

Incorporating Bortezomib into the Treatment of Lung Cancer

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Abstract Bortezomib, a small-molecule proteasome inhibitor, has activity in lung cancer both as a single agent and in combination with agents commonly used in lung cancer. The ability of bortezomib to favorably modulate the expression of apoptosis-associated proteins, along with its moderate toxicity as a single agent, provides the basis for its combination with cytotoxic agents in the treatment of lung cancer. In non-small cell lung cancer, bortezomib as a single agent has limited activity but in combination with chemotherapy has shown encouraging activity without significantly adding to toxicity. Bortezomib as a single agent has shown minimal activity in small cell lung cancer. Although the role of bortezomib in lung cancer is uncertain, it is likely to have its greatest clinical benefit when given in combination with other therapeutics. Ongoing studies are focused on optimizing the scheduling of bortezomib with chemotherapy, investigating its combination with targeted agents and radiation, and examining its efficacy in a specific subgroup, bronchioloalveolar carcinoma.

The Proteasome as a Target for Lung Cancer

Bortezomib (PS-341, Velcade, Millennium Pharmaceuticals, Inc.) is a dipeptidyl boronic acid that functions as a specific and selective reversible inhibitor of the 26S proteasome. The proteasome is a multicatalytic complex that serves to eliminate misfolded and damaged proteins as well as proteins regulated throughout the cell cycle. Protein degradation via the ubiquitin-proteasome pathway is critical to the regulation of multiple cellular processes, including cell cycle progression and apoptosis (see Fig. 1). Inhibition of the proteasome results in disruption of protein homeostasis that adversely affects cell signaling cascades (1–5).

Although bortezomib has shown its greatest benefit in the treatment of refractory multiple myeloma, it targets many key cell cycle regulators that are relevant to tumor progression and therapy resistance in lung cancer (see Table 1). Bortezomib can facilitate apoptosis by reducing expression and/or activity of survival factors, such as nuclear factor- κ B (NF- κ B), which results in decreased levels of Bcl-2 and Bcl-xL. Bcl-2 is reported to be overexpressed in up to 90% of small cell lung cancer (SCLC) tumors (6–9) and is associated with chemotherapy resistance (10). The ability of bortezomib to overcome Bcl-2-mediated resistance to apoptosis and to stabilize the proapoptotic Bax, a binding partner of Bcl-2, are two of the proposed mechanisms by which bortezomib is

thought to be of potential therapeutic benefit, particularly in SCLC (11, 12).

The inhibition of proteasome function may lead, through multiple mechanisms, to arrested growth of malignant cells, impaired tumor angiogenesis, decreased metastasis, sensitization of cells to chemotherapeutic agents, and decreased chemoresistance (13–16). In addition, preclinical data suggest that proteasome inhibition may reverse platinum resistance, which is a common cause of treatment failure and disease progression in lung cancer, although its mechanism is not known (17).

Bortezomib Monotherapy Studies

Initial phase I studies showed modest single-agent activity with bortezomib in non-SCLC (NSCLC; refs. 18, 19), which formed the basis for subsequent investigations in this tumor type. A randomized phase II study of bortezomib versus bortezomib plus docetaxel confirmed the single-agent activity of bortezomib as second-line therapy of advanced NSCLC (20). Patients receiving bortezomib alone had an 8% response rate and a 21% stable disease rate, which is comparable with other second-line therapies in advanced NSCLC. This trial will be discussed in more detail below.

Activity was also seen in the histologic subtype of bronchioloalveolar cancer in early phase studies with bortezomib. In a histologic subtype anecdotally reported to have minimal response with chemotherapy, novel agents are of particular interest. Thus, two ongoing trials are examining the use of bortezomib in bronchioloalveolar cancer. Two different schedules are being used in each trial, an industry-sponsored trial with the standard twice-weekly schedule (1.3 mg/m²) and a California Cancer Consortium study using a weekly schedule (dosed at 1.6 mg/m²).

Despite a strong preclinical rationale for single-agent bortezomib in SCLC, efficacy was limited in a phase II trial for extensive-stage disease (Southwest Oncology Group 0327).

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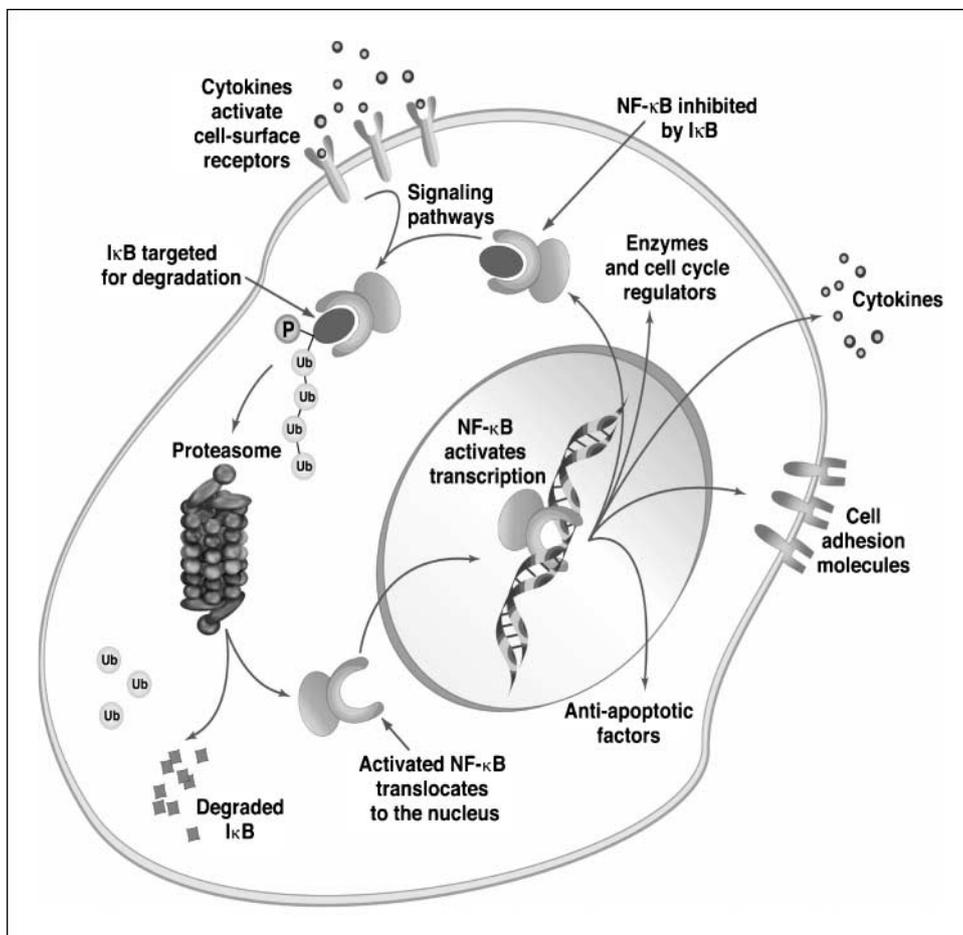


Fig. 1. The proteasome: target of bortezomib.

Heavily pretreated SCLC patients with either platinum-sensitive ($n = 28$) or platinum-refractory disease ($n = 28$) were treated with 1.3 mg/m² bortezomib on days 1, 4, 8, and 11 of a 21-day cycle (21). Only one patient with platinum-refractory disease had a confirmed partial response. Although this could be viewed as a positive finding, given that platinum-refractory patients rarely respond to treatment, the lack of a predictive biomarker in this setting limits its potential clinical utility if only a small proportion of patients are likely to benefit from bortezomib. Clinical testing of bortezomib in combination with an apoptotic trigger, such as cytotoxic chemotherapy, seems to be a more rational approach in SCLC.

Bortezomib Combination Studies

Bortezomib is expected to synergize with chemotherapy as a result of its ability to lower the apoptotic threshold of cancer

cells. However, in many preclinical models, treatment with bortezomib results in cell cycle arrest in G₁ and G₂-M. Given the effect of proteasome inhibition on cell cycle regulation, some authors have postulated that the sequence in which bortezomib is given with other chemotherapeutics may affect efficacy (4, 22). The underlying molecular profile of the tumor is likely to influence this. In cell types where bortezomib is principally cytostatic, pretreatment may diminish chemotherapeutic activity, whereas concurrent treatment or posttreatment may potentiate chemotherapy. To investigate the concept of bortezomib sequencing further, the California Cancer Consortium is leading a multi-institutional randomized phase II study testing the preferred preclinical sequence of docetaxel (day 1) followed by bortezomib (days 2 and 8) versus concurrent administration of both agents on day 1 and bortezomib again on day 8 (Fig. 2). Although the sequencing of bortezomib with chemotherapy is a theoretical concern that needs to be tested

Table 1. Bortezomib (PS-341): selected targets relevant to lung cancer (33)

Protein	Protein function	Role in lung cancer	Effect of PS-341
p27 ^{KIP1}	Cell cycle inhibition, apoptosis	Tumor suppressor	Stabilization
p53	DNA damage repair, cell cycle inhibition, apoptosis	Tumor suppressor, therapy resistance	Stabilization
NF-κB	Transcription factor, apoptosis suppressor	Cell survival, therapy resistance	Down-regulation
Bcl-2, Bcl-xL	Antiapoptosis	Cell survival, therapy resistance	Down-regulation
Bax	Proapoptosis	Promote apoptosis	Stabilization
Cyclin D, E, A	Cell cycle progression	Oncogenic	Stabilization

prospectively, the tolerability of bortezomib combined with chemotherapy has been shown. Bortezomib has been successfully combined with many cytotoxic agents commonly used in the treatment of NSCLC at therapeutic doses without significant overlapping toxicity, including gemcitabine, carboplatin, docetaxel, and pemetrexed (20, 21, 23–26).

Bortezomib plus Docetaxel

In a phase I trial conducted by the California Cancer Consortium of bortezomib and docetaxel in metastatic NSCLC and other solid tumors, the maximum tolerated dose was 1.0 mg/m² for bortezomib (days 1, 4, 8, and 11) with 75 mg/m² docetaxel (21). Two (6%) patients with NSCLC achieved a partial response, and seven (19%) patients achieved stable disease (including six patients with NSCLC). The combination of bortezomib and docetaxel at the maximum tolerated dose was generally well tolerated, and no additive toxicities were observed.

A randomized phase II study of bortezomib alone (1.5 mg/m² i.v. on days 1, 4, 8, and 11 of a 21-day schedule) or in combination with docetaxel (75 mg/m² i.v. on day 1) in 155 previously treated patients with advanced NSCLC (20) showed similar response rates in both arms (8% for bortezomib alone versus 9% for the combination) with time to disease progression improved in patients receiving the combination (1.5 versus 4 months; ref. 20). The study was not powered to compare survival; however, the combination does not seem to be additive, with survival being similar in both the combination and the bortezomib alone arm (median survival, 7.8 versus 7.4 months). Survival may have been affected by subsequent therapy. Although patients in the combination arm experienced more hematologic toxicity due to the docetaxel (4% versus 65% grade 3/4 neutropenia and 5% versus 13% grade 3 anemia for bortezomib versus bortezomib + docetaxel, respectively), there did not seem to be additive toxicity. Grade 3 peripheral neuropathy occurred more commonly in the bortezomib alone arm (15% versus 5%) likely due to the higher dose used.

Although the response rate for bortezomib alone was comparable with other second-line single agents, the time to progression was much shorter, suggesting its role as a single agent in an unselected NSCLC population is limited. In addition, it is unclear from this study whether bortezomib added to the efficacy of docetaxel, given that it was not compared with docetaxel alone.

Bortezomib plus Pemetrexed

The efficacy and favorable toxicity profile of pemetrexed in the second-line setting in NSCLC (27) make it an ideal agent to combine with novel therapeutics such as bortezomib. A phase I trial at the University of California, Davis, examined two different schedules of bortezomib (days 1, 4, 8, and 11 versus weekly) in combination with pemetrexed in advanced NSCLC and other solid tumors (20). Both schedules were well tolerated and were able to be combined at therapeutic doses (pemetrexed 500 mg/m² and bortezomib 1.3 mg/m² on days 1, 4, 8, 11 or 1.6 mg/m² on days 1 and 8). However, there was significantly more grade 3/4 neutropenia in the twice-weekly bortezomib arm (66% versus 8%). Of 26 evaluable patients, 2 had a partial response (both NSCLC patients) and 14 had stable disease. A randomized, multi-institutional phase II study will examine the efficacy of these two schedules in patients with NSCLC. In addition, an industry-sponsored randomized phase II trial is ongoing in Europe of bortezomib versus pemetrexed versus the combination.

Bortezomib plus Gemcitabine/Carboplatin

Gemcitabine/carboplatin is a commonly used platinum doublet in the first-line treatment of advanced NSCLC. Preclinical data from the University of California, Davis, have shown sequence-specific synergy with this doublet in combination with bortezomib (11). A phase I trial in the California Cancer Consortium determined the maximum tolerated dose to be 1.0 mg/m² bortezomib on days 1, 4, 8, and 11; 1,000 mg/m² gemcitabine on days 1 and 8; and carboplatin area under the curve of 5 on day 1 of a 21-day schedule (25). The combination was well tolerated, with thrombocytopenia and neutropenia as the most common grade 3/4 toxicities. Among 21 evaluable patients, 10 patients (48%) achieved a partial response, and stable disease was observed in 6 patients.

The promising efficacy of this combination was further examined in a Southwest Oncology Group phase II study (S0339); results were presented in the Lung Oral Session at the American Society of Clinical Oncology meeting in June of 2006 (28). In this trial, 114 chemotherapy-naïve stage IV and selected stage IIIB (pleural effusion) NSCLC patients received gemcitabine/carboplatin with bortezomib at the doses and schedule used in the phase I trial (see Table 2). Response Evaluation Criteria in Solid Tumors (RECIST) responses were seen in 20% of patients and 45% had stable disease for a disease control rate of 66%. Progression-free and median overall survival were 5 and 11 months, respectively. The 1-year survival rate was 46% (95% confidence interval, 37–55%). The most common grade 3/4 toxicities were, as expected, neutropenia (52%) and thrombocytopenia (63%); however, these adverse events were not associated with bleeding or increased rates of febrile neutropenia. Ongoing correlative studies are examining



California/Pittsburgh Cancer Consortium Randomized Phase II NCI Trial

NSCLC Advanced Stage 1 prior chemotherapy	R A N D O M I Z E	<p>Concurrent Bortezomib + Docetaxel</p> <p>Sequential Docetaxel → Bortezomib</p>
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Concurrent: Docetaxel 75 mg/m² d 1, PS-341 1.6 mg/m² d 1 & 8
 Sequential: Docetaxel 75 mg/m² d 1, PS-341 1.6 mg/m² d 2 & 9

Fig. 2. California/Pittsburgh Cancer Consortium randomized phase II study evaluating concurrent versus sequential administration of bortezomib with docetaxel.

markers of proteasome inhibition (e.g., Bcl-2 family, NF- κ B, and I κ B) and hypoxia (e.g., plasminogen activator inhibitor-1, vascular endothelial growth factor, osteopontin, and hypoxia-induced factor-1) in tumor tissue and surrogate specimens. Although the 11-month median survival was promising in advanced NSCLC (compared with prior Southwest Oncology Group trials), and this trial met its prespecified end point to move forward with a phase III trial, the therapeutic landscape has changed with the introduction of bevacizumab into front-line platinum therapy. Thus, it is unclear where bortezomib will now fit in the front-line setting.

Bortezomib and Targeted Agents

With the advent of many new targeted drugs showing efficacy in NSCLC, the potential benefit of combining agents, such as the epidermal growth factor receptor tyrosine kinase inhibitors with bortezomib, is of particular interest. A preclinical model has shown schedule-dependent activity for the combination of erlotinib and bortezomib in erlotinib-sensitive H358 bronchioloalveolar cells (29). Whereas some hypothesize that bortezomib would inhibit the degradation of activated epidermal growth factor receptor and its ligand, others have hypothesized synergy by promotion of cell-cell adhesion and migration (30). The efficacy of this combination is now being tested in advanced NSCLC in a randomized phase II study of erlotinib versus erlotinib plus bortezomib, with results anticipated for presentation at the 2007 American Society of Clinical Oncology annual meeting. Preclinical data also support the combination of bortezomib with the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA; ref. 1).

Bortezomib and Radiation Therapy

Bortezomib is a potent radiosensitizer and modulator of apoptotic sensitivity in preclinical models. Because NF- κ B activation is thought to be induced by radiation and its activation inhibited by bortezomib, preclinical models have examined pretreatment of cells with bortezomib before radiation and found increased apoptosis and decreased cell growth and clonogenic survival compared with radiation alone in myeloma and colon cancer cells (31, 32). In a preclinical head and neck cancer model, administration of bortezomib with radiation induced NF- κ B localization, apoptosis, and

increased expression of NF- κ B–modulated genes and cytokines in tumor and serum and was associated with tumor reduction (34). Ongoing studies are examining bortezomib in combination with chemoradiation (paclitaxel/carboplatin) in locally advanced NSCLC as well as with cisplatin/etoposide and radiation in limited-stage SCLC (Table 3).

Conclusions

Inhibition of the proteasome with bortezomib is a novel approach to the treatment of lung cancer. Single-agent responses are modest, yet at 8% are in keeping with other approved second-line therapies. Although bortezomib has shown some antitumor activity alone in lung cancer, it is likely to have its greatest clinical benefit when given in combination with other therapeutics. The phase II Southwest Oncology Group study of bortezomib in combination with gemcitabine/carboplatin yielded promising progression-free and overall survival rates; however, a phase III trial is required to confirm these findings.

Although the preclinical rationale to proceed with the development of bortezomib was strong, with the plethora of new agents being investigated in lung cancer, it is hard to predict where bortezomib will fit into the therapeutic landscape. Results from ongoing studies of erlotinib/bortezomib in combination and bortezomib in bronchioloalveolar cancer will shed some light on the potential therapeutic roles for bortezomib. One of the greatest challenges with all these new drugs that show some activity but not spectacular efficacy is finding biomarkers that will predict for response. Preclinical and correlative studies are attempting to identify markers in serum and tissue that may help predict which patient subgroups are most likely to benefit from proteasome inhibition and ultimately determine whether bortezomib will have a role in the treatment of lung cancer.

Open Discussion

Dr. Thomas Lynch: The cell kill assays you showed illustrated the sequence dependency of how you use the drugs. Do others think that the outcome with the sequential regimen justifies a large randomized trial, because it would probably require a 700- to 800-patient study to try to answer that question. If not, does this mean the end of bortezomib?

Dr. Philip Bonomi: I don't have high hopes that giving bortezomib days 2 and 9 rather than days 1 and 8 is going to be a major therapeutic advance in the clinic.

Dr. Bruce Johnson: With the preclinical data that you showed, you are working at 10 micromolar concentrations of bortezomib and 10 micromolar concentrations of your chemotherapeutic doses. For the taxanes that is high, relative to what we achieve in patients. Given what you now know clinically, what do you think about the relevance of the preclinical data, working concentrations that high and extrapolating from them?

Dr. Davies: That is a challenge when we are choosing doses preclinically in our lab, and I think that particularly with the taxanes that has been a problem with a number of models.

Dr. Ramaswamy Govindan: We have to be careful in using historic controls, particularly with the widespread use of PET

Table 2. Treatment schema for phase II trial (Southwest Oncology Group 0339) of gemcitabine and carboplatin in combination with bortezomib

	Day 1	Day 4	Day 8	Day 11
Gemcitabine*	X		X	
Carboplatin †	X			
Bortezomib ‡	X	X	X	X

*1,000 mg/m².

† Area under the curve of 5.0.

‡ 1.0 mg/m².

Table 3. Radiation and bortezomib: ongoing studies

Phase	Combination	Tumor type
I	Bortezomib and concurrent external beam radiation	Advanced solid tumors
I/II	Bortezomib in combination with paclitaxel /carboplatin and radiation	Lung (NSCLC)
I	Bortezomib and radiation therapy	Head and neck, central nervous system, cervix
I	Bortezomib and radiation therapy	Recurrent metastatic head and neck
I	Bortezomib and paclitaxel with radiation	Biliary tract, pancreas
II	Bortezomib and cisplatin/etoposide with radiation	SCLC

scan to stage the tumors. This not a 10% drug, it's probably a 2% drug. Is it really worth our effort to identify the subgroup sensitive to bortezomib? My question for the basic scientists is, why does it work in myeloma this well? The cell line looked so impressive. Why does it not work in lung cancer?

Dr. Roman Perez-Soler: This is an impressive agent that kills almost every cell line at less than 1 micromolar concentrations. The problem to me has always been that the drug needs help in terms of finding the right dosing schedule. It has an extremely short half-life. I do not think we have learned how to use it.

Dr. John Heymach: It is a complicated drug and we are not exactly sure how it works. Nobody knew that it was going to work in multiple myeloma, but *post hoc* people can identify a mechanism. Ken Anderson's lab has shown antiangiogenic effects, with a reduction in VEGF and other factors. We have looked at this in lung cancer cell lines, and in the right settings, you actually get transient increases in HIF and in VEGF. Now, that does not happen consistently and it seems to be context dependent, but it makes the point that this is not a straightforward drug to study.

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