Phase II Study of the Proteasome Inhibitor Bortezomib (PS-341) in Patients with Metastatic Neuroendocrine Tumors

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ABSTRACT

Purpose: **This phase II study was undertaken to assess objective response, toxicity, tumor marker response, and pharmacodynamics of bortezomib in patients with metastatic neuroendocrine (carcinoid and islet cell) tumors.**

Experimental Design: **A total of 16 patients with measurable metastatic carcinoid ($n = 12$) or islet cell ($n = 4$) tumors received i.v. bolus of single agent bortezomib at a dose of 1.5 mg/m^2 on days 1, 4, 8, and 11 every 21 days. Tumor response was assessed at 12-week intervals using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. All patients were chemotherapy naïve and had Eastern Cooperative Oncology Group performance status of 0 to 1.**

Results: **No patient achieved a partial or a complete remission. The patients received total of 264 doses of therapy with a median of 15 doses per patient. Grade 4 toxicities were not observed. The most common grade 3 adverse events included peripheral sensory neuropathy (37%), diarrhea (25%), vomiting (18%), and ileus (18%). Six of 10 patients who experienced grade 2 to 3 peripheral sensory neuropathy also had grade 2 to 3 dizziness ($n = 2$), orthostatic hypotension ($n = 2$), syncope ($n = 1$), ileus ($n = 2$), or abdominal cramps ($n = 1$). Changes in tumor marker levels did not correlate with tumor response. The mean percentage of 20S proteasome inhibition achieved in whole blood at 1 and 24 hours after bortezomib administration was 68 and 30%, respectively.**

Conclusions: **Despite achieving the surrogate biologic end point, single-agent bortezomib did not induce any objective responses in patients with metastatic carcinoid or islet cell tumors. Additional investigation is warranted to clarify the possible association of autonomic neuropathy with bortezomib.**

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INTRODUCTION

Because of the pivotal role of the proteasome in controlling key cellular processes, the proteasome has emerged as an attractive novel target for the development of anticancer therapy (1). The 26S proteasome is an ATP-dependent multicatalytic protease that is central to the ubiquitin-proteasome-degradative pathway. The 26S proteasome acts as a housekeeper to eliminate damaged or misfolded proteins. In addition, many regulatory proteins governing the cell cycle, transcription factor activation, apoptosis, and cell trafficking, are the substrates for proteasome-mediated degradation (1). The proteasome plays a significant role in degradation of cyclin-dependent kinase inhibitors (p21, p27; refs. 2, 3) and tumor suppressor (p53; ref. 4) proteins that are required for cell cycle arrest. The proteasome is also required for activation of transcription factor nuclear factor-κB by degradation of its inhibitory protein inhibitor of nuclear factor-κB (5). Nuclear factor-κB is necessary, in part, to maintain cell viability through transcription of inhibitors of apoptosis in response to stress or cytotoxic agents. Nuclear factor-κB has also been implicated in controlling gene expression of endothelial cell surface adhesion molecules such as intercellular adhesion molecule 1, vascular cell adhesion molecule, and E-selectin (6), which are involved in tumor metastasis and angiogenesis. Furthermore, the proteasome is implicated in *in vivo* angiogenesis, a phenomenon essential for tumor growth and metastasis (7).

Bortezomib [Velcade (Millennium Pharmaceuticals, Inc., Cambridge, MA), previously known as PS-341] is a dipeptidyl boronic acid that is a specific, potent and reversible inhibitor of the 26S proteasome. Preclinical work revealed significant antitumor activity of bortezomib *in vitro* and *in vivo*. In the cell line screen of the National Cancer Institute, bortezomib demonstrated a unique pattern of growth inhibitory and cytotoxic activity against a broad range of solid tumors (8). Bortezomib also significantly reduced tumor volumes in several murine and human tumor xenograft models including the Lewis lung, HT-29 human colon, PC-3 human prostate, squamous cell carcinoma, and pancreatic cancer (9–13). The initial dose and schedule of bortezomib for phase I clinical trials was chosen based on the acute and multiple dose toxicity studies performed on rodents and primates (14). Preclinical studies in animals showed that bortezomib was rapidly removed from the vascular compartment and distributed widely, quickly approaching the limits of detection. Therefore, a sensitive, accurate and reproducible *ex vivo* 20S proteasome inhibition assay to monitor bortezomib activity in whole blood was developed (15). Several phase I and/or II clinical trials done to date showed that the

target proteasome inhibition of ~70% can be achieved in cancer patients with a reasonable safety profile. Moreover, complete responses, partial responses, or minor responses were observed in the variety of solid tumors and hematologic malignancies (16–20). Bortezomib was recently approved by the Food and Drug Administration for its use in the patients with refractory or relapsed multiple myeloma.

Carcinoid and islet cell tumors are generally classified at the less-aggressive end of the spectrum of neuroendocrine tumors. They are thought to derive from enterochromaffin cells, which are distributed throughout the gastrointestinal and respiratory system. Although plasma chromogranin A and 24-hour urine for 5-hydroxy indole acetic acid are known prognostic markers for survival in patients with carcinoid tumors, the role of other tumor markers is not well described (21, 22). Although local or locoregional carcinoid or islet cell tumors are surgically manageable, metastatic disease is present in ~50% of patients at the time of diagnosis, and the overall 5-year survival for patients with distant metastasis is only 22%. Somatostatin analogues, IFN-α or hepatic artery chemoembolization provide good palliation of the symptoms of carcinoid syndrome associated with such tumors. However, no systemic therapy has been shown to consistently elicit tumor responses and prolong survival. The ineffectiveness of systemic chemotherapy in metastatic neuroendocrine tumors may relate to their unique biological features such as slow growth pattern or hypervascularity.

Preclinical *in vitro* and *in vivo* work suggests that bortezomib has antitumor activity in a broad spectrum of solid tumors, including the PC-12 neuroendocrine (pheochromocytoma) tumor cell line (23). Although primarily targeting the proteasome pathway, bortezomib has been shown to affect key proteins involved in cell cycle regulation, angiogenesis, and apoptosis. On the basis of this and the unique antitumor mechanisms of bortezomib, we hypothesize that it may have clinical activity in metastatic carcinoid and islet cell tumors. We thus conducted a phase II clinical trial in patients with metastatic carcinoid and islet cell tumors. On the basis of toxicity and pharmacodynamic data available from initial phase I clinical trials in solid tumor and hematologic malignancies, the dose of 1.5 mg/m^2 administered as an i.v. bolus on days 1, 4, 8, and 11 every 21 days was considered optimal for our trial. We report the results of the first prospective phase II study of bortezomib in patients with metastatic neuroendocrine tumors.

PATIENTS AND METHODS

Patient Selection. Eligibility criteria included histologically confirmed well-differentiated neuroendocrine carcinoma; metastatic and measurable disease; no more than one prior systemic chemotherapy regimen; no IFN-α, systemic chemotherapy, or radiation therapy within the past 4 weeks; no hepatic artery chemoembolization within the past 12 weeks; age ≥ 18 years; Eastern Cooperative Oncology Group performance status 0 to 2; life expectancy ≥ 6 months; and adequate organ functions: total bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase/alanine aminotransferase ≤ 2.5× upper limit of normal, absolute neutrophil count ≥ 1500/μL, platelet count ≥ 100,000/μL, and serum creatinine of ≤1.5 mg/dL. The standard dose (10 to 40 mg every 3 to 4 weeks) of intramuscular long-acting octreotide [Sandostatin LAR (Novartis Pharmaceuticals Co., East Hanover, NJ)] was permitted for the control of carcinoid syndrome symptoms provided that the dose was stable for 3 months before study entry. Exclusion criteria were pregnancy, breast-feeding, and uncontrolled intercurrent illness.

Study Design. Bortezomib was administered as an i.v. bolus at a dose of 1.5 mg/m^2 on days 1, 4, 8, and 11 every 21 days. Antiemetic therapy or growth factor support was not used on a prophylactic basis. Therapy was given for a total of 24 weeks unless patients met one of the following criteria: progressive disease; unacceptable adverse event; off of study drug for >2 weeks; or patient withdrawal from the study. Patients were maintained at the full dose of 1.5 mg/m^2 unless patients had grade 3 or 4 adverse event. In case of grade 3 or 4 adverse event, treatment was withheld for 1 week. Upon reevaluation, patients who showed a partial (improvement to grade 1 or 2 adverse event) or a full resolution were started on bortezomib at the reduced dose of 1.0 mg/m^2 that was escalated to 1.3 mg/m^2 after 1 week and to 1.5 mg/m^2 after the second week as tolerated. The patients with persistent grade 3 or 4 adverse event were taken off of the protocol.

History, physical examination, complete blood count, and serum chemistry were obtained within 14 days before initiation of therapy and within 2 to 4 weeks after the last dose of bortezomib (posttreatment). Baseline tumor measurements were performed with computed tomography scan within 4 weeks before initiation of therapy and repeated every 12 weeks during study and at the posttreatment visit. In addition, patients had a history and physical examination performed every 6 weeks and had complete blood count, serum chemistries, and adverse event evaluation performed once a week during their treatment weeks (week 1, 2, 4, 5, and so on). Objective response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and toxicity was assessed according to National Cancer Institute Common Toxicity Criteria, version 2.0 (24).[6]

Tumor Marker Studies. Serum tumor markers (pancreastatin, gastrin, calcitonin, pancreatic polypeptide, vasoactive intestinal peptide, neurotensin, substance-P, gastrin-releasing peptide, glucagon, somatostatin, and serotonin) and 24-hour urine for 5-hydroxy indole acetic acid were obtained within 14 days before initiation of therapy every 12 weeks during therapy and within 2 to 4 weeks posttreatment.

Pharmacodynamic Studies. We used an *ex vivo* 20S proteasome inhibition assay to monitor bortezomib activity in whole blood using the previously described method (15). This fluorogenic kinetic assay consisted of measuring proteasome activity at chymotryptic and tryptic sites within the 20S core of the proteasome and determining the degree of inhibition conferred by bortezomib. Using the ratio of these chymotryptic: tryptic activities and the catalytic mechanism of the proteasome, percentage of inhibition was calculated compared with predose whole blood obtained from the same patient.

Blood samples were collected at 0 hour (just before administration of bortezomib), 1 hour, and 24 hours after bortezomib

[6] Internet address: http://ctep.info.nih.gov/reporting/ctc.html.

on days 1 and 4 of the first course of therapy. For each time point, 8-mL of blood were collected in one heparinized green top tube, immediately placed on ice, and then frozen at −70°C. Batched samples were shipped on dry ice to Millennium Pharmaceuticals, Inc., for performing an assay. On the basis of the preclinical efficacy and toxicity studies, a target level of ~70% proteasome inhibition was considered optimal.

Statistical Considerations. For this phase II study, the minimax two-stage design of Simon was chosen, resulting in a trial with a decision to proceed to the second stage based on efficacy seen in the first 16 patients. Bortezomib was to be considered ineffective or uninteresting if the true response probability was <10% (p_0). The regimen was to be worthy of further study if the true response probability or target response rate was ≥30% (p_1). These figures resulted in a two-stage design of 16 and 25 patients, with an α of 0.10 and β of 0.10. If one or no responses were seen in the first 16 patients, the study was to be terminated early, and this regimen was deemed ineffective for this patient population. If two or more patients respond in the first 16, an additional 9 patients were to be treated for a total of 25.

The primary end point was to assess the objective response (partial remission or complete remission) of bortezomib in metastatic carcinoid and islet cell tumors. Stable disease was not considered an objective response to therapy given the relatively slow-growing nature of these cancers and due to a single-arm study design. Patients who had stable disease were taken off from the protocol at 24 weeks of therapy. Secondary end points were to assess the toxicity of bortezomib in patients with metastatic neuroendocrine tumors, to assess tumor marker response, and to evaluate pharmacodynamics of bortezomib by *ex vivo* 20S proteasome inhibition assay.

RESULTS

Patients. After obtaining informed consent, 16 patients with metastatic neuroendocrine tumor were enrolled on to the Institutional Review Board-approved phase II study at The Ohio State University ($n = 14$) and at University of Chicago ($n = 2$) between May 2001 and December 2001. Patient characteristics are outlined in Table 1. A majority of patients ($n = 12$; 75%) had carcinoid tumors, whereas the rest ($n = 4$, 25%) had islet cell tumors. Of the four patients with islet cell tumors, one patient had symptoms of diarrhea related to carcinoid syndrome, whereas the rest of the patients had no symptoms associated with abnormally high hormone production (pancreatic polypeptide, gastrin, glucagon, or calcitonin) related to their islet cell tumors.

Table 1 Patient characteristics

Characteristic	No.	%
Total patients	16	
Age (y)		
Median	60	
Range	26–72	
Sex		
Female	10	62
Male	6	38
Eastern Cooperative Oncology Group performance status		
0	13	81
1	3	19
Type of neuroendocrine tumor		
Carcinoid tumor	12	75
Islet cell tumor	4	25
Primary sites		
Pancreas	4	25
Ileocecal	7	43
Colon	1	6
Stomach	1	6
Lung	1	6
Unknown	2	12
Metastatic sites		
Liver alone	6	37
Liver and lymph nodes	6	37
Liver, lymph nodes, and bone	4	25
Carcinoid syndrome/concurrent octreotide therapy		
Present	6	38
Absent	10	62
Prior treatment		
Debulking or palliative surgery	11	68
Hepatic artery chemoembolization	6	38
Systemic chemotherapy	0	0
Baseline elevation of serum tumor markers		
Pancreastatin	13	81
Glucagon	5	31
Neurotensin	5	31
Gastrin	4	25
Pancreatic polypeptide	2	12
Calcitonin	2	12

Treatment Administered. If the best response achieved was stable disease, treatment with bortezomib was continued for up to 24 weeks (32 doses). All 16 patients received median of 15 doses (range, 1 to 32 doses), with a median cumulative total dose of 21.8 (range, 1.5 to 48) mg/m^2. Of the total 264 doses given in the study, 42 doses in seven patients were given at the reduced doses per protocol guidelines because of grade 3 adverse events [neutropenia ($n = 2$), peripheral neuropathy ($n = 2$), ileus ($n = 2$), and thrombocytopenia ($n = 1$)] or recurrent grade 2 vomiting. The median duration of therapy for all patients was 12 weeks (range, 0.5 to 24 weeks) and only 4 of 16 patients (25%) completed 24 weeks of therapy. The reasons for leaving the study before 24 weeks of planned therapy in the 12 patients included progressive disease ($n = 3$), persistent grade 3 adverse events [peripheral neuropathy ($n = 2$), diarrhea ($n = 1$), fatigue ($n = 1$)], and patient withdrawal [grade 3 hypertension/atrial fibrillation ($n = 1$); grade 2 nausea ($n = 1$), vomiting ($n = 1$) or seizure ($n = 1$); and social reason ($n = 1$)] (Fig. 1).

Objective Response. All 16 patients were considered evaluable for response in an intent-to-treat analysis. No patients achieved a partial response or a complete response. Stable disease was noted in 11 of 16 patients (69%) at the median evaluation time of 12 weeks (range, 3 to 24 weeks) after the start of therapy. Five patients (31%) had progressive disease noted at weeks 0.5 ($n = 1$), 12 ($n = 2$), 16.5 ($n = 1$), and 24 ($n = 1$).

Tumor Marker Response. Serum pancreastatin was consistently elevated at the prestudy evaluation in 13 patients, whereas other tumor markers (pancreatic polypeptide, gastrin, glucagon, calcitonin, or neurotensin) were elevated in only a few patients at baseline (Table 1). Tumor markers were evaluable in 10 patients, and marker levels did not correlate with

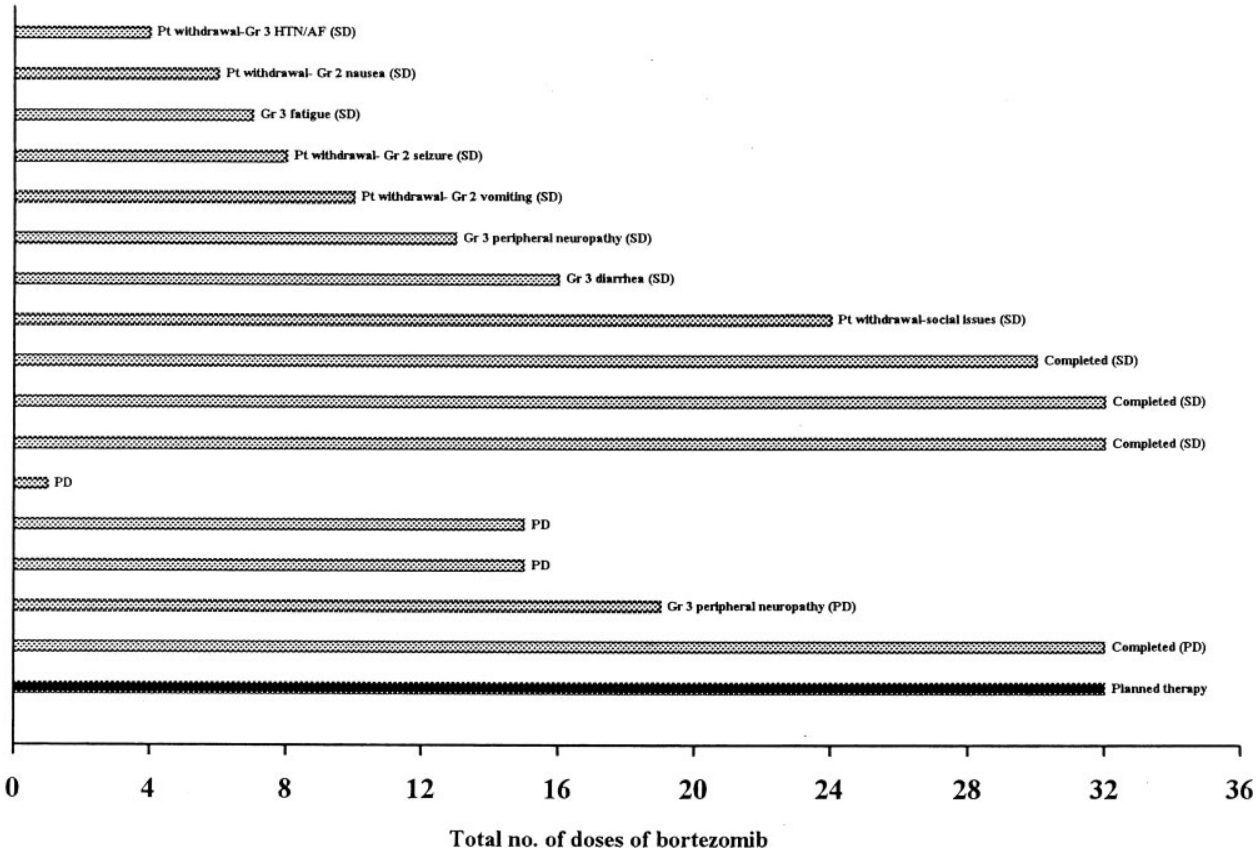

Fig. 1 Treatment administered and reasons for off study. ■ indicates maximum doses planned, ▩ indicates individual patient and data label indicates the reason for off study (type of response). PD, progressive disease; SD, stable disease; HTN, hypertension, AF, atrial fibrillation.

objective tumor response in most patients. Table 2 summarizes serum pancreastatin results in 10 evaluable patients. Of eight patients who showed stable disease, three patients had an 11 to 24% reduction in serum pancreastatin, whereas five patients had an increase (median increase, 44%; range, 7 to 55%) in serum pancreastatin compared with the prestudy levels. Serum pancreastatin was increased by 13 to 18% as compared with baseline in patients who showed progressive disease.

Pharmacodynamic Studies. A pharmacodynamic assay was performed to correlate the degree of proteasome inhibition with tumor response or adverse events. The percentage of 20S proteasome inhibition was compared with the predose (0 hour) value obtained on the same day in each individual patient. Peripheral blood samples were evaluable in 15 of total 16 patients on the study. The mean percentage of 20S proteasome inhibition achieved in whole blood at 1 and 24 hours after

Table 2 Correlation of serum tumor marker response with objective response

Subject no.	Serum pancreastatin (pg/mL) (normal value < 135 pg/mL)			Best clinical response
	Pretherapy	Posttherapy	% change with therapy	
105	851	755	−11	SD
110	346	260	−21	SD
113	1,580	1,200	−24	SD
112	1,520	1,620	7	SD
108	1,070	1,420	33	SD
107	12,500	8,210	44	SD
104	555	853	54	SD
101	5,650	8,790	55	SD
106	343	389	13	PD
103	484	570	18	PD

Abbreviations: SD, stable disease; PD, progressive disease.

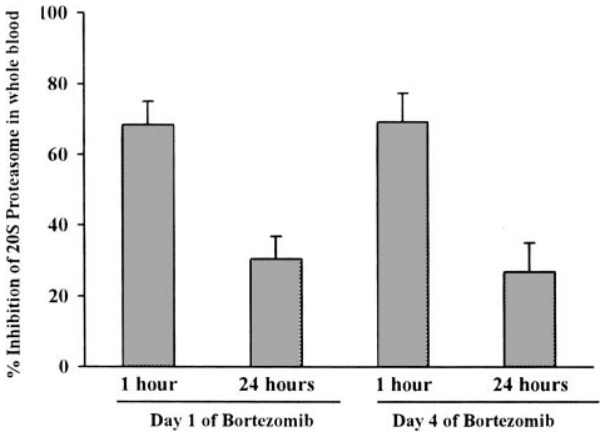

Fig. 2 Pharmacodynamic assay for bortezomib ($n = 15$). Percentage of 20S proteasome inhibition in whole blood at indicated time points during the first course of bortezomib (mean ± SD). Percentage of 20S proteasome inhibition is compared with the predose value obtained on the same day in each individual patient.

bortezomib administration on day 1 was 68 (SD ±6) and 30 (SD ±6), respectively. Similar results were achieved on day 4 of bortezomib administration (Fig. 2). The target level of 20S proteasome inhibition was achieved in our study patients, and there was no correlation with type or degree of adverse events or clinical outcome.

Adverse Events. Bortezomib was generally well tolerated. There were no grade 4 adverse events or deaths related to the study. All of the drug-related adverse events reported in the 16 study patients are outlined in Table 3. The worst grade experienced by individual patient was used to report the adverse events. Although the most common adverse event seen was nausea (74%), the most common grade 3 toxicities were peripheral sensory neuropathy (37%), followed by diarrhea (25%). It is noteworthy that four patients (25%) developed viral-associated infections during the study period. Three of these patients had recurrent grade 2 cold sores, whereas one patient had grade 3 conjunctivitis in absence of neutropenia. Three patients (18%) had ileus occur at the cumulative dose (mg/m^2) of 6, 7.5, or 10.5. All of these patients had prior laparotomy, two patients had active mesenteric carcinoid tumor, and one patient was on a stable dose of tincture of opium. Ileus resolved within 2 to 3 days of hospitalization with conservative treatment, and patients subsequently received one, three, or eight doses of bortezomib without recurrent ileus. Of the two patients who experienced grade 3 abdominal cramps, one had ileus as noted above.

A drug-related grade 2 to 3 peripheral sensory neuropathy manifested by pain, tingling, and numbness occurred in 10 patients (62%). In general, tingling and numbness were more intense in the feet and legs than in the hands, whereas neuropathic pain was mainly localized to legs and feet. All of these patients required narcotics and gabapentin for pain control. The median cumulative dose at the onset of neuropathy was 13.3 (range, 1.5 to 28.5) mg/m^2 (Table 4). Five of these patients had worsening of neuropathy during the off-study period at a median of 3.5 weeks (range, 3 to 9 weeks) after the last dose of bortezomib. Moreover, one patient had neuropathy symptoms starting at 3 weeks after the last of bortezomib. Grade 3 neuropathy symptoms in this patient improved to grade 2 and to grade 1 at week 12 and at week 18 after the last of bortezomib, respectively, despite subsequent treatment with etoposide and cisplatin. Although peripheral neuropathy is a common side effect of cisplatin, it is usually cumulative and progressive during the course of cisplatin chemotherapy. Thus, spontaneous improvement of neuropathy from grade 3 to grade 1 in our patient during the six cycles of cisplatin-based chemotherapy indicates its likely attribution to bortezomib. Seven of 10 patients had improvement up to grade 1 ($n = 5$) or grade 0 ($n = 2$) peripheral neuropathy at a median of 18 weeks (range, 2 to 76 weeks) after the last dose of bortezomib.

DISCUSSION

Given the broad spectrum of *in vitro* and *in vivo* antineoplastic activity and safety of single-agent bortezomib, we studied its efficacy in patients with metastatic neuroendocrine tumors. Despite achieving the surrogate biological end point of 20S proteasome inhibition in peripheral blood mononuclear cells obtained from 15 patients, our study failed to show any objective tumor response in this patient population. Although stable disease was noted in 11 of 16 patients (69%) at the median evaluation time of 12 weeks (range, 3 to 24 weeks) after

Table 3 Bortezomib-related adverse events reported in all 16 patients

Adverse event	Number (%)		
	Grade 1	Grade 2	Grade 3
Gastrointestinal			
Anorexia	4 (25)	5 (31)	0
Nausea	1 (6)	9 (56)	2 (12)
Vomiting	1 (6)	3 (18)	3 (18)
Diarrhea	3 (18)	1 (6)	4 (25)
Constipation	1 (6)	4 (25)	0
Ileus	0	0	3 (18)
Abdominal cramps	0	0	2 (12)
Dehydration	0	3 (18)	0
Dysgeusia	3 (18)	1 (6)	0
Neurological			
Neuropathic pain	0	4 (25)	6 (37)
Neuropathy-sensory	0	4 (25)	6 (37)
Dizziness	1 (6)	1 (6)	0
Syncope	0	0	1 (6)
Seizure	0	1 (6)	0
Constitutional			
Fatigue	7 (43)	5 (31)	1 (6)
Weight loss	2 (12)	1 (6)	0
Hematologic			
Neutropenia	0	1 (6)	2 (12)
Thrombocytopenia	1 (6)	1 (6)	2 (12)
Others			
Skin rash	2 (12)	2 (12)	0
Mouth sores (cold sores)	0	3 (18)	0
Infection without neutropenia	1 (6)	2 (12)	0
Hyperglycemia	1 (6)	1 (6)	1 (6)
Orthostatic hypotension	0	2 (12)	0
Hypertension	0	0	1 (6)
Atrial fibrillation	0	0	1 (6)
Conjunctivitis	0	0	1 (6)

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