Phase I Trial of Bortezomib in Combination with Docetaxel in Patients with Advanced Solid Tumors

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Abstract

Purpose: Bortezomib (PS-341), a first-in-class proteasome inhibitor, is metabolized by deboronation involving cytochrome P4503A (CYP3A), which also metabolizes docetaxel. Preclinical studies have shown synergy between bortezomib and taxanes. We conducted a phase I study combining bortezomib and docetaxel in refractory solid tumor patients.

Experimental Design: Patients received escalating doses of weekly docetaxel (days 1 and 8) and twice weekly bortezomib (days 2, 5, 9, and 12) in 3-week cycles. Two subjects were enrolled at each dose level, with cohort expansion to six for dose-limiting toxicity (DLT). Dose levels 1, 2, and 3 consisted of docetaxel/bortezomib 25/0.8, 25/1.0, and 30/1.0 mg/m2, respectively. CYP3A activity and docetaxel pharmacokinetic studies were conducted, and proteasome inhibition was assessed.

Results: Fourteen patients received a total of 34 cycles of treatment. Dose level 2 was expanded for DLT that occurred in two of six patients consisting of febrile neutropenia in one patient and grade 3 thrombocytopenia in one patient. One patient received two cycles at dose level 3 with dose reduction to dose level 2, where grade 3 thrombocytopenia occurred at cycle 3. Both episodes of grade 3 thrombocytopenia were transient (<7 days). Dose level 1 was then expanded to six patients where no DLTs occurred. CYP3A activity and docetaxel clearance did not change between weeks 1 and 5.

Conclusions: The maximum tolerated dose was docetaxel 25 mg/m2 (days 1 and 8) with bortezomib 0.8 mg/m2 (days 2, 5, 9, and 12) given every 21 days. Bortezomib treatment did not alter CYP3A activity and docetaxel clearance.

Bortezomib (Velcade, formerly PS-341) is a first-in-class reversible inhibitor of the 26S proteasome, which degrades proteins involved in cell cycle regulation and cell signaling (1). Bortezomib is approved by the Food and Drug Administration for the treatment of multiple myeloma (2). Several phase I trials of bortezomib in solid tumor patients have been completed, with the primary dose-limiting toxicities (DLT) being diarrhea, fatigue, and sensory neurotoxicity (3–5). Because proteasome inhibition may alter the sensitivity of cancer cells to therapeutic agents, there is interest in combining bortezomib with cytotoxic chemotherapy.

Docetaxel is a semisynthetic taxane with wide activity in a number of solid tumors, including breast, lung, and prostate cancer (6). Both weekly and once every 3 weeks (3-weekly) schedules have been explored, with schedule-dependent toxicities observed despite similar pharmacokinetics (7). Docetaxel has been shown to function in part by phosphorylation of bcl-2, thereby suppressing the normal antiapoptotic function of this protein (8). Interestingly, proteasome inhibitors have also been shown to overcome bcl-2-mediated protection from apoptosis (9). Thus, there is potential for significant antitumor activity with the combined use of docetaxel and bortezomib, and this has been shown in preclinical studies (10). Significantly, the administration of docetaxel before bortezomib has been found to produce greater tumor cell kill than the reverse order (11).

Docetaxel undergoes extensive metabolism by cytochrome P450 (CYP) 3A4 and 3A5, and the predominant route of elimination is via biliary excretion (12, 13). Docetaxel metabolites show substantially reduced cytotoxic activity compared with the parent drug, making biotransformation by CYP3A a major route of inactivation (14). Substantial intrapatient variability in docetaxel pharmacokinetics has been seen, and decreased docetaxel clearance (hence high plasma concentrations) has been associated with increased frequency of grade 4 neutropenia and febrile neutropenia in a population pharmacokinetic-pharmacodynamic analysis (15). The primary route of metabolism for bortezomib is deboronation by several CYP enzymes, including CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2...
(16). Because bortezomib binds the proteasome via the boronic acid moiety, deboronation is the principal route of bortezomib detoxification (17). Bortezomib also may affect the intracellular concentration of multiple CYP isoenzymes by inhibiting their degradation after induction (18, 19). Thus, the potential for a significant interaction between bortezomib and docetaxel exists.

The primary objective of this phase I study was to determine the DLT and maximum tolerated dose of bortezomib administered twice weekly combined with weekly docetaxel in patients with advanced solid malignancies. Secondary objectives included the following: (a) to assess the pharmacokinetics of docetaxel administered alone and in combination with bortezomib, (b) to determine the effects of the combination on CYP3A4 activity using the erythromycin breath test, and (c) to explore the pharmacodynamic effects of bortezomib combined with docetaxel using the 20S proteasome inhibition assay on peripheral blood mononuclear cells.

**Patients and Methods**

**Eligibility.** Patients with histologically confirmed advanced solid malignancies without conventional treatment options were eligible for the trial. Inclusion criteria included age ≥18 years; Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (Karnofsky performance status ≥ 50%); life expectancy >12 weeks; at least 4 weeks elapsed since prior chemotherapy or radiation therapy if 6 weeks if the regimen included 1,3-bis(2-chloroethyl)-1-nitrosourea or mitomycin C, without receiving >3 cycles of mitomycin C total); at least 6 months elapsed since previous weekly docetaxel treatment; adequate organ function [leukocytes ≥3,000/µL, hemoglobin ≥8 mg/dL, absolute neutrophil count ≥1,500/µL, platelets ≥100,000/µL, total bilirubin within normal institutional limits (WNL), creatinine WNL or creatinine clearance ≥60 mL/min/1.73 m² for patients with creatinine levels above institutional normal]. Patients were excluded if they had known brain metastases, hypersensitivity to taxanes or corticosteroids, intolerance of corticosteroids, peripheral neuropathy >grade 1 (Common Toxicity Criteria version 2), pregnancy, HIV infection, or within 14 days of study drug administration total bilirubin above institutional normal limits, alanine aminotransferase/aspartate aminotransferase >1.5 upper limit of normal, alkaline phosphatase > 2.5 upper limit of normal (unless shown to be bone-derived whereas alanine aminotransferase/aspartate aminotransferase < 1.5 × upper limit of normal).

The clinical protocol was approved by the Johns Hopkins Institutional Review Board and all subjects provided written informed consent before study drug administration.

**Drug dosage and administration.** Both bortezomib and docetaxel were dosed i.v. by body surface area. Bortezomib was administered on days 2, 5, and 12, and docetaxel was given on days 1 and 8, of a 21-day cycle (Fig. 1). Dose levels, outlined in Table 1, were as follows: dose level 1, 0.8 mg/m² bortezomib and 25 mg/m² of docetaxel; dose level 2, 1.0/25; and dose level 3, 1.0/30. There was no inpatient dose escalation. Two patients were enrolled at each dose level, with cohort expansion to six subjects when a DLT was seen. For docetaxel pharmacokinetic studies, the combination on CYP3A4 activity using the erythromycin breath test, and during week 5. The 20S proteasome assay was done during the first dose of bortezomib, *docetaxel pharmacokinetic studies, +* 20S proteasome inhibition assay. 

**Toxicity assessment.** Toxicity was assessed weekly using the National Cancer Institute Common Toxicity Criteria version 2. DLT was defined as dose delays > 2 weeks or treatment-related grade 3 thrombocytopenia (platelet count < 50,000/mm³), grade 4 neutropenia lasting ≥7 days, febrile neutropenia (>38.5 °C), grade 4 anemia (hemoglobin < 6.5 g/dL), or any grade ≥3 nonhematologic toxicity occurring during cycle 1 or 2 except inadequately treated nausea, vomiting, or diarrhea. If the delivered dose of docetaxel was < 75% planned in the first two cycles, or similarly <80% of planned bortezomib during cycles 1 and 2, it was considered a DLT. The maximum tolerated dose (recommended dose for phase II testing) was considered to be the dose level where none or one of six subjects experienced DLT.

**Pretreatment and follow-up studies.** Baseline evaluations were conducted within 1 week of study entry and included medical history (including performance status), concurrent medications, vital signs, physical exam, complete blood count with differential, serum chemistry (sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, phosphorus, and total protein), and electrocardiography. Radiologic evaluations were done within 4 weeks of study entry. Vital signs were recorded on each treatment day and complete blood counts, serum chemistries, and adverse event evaluations were done weekly. Physical exams were repeated once per cycle. Response of measurable lesions was done every 2 cycles (6 weeks) using Response Evaluation Criteria in Solid Tumors (20). A 30-day off-study follow-up evaluation of toxicities and blood tests was done.

**Drug assay and pharmacokinetic analysis.** Docetaxel pharmacokinetic studies were done at week 1 (during docetaxel monotherapy in which bortezomib was held) and week 5 (during combination therapy).
treatment with bortezomib). Serial sampling of venous blood was done at the following time points: immediately pretreatment, 30 minutes into the infusion, at 59 minutes (just before the end of the docetaxel infusion), and postinfusion at 10 minutes, 30 minutes, 1 hour, 3 hours, 7.5 hours, and the morning of days 2 (24 hours), 3 (48 hours), and 8. Docetaxel concentrations in plasma were quantitated in the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Analytical Pharmacology Core Laboratory (Baltimore, MD) using a validated analytic assay consisting of high-performance liquid chromatography with mass spectrometric detection (liquid chromatography/tandem mass spectrometry) as previously described (7). Plasma docetaxel concentrations were quantitated over a range of 0.50 to 100 nmol/L. The accuracy and precision of quality control samples was <15%. Samples with docetaxel concentrations >100 nmol/L were diluted with analyte-free human plasma before extraction and quantitation.

Individual docetaxel pharmacokinetic variables were estimated by model-dependent methods as implemented in Adapt II, release 4 (Biomedical Simulations Resource, Los Angeles, CA). Data were fit with either a two- or three-compartment model by use of weighted least squares as the estimation procedure and inverse variance of the output error (linear) as the weighting option. Maximum plasma concentrations ($C_{max}$) values were obtained from the model-estimated plasma concentration at the end of the docetaxel infusion. Calculated secondary pharmacokinetic variables included half-life during the terminal phase of the disposition curve ($t_{1/2}$), area under the plasma concentration-time curve ($AUC_{0-\infty}$), and systemic clearance.

The area under the plasma concentration-time curve was calculated as dose divided by systemic clearance.

Assessment of CYP3A4 activity. CYP3A4 activity was assessed using the erythromycin breath test as previously described (21). The test was administered immediately pretreatment on day 1 of cycle 1 and on day 12 of cycle 2. The erythromycin breath test is based on detection of $^{14}$C-labeled CO$_2$ after $N$-demethylation of erythromycin by hepatic CYP3A4. The erythromycin breath test dose, consisting of 0.04 mg [1$^{14}$C]-N-methyl[erythromycin (containing 3 $\mu$Ci of radioactivity), and collection balloons were obtained from Metabolic Solutions (Nashua, NH). The dose was dissolved in 4.5 mL of 5% dextrose solution and administered as an i.v. injection over 1 minute. Postinjection breath samples were collected in balloons at 5, 10, 15, 20, 25, 30, and 40 minutes. Samples were shipped to Metabolic Solutions for measurement of breath carbon dioxide. The data were reported as the flux of $^{14}$CO$_2$ and expressed as a percentage of dose exhaled per minute at each collection time point assuming a CO$_2$ output of 5 mmol/min/m$^2$ body surface area (22). The conventional erythromycin breath test variable, percentage $^{14}$C metabolized per hour ($^{14}$C exhaled/h), was calculated using the equation $y = -65.988x^2 + 54.645x + 0.0377$, where $x$ is the value for $^{14}$C exhaled/min at the 20-minute time point (23).

Although it was not strictly forbidden in the protocol, subjects were strongly discouraged from using food supplements or herbal preparations.

20S proteasome assay. Preclinical studies have shown that although bortezomib has a short plasma half-life measured in minutes, a dose-dependent decrease in peripheral blood mononuclear cell proteasome activity is seen 1 hour after drug administration and returns to baseline in 24 to 48 hours. Whole blood samples for determination of 20S proteasome inhibition assays were collected at the first dose of bortezomib (cycle 1, day 9) immediately pretreatment, and posttreatment at 1, 24, and 48. Assays were done by Millenium Pharmaceuticals (Cambridge, MA) using a published spectrofluorometric method (24).

Statistical considerations. All study subjects who received at least one dose of study drugs are included in the toxicity and efficacy analysis. For pharmacokinetic analysis, variables are presented as mean values ± SD, and for all tests the a priori cutoff for statistical significance was taken at $P < 0.05$. Differences between pharmacokinetic variables and CYP3A activity were compared by a two-sided paired Student’s $t$ test. Statistical calculations were done with the software package JMP version 3.2.6 (SAS Institute, Cary, NC).

Results

Fourteen patients were enrolled and pretreatment characteristics are summarized in Table 2. A variety of solid tumor types were enrolled, with the most frequent being non–small cell

<table>
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<td>1</td>
<td>11</td>
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Table 1. Dose escalation scheme and incidence of DLT

<table>
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<tr>
<th>Dose level</th>
<th>Bortezomib dose (mg/m$^2$)</th>
<th>Docetaxel dose (mg/m$^2$)</th>
<th>No. patients</th>
<th>No. cycles</th>
<th>DLT (no.)</th>
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<td>1</td>
<td>3*</td>
<td>0</td>
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</table>

*One patient not evaluable for toxicity.
+Patient reduced to dose level 2 after one cycle.

Table 2. Patient characteristics

Abbreviations: ECOG, Eastern Cooperative Oncology Group.
lung cancer (n = 4), bladder (n = 2), and prostate cancer (n = 2). In all, 38 three-week cycles of bortezomib/docetaxel were administered. The median number of cycles was 2 (range, 0.67-8). One patient did not complete cycle 1 due to rapid disease progression. Thirteen patients completed at least two cycles. The third dose level was explored in only one patient due to a late-occurring DLT at the second dose level, at which time the second dose level was further explored.

**DLT and maximum tolerated dose.** DLT was observed in two patients at dose level 2 of 1.0 mg/m² bortezomib and 25 mg/m² docetaxel (grade 3 thrombocytopenia and febrile neutropenia each in one patient). No other treatment-related grade 4 toxicities occurred. One patient at dose level 3 of 1.0 mg/m² bortezomib and 30 mg/m² docetaxel experienced grade 3 thrombocytopenia during cycle 3. The maximum tolerated dose and recommended phase II dose at this schedule is 0.8 mg/m² bortezomib and 25 mg/m² docetaxel.

**Toxicity.** The adverse events are summarized in Table 3. The most common adverse events were cytopenias, especially thrombocytopenia and anemia, as well as fatigue. Thrombocytopenia was delayed (both grade 3 events occurred during cycle 2, week 3) and short-lived (lasting <7 days), and no bleeding episodes occurred. One episode of febrile neutropenia was seen without documented infection or sequelae. Infusion reactions and lower extremity edema, likely related to docetaxel, also occurred. No other grade 4 adverse events were encountered.

Of the toxicities encountered, cytopenias were the only side effects that seemed to be dose dependent, albeit a limited number of subjects were treated at each dose level. At dose level 3, one of one patient had grade 3 thrombocytopenia; at dose level 2, five of six patients had some type of grade 2 to 3 cytopenia; and at dose level 1, none of seven patients had grade 2 to 3 cytopenias (Table 3). There were no unexpected toxicities.

**Pharmacokinetic analysis.** All patients were evaluated for docetaxel pharmacokinetics during week 1, where docetaxel was administered alone, and week 5, when docetaxel and bortezomib were administered together. One patient withdrew early from the study due to disease progression before week 5. Docetaxel pharmacokinetic variables for weeks 1 and 5 are summarized in Table 4. Mean (SD) values for docetaxel clearance were similar during weeks 1 and 5 [26 (12) L/h versus 24 (13) L/h, respectively; \( P = 0.28 \)]. No significant differences were observed for other docetaxel pharmacokinetic variables listed in Table 4 between week 1 and week 5, indicating a lack of effect of bortezomib administration on docetaxel pharmacokinetics.

**CYP3A4 activity.** Mean (SD) values for the erythromycin breath test variable \%^{14}C exhaled/h during weeks 1 and 5 were similar [2.13% (0.83%) versus 2.16% (0.76%), respectively;
with 1.0 mg/m² in a phase II trial in multiple myeloma (26). In Drug Administration–approved dosing of bortezomib monotherapy typically administered at a dose of 30 mg/m², and the Food and reported results from bortezomib monotherapy studies (3–5). Proteasome inhibition studies reflecting the activity of bortezomib showed profiles that are consistent with previously limited, a pharmacokinetic interaction between these agents was not seen with regard to docetaxel metabolism, and CYP3A phenotyping studies did not show a significant difference in response to docetaxel metabolism, and CYP3A activity as assessed by erythromycin breath test was not altered by the administration of bortezomib in combination with docetaxel.

Proteasome inhibition assay. Eleven subjects had evaluable results for the proteasome inhibition assay at all time points. In all cases, maximal inhibition was seen at 1 hour, with progressive decreases at 24 and 48 hours, which is consistent with previous studies. No significant difference was seen between patients treated at dose level 1 (n = 6, 0.8 mg/m²), where the mean (SD) inhibition was 46.8% (7.8%) and dose level 2 (n = 4, 1.0 mg/m²), where it was 44.0% (9.4%). There was no difference in inhibition between the patients with stable disease (n = 3) and progressive disease (n = 7; data not shown). Response. No objective responses were seen in this patient population. Four subjects (two non–small cell lung, one bladder, one prostate) had stable disease after four cycles. One patient with non–small cell lung had stable disease for eight cycles of treatment.

Discussion

This phase I trial of twice-weekly bortezomib and weekly docetaxel establishes the recommended dose at 0.8 mg/m² (days 2, 5, 9, and 12) and 25 mg/m² (days 1 and 8), respectively, every 21 days. The DLTs were thrombocytopenia and febrile neutropenia. Other common side effects were anemia and fatigue. Although the number of patients was limited, a pharmacokinetic interaction between these agents was not seen with regard to docetaxel metabolism, and CYP3A phenotyping studies did not show a significant difference in enzyme activity before and after combination treatment. Proteasome inhibition studies reflecting the activity of bortezomib showed profiles that are consistent with previously reported results from bortezomib monotherapy studies (3–5).

When given on a weekly schedule, docetaxel monotherapy is typically administered at a dose of 30 mg/m², and the Food and Drug Administration–approved dosing of bortezomib monotherapy is 1.3 mg/m² twice weekly (days 1, 4, 8, and 11 of a 21-day cycle; refs. 2, 25). Therefore, the recommended dose based on this study includes a 17% dose reduction of docetaxel and a 38% dose reduction of bortezomib when given in combination compared with monotherapy. Particularly for bortezomib, the decreased dose may be clinically significant given that slightly higher response rates were seen at 1.3 mg/m² compared with 1.0 mg/m² in a phase II trial in multiple myeloma (26). In addition, the recommended phase II dose in patients with solid tumors receiving single-agent bortezomib in a twice-weekly schedule was 1.56 mg/m², which is nearly double the dose obtained in this trial (3). In a more recent study with pharmacodynamic end points using a days 1 and 4 schedule every 2 weeks, the recommended dose was 3.0 mg (equivalent to 1.75 mg/m²) because reversible inhibition of proteosome activity best fit a total dose (mg) per fraction rather than mg/m² (5). These data were not available, however, before completion of our study.

Bortezomib and docetaxel are known to have overlapping toxicities when given as single agents. For bortezomib, thrombocytopenia (29%) was the most common grade ≥3 adverse event in the SUMMIT and CREST multiple myeloma trials, followed by neutropenia (15%), fatigue (11%), and peripheral neuropathy (11%; ref. 2). In the phase I monotherapy studies in solid tumor patients, the DLTs of bortezomib were diarrhea, fatigue, and sensory neuropathy, and hematologic toxicities were generally not dose limiting (3–5). The side effect profile of docetaxel depends in part on the schedule and patient characteristics. Weekly docetaxel is associated with less frequent neutropenia (4–14%) compared with 3-weekly schedules (27, 28). Thrombocytopenia following administration of docetaxel is relatively infrequent with both 3-weekly (1–4%) and weekly (0%) schedules. Thus, the thrombocytopenia seen in this study at these low doses was greater than expected despite the potential for overlap. Of note, due to safety concerns, the criterion for dose-limiting thrombocytopenia (grade 3) in this trial was more conservative than other studies with bortezomib, where grade 4 was selected as a DLT. A more liberal DLT definition likely would have allowed the exploration of higher dose levels.

One explanation for the grade 3 thrombocytopenia may have been the heavy pretreatment of the individual patients who experienced it. Both patients had prostate cancer and had previously received wide-field radiation therapy in addition to multiple cytotoxic chemotherapy regimens. The patient who experienced febrile neutropenia also had received multiple cycles of conventional chemotherapy before enrollment. However, in the phase I trial of single-agent bortezomib where twice-weekly doses up to 1.56 mg/m² were explored with only 2 of 12 subjects experiencing grade 3 hematologic toxicity, 24 (50%) of 48 patients had received definitive or palliative radiotherapy and all subjects had received prior chemotherapy (median = 4, range 1-16). The short-lived (<7 days) length of grade 3 thrombocytopenia seen in this trial and lack of clinical sequelae indicate that this side effect may be tolerable for future studies of this combination, and perhaps more permissible variables of tolerable thrombocytopenia could be incorporated.

Sensory neuropathy (any grade) is seen in 20% to 30% of patients receiving docetaxel therapy in 3 weekly and weekly schedules. Given that neuropathy is one of the DLTs typically seen with bortezomib, the potential for overlap in our trial was

<table>
<thead>
<tr>
<th>Table 4. Pharmacokinetic variables for docetaxel during week 1 (monotherapy) and week 5 (combination therapy with bortezomib)</th>
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<tr>
<td></td>
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<tr>
<td>Week 1 (n = 14)</td>
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<tr>
<td>Week 5 (n = 13)</td>
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NOTE: All values are mean (SD).
Abbreviations: AUClast = area under the concentration-time curve; t1/2, = terminal half-life; Vss, steady-state volume of distribution.

"Cmax and area under the concentration-time curve were normalized to a dose of 25 mg/m² for one patient who received 30 mg/m²."
significant. The lack of neurotoxicity may be due to the relatively low doses that were explored. In most trials of bortezomib, neuropathy was not reported at doses <1.2 mg/m², and dose-limiting neuropathy was reported at doses >1.5 (3, 5). Neuropathy from taxanes tends to be cumulative, which in addition to the low dose may partially explain the low incidence of neuropathy seen in this trial because the majority of the patients received only two cycles (6 weeks) of study drugs.

The results of this trial indicate that weekly docetaxel and twice-weekly bortezomib can be safely combined, albeit at slightly reduced doses compared with each agent alone. No interaction was detected in an analysis of docetaxel pharmacokinetics, and no change in CYP3A4 activity was detected using inhibition seen at these doses was as anticipated. Clinical activity was modest in this pretreated population.

The tested schedule in this study required that patients receive treatment three times per week for 2 weeks (days 1, 2, 5, 8, 9, and 12), followed by 1 week off. Study subjects informally reported that this was an inconvenient schedule. A phase I/II study of docetaxel/bortezomib in prostate cancer patients using a weekly schedule for each agent (docetaxel days 1 and 8 and bortezomib days 2 and 9) has been reported without DLTs at docetaxel 40 mg/m² and bortezomib 1.3 mg/m² (29). Four of 12 patients has a ≥50% decline in prostate-specific antigen values in that study, and grade 3/4 thrombocytopenia was not reported despite the fact that six subjects had received prior radiotherapy. The effects on efficacy of dropping one of the weekly doses of bortezomib are unknown. Further evaluation of this combination is warranted, although perhaps with an altered schedule of weekly bortezomib, an exclusion criterion for heavily pretreated patients, and/or permissible transient thrombocytopenia. Due to the inconvenience of the schedule in this study, combined with promising clinical activity seen early trials of once-weekly combination regimens, further exploration of this schedule was not done.

References

Phase I trial of bortezomib in combination with docetaxel in patients with advanced solid tumors.


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