



CITINGS

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VELCADE® (BORTEZOMIB) ISSUE

THE INTERNATIONAL MYELOMA FOUNDATION (IMF) is pleased to present our first VELCADE® (bortezomib)-focused edition of CITINGS for 2005, a relatively recent publication featuring the most up-to-date information on new therapies for multiple myeloma. VELCADE is the first of a new class of drugs called proteasome inhibitors. Because it is a new type of drug, VELCADE represents a new treatment option for patients who have relapsed on other standard therapies. This issue of CITINGS has been prepared by the IMF to correspond with the annual meeting of the American Society of Clinical Oncology (ASCO) in Orlando, Florida. In this issue, readers will find three key resources related to VELCADE:

- 1) a list of selected bortezomib data being presented at the ASCO meeting, along with dates and times of each presentation,*
- 2) a list of selected bortezomib-related studies presented at the 10th International Myeloma Workshop in Sydney, Australia from April 10th - 14th 2005, and*
- 3) references to the latest published studies on bortezomib.*

We hope this issue will provide readers with a detailed update on the VELCADE literature and will be a useful tool for navigating the ASCO meeting. Please feel free to contact the IMF at (800) 452-CURE or by clicking on www.myeloma.org.

--Susie Novis, President, IMF

AMERICAN SOCIETY OF CLINICAL ONCOLOGY PRESENTATIONS 2005

Oral Presentation:

[6501] Bortezomib Appears to Overcome Poor Prognosis Conferred by Chromosome 13 Deletion in Phase 2 and 3 Trials

Date/Time: Sunday May 14, 9:30 am-10:45am

Authors: Sundar Jagannath, Paul G. Richardson, Pieter Sonneveld, Michael W. Schuster, David Irwin, Edward A. Stadtmauer, Thierry Facon, Jean-Luc Harousseau, Janet M. Cowan, Kenneth C. Anderson

Session Info: Integrated Educational Session Level 2, 230A: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)* (8:00am-12:00pm)

Poster Discussions:

[6535] Health-Related Quality of Life Associated With Bortezomib Compared With High-Dose Dexamethasone in Relapsed Multiple Myeloma: Results From The APEX Study

Date/Time: Monday May 16, 4:30pm-5:30pm

www.myeloma.org

(800) 452 - CURE (2873)

Funded by an educational grant from Millennium Pharmaceuticals, Inc.

Authors: Stephanie J. Lee, Paul G. Richardson, Pieter Sonneveld, Michael Schuster, David Irwin, J. Massaro, Bruce Crawford, R. Dhawan, S. Gupta, Kenneth C. Anderson

Session Info: Poster Discussion Level 2, Hall F1: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)*
1:30pm-5:30pm

[6533] Safety and Efficacy of Bortezomib in High-Risk and Elderly Patients With Relapsed Myeloma

Date/Time: Monday, May 16, 4:30pm-5:30pm

Authors: Paul G. Richardson, Pieter Sonneveld, Michael W. Schuster, David Irwin, Edward A. Stadtmauer, Thierry Facon, Jean-Luc Harousseau, Dina Ben-Yehuda, Sagar Lonial, Kenneth C. Anderson

Poster Info: Poster Discussion Level 2, Hall F1: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)*
1:30pm-5:30pm

[6536] Response to Bortezomib (BOR) and Bone Metabolism in Multiple Myeloma Patients

Date/Time: Monday, May 16

Authors: Zangari Maurizio, Esseltine Dixie-Lee, Najarian Kevin, Elice Francesca, Lee Choon-Kee, Yacoby Shmuel, Barlogie Bart, Tricot Guido

Poster Info: Poster Discussion: Level 2, Hall F1: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)*
4:30pm-5:30pm

General Poster Sessions:

[6653] Bortezomib (VELCADE®) Plus Dexamethasone as Induction Treatment Prior to Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma: Results of an IFM Phase II Study

Date/Time: Tuesday May 17

Authors: Jean-Luc Harousseau, Michel Attal, Xavier Leleu, Jacques Troncy, Rémy Gressin, Anne-Marie Stoppa, Cyrille Hulin, Lofti Benboubker, Jean-Gabriel Fuzibet, François Guilhot, on behalf of the IFM

Poster Info: General Poster Session Level 2, Hall C: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)* 8:00am-12:00pm

[6610] Bortezomib-Associated Transient and Cyclical Thrombocytopenia:

Evidence for Lack of Marrow Cytotoxicity

Date/Time: Tuesday May 17

Authors: Sagar Lonial, Edmund K. Waller, Paul G. Richardson, Sundar Jagannath, Robert Z. Orlowski, Cynthia R. Giver, David L. Jaye, Bart Barlogie, Leonard T. Heffner, and Kenneth C. Anderson, for the SUMMIT/CREST Investigators

Poster Info: General Poster Session Level 2, Hall C: *Leukemia, Lymphoma, Myeloma, and Transplantation (Adult)* 8:00am-12:00pm

Pre-Clinical Poster Session

[2081] Bortezomib's Effect on NFkB Nuclear Localization Is Not Sufficient Information for Predicting its Modulation of Chemotherapy-Induced Cytotoxicity.

Date/Time: Sunday May 15

Authors: R.L. Dubowy, N. Schiff, B. Toms

Poster Info: General Poster Session Level 2, Hall C: *Development Therapeutics: Cytotoxic Chemotherapy*
8:00am – 12:00pm

10TH INTERNATIONAL MYELOMA WORKSHOP PRESENTATIONS

A complete summary of the all plenary sessions that took place in Sydney can be found at www.myeloma.org. A printed guide to the workshop with a companion DVD containing key sessions and interviews will be published shortly by the IMF. Abstracts of the posters and presentations were published in a special supplement of the journal *Haematologica* as part of the April 20, 2005 issue.

Oral Presentations:

Phase I Study of the safety and efficacy of bortezomib (Velcade) in combination with lenalidomide (Revlimid) in relapsed and refractory multiple myeloma.

Richardson PG, Schlossman R, Munshi N, *et al.*

Plenary Session 5: New Therapeutic Agents

Because both agents are antiangiogenic and have immunomodulatory effects, the expectation was that the combination would overcome resistance to therapy and enhance overall efficacy. The objective of this study was to identify the maximum tolerated dose (MTD) and recommended dose for a phase II trial. At this stage the researchers presented results from 10 of 11 patients enrolled and showed an overall response of 91%. The MTD has not yet been reached and the last available cohort received 1.3mg/m² bortezomib and 10mg of lenalidomide. Dr. Richardson indicated that the future trials will include a phase II study in relapsed/refractory patients and a phase II study in newly-diagnosed patients.

Total therapy for newly diagnosed multiple myeloma: the Arkansas experience

Barlogie B

Plenary Session 4: Autologous Transplantation

The presentation was an update on total therapy 2 (TT 2) versus total therapy 1 (TT 1). Dr. Barlogie reviewed data supporting the superiority of TT 2 over TT 1 with improved CR duration and doubled EFS. TT 3, a successor protocol including Velcade with DT PACE, shortens the induction phase to 2 cycles to allow for completion of tandem transplants. Dr. Barlogie cautioned that the study is ongoing and that results will be discussed at future meetings in 2005

In vitro activity of a novel small molecule cyclin dependent kinase inhibitor, CYC202 (seliciclib or RRoscovotine), in multiple myeloma

Raje N

Focus Session 11: Experimental Agents

CYC202 (seliciclib or R-Roscovotine) is a purine analog that has shown activity in 19 human cancer cell lines and is currently being evaluated in ongoing phase I trials. Within 24 hours, CYC202 induces cytotoxicity in myeloma cells sensitive or resistant to conventional chemotherapy or steroids. Dr. Raje has also shown that CYC202 is synergistic with Velcade and doxorubicin; a situation which should be explored in future trials.

Combined farnesyl transferase inhibition and proteasome inhibition synergistically induce apoptosis via downregulation of p-AKT

Lonial S

Focus Session 11: Experimental Agents

The farnesyl transferase inhibitor, tipifamib, blocks the RAS pathway and induces apoptosis in myeloma cells while Velcade has proven efficacy in myeloma in several clinical settings. The author of this study shows that the combination of these two agents results in greater response than with either given individually. In combination rapid caspase dependant and independent apoptosis is induced.

Lack of Mcl-1 confers resistance to bortezomib and melphalan but not doxorubicin

Le Gouill S

Focus Session 12: Drug resistance, mechanisms and treatment strategies

Mcl-1 is an antiapoptotic protein that protects myeloma cells against spontaneous and dexamethasone-induced apoptosis. This particular study investigated the role of Mcl-1 in bortezomib-induced apoptosis in comparison to conventional therapies doxorubicin and melphalan. Dr. Le Gouill's analysis suggests that bortezomib and melphalan, but not doxorubicin, triggers Mcl-1-dependent-induced apoptosis pathways.

Tumor immune interactions in myeloma

Dhodapkar M

Plenary Session 11: Immune Biology

Dr. Dhodapkar discussed some of his current research including phase I trial data exploring whether natural killer (NKT) cells could be reliably and specifically manipulated in patients. He showed that it is possible to expand the number of NKT cells in patients but these cells mediate activation of T cell immunity by a third party dendritic cell (DC) in vivo. The question of how to maintain the expansion of NKT cells in patients by vaccines is being explored. Dr. Dhodapkar postulated that effective suppression of myeloma requires that myeloma cells and DC be targeted by a proteasome inhibitor such as Velcade.

The role of Wnt signaling in myeloma and its interaction with marrow stromal cells

Tian E

Focus Session 8: Bone and Tumour Microenvironment

Dr. Tian examined the role of over expressed DKK1 in patients with myeloma bone disease. In a mouse model, a monoclonal antibody used against DKK1 showed increased numbers of osteoblasts, reduced number of osteoclasts, reduced bone loss, and reduced tumor burden. Additionally, data shows that DKK1 can be activated by genotoxic and non-genotoxic agents in other tumor cells, activated by tumor and non-tumor cells, activated by thalidomide and other drugs, but not activated by Velcade or other proteasome inhibitors.

Poster Sessions:

[PO.720] Bortezomib demonstrates superior efficacy compared with high-dose dexamethasone, with predictable toxicity.

Richardson PG, Sonneveld P, Schuster MW, Irwin D, *et al.*

This is the final report from the multi-center, international APEX trial; the largest study to date in relapsed myeloma. Patients who had previously received 1-3 prior therapies were randomized to receive either bortezomib 1.3 mg/m² or dex 40 mg (669 patients total). The results showed bortezomib to be superior to dex, demonstrating a highly significant 78% improvement in median time to progression (hazard ratio 0.55, $p < 0.0001$), higher response rates using EBMT criteria (complete + partial response, 38% vs 18%; $p < 0.0001$), and an improvement in 1-year survival (80% vs 66%, $p = 0.0025$). The safety profile of bortezomib was predictable and manageable.

[PO.721] Bortezomib at first relapse is superior to high-dose dexamethasone and more effective than when given later in relapsed multiple myeloma

Sonneveld P, Richardson PG, Schuster MW, Irwin D, *et al.*

This paper is further analysis of the APEX trial data. The key observation made in this paper was that Velcade appeared to result in a longer time to progression (TTP) and higher response rate (RR) when used earlier as second line compared with its use as later salvage therapy. It is also important to note that it was unaffected by type of prior therapy, except when that prior therapy included thalidomide.

[PO.722] Bortezomib induces remissions in patients with relapsed/refractory myeloma independent of their cytogenetic risk profile and addition of dexamethasone or dexamethasone plus chemotherapy can restore responsiveness.

Ludwig H, Zojer N, Ackermann J, Kaufmann H, *et al.*

This study involved 30 pre-treated patients and looked at the efficacy of Velcade in relation to the cytogenetics of particular patients. Interestingly the paper showed that: (a) Velcade was effective regardless of cytogenetics present [including one with del(13q) plus translocation t(4;14)(p16;q32)] with an overall response of 42% for Velcade alone and (b) the addition of dex can induce a further response after the initial response to Velcade has faded.

[PO.724] Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma. Preliminary results of an IFM Phase II study

Harousseau JL, Attal M, Leleu X, Gressin R, *et al.*

The preliminary data reported here includes 48 patients recruited to the trial as of August 2004. So far the overall response rate was 75% and the CR rate was 21%. The side effects observed were usually mild (grade 1/2) only and in all cases stem cells could be adequately collected. Complete results will be reported later in 2005.

[PO.725] Bortezomib therapy alone and in combination with dexamethasone for patients with previously untreated multiple myeloma

S Jagannath S, Durie BMG, Wolf J, Camacho E, *et al.*

In this study Velcade (1.3 mg/m²) was administered on days 1, 4, 8, and 11 of a 3-week cycle for a maximum of 6 cycles. Oral dex 40 mg was given to patients who achieved < partial response (PR) after 2 cycles or < complete response (CR) after 4 cycles. Initial data includes results from 40 patients. Bortezomib alone or in combination with dex was highly active in the first-line treatment of patients with myeloma overall response rate (ORR) 85%, CR/nCR 20%. The combination of bortezomib + dex demonstrated additional benefit. Toxicities were manageable and reversible. Although experience has been limited to date, stem cell transplantation was successful in all attempts.

[PO.726] A Phase I/II national, multiple-center, open-label study of Velcade plus melphalan and prednisone (V-MP) in elderly untreated multiple myeloma patients

Mateos MV, Blade J, Diaz Mediavilla J, Lahuerta JJ, *et al.*

This study includes 47 patients - 12 in the phase I and 35 in the phase II. The results of the phase I section of the trial recommended a phase II dose of 1.3 mg/m² of Velcade in combination with melphalan and prednisone. So far, no patient has developed dose limiting toxicity (DLT.) The combination of V-MP is well tolerated with a manageable toxicity. Significant M-protein responses have been observed. Initial results of the phase II trial show a 92% overall response. Complete results will be presented later in the year.

[PO.727] Bortezomib in combination with dexamethasone for relapsed multiple myeloma

Kropff M, Bisping G, Schuck E, Berde W, *et al.*

Fifteen consecutive patients with relapsed multiple myeloma were enrolled in this study and scheduled to receive bortezomib 1.3 mg/m² for up to 8 cycles, in combination with dexamethasone 20mg PO once daily on the day of bortezomib injection and the day thereafter. Results are not complete but preliminary analysis suggests that bortezomib may be safe even in patients with poor bone marrow reserve, who would not have been candidates for the SUMMIT trial. Though the remission rate was high, remissions often were not durable. This fact underlines the need for consolidating treatment and evaluation of bortezomib combinations with other anti-myeloma agents.

[PO.728] Bortezomib in combination with melphalan in the treatment of relapsed or refractory multiple myeloma: A phase I/II study

Berenson JR, Yang HH, Swift R, *et al.*

Twenty-two heavily pretreated patients have been accrued to the study. Responses were observed in 70% (21/30) of patients [CR/PR 50%, median time to progression (TTP) and overall survival not reached]. The complete response (CR) and near CR occurred in patients receiving bortezomib 1.0 mg/m² in combination with melphalan .025 mg/kg however the maximum tolerated dose (MTD) was 1.0 mg/m² bortezomib, 0.10 mg/kg melphalan. Partial response (PR) or better was independent of prior type of therapy, and was also observed among patients who had previously received melphalan or bortezomib.

[PO.730] Bortezomib and pegylated liposomal doxorubicin as initial therapy for adult patients with symptomatic multiple myeloma: CALGB Study 10301

Orlowski RZ, Peterson BL, Caligiuri MA, Kelly M, *et al.*

Previous studies have shown combinations of anthracycline and proteasome inhibitors to have enhanced, possibly synergistic anti-tumor activity in both in vitro and in vivo model systems. This particular research builds on a previous phase I study [36% CR, 73 % OR] and enrolled patients will receive Velcade at 1.3 mg/m² on days 1, 4, 8, and 11 of every 21-day cycle, while pegLD is being given at 30 mg/m² on day 4. Accrual is now complete; preliminary shows 80 % RR in 15 evaluable patients. Complete data will be presented later in the year.

[PO.731] Velcade, doxil and low-dose thalidomide as salvage regimen for patients with relapsed or refractory multiple myeloma and Waldenstroms Macroglobulinemia: Preliminary results of a phase II study

Chanan-Khan A, Millar KC, DiMiceli LA, McCarthy P, *et al.*

The idea behind this study is to target the bone marrow micro environment (ME) at the same time as the malignant myeloma cells in order to overcome resistance in patients with refractory myeloma. Velcade targets the ME by down regulation of IL-6 through inhibitory effect on NFkB, while thalidomide, exerts its anti-myeloma effect through perturbation of the myeloma ME via down regulation of IL-6, VEGF and TNF-a. The authors of this study combined VT (to target the ME) with doxil (D) (to target myeloma cell). Initial results are promising and show that of 16 patients enrolled, 63% showed a clinical response 28% CR IF-, 38% PR.

[PO.732] Combination therapy of PS-341 (bortezomib), adriamycin and dexamethasone (PAD) for untreated patients with multiple myeloma.

Popat R, Oakervee H, Curry N, Morris C, *et al.*

This is a very exciting study that has shown at least a partial response (PR) in 95% of 21 patients in the first cohort. Preliminary data suggests that PAD chemotherapy is not only well tolerated, but highly efficacious in the front line therapy of multiple myeloma. Stem cell collection is not affected. The early results for cohort 2 imply that the toxicity profile is improved with the lower dose of bortezomib (1.0 mg/m² vs. 1.3 mg/m²) although sufficient response data is not yet available to make conclusions. Initial data shows a response rate (RR) of 83% at the lower dose; complete results will be reported later in the year.

[PO.813] Combination of receptor tyrosine kinase inhibition, proteasome inhibition and dexamethasone enhances apoptosis in cytogenetically defined multiple myeloma subgroups

Bisping G, Wenning D, Dreyer B, Kropff M, *et al.*

This study explored whether combinations of highly selective targeted strategies, such as RTK inhibition, blocking VEGF and FGF signaling, and more unspecific antimyeloma agents, including Velcade and dexamethasone, are capable of enhancing apoptosis in cytogenetically defined myeloma subgroups. The results displayed significant induction of apoptosis in t(4;14) and t(14;16) positive myeloma by incubation with the receptor tyrosine kinase inhibitor BIBF1000. Co-incubation with the Velcade, or dexamethasone or a combination of these drugs revealed an increase of apoptosis. In parallel, a markedly higher proportion of cleaved caspase-3, caspase-8 and PARP was found, while caspase-9 was not activated when combining BIBF1000, Velcade, or dexamethasone. This study provides the rationale for clinical trials of these combinations

[PO.901] Bortezomib targets multiple myeloma endothelial cells

Roccaro AM, Hideshima T, Raje N, Kumar S, *et al.*

Investigators in this study evaluated whether anti-angiogenesis may contribute to the anti-myeloma activity of Velcade; endothelial cells (ECs) were isolated from the bone marrow of patients with myeloma. Velcade inhibited *in vitro* multiple myeloma endothelial cells (MMEC) and HUVEC functions related to angiogenesis, including proliferation, chemotaxis, spreading on FN, and capillary formation. A significant concentration-dependent reduction of VEGF and IL-6 production was observed. Importantly, binding of MM.1S cells to MMECs triggers tumor cell proliferation; which was also inhibited.

 **Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impaired renal function.**

Jagannath S, Barlogie B, Berenson JR, Singhal S, *et al.*
Cancer. 2005 Mar 15;103(6):1195-200.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15690325

This is the first study to look specifically at the activity of Velcade in patients with impaired kidney function. Efficacy of Velcade was assessed in relation to baseline creatinine clearance (CrCl); 256 relapse patients were involved and received a 21-day cycle at 2 doses, 1.0 mg/m² (n = 28 patients) and 1.3 mg/m² (n = 228 patients). Results suggest that bortezomib provides clinical benefit with manageable toxicities in this high-risk population.

 **Phase I trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies.**

Orlowski RZ, Voorhees PM, Garcia RA, *et al.*
Blood. 2005 Apr 15;105(8):3058-65. [Epub 2004 Dec 30].

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15626743

It has been shown previously that proteasome inhibitors enhance the antitumor efficacy of anthracyclines. This study looks at the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of Velcade and pegylated liposomal doxorubicin (PegLD). The combination showed complete response (CR) or partial response (PR) in 16 of the 22 myeloma patients involved (including several with anthracycline-refractory disease).

 **Efficacy of bortezomib therapy for extramedullary relapse of myeloma after autologous and non-myeloablative allogeneic transplantation.**

Patriarca F, Prosdocimo S, Tomadini V, *et al.*
Haematologica. 2005 Feb; 90(2):278-9.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15710593

This paper described the successful treatment of extramedullary disease in relapse with Velcade.

 **A Phase I and pharmacologic trial of two schedules of the proteasome inhibitor, PS-341 (Bortezomib, Velcade), in patients with advanced cancer.**

Dy GK, Thomas JP, Wilding G, Bruzek L, *et al.*
Clin Cancer Res. 2005 May 1;11(9):3410-6.

 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15867242

This study looked at the relative toxicities of two schedules for the administration of Velcade (44 patients total). The researchers concluded that Velcade was better tolerated if given 1.5 mg/m² twice weekly for 2 of every 3 weeks rather than twice weekly for 4 of 6 week

-  **Activity probe for in vivo profiling of the specificity of proteasome inhibitor bortezomib.**
Berkers CR, Verdoes M, Lichtman E, *et al.*
Nat Methods. 2005 Apr 21; 2(5):357-362 [Epub ahead of print].
 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15846363
This report describes the synthesis and use of a cell-permeant active site-directed probe, which allows profiling of proteasomal activities in living cells. When compared proteasome activity patterns in cultured cells and crude cell extracts with this probe, substantial differences were observed, stressing the importance for bioassays compatible with live cells to ensure accuracy of such measurements.
-  **High serum bone-specific alkaline phosphatase level after bortezomib-combined therapy in refractory multiple myeloma: possible role of bortezomib on osteoblast differentiation.**
Shimazaki C, Uchida R, Nakano S, Namura K, *et al.*
Leukemia. 2005 Apr 14; [Epub ahead of print].
 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15830008
-  **Mitochondrial-mediated disregulation of Ca²⁺ is a critical determinant of Velcade (PS-341/Bortezomib) cytotoxicity in myeloma cell lines.**
Landowski TH, Megli CJ, Nullmeyer KD, *et al.*
Cancer Res. 2005 May 1;65(9):3828-36.
 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15867381
Although Velcade has been shown to be very active in myeloma, the actual mechanism of action is not well understood. In this study oligonucleotide microarray analysis of the 8226 multiple myeloma cell line support the hypothesis that intracellular Ca(2+) disregulation is a critical determinant of bortezomib cytotoxicity.
-  **Combining proteasome inhibition with TNF-related apoptosis-inducing ligand (Apo2L/TRAIL) for cancer therapy.**
Sayers TJ, Murphy WJ.
Cancer Immunol Immunother. 2005 Apr 28; [Epub ahead of print].
 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15864587
Recent studies have shown that apoptosis in myeloma cell can be induced with exposure to members of the tumor necrosis factor (TNF) superfamily. This study expands upon that work and explores the possibility of combining the Apo2L/TRAIL (TNF-related apoptosis-inducing ligand) with Velcade.
-  **Bik/NBK accumulation correlates with apoptosis-induction by bortezomib (PS-341, Velcade) and other proteasome inhibitors.**
Zhu H, Zhang L, Dong F, Guo W, *et al.*
Oncogene. 2005 Apr 11; [Epub ahead of print].
 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15824729

 The proteasome inhibitor bortezomib sensitizes cells to killing by death receptor ligand TRAIL via BH3-only proteins Bik and Bim.

Nikrad M, Johnson T, Puthalalath H, *et al.*
Mol Cancer Ther. 2005 Mar; 4(3):443-9.



http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15767553

 p38 MAPK inhibition enhances PS-341 (bortezomib)-induced cytotoxicity against multiple myeloma cells.

Hideshima T, Podar K, Chauhan D, *et al.*
Oncogene. 2004 Nov 18;23(54):8766-76.



http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15480425

It has been shown previously that heat shock protein (Hsp)27 is upregulated after PS-341 treatment, that over expression of Hsp27 confers PS-341 resistance, and that inhibition of Hsp27 overcomes PS-341 resistance. In this study, although p38 MAPK inhibitor SCIO-469 alone did not induce significant growth inhibition, it blocked baseline and PS-341-triggered phosphorylation of p38 MAPK as well as upregulation of Hsp27, associated with enhanced cytotoxicity in MM.1S cells. Importantly, SCIO-469 enhanced phosphorylation of c-Jun NH2-terminal kinase (JNK) and augmented cleavage of caspase-8 and poly(ADP)-ribose polymerase.

LICENSING UPDATE:

Velcade receives approval from both the Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMA) as a second line treatment for myeloma. This approval expands the label to include the treatment of multiple myeloma patients who have received at least one prior therapy. The approval was based on data from the randomized phase III APEX study that compared single-agent Velcade to high-dose dexamethasone (669 patients with relapsed or refractory myeloma at 93 centers in North America, Europe and Israel). The study demonstrated a statistically significant survival advantage in the Velcade arm of the study.

CLINICAL TRIALS UPDATE

Phase III Vista Trial (VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone)

This is a large, multicenter, international phase III clinical trial of Velcade in combination with melphalan and prednisone versus melphalan and prednisone in newly diagnosed patients who are not planning a stem cell transplants. It will assess efficacy, overall safety and tolerability of the combination versus melphalan and prednisone alone.

Phase IV Everest Trial (Evaluation of VELCADE Employed as Retreatment for Efficacy, Safety and Tolerability)

The Everest Trial is a multicenter phase IV clinical trial of Velcade designed to evaluate the efficacy of retreatment in patients who have previously responded to Velcade and relapsed following a treatment-free remission. It will involve 80 sites in the United States.

Other current trials include:

- **UCLA-0409110-01, JJPRD-26866138-MMY-3002** - Phase III Randomized Study of Melphalan and Prednisone With Versus Without Bortezomib in Older Patients With Newly Diagnosed Multiple Myeloma
- **DOXIL MMY 3001 (NCT00103506)** - Phase III of Doxil/Caelyx and Velcade or Velcade Monotherapy for the Treatment of Relapsed Multiple Myeloma
- **UCLA-0306106, MILLENNIUM-MM2003 (NCT00084747)** - Phase I/II Study of Adjuvant Bortezomib as Maintenance Therapy After Autologous Peripheral Blood Stem Cell Transplantation in Patients With Intermediate or Advanced Multiple Myeloma
- **UARK 2001-37, (NCT00083460)** - Study of Combination Velcade and Thalidomide in Multiple Myeloma
- **UARK 2003-33 (NCT00081939)** - Total Therapy III
- Phase I Study of Velcade with Revlimid in Relapsed and Refractory MM: The RevVel Study



www.myeloma.org