



# CITINGS

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## VELCADE® (bortezomib) Issue

Welcome to the **The International Myeloma Foundation's** (IMF) special edition of *CITINGS*, our premiere publication featuring the most up-to-date information on myeloma treatment. This issue focuses on VELCADE (bortezomib), the first of a new class of drugs called proteasome inhibitors. In this issue, we provide a list of selected bortezomib data being presented at the annual American Society of Clinical Oncology (ASCO) meeting to be held June 2-6, 2006. As always, readers will also find a comprehensive list of references to the latest published studies on bortezomib from both national and international medical journals and publications.

We hope that *CITINGS* provides a detailed and informative update of the VELCADE literature, as well as assists in navigating the ASCO meeting. Please feel free to contact the IMF at (800) 452-CURE or [www.myeloma.org](http://www.myeloma.org)

– Susie Novis, President, IMF

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## American Society of Clinical Oncology Presentations 2006

*Saturday, June 3, 2006*

**8:00 AM – 12:00 PM**

■ Extended follow-up of outcome measures and analysis of prognostic factors in multiple myeloma patients treated on a phase I study with bortezomib and pegylated liposomal doxorubicin.

Presenter: Suzanne E Biehn, BA

Abstract No: 7617 Poster No: Y7

*General Poster Session*

■ In vivo changes in gene expression profiles (GEP) after bortezomib (V) for multiple myeloma (MM): Differential effects on plasma cells (PC) and micro-environment (ME).

Presenter: John D Shaughnessy

Abstract No: 7603 Poster No: X4

*General Poster Session*

*Saturday, June 3, 2006 • 8:00 AM – 12:00 PM, continued*

■ **Lenalidomide and bortezomib induce osteoclast cytotoxicity and decrease BAFF secretion in osteoclasts in human multiple myeloma: Clinical implications.**

Presenter: Iris Breitzkreutz

Abstract No: 7606 Poster Number: X8

*General Poster Session*

■ **Phase I study of bortezomib and <sup>153</sup>Sm-lexidronam combination for refractory and relapsed multiple myeloma.**

Presenter: Howard S Yeh

Abstract No: 7614 Poster No: Y3

*General Poster Session*

■ **A phase I/II study of arsenic trioxide, bortezomib, and ascorbic acid in relapsed or refractory multiple myeloma.**

Presenter: James R Berenson

Abstract No: 7611 Poster No: X13

*General Poster Session*

## ***Sunday, June 4, 2006***

***10:00 AM – 10:15 AM***

■ **Single-agent bortezomib in previously untreated multiple myeloma (MM): Results of a phase II multicenter study.**

Presenter: Kenneth Anderson

Abstract No: 7504

*Clinical Science Symposium*

***2:00 PM – 6:00 PM***

■ **Phase 1 clinical trial of KOS-953 + bortezomib (BZ) in relapsed refractory multiple myeloma (MM).**

Presenter: Asher Chanan-Khan

Abstract No: 3066 Poster No: Y8

*General Poster Session*

## ***Monday, June 5, 2006***

***10:00 AM – 10:15 AM***

■ **High CR and near-CR rate with bortezomib incorporated into up-front therapy of multiple myeloma with tandem transplants.**

Presenter: Bart Barlogie

Abstract No: 7519

*Oral Presentation*

***2:00 PM – 6:00 PM***

■ **Impact of prior autologous stem cell transplant (ASCT) in patients receiving bortezomib or dexamethasone for relapsed/refractory multiple myeloma in the APEX trial.**

Presenter: Dan T. Vogl

Abstract No: 7546 Poster No: 22

*Poster Discussion*

■ **A prospective study of the effects of once weekly bortezomib on markers of bone metabolism in patients with multiple myeloma (MM).**

Presenter: Shachar Peles, MD

Abstract No: 7548 Poster No: 24

*Poster Discussion*

■ **Weekly bortezomib in the treatment of patients (pts) with previously treated multiple myeloma: A phase II trial of the Minnie Pearl Cancer Research Network.**

Presenter: Frank A Greco

Abstract No: 7547 Poster Number: 23

*Poster Discussion*

## 2nd Quarter 2006 VELCADE® (bortezomib) Publications

### ***Bortezomib (Velcade) for progressive myeloma after autologous stem cell transplantation and thalidomide.***

Musto P, Falcone A, Sanpaolo G, Guglielmelli T, Zambello R, Balleari E, Catalano L, Spriano M, Cavallo F, La Sala A, Mantuano S, Nobile M, Melillo L, Scalzulli PR, Dell'Olio M, Bodenizza C, Greco MM, Carella AM Jr, Merla E, Carella AM, Boccadoro M, Cascavilla N, Palumbo A.

*Leuk Res.* 2006 Mar;30(3):283-5. Epub 2005 Aug 18.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16111749&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16111749&query_hl=7&itool=pubmed_DocSum)

The authors conclude that bortezomib alone may induce high quality responses as third-line salvage therapy with acceptable toxicity in a significant proportion of homogeneously pre-treated myeloma patients with progressive disease after autologous transplantation and thalidomide.

### ***Crystal structure of the boronic acid-based proteasome inhibitor bortezomib in complex with the yeast 20S proteasome.***

Groll M, Berkers CR, Ploegh HL, Ovaa H.

*Structure.* 2006 Mar;14(3):451-6.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16531229&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16531229&query_hl=7&itool=pubmed_DocSum)

The authors determine the crystal structure of the yeast 20S proteasome in complex with bortezomib to establish the specificity and binding mode of bortezomib to the proteasome's different catalytically active sites. This structure should enable the rational design of new boronic acid derivatives with improved affinities and specificities for individual active subunits.

### ***Cutaneous leucoclastic vasculitis (LV) following bortezomib therapy in a myeloma patient; association with pro-inflammatory cytokines.***

Min CK, Lee S, Kim YJ, Eom KS, Lee JW, Min WS, Kim CC, Cho CS, Park G.

*Eur J Haematol.* 2006 Mar;76(3):265-8.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16451401&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16451401&query_hl=7&itool=pubmed_DocSum)

The authors report a patient with myeloma who developed a cutaneous leucoclastic vasculitis (LV) after bortezomib treatment. The patient with LV exhibited a marked increase in serum levels of IL-6, TNF-alpha, and C-reactive protein. Bortezomib administration may enhance the release of non NF-kappa  $\beta$  mediated pro-inflammatory cytokines, which might play a role in bortezomib-induced cutaneous LV.

👁 ***Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: final time-to-event results from the SUMMIT trial.***

Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin DH, Rajkumar SV, Srkalovic G, Alsina M, Anderson KC.

*Cancer*. 2006 Mar 15;106(6):1316-9.

🖥 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16470606&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16470606&query_hl=7&itool=pubmed_DocSum)

The results of this study suggest that treatment with bortezomib results in no cumulative toxicity, and other meaningful long-term benefit for patients with relapsed and refractory myeloma

👁 ***Extramedullary relapse of multiple myeloma presenting as hematemesis and melena.***

Dawson MA, Polizzotto MN, Gordon A, Roberts SK, Spencer A.

*Nat Clin Pract Oncol*. 2006 Apr;3(4):223-226.

🖥 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16596146&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16596146&query_hl=7&itool=pubmed_DocSum)

The authors assess a 60-year-old woman with multiple myeloma relapsed after a good partial response to high-dose chemotherapy (melphalan 200 mg/m<sup>2</sup>) and autologous stem-cell transplantation, followed by thalidomide and prednisolone maintenance therapy. She presented with hematemesis and melena following salvage chemotherapy with dexamethasone, cyclophosphamide, etoposide, cisplatin, and rescue therapy with single-agent bortezomib. The authors diagnose the patient with multifocal extramedullary relapse of multiple myeloma involving the stomach and duodenum and suggest management via high-dose infusion of omeprazole, blood product support, palliative analgesics, and anxiolytic agents.

👁 ***Investigation of drug-drug interaction potential of bortezomib in vivo in female Sprague-Dawley rats and in vitro in human liver microsomes.***

Lu C, Gallegos R, Li P, Xia CQ, Pusalkar S, Uttamsingh V, Nix D, Miwa GT, Gan LS.

*Drug Metab Dispos*. 2006 Apr;34(4):702-8. Epub 2006 Jan 27.

🖥 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16443666&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16443666&query_hl=7&itool=pubmed_DocSum)

The authors address a preclinical toxicology study in which treatment of the rats with bortezomib resulted in liver enlargement (35%). To address the likelihood of clinical drug-drug interactions, the P450 inhibition potential of bortezomib and its major deboronated metabolites M1 and M2 and their dealkylated metabolites M3 and M4 was evaluated in human liver microsomes for the major P450 isoforms 1A2, 2C9, 2C19, 2D6, and 3A4/5. The results of this study suggest that no major P450-mediated clinical drug-drug interactions are anticipated for bortezomib or its major metabolites.

 ***New treatment strategy of multiple myeloma for cure [in Japanese].***

Murakami H, Handa H.

*Gan To Kagaku Ryoho (Cancer & Chemotherapy)*. 2006 Apr;33(4):417-23.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16612147&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16612147&query_hl=7&itool=pubmed_DocSum)

The authors address the treatment advances made in the field of multiple myeloma, including the novel drugs (thalidomide, thalidomide/dexamethasone, lenalidomide, bortezomib) that have been introduced in the treatment of patients with relapsed/refractory multiple myeloma, and the improved prognosis and life span of these patients.

 ***Oxidative deboronation of the peptide boronic acid proteasome inhibitor bortezomib: contributions from reactive oxygen species in this novel cytochrome p450 reaction.***

Labutti J, Parsons I, Huang R, Miwa G, Gan LS, Daniels JS.

*Chem Res Toxicol*. 2006 Apr;19(4):539-46.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16608165&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16608165&query_hl=7&itool=pubmed_DocSum)

This study addresses bortezomib as a potent first-in-class dipeptidyl boronic acid proteasome inhibitor employed in the treatment of patients with relapsed multiple myeloma, where the disease is refractory to conventional lines of therapy. The potency of bortezomib is owed primarily to the presence of the boronic acid moiety, one that is suited to establish a tetrahedral intermediate with the active site N-terminal threonine residue of the proteasome. The authors' findings indicate that the oxidase activity of P450 enzymes (i.e., formation of reactive oxygen species) represents a mechanism of deboronation.

 ***Proteasome inhibition: novel therapy for multiple myeloma.***

Kaufman JL, Lonial S.

*Onkologie*. 2006 Apr;29(4):162-8. Epub 2006 Mar 29.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16601373&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16601373&query_hl=7&itool=pubmed_DocSum)

The authors address bortezomib, a novel proteasome inhibitor, as a therapeutic option for patients with myeloma. The success of proteasome inhibition in the treatment of myeloma is a model for effective translation of preclinical research into tangible clinical benefits for patients with cancer.

 ***Complete remission upon bortezomib-dexamethasone therapy in three heavily pretreated multiple myeloma patients relapsing after allogeneic stem cell transplantation.***

Tosi P, Zamagni E, Cangini D, Tacchetti P, Perrone G, Ceccolini M, Baccarani M, Cavo M.

*Ann Hematol*. 2006 Apr 13; Epub ahead of print.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16614846&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16614846&query_hl=7&itool=pubmed_DocSum)

Letter.

***👁 Inhibition of p38alpha MAPK enhances proteasome inhibitor-induced apoptosis of myeloma cells by modulating Hsp27, Bcl-X(L), Mcl-1 and p53 levels in vitro and inhibits tumor growth in vivo.***

Navas TA, Nguyen AN, Hideshima T, Reddy M, Ma JY, Haghazari E, Henson M, Stebbins EG, Kerr I, O'young G, Kapoun AM, Chakravarty S, Mavunkel B, Perumattam J, Luedtke G, Dugar S, Medicherla S, Protter AA, Schreiner GF, Anderson KC, Higgins LS.

*Leukemia*. 2006 Apr 13; Epub ahead of print.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16617327&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16617327&query_hl=7&itool=pubmed_DocSum)

The authors show that continued treatment of multiple myeloma (MM) cells with bortezomib leads to a SCIO-469-enhanced downregulation of Hsp27 and to increased MM apoptosis, and that p38 inhibition enhances the bortezomib-induced MM apoptosis by upregulation of p53 and downregulation of Bcl-X(L) and Mcl-1. They conclude that in addition to its role in suppressing an activated MM microenvironment, co-treatment with a p38 inhibitor, such as SCIO-469, may enhance the cytotoxicity of bortezomib by modulating pro-apoptotic and anti-apoptotic factors in MM cells, suggesting great potential for co-therapy.

***👁 Remarkable activity of novel agents bortezomib and thalidomide in patients not responding to donor lymphocyte infusions following nonmyeloablative allogeneic stem cell transplantation in multiple myeloma.***

van de Donk NW, Kroger N, Hegenbart U, Corradini P, San Miguel JF, Goldschmidt H, Perez-Simon JA, Zijlmans M, Raymakers RA, Montefusco V, Ayuk FA, van Oers MH, Nagler A, Verdonck LF, Lokhorst HM.

*Blood*. 2006 Apr 15;107(8):3415-6.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16597603&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16597603&query_hl=7&itool=pubmed_DocSum)

Letter.

***👁 Bortezomib: an effective agent in extramedullary disease in multiple myeloma.***

Laura R, Cibeira MT, Uriburu C, Yantorno S, Salamero O, Blade J, Montserrat E.

*Eur J Haematol*. 2006 May;76(5):405-8. Epub 2006 Mar 9.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16529604&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16529604&query_hl=7&itool=pubmed_DocSum)

The authors address the lack of information on the effect of bortezomib on extramedullary myeloma. In their study, 4 of 23 patients treated with bortezomib at their institution had extramedullary involvement at the time of relapse. In 3 of these patients, large soft-tissue plasmacytomas disappeared, indicating that bortezomib may be useful in clinical situations of extramedullary disease in which other agents, such as thalidomide, may not be effective.

 ***Novel treatment approaches for patients with relapsed and refractory multiple myeloma.***

Sinha R, Lonial S.

*Curr Treat Options Oncol.* 2006 May;7(3):246-57.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16615880&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16615880&query_hl=7&itool=pubmed_DocSum)

The authors address the newly developing treatment options for patients with relapsed myeloma. They note that the next generation of novel agents targeting heat shock proteins, the mitogen-activated protein kinase pathway, and monoclonal antibodies are further expanding the list of future potential agents and that the rapid clinical development of targeting agents will allow for more options to treat patients with relapsed or refractory myeloma, thereby improving quality of life and overall survival.

 ***Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma.***

Miyakoshi S, Kami M, Yuji K, Matsumura T, Takatoku M, Sasaki M, Narimatsu H, Fujii T, Kawabata M, Taniguchi S, Ozawa K, Oshimi K.

*Blood.* 2006 May 1;107(9):3492-4. Epub 2006 Jan 12.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16410442&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16410442&query_hl=7&itool=pubmed_DocSum)

The authors report that between June 2004 and September 2005, 13 Japanese patients with multiple myeloma were treated with bortezomib. Four of them developed severe pulmonary complications, and 2 died of respiratory failure without progression of underlying disease. To the authors' knowledge, this is the first report on life-threatening pulmonary adverse effects after bortezomib therapy. Previous clinical studies on bortezomib, mostly in the United States and Europe, have shown low incidences of pulmonary adverse effects. These incidences suggests that bortezomib can cause serious lung injury, and that its incidence might vary among different ethnicities. Clinicians need to be alert to the possibility.

 ***Perifosine, an oral bioactive novel alkylphospholipid, inhibits Akt and induces in vitro and in vivo cytotoxicity in human multiple myeloma cells.***

Hideshima T, Catley L, Yasui H, Ishitsuka K, Raje N, Mitsiades C, Podar K, Munshi NC, Chauhan D, Richardson PG, Anderson KC.

*Blood.* 2006 May 15;107(10):4053-62. Epub 2006 Jan 17.

 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16418332&query\\_hl=7&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16418332&query_hl=7&itool=pubmed_DocSum)

The authors address perifosine, a synthetic novel alkylphospholipid and a new class of antitumor agent which targets cell membranes and inhibits Akt activation, concluding that perifosine augments dexamethasone, doxorubicin, melphalan, and bortezomib-induced multiple myeloma cell cytotoxicity and demonstrates significant antitumor activity in a human plasmacytoma mouse model, associated with down-regulation of Akt phosphorylation in tumor cells.



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