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# Clinical potential of proteasome inhibition in solid tumours ☆

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**Abstract**

The proteasome plays a central role in the regulation of many processes critical to solid tumour growth. Proteasome inhibition activates multiple mechanisms capable of arresting tumour proliferation, tumour metastasis, and angiogenesis. In preclinical testing, the novel proteasome inhibitor bortezomib displays a unique pattern of cytotoxicity against a broad spectrum of tumour cell lines. In experimental models of breast, lung, colon, prostate, pancreatic, and ovarian cancer, bortezomib shows additive or synergistic activity when combined with chemotherapeutic agents such as irinotecan, gemcitabine, 5-fluorouracil, cisplatin, paclitaxel, docetaxel, and doxorubicin. Bortezomib is currently being investigated both as a single agent and in combination regimens for the treatment of a broad range of solid tumours including non-small cell lung cancer (NSCLC), renal cell, breast, ovarian, prostate, colon, gastric, and pancreatic cancer. In an ongoing, single-agent phase II trial in NSCLC, one partial response and six instances of stable disease were documented in 15 evaluable patients. Pharmacodynamic studies showed inhibition of NF-κB. Two single-institution phase II trials in renal cell cancer showed four partial responses in 37 patients and one partial response in 21 patients, respectively. Randomised phase II trials of bortezomib with or without docetaxel in patients with NSCLC and with or without irinotecan in patients with colon cancer are ongoing, as are single-agent phase II studies in colon, breast, and ovarian cancer. Bortezomib is also being studied in combination with irinotecan in patients with gastro-oesophageal cancer, with gemcitabine in patients with pancreatic cancer, and with docetaxel in patients with breast and prostate cancer.


*Keywords:* Proteasome; Bortezomib; NF-κB; Dipeptides; Boronic acids

## 1. Introduction

The proteasome plays a central role in the regulation of many processes critical to solid tumour growth and metastasis. In addition to haematological malignancies, there is a strong preclinical rationale for the use of proteasome inhibition in the treatment of a broad array of solid tumours. Inhibition of the proteasome activates multiple mechanisms capable of arresting tumour proliferation, tumour spread, and angiogenesis. Combining these mechanisms offers a potentially new approach to cancer treatment [1].

As described in detail by Dr. Kenneth Anderson [*Eur J Cancer Suppl.*], proteasome activity is required for activation of the transcriptional regulator NF-κB. Inhibition of NF-κB renders cells more sensitive to the effects of chemotherapy and radiation and blocks NF-κB mediated resistance to chemotherapy-induced apoptosis [1–3]. In addition, proteasome inhibition downregulates expression of the antiapoptotic protein Bcl-2 and stabilises the tumour suppressor p53 and cyclin-dependent kinase inhibitors p21 and $p27^{KIP1}$ [1,3,4].

Bortezomib is a novel boronic acid dipeptide proteasome inhibitor. In preclinical testing, bortezomib is cyotoxic against a wide range of both drug-sensitive and drug-resistant tumour cell lines [1,5]. Cell culture and xenograft data suggest that bortezomib may be active in a broad spectrum of tumour types [3]. In experimental models of breast, lung, colon, prostate, pancreatic, and ovarian cancer, bortezomib shows additive or synergistic activity both *in vitro* and *in vivo* when combined with chemotherapeutic agents such as irinotecan, gemcitabine, 5-fluorouracil, cisplatin, paclitaxel, docetaxel, and doxorubicin [1,2,6].

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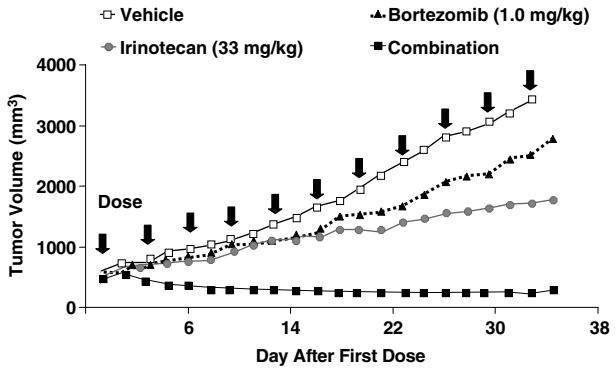


Fig. 1. Growth of LOVO colorectal cancer xenografts in mice. Combination treatment with bortezomib and irinotecan produced a significantly greater tumouricidal response compared with either agent alone. $N = 12$–14 per group [1].

One of the most promising results from preclinical investigation is the finding that bortezomib can bypass mechanisms leading to chemoresistance or can act to resensitise cells to chemotherapy [1,3]. In human colon cancer LOVO cells, pretreatment with bortezomib inhibited activation of NF-κB in response to treatment with SN-38, the active metabolite of irinotecan, and resulted in a significantly higher level of growth inhibition compared with either bortezomib or irinotecan alone (Fig. 1) [1,2]. Levels of apoptosis were 80–90% in the combination treatment group, compared with 10% in the single-agent groups [2]. These results demonstrate that bortezomib can augment chemosensitivity and enhance apoptosis through blockade of chemotherapy-induced NF-κB activation [2].

In phase I testing, as discussed by Prof. Stanley Kaye (*Eur J Cancer Suppl*), in eight patients with non-small cell lung cancer (NSCLC), one partial response was documented in a patient with bronchioloalveolar carcinoma. The patient, who had progressed on multiple prior chemotherapeutic agents, showed resolution of an infiltrative tumour mass by computed tomography (CT) scan and experienced significant relief of his tumour-related symptoms. In addition, one patient each with malignant melanoma, nasopharyngeal carcinoma, and renal cell carcinoma experienced stable disease [7].

## 2. Phase II testing in non-small cell lung carcinoma

A phase II study of antitumour efficacy and pharmacodynamics was performed in patients with advanced NSCLC [8]. Patients with histologically confirmed Stage IIIB/IV NSCLC were treated with bortezomib 1.5 mg/m$^2$ on days 1, 4, 8, and 11 every 21 days. Eligibility criteria included measurable disease; no more than one previous treatment regimen for NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; and peripheral neuropathy $\leqslant$ grade 1 at study entry. Response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria every two cycles, and pharmacodynamics were evaluated on day 1 of the first treatment cycle.

Of 19 patients enrolled in the ongoing trial, seven had received prior chemotherapy, one had received prior radiotherapy, three had received both chemotherapy and radiation, and eight had received no prior therapy. Fifteen patients were evaluable for response. One patient who had progressed on prior paclitaxel and carboplatin treatment experienced a partial response. As shown in Fig. 2(a), the patient presented with a malignant pleural effusion and parenchymal involvement of the right middle and lower lobes. As shown in Fig. 2(b), a partial response was documented after four cycles of bortezomib treatment, with further improvement after cycle 8 (Fig. 2(c)). Stable disease was noted in six patients, three of whom received >six cycles of treatment [8].

The principal toxicities observed in the trial included nausea, fatigue, peripheral neuropathy, and diarrhoea, primarily grades 1–2 in severity. Grade 3 nausea, neuropathy, thrombocytopaenia, rash, and constipation were seen in one patient each. Pharmacodynamic analysis of patient peripheral blood mononuclear cells showed loss of p65(relA) expression at 24 h, consistent with NF-κB inhibition. Patient accrual and pharmacodynamic analyses are ongoing [8].

## 3. Phase II testing in renal cell carcinoma

Two phase II studies have been conducted in patients with advanced renal cell carcinoma (RCC), both at single institutions.

The first trial included patients with advanced RCC who had received no more than one prior cytokine regimen and no prior chemotherapy [9]. Additional eligibility criteria were Karnofsky performance status (PS) $\geqslant$70 and absence of peripheral neuropathy at the time of study entry. Initially, patients were treated with bortezomib 1.5 mg/m$^2$ twice weekly for 2 weeks, every 21 days. Based on observed toxicity in the first 25 patients, the starting dose was decreased to 1.3 mg/m$^2$. Thirty-seven patients were enrolled. Overall, there were four partial responses and 14 patients with stable disease. The 6-month progression-free survival was 24%. Grade 2/3 toxicities at the 1.3 mg/m$^2$ dose included constipation (58%), dysponea (33%), fatigue (25%), nausea (25%), neuropathy (25%), and diarrhoea (16%) [9].

The second trial included a similar patient population with Stage IV RCC [10]. Bortezomib 1.5 mg/m$^2$ was administered twice weekly for 2 weeks every 21 days. Twenty-three patients were enrolled and 21 were evaluable for response. Eighteen patients completed at least three cycles of treatment. One partial remission was

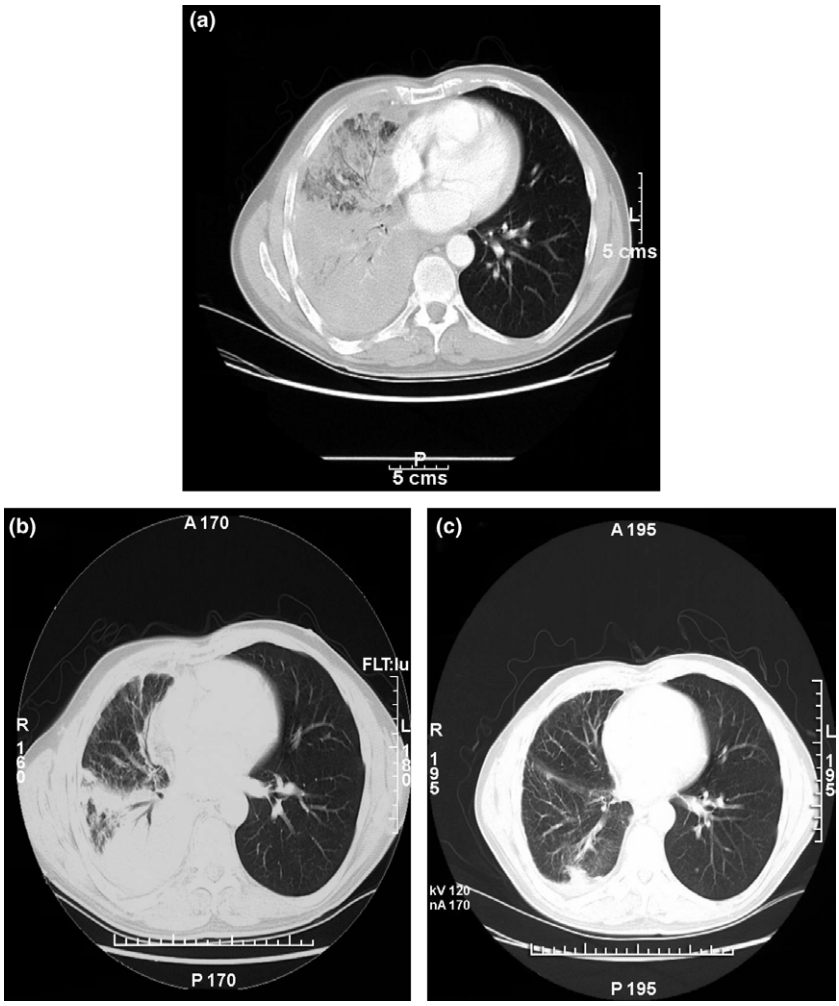


Fig. 2. (a) Baseline chest computed tomography (CT) scan in a 55-year-old male with Stage IIIB NSCLC. (b) Chest CT after four cycles of treatment. (c) Chest CT after eight cycles of treatment [8].

observed. Toxicities were similar to those observed by Drucker *et al.* [9] and Davis *et al.* [10].

The explanation for the contrasting efficacy results obtained in the two phase II trials remains unclear. Further study is ongoing to elucidate more clearly the role of bortezomib in RCC.

## 4. Phase I/II testing in other solid tumours

Bortezomib is currently being investigated, both as a single agent and in combination, for treatment of a broad range of solid tumours. As discussed, experimental data provide evidence of synergistic effects between bortezomib and chemotherapeutic agents such as irinotecan, gemcitabine, paclitaxel, docetaxel, and cisplatin in murine xenograft models of breast, lung, colon, ovarian, prostate, and pancreatic cancer [1,2,6].

A randomised phase II study in which patients with advanced NSCLC receive bortezomib with or without docetaxel is currently accruing patients. Patients are eligible for enrollment following failure of first-line treatment. The primary study endpoint is overall response rate. Secondary endpoints include time to tumour progression, overall survival, and quality of life assessment. Bortezomib is also being studied in patients with NSCLC in combination with gemcitabine alone and gemcitabine combined with carboplatin ([1]; Millennium Pharmaceuticals, Inc. Data on file).

Studies are being conducted in a broad spectrum of solid tumours in addition to NSCLC and RCC. Single-agent phase II studies are ongoing in sarcoma and in colon, breast, and ovarian cancer. A randomised phase II trial of bortezomib with or without irinotecan is being conducted in patients with relapsed colorectal cancer. In addition, bortezomib is being studied in combination with irinotecan in patients with gastro-oesophageal cancer, with gemcitabine in patients with pancreatic cancer, and with docetaxel in patients with breast and prostate cancer. An overview of the

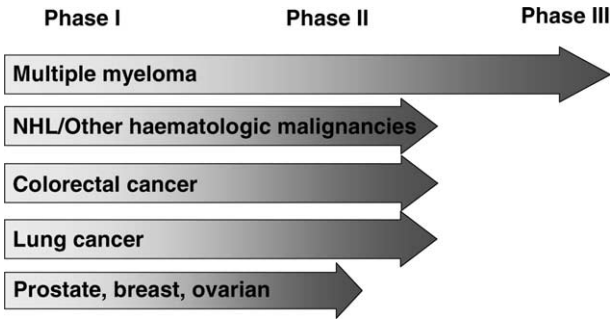


Fig. 3. Overview of the bortezomib clinical development program.

bortezomib clinical development program is shown in Fig. 3 ([1,11]; Millennium Pharmaceuticals, Inc. Data on file.).

## 5. Summary and conclusions

In summary, inhibition of the proteasome activates multiple mechanisms that can arrest tumour growth, metastasis, and angiogenesis. Proteasome inhibition thus offers a potentially new approach to cancer treatment. The proteasome inhibitor bortezomib has already demonstrated activity in the treatment of solid tumours including patients with NSCLC. Toxicities associated with bortezomib treatment appear manageable, even in patients who have received extensive prior therapy. In preclinical experiments, bortezomib demonstrates a unique pattern of activity against a broad range of tumour types and shows additive or synergistic activity when combined with a number of widely used chemotherapeutic agents. Based on these results, bortezomib is currently being investigated both as a single agent and in combination for treatment of advanced NSCLC, RCC, colon, breast, ovarian, prostate, and pancreatic cancer. A randomised phase II trial of bortezomib with or without docetaxel in patients with NSCLC is ongoing.

## Conflict of interest statement

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