = 16 months

In patients with a complete or partial response:
89% had a hemoglobin increase of at least 1g/dL
None needed transfusions after cycle 4
Increase in platelet counts
Increase in performance status
Improvement in mean global QoL score, disease symptoms

Prognostic Factors:
No Influence: sex, type of myeloma, serum level of beta$_2$-microglobulin, type or number of previous therapies

Negative Influence: Age (≥65) and >50% plasma cells in bone marrow had lower responses

Most common adverse effects: gastrointestinal (mild to moderate and manageable with routine care), fatigue, thrombocytopenia, sensory neuropathy

Most common grade 3 AE's: thrombocytopenia, fatigue, neuropathy, neutropenia

Most common grade 4 AE's: thrombocytopenia, neutropenia (1 case of febrile neutropenia); all other grade 4 events were in <1%.

Discontinuation due to drug-related AD's: 18%
Death possibly due to bortezomib: 2 patients</td>
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<tr><th>Supportive Data</th><th></th><th></th><th></th></tr>
<tr>
<td>Orlowski et al. 2002[16]
Phase I
Dose escalaltion/safety

Bortezomib 0.4mg/m^2/dose Days 1,4,8,11,15,18,22,25 followed by 2 week rest Increase according to modified Fibonacci schema.

Supported by Leukemia and Lymphoma Society grants, Lymphoma Foundation, & the General Clinical Research Centers program of the NIH</td>
<td>Hematologic malignancy refractory to standard therapy or for whom there is no standard therapy
ECOG PS 0-2
No radiation/chemo in previous 4 weeks
Creatinine clearance ≥50ml/min; modified to serum creatinine ≤2.5mg/dL due to high activity in patients with multiple myeloma who often have disease-induced renal dysfunction.</td>
<td>
<table>
<tr><th>Characteristic (N=27)</th><th>Value</th></tr>
<tr><td>Age, mean</td><td>56</td></tr>
<tr><td>Male %</td><td>63</td></tr>
<tr><td>Diagnosis (No.)</td><td></td></tr>
<tr><td>Hodgkin’s</td><td>4</td></tr>
<tr><td>NHL</td><td>10</td></tr>
<tr><td>Multiple myeloma</td><td>11</td></tr>
<tr><td>MDS with excess blasts</td><td>1</td></tr>
<tr><td>Prior Therapy</td><td></td></tr>
<tr><td>Chemotherapy Regimens (med)</td><td>3</td></tr>
<tr><td>Radiation (no.)</td><td>13</td></tr>
<tr><td>BMT (no.)</td><td>10</td></tr>
<tr><td></td><td></td></tr>
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<td>
<table>
<tr><th>Result</th><th>Value</th></tr>
<tr><td>Dose escalation</td><td></td></tr>
<tr><td>0.4mg/m^2</td><td>3</td></tr>
<tr><td>1.04mg/m^2</td><td>12</td></tr>
<tr><td>1.2mg/m^2</td><td>7</td></tr>
<tr><td>1.38mg/m^2</td><td>5</td></tr>
<tr><td>Inhibition of proteasome activity</td><td></td></tr>
<tr><td>0.4mg/h^2</td><td>36%</td></tr>
<tr><td>1.04mg/m^2</td><td>60</td></tr>
<tr><td>1.2mg/m^2</td><td>65</td></tr>
<tr><td>1.38mg/m^2</td><td>74</td></tr>
<tr><td>Antitumor activity
Multiple myeloma
At 1.04mg/m^2</td><td>1 CR, 2 PR, 3SD, 1MR, 1PD(?)</td></tr>
<tr><td>Non-Hodgkin’s lymphoma
At 1.38mg/m^2</td><td>2PR (1 Mantle cell, 1 follicular).</td></tr>
</table>
Adverse Events:
Thrombocytopenia 74% (most common gr 3 event)
Anemia 48%
Leukopenia 48%
Fatigue 59%
Nausea 52%
Vomiting 30%
Neuropathy in 5, related to PS341 in 3

Late toxicities:
Rash, hyperbilirubinemia, AST/ALT elevation
</td>
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<tr>
<td>Aghajanian et al. 2002[17]
Phase I
Dose escalation/safety

Bortezomib 0.13mg/m^2/dose twice a week for 2 weeks followed by 1 week of rest. Dose escalated to a maximum of 1.556mg/m^2

Supported by grants from the NCI and Millennium Pharmaceuticals</td>
<td>Patients with solid tumors refractory to therapy or for whom no therapy existed</td>
<td>
<table>
<tr><th>Characteristic (N=43)</th><th>Value</th></tr>
<tr><td>Age (median)</td><td>53</td></tr>
<tr><td>Male %</td><td>44</td></tr>
<tr><td>Tumor type</td><td></td></tr>
<tr><td>NSCLC</td><td>8</td></tr>
<tr><td>Colon</td><td>6</td></tr>
<tr><td>Head and Neck</td><td>5</td></tr>
<tr><td>Melanoma</td><td>4</td></tr>
<tr><td>Ovary</td><td>4</td></tr>
<tr><td>Prostate</td><td>4</td></tr>
<tr><td>Renal</td><td>4</td></tr>
<tr><td>Pancreas</td><td>2</td></tr>
<tr><td>Bladder</td><td>1</td></tr>
<tr><td>Cervix</td><td>1</td></tr>
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<td>
<table>
<tr><th>Result</th><th>Value</th></tr>
<tr><td>Dose escalation</td><td></td></tr>
<tr><td>0.13mg/m^2</td><td>3</td></tr>
<tr><td>0.25mg/m^2</td><td>4</td></tr>
<tr><td>0.4mg/m^2</td><td>5</td></tr>
<tr><td>0.6mg/m^2</td><td>4</td></tr>
<tr><td>0.75mg/m^2</td><td>3</td></tr>
<tr><td>0.9mg/m^2</td><td>6</td></tr>
<tr><td>1.08mg/m^2</td><td>3</td></tr>
<tr><td>1.3mg/m^2</td><td>3</td></tr>
<tr><td>1.56mg/m^2</td><td>12</td></tr>
<tr><td>Proteasome Inhibition</td><td></td></tr>
<tr><td>0.13mg/m^2</td><td></td></tr>
<tr><td>0.25mg/m^2</td><td></td></tr>
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		Endometrial 1 Esophagus 1 Gastric 1 Unknown primary 1 Prior chemotherapy Median 4 Prior radiation Definitive 12 Palliative 12	0.4mg/m^2 31% 0.6mg/m^2 42 0.75mg/m^2 48 0.9mg/m^2 57 1.08mg/m^2 46 1.3mg/m^2 65 1.56mg/m^2 68 Antitumor Activity NSCLC 1PR Nasopharyngeal 1SD Melanoma 1SD Renal Cell 1SD Adverse Events: Hematologic: Thrombocytopenia - occurred at doses >0.75mg/m^2; no clinical adverse outcomes (e.g. bleeding) at higher doses Neutropenia – occurred at doses >0.75mg/m^2; one case of febrile neutropenia that resolved in 24 hours Non-hematologic: Dose Limiting – diarrhea and sensory neuropathy Diarrhea-watery, profuse, self limited, dose related Neuropathy – mainly in heavily pre-treated patients with pre-existing neuropathy
Jagannath et al. 2002[18] Phase II, MC, R Bortezomib 1mg/m^2/dose or 1.3mg/m^2/dose in days 1,4,8,11 of a 21 day cycle; add dexamethasone if PD or SD after 2 & 4 cycles, respectively	Patients who progressed on or relapsed after 1st line chemotherapy		N=54 Response rate: 1mg/m^2 23% 1.3mg/m^2 35% p not significant; 1 CR at each dose level

MC=multicenter, OL=open-label, NR=non-randomized, IVB=IV bolus, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, MR=minimal response, NHL=non-hodgkin's lymphoma, MDS=myelodysplastic syndrome, BMT=bone marrow transplant, R=randomized

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