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SPECIAL EDITION: ASH 2004

Velcade® (bortezomib) Issue

The International Myeloma Foundation (IMF) is pleased to present our first VELCADE® (bortezomib)-focused edition of CITINGS, our newest 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 46th American Society of Hematology (ASH) annual meeting in San Diego, California. In this issue, readers will find three key resources related to VELCADE: 1) a list of selected bortezomib data being presented at the ASH meeting, along with dates and times of each presentation, 2) a list of selected bortezomib-related studies presented at the European Hematology Association meeting, 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 ASH 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 Hematology Presentations 2004

[929] Addition of Bortezomib (VELCADE) to High-Dose Melphalan (Vel-Mel) as an Effective Conditioning Regimen with Autologous Stem Cell Support in Multiple Myeloma (MM).

Session Type: Poster Session 83-I

Authors: Klaus Hollmig, Julie Stover, Giampalamo Talamo, Maurizio Zangari, Raymond Thertulien, Frits van

Rhee, Athanasios Fassas, Elias Anaissie, Guido Tricot, Bart Barlogie

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Autologous Transplantation in Multiple Myeloma and Amyloidosis (6:00 -7:30 PM)

[1478] PAD Combination Therapy (PS-341/Bortezomib, Adriamycin and Dexamethasone) for Previously Untreated Patients with Multiple Myeloma.

Session Type: Poster Session 632-I

Authors: James D. Cavenagh, Rakesh Popat, Nikki Curry, Jim Stec, Treen C. Morris, Mary Drake, Samir

Agrawal, Patricia Smith, David P. Schenkein, Dixie-Lee Esseltine, Heather Oakervee

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant I (6:00 -7:30 PM)

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[1480] Marked Activity of VELCADE Plus Thalidomide (V+T) in Advanced and Refractory Multiple Myeloma (MM).

Session Type: Poster Session 634-I

Authors: Maurizio Zangari, Bart Barlogie, Klaus Hollmig, Athanasios Fassas, Erik Rasmussen, Raymond

Thertulien, Giampaolo Talamo, Choon-Kee Lee, Guido Tricot

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant I (6:00 PM-7:30 PM)

[1481] Predicting Event-Free and Overall Survival after Treatment of Myeloma with the Proteasome Inhibitor Bortezomib with Pre-Treatment and 48-Hour Post-Therapy Gene Expression Patterns.

Session Type: Poster Session 635-I

Authors: William Barlow, Zhan Fenghuang, Yongsheng Huang, Sisi Kapp, Erik Rasmussen, Bart Barlogie, John

Crowley, John Shaughnessy

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant I (6:00 PM-7:30 PM)

[1486] Circulating Proteasome Level Is an Independent Prognostic Factor for Survival in Patients with Multiple Myeloma.

Session Type: Poster Session 640-I

Authors: Christian Jakob, Karl Egerer, Eugen Feist, Ivana Zavrski, Jan Eucker, Ulrike Heider, Gerd Burmester,

Kurt Possinger, Peter M. Kloetzel, Orhan Sezer Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant I (6:00 PM-7:30 PM)

[1490] Bortezomib (VELCADE) 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.

Session Type: Poster Session 644-I

Authors: Jean-Luc Harousseau, Michel Attal, Xavier Leleu, Remy Gressin, Cyrille Hulin, Jean-Gabriel Fuzibet, Jacques Troncy

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant I (6:00 -7:30 PM)

[1651] Results of Bortezomib (BTZ) Therapy for Myeloma (MM) Patients Relapsing after an Allogeneic Transplant. Preliminary Results Show Efficacy without Induction of GVHD.

Session Type: Poster Session 805-I

Authors: Sergio Giralt, Ana Aleman, Xin Lei, Marilyn Davis, Kerry Mickler, Donna Weber, Michael Wang,

Richard Champlin

Date/Time: Saturday, December 4, 2004 - 6:00 PM

Session Info: Poster Session: Relapse, Immune Responses, and Immunotherapy after Transplantation

(6:00 PM-7:30 PM)

[2399] Bortezomib (VELCADE) + Adriamycin + Thalidomide + Dexamethasone (VATD) as an Effective Regimen in Patients with Refractory or Relapsed Multiple Myeloma (MM).

Session Type: Poster Session 612-II

Authors: Klaus Hollmig, Julie Stover, Giampaolo Talamo, Athanasios Fassas, Choon-Kee Lee, Elias Anaissie,

Guido Tricot, Bart Barlogie

Date/Time: Sunday, December 5, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant III (6:00 -7:30 PM)

[2421] A Phase II Study of VELCADE (V), Doxil (D) in Combination with Low-Dose Thalidomide (T) as Salvage Therapy for Patients (pts) with Relapsed (rel) or Refractory (ref) Multiple Myeloma (MM) and Waldenstrom Macroglobulinemia (WM): Encouraging Preliminary Results.

Session Type: Poster Session 634-II

Authors: Asher Alban Chanan-Khan, Kena C. Miller, Philip McCarthy, Laurie A. DiMiceli, Jihnee Yu, Zale P.

Bernstein, Myron S. Czuczman

Date/Time: Sunday, December 5, 2004 - 6:00 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant III (6:00 -7:30 PM)

[209] Bortezomib in Combination with Melphalan in the Treatment of Relapsed or Refractory Multiple

Myeloma: A Phase I/II Study. Session Type: Oral Session

Authors: James Berenson, H. Yang, R. Swift, K. Sadler, R. Vescio, J. Adams, D. Schenkein

Date/Time: Monday, December 6, 2004 - 7:30 AM

Session Info: Simultaneous Session: Myeloma Therapy (7:30 -9:00 AM)

[210] VTD (VELCADE, Thalidomide, Dexamethasone) as Primary Therapy for Newly-Diagnosed Multiple Myeloma.

Session Type: Oral Session

Authors: Raymond Alexanian, Luhua M. Wang, Donna M. Weber, Kay B. Delasalle

Date/Time: Monday, December 6, 2004 - 7:30 AM

Session Info: Simultaneous Session: Myeloma Therapy (7:30 -9:00 AM)

[268] Economic Evaluation of Bortezomib (VELCADE) for Relapsed and Refractory Multiple Myeloma.

Session Type: Oral Session

Authors: Adrian Bagust, Alan R. Haycox, Angela Boland, Patrick Chu, Gareth J. Morgan, Ruben E. Mujica

Mota, Dominique Dubois, Ravinder Dhawan

Date/Time: Monday, December 6, 2004 - 11:00 AM

Session Info: Simultaneous Session: Clinical Trials and Drug Approval (11:00 AM-12:30 PM)

[333] A Phase 2 Study of Bortezomib as First-Line Therapy in Patients with Multiple Myeloma.

Session Type: Oral Session

Authors: Sundar Jagannath, Brian Durie, Jeffrey L. Wolf, Elber Camacho, David Irwin, Jose Lutzky, Marti

McKinley, Eli Gabayan, Amitabha Mazumder, John Crowley, David Schenkein

Date/Time: Monday, December 6, 2004 - 11:30 AM

Session Info: Simultaneous Session: Myeloma Therapy Novel Agents (11:00 AM-12:30 PM)

[336] Phase II Trial of Single Agent Bortezomib (VELCADE) in Patients with Previously Untreated Multiple Myeloma (MM).

Session Type: Oral Session

Authors: Paul G. Richardson, Asher Chanan-Khan, Robert L. Schlossman, Nikhil C. Munshi, Patrick Wen,

Hannah Briemberg, David Kuter, Anne-Louise Oaklander, Sagar Lonial, Hani Hassoun, Deborah Doss,

Kathleen Colson, Mary McKenney, Karen Hande, Alexandra Koryzna, Barbara Stoklas, Laura Lunde, Svetlana Gorelik, Cliona McAlister, Andrea Freeman, Diane Warren, Denise Collins, Dixie Esseltine, Anthony Amato,

Kenneth C. Anderson

Date/Time: Monday, December 6, 2004 - 11:00 AM

Session Info: Simultaneous Session: Myeloma Therapy Novel Agents (11:00 AM-12:30 PM)

[336.5] Bortezomib Demonstrates Superior Efficacy to High-Dose Dexamethasone in Relapsed Multiple Myeloma: Final Report of the APEX Study.

Session Type: Oral Session

Authors: Paul Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. Harousseau, D. Ben-Yehuda, S. Lonial, H. Goldschmidt, D. Reece, J. San Miguel, J. Blade, M. Boccadoro, J. Cavenagh, W.

Dalton, A. Boral, D. Schenkein, K. Anderson

Date/Time: Monday, December 6, 2004 - 11:00 AM

Session Info: Simultaneous Session: Myeloma Therapy Novel Agents (11:00 AM-12:30 PM)

[538] Total Therapy 3 (TT 3) for Newly Diagnosed Myeloma, Incorporating VELCADE into Remission Induction with DT PACE: Early Results Regarding Efficacy, PBSC Mobilization and Toxicities.

Session Type: Oral Session

Authors: Bart Barlogie, Klaus Hollmig, Maurizio Zangari, Julie Stover, Lisa Jackson, Teresa Milner, Athanasios

Fassas, Guido Tricot

Date/Time: Monday, December 6, 2004 - 3:30 PM

Session Info: Simultaneous Session: Autologous Stem Cell Transplantation in Multiple Myeloma and

Amyloidosis (3:30 -5:30 PM)

[541] Bortezomib Given in Sequence with Anthracycline and Thalidomide-Containing Regimens Does Not Adversely Affect Stem Cell Mobilization and Engraftment in Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation.

Session Type: Oral Session

Authors: Geoffrey L. Uy, Nicholas M. Fisher, Steven M. Devine, Hanna J. Khoury, Douglas R. Adkins,

Michael H. Tomasson, Timothy A. Graubert, John F. DiPersio, Ravi Vij

Date/Time: Monday, December 6, 2004 - 3:30 PM

Session Info: Simultaneous Session: Autologous Stem Cell Transplantation in Multiple Myeloma and

Amyloidosis (3:30 -5:30 PM)

[3462] A Phase I/II National, Multi-Center, Open-Label Study of Bortezomib Plus Melphalan and Prednisone (V-MP) in Elderly Untreated Multiple Myeloma Patients.

Session Type: Poster Session 732-III

Authors: M.V. Mateos, Joan Blade, J. Diaz Mediavilla, J.J. Lahuerta, M.J. Terol, J. Hernández, M.J. Moro, J. Bargay, J.M. Ribera, J. de la Rubia, A. Sureda, D. Carrera, F. de Arriba, L. Palomera, M. Hernández, J. García

Laraña, A. Alegre, F. Prosper, P. Rivas, D.L. Esseltine, D. Schenkein, J.F. San Miguel

Date/Time: Monday, December 6, 2004 - 5:30 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant III (5:30 -7:00 PM)

[3468] Use of Patient-Reported Outcomes (PROs) to Assess Prognosis, Toxicity, and Response: The Bortezomib Experience in Relapsed and Refractory Multiple Myeloma (MM).

Session Type: Poster Session 738-III

Authors: Dominique Dubois, Dhawan Ravinder, Helgi van de Velde, Dixie Esseltine, Sanjay Gupta, Muriel

Viala, Christine de la Loge

Date/Time: Monday, December 6, 2004 - 5:30 PM

Session Info: Poster Session: Myeloma Therapy - Non-Transplant III (5:30 PM-7:00 PM)

European Hematology Association Presentations 2004

Survival, Duration of Response, and Time to Progression with Bortezomib in Patients with Relapsed and Refractory Multiple Myeloma: An Update with Additional Follow-Up. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Srkalovic G, Alsina M, Alexanian R, Siegel D, Orlowski R, Kuter D, Hideshima T, Esseltine DL, Anderson KC.

Hematology Journal 2004; 5(supplement 2):S103-4.

Meaningful long-term survival benefits were observed with additional bortezomib therapy beyond 8 cycles and with long-term follow-up in patients enrolled in a phase 2 trial, SUMMIT.

Bortezomib in Combination With Dexamethasone for the Treatment of Patients With Relapsed and/or Refractory Multiple Myeloma. Jagannath S, Richardson PG, Barlogie B, Berenson JR, Singhal S, Irwin D, Srkalovic G, Schenkein D, Esseltine D, Anderson KC.

Hematology Journal 2004; 5(supplement 2):S130.

Bortezomib in combination with dexamethasone provided additional clinical responses in patients with relapsed and/or refractory myeloma. There was preliminary evidence that bortezomib could overcome previous dexamethasone resistance in a subset of patients with dexamethasone-refractory disease.

Evaluation of the Severity and Risk of Thrombocytopenia With Bortezomib Therapy in Relapsed and Refractory Multiple Myeloma. Lonial S, Waller EK, Richardson PG, Jagannath S, Francis D, Lehman M, Torre C, Barlogie B, Berenson JR,

Singhal S, Schenkein D, Esseltine DW, Anderson J, Xiao H, Heffner LT, Anderson KC.

Hematology Journal 2004; 5(supplement 2):S130-1.

The authors reported that when thrombocytopenia occurs with bortezomib therapy, it is predictable and transient, with a return to baseline levels during rest periods among patients. The rapidity of platelet recovery suggested that the mechanism of thrombocytopenia is not related to marrow destruction, and thus may not be dose limiting.

Factors Predictive of Clinical Outcome With Bortezomib (VELCADE) in Patients With Relapsed, Refractory Multiple Myeloma. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Hideshima T, Bryant, Xiao H, Esseltine DL, Schenkein D, Anderson K.

Hematology Journal 2004; 5(supplement 2):S128.

In a multivariate analysis, the authors found that factors predictive of outcome with bortezomib in patients with relapsed, refractory myeloma tended to be associated with high tumor burden. Patients \geq 65 years of age who respond to bortezomib may experience the same clinical benefit as younger patients.

The Safety of Prolonged Therapy With the Proteasome Inhibitor Bortezomib (VELCADE) in Relapsed and/or Refractory Multiple Myeloma. Berenson JR, Jagannath S, Barlogie B, Siegel D, Alexanian R, Irwin D, Grkalovic G, Richardson PG, Ellestine DL, Anderson KC.

Hematology Journal 2004; 5(supplement 2):S129.

The authors described clinical experience with bortezomib beyond 8 cycles and reported that bortezomib ± dexamethasone can be administered for up to 32 cycles and have a safety profile that is similar to that of the first 8 cycles of treatment.

Phase 1 Study of the Proteasome Inhibitor Bortezomib and Pegylated Liposomal Doxorubicin in Patients With Advanced Hematology Malignancies. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Adams J, Esseltine DL, Gabriel DA, Shea TC, van Deventer HW, Mitchell BS, Dees EC.

Hematology Journal 2004; 5(supplement 2):S131.

The combination of bortezomib and pegylated liposomal doxorubicin was well tolerated and had significant activity in patients with multiple myeloma.

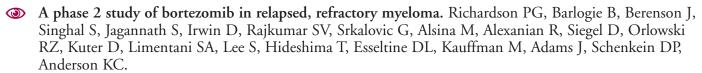
Characterization and Reversibility of Peripheral Neuropathy in Patients With Advanced Multiple Myeloma Treatment With Bortezomib (VELCADE). The SUMMIT and CREST Study Group.

Richardson R, Briemberg H. Jagannath S, Barlogie B, Berenson JR, Singhal S, Siegel DT, Irwin DH, Schuster MW, Srkalovic G, Orlowski R, Esseltine D, Wen P, Amato A, Anderson KC.

Hematology Journal 2004; 5(supplement 2):S129.

In a detailed analysis of the frequency, severity and clinical course of peripheral neuropathy in patients treated with bortezomib, the investigators concluded that peripheral neuropathy was reported in 35% of patients, was usually of mild to moderate severity, and had the potential for improvement or resolution during or after treatment in the majority of patients.

2004 VELCADE (BORTEZOMIB) Publications



New England Journal of Medicine 2003 Jun 26;348(26):2609-17.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1 2826635

Bortezomib was found to be active in patients with relapsed multiple myeloma that was refractory to conventional chemotherapy in this important phase 2 study. Treatment with bortezomib alone produced a rate of response of 35 percent in patients evaluated using the criteria of the European Group for Blood and Marrow Transplantation.

- Treatment with a proteasome inhibitor, bortezomib, for thalidomide-resistant multiple myeloma. Takatoku M, Noborio-Hatano K, Takahashi S, Kikuchi S, Mori M, Muroi K, Komatsu N, Ozawa K. Rinsho Ketsueki. 2004 Feb;45(2):144-8.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=150 45823

This is the first report of the use of bortezomib in the treatment of refractory multiple myeloma in Japan.

- New developments with bortezomib in treating multiple myeloma. Reddy GK. Clinical Lymphoma 2004 Mar;4(4):215-6.
- www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15072611
 No abstract available.
- A review of the proteasome inhibitor bortezomib in multiple myeloma. Richardson PG. Expert Opinion on Pharmacotherapy 2004 Jun;5(6):1321-31.
- www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163277
 The first-in-class proteasome inhibitor, bortezomib was recently approved in the US for the treatment of patients with MM who have received at least two prior therapies and are progressing on their last therapy. Its use in earlier-stage MM, other hematological malignancies, in solid tumors as monotherapy, and in combination therapy is currently under investigation.
- © Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. Mehta J, Duff SB, Gupta S. Managed Care Interface 2004 Sep; 17(9):52-61.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1 5521286

In a cost effectiveness analysis, bortezomib was found to be cost effective relative to best supportive care and thalidomide in patients with relapsed, refractory myeloma. The analysis suggested that bortezomib provided the best value in terms of cost/life-year gained among the currently available therapeutic options for relapsed, refractory myeloma.

- A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, Niesvizky R, Alexanian R, Limentani SA, Alsina M, Adams J, Kauffman M, Esseltine DL, Schenkein DP, Anderson KC.

 British Journal of Haematology 2004 Oct 11;127(2):165-72.
- http://www.blackwellsynergy.com/openurl?genre=article&sid=nlm:pubmed&issn=00071048&date=2004 &volume=127&issue=2&spage=165

 The authors found that bortezomib alone or in combination with dexamethasone demonstrated therapeutic activity in patients with multiple myeloma who relapsed after frontline therapy. Activity was demonstrated at two
 - The authors found that bortezomib alone or in combination with dexamethasone demonstrated therapeutic activity in patients with multiple myeloma who relapsed after frontline therapy. Activity was demonstrated at two dose levels, 1.3 and 1.0 mg/m2, when bortezomib was administered on days 1, 4, 8 and 11 of a 21-day cycle.
- Tumour lysis syndrome in multiple myeloma after bortezomib (VELCADE) administration. Terpos E, Politou M, Rahemtulla A.
 - Journal of Cancer Research and Clinical Oncology 2004 Oct;130(10):623-5.
- www.springerlink.com/app/home/contribution.asp?wasp=2dyrygwhvjckncjtxxww&referrer=parent&back to=issue,8,8;journal,3,92;linkingpublicationresults,1:101168,1
 - The authors conclude that bortezomib therapy, due to the rapidity of its action, may result in TLS in myeloma patients who have rapidly proliferative disease with a high tumor burden. Therefore, TLS should be looked for during the first cycle of bortezomib treatment and suitable precautions should be considered.
- Multiple Myeloma: The Emerging Role of Novel Therapies. Richardson PG, Mitsiades C. Oncology Special Edition 2004 Oct (web only).
- http://www.oncologyse.com/indexpub.cfm?pubid=16

 Novel therapeutic agents for the treatment of multiple myeloma offer encouraging new treatment options that may extend survival and offer the potential for cure. Among the agents described in this review are bortezomib, thalidomide and its analogs, and histone deacetylase inhibitors.



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