CITINGS

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VELCADE® (bortezomib) Issue

Welcome to 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 50th Annual American Society of Hematology (ASH) Meeting to be held December 6–9, 2008. Furthermore, 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 published in the fourth quarter of this year.*

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

– Susie Novis, President, IMF

American Society of Hematology Presentations 2008

Saturday, December 6, 2008

Genetic Origin of Myeloma
Marta Chesi, Peter Leif Bergsagel, and Michael Kuehl
Abstract No.: n/a **Location: 304-306-308 - South (Moscone Center)**
Time: 2:00 PM
High-Risk Myeloma (Scientific Program)

The Administration of Bortezomib, Dexamethasone and Thalidomide (VTD) after ASCT in Myeloma Patients Who Do Not Receive Bisphosphonates Normalizes sRANKL, Dickkopf-1 and Improves Abnormal Osteoclast Function and Impaired Angiogenesis
Evangelos Terpos, Efstathios Kastritis, Dimitrios Christoulas, Magdalini Migkou, Maria Gavriatopoulou and Meletios A. Dimopoulos
Time: 5:30 PM – 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 1728 **Poster Board: I-833**
Myeloma – Therapy, Excluding Transplantation Poster I

Antitumor Activity in a Human Multiple Myeloma (MM) Model Using Sorafenib, Bortezomib, and Dexamethasone Treatment
Julia Schüler, Dagmar Wider, Dietmar Pfeifer, Martin Wagner, Heinz-Herbert Fiebig and Monika Engelhardt
Abstract No.: 1720 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-825**
Myeloma – Pathophysiology and Preclinical Studies Excluding Therapy Poster I

Funded by an unrestricted educational grant from Millennium: The Takeda Oncology Company

Bortezomib Improves Endothelial Thromboresistance Via Induction of KLF Transcription Factors
Toyoko Hiroi, Clayton B Deming, Haige Zhao, Baranda S Hansen, Elisabeth K Arkenbout, Thomas J Myers, William J Riordan, Michael A McDevitt and Jeffrey J Rade
Abstract No.: 1890 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-995**
Vascular Wall Biology, Endothelial Progenitor Cells, and Platelet Adhesion Poster I

Bortezomib–Melphalan–Prednisone (VMP) in Newly Diagnosed Multiple Myeloma Patients with Impaired Renal Function: Cohort Analysis of the Phase III VISTA Study
Meletios A Dimopoulos, Paul Richardson, Rudolf Schlag, Nuriet K Khuageva, Ofer Shpilberg, Efstathios Kastritis, Martin H Kropff, Maria Teresa Petrucci, Michel Delforge, Julia A Alexeeva, Rik Schots, Tamas Masszi, Maria-Victoria Mateos, William Deraedt, Kevin Liu, Andrew Cakana, Helgi van de Velde and Jesus F San Miguel
Abstract No.: 1727 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-832**
Myeloma – Therapy, Excluding Transplantation Poster I

Bortezomib Overcomes Cell Adhesion-Mediated Drug Resistance Via Down-Regulation of VLA-4 Expression in Multiple Myeloma
Kaoru Hatano, Jiro Kikuchi, Masaaki Takatoku, Rumi Shimizu, Taeko Wada, Masuzu Ueda, Masaharu Nobuyoshi, Iekuni Oh, Kazuya Sato, Takahiro Suzuki, Katsutoshi Ozaki, Masaki Mori, Tadashi Nagai, Kazuo Muroi, Yasuhiko Kano, Yusuke Furukawa and Keiya Ozawa
Abstract No.: 1634 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-739**
Molecular Pharmacology, Drug Resistance Poster I

Bortezomib Targets Stroma-Mediated APO2L/TRAIL Apoptosis Resistance in Multiple Myeloma
Lia Perez, Nancy Parquet, Claudio Anasetti and William Dalton
Abstract No.: 1665 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-770**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster I

Immunomodulatory Effects of Lenalidomide and Bortezomib on Bone Marrow Stroma Cell and CD4 T Cell Interaction in Multiple Myeloma
Gullu Gorgun, Elisabetta Calabrese, Teru Hideshima, Hiroshi Ikeda, Giulia Perrone, Loredana Santo, Diana Cirstea, Paul G Richardson and Kenneth C Anderson
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 1690 **Poster Board: I-795**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster I

Lenalidomide, Bortezomib, and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Encouraging Response Rates and Tolerability with Correlation of Outcome and Adverse Cytogenetics in a Phase II Study
Paul Richardson, Sundar Jagannath, Andrzej Jakubowiak, Sagar Lonial, Noopur Raje, Melissa Alsina, Irene Ghobrial, Amitabha Mazumder, Nikhil C Munshi, David H Vesole, Kathleen Colson, Mary L McKenney, Laura Lunde, Sarah Kennedy, Kara Kosakowski, Constantine Mitsiades, Teru Hideshima, Robert D Knight, Dixie-Lee Esseltine, and Kenneth C Anderson
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 1742 **Poster Board: I-847**
Myeloma – Therapy, Excluding Transplantation Poster I

Primary Therapy with Bortezomib—the Role of Induction, Maintenance, and Re-Induction in Patients with High Risk Myeloma. Update of Results from E2A02
Angela Dispenzieri, Susanna Jacobus, David H. Vesole, S. Vincent Rajkumar and Philip R. Greipp
Abstract No.: 1738 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-843**
Myeloma – Therapy, Excluding Transplantation Poster I

Proteomic Profiling of Multiple Myeloma: Correlation of Protein and Gene Expression Data
Ricky D Edmondson, Sheeno P Thyparambil, Veronica MacLeod, Bart Barlogie, and John D. Shaughnessy Jr.
Abstract No.: 1705 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-810**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster I

Reversibility of Renal Impairment of Multiple Myeloma Patients Treated with Bortezomib-Based Regimens: Identification of Predictive Factors
Meletios A. Dimopoulos, Maria Roussou, Efstathios Kastritis, Maria Gavriatopoulou, Flora Zagouri, Magdalini Migkou, Charis Matsouka, Despina Barmparousi, Dimitrios Christoulas, Erasmia Psimenou, Irini Grapsa and Evangelos Terpos
Abstract No.: 1725 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: I-830**
Myeloma – Therapy, Excluding Transplantation Poster I

Treatment of Relapsed and Refractory Multiple Myeloma in Patients with p53 Deletion
Donna E. Reece, Young Trieu, Hong Chang, Wei Xu, Peter Anglin, Christine Chen, Vishal Kukreti, Suzanne Trudel, and Joseph Mikhael
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 1724 **Poster Board: I-829**
Myeloma – Therapy, Excluding Transplantation Poster I

Treatment of Patients with Relapsed/Refractory Multiple Myeloma (MM) with Lenalidomide and Dexamethasone with or with Bortezomib Depending on Prior Neurotoxicity: Prospective Evaluation of the Impact of Cytogenetic Abnormalities and Assessment
Meletios A. Dimopoulos, Efstathios Kastritis, Dimitrios Christoulas, Magdalini Migkou, Maria Gavriatopoulou, Flora Zagouri and Evangelos Terpos
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 1726 **Poster Board: I-831**
Myeloma – Therapy, Excluding Transplantation Poster I

Sunday, December 7, 2008

Lenalidomide, Bortezomib, and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Encouraging Efficacy in High Risk Groups with Updated Results of a Phase I/II Study
Paul Richardson, Sagar Lonial, Andrzej Jakubowiak, Sundar Jagannath, Noopur S Raje, David Avigan, Irene M Ghobrial, Robert L Schlossman, Amitabha Mazumder, Nikhil C Munshi, David H Vesole, Robin Joyce, Deborah Doss, Diane L Warren, Stephen W Hayes, Sarah Kaster, Carol Delaney, Marisa Lauria, Constantine Mitsiades, Teru Hideshima, Robert D. Knight, Dixie-Lee Esseltine, and Kenneth C Anderson
Time: 4:45 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 92
Myeloma Therapy: Newly Diagnosed Myeloma

Bortezomib Induces Thrombocytopenia by Inhibiting Proplatelet Formation but Not Proliferation and Endomitosis in Human Primary Megakaryocytes Clinically Relevant Abstract
Wataru Nogami, Akiko Yamane, Takanori Nakamura, Eri Matsuki, Yasuo Ikeda and Yoshitaka Miyakawa
Abstract No.: 87 **Location: 120-121-122-123-124-125 - North (Moscone Center)**
Time: 5:00 PM
Inherited and Acquired Platelet Disorders

Safety and Efficacy of Novel Combination Therapy with Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide in Newly Diagnosed Multiple Myeloma: Initial Results from the Phase I/II Multi-Center EVOLUTION Study
Shaji Kumar, Ian W Flinn, Stephen J. Noga, Parameswaran Hari, Robert M. Rifkin, Natalie Scott Callander, Manish Bhandari, Jeffrey Lee Wolf, Cristina Gasparetto, Amrita Krishnan, Daren D Grosman, Jonathan Glass, Entezam Asim Sahovic, Hongliang Shi, Iain J. Webb, Paul Richardson, and S. Vincent Rajkumar
Time: 5:00 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 93
Myeloma Therapy: Newly Diagnosed Myeloma

A Phase II Study of Bortezomib (VELCADE®), Cyclophosphamide (Cytoxan®), Thalidomide (Thalomid®) and Dexamethasone as First-Line Therapy for Multiple Myeloma
William Bensinger, Sundar Jagannath, Robert Vescio, Elber S. Camacho, Jeffrey Lee Wolf, David H Irwin, Gerardo Capo III, Marti McKinley, Phyllis Potts, David H. Vesole, Amitabha Mazumder, Dixie-Lee Esseltine, Pamela Becker, John Crowley, and Brian GM Durie.
Time: 5:15 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 94
Myeloma Therapy: Newly Diagnosed Myeloma

Acquired Resistance to Bortezomib in Human RPMI-8226 Multiple Myeloma Cells: Molecular Characterization, Cross-Resistance with Other Proteasome Inhibitors but Marked Sensitization to Glucocorticoids
Niels E Franke, Gertjan L Kaspers, Nynke van den Berg, Ina van Zantwijk, Katarina Vojtekova, Uzma Yaqub, Serge Smeets, Bauke Ylstra, Sonja Zweegman, Gerrit Jansen, and Jacqueline Cloos,
Abstract No.: 2640 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-734**
Molecular Pharmacology, Drug Resistance Poster II

Bortezomib and Dexamethasone as Maintenance therapy in Relapse/Refractory multiple myeloma Patients
Giulia Benevolo, Alessandra Larocca, Patrizia Pregno, Francesca Gay, Barbara Botto, Lorella Orsucci, Andrea Evangelista, Antonio Palumbo, Umberto Vitolo, and Mario Boccadoro
Abstract No.: 2771 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-865**
Myeloma – Therapy, Excluding Transplantation Poster II

Bortezomib, Intravenous Cyclophosphamide and Dexamethasone (VelCD) for Previously Untreated Multiple Myeloma: An Interim Analysis of the German DSMM XIa Trial
Stefan Knop, Peter Liebisch, Hannes Wandt, Martin Kropff, Volker Kunzmann, Katja Weisel, Daniel Franke, Monika Engelhardt, Lorenz H. Truemper, Nikolaus Kroeger, Burkhard Hennemann, Michael Pfreundschuh, Martin Gramatzki, Bernd Metzner, Christian Peschel, Herbert G. Sayer, Orhan Sezer, Heinz A Duerk, Bernd Hertenstein, Hans-Guenther Mergenthaler, Hella Gollasch, Hans-Heinrich Wolf, Georgia Schilling, Claas Frohn, and Hermann Einsele
Abstract No.: 2776 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-870**
Myeloma – Therapy, Excluding Transplantation Poster II

Bortezomib Retreatment in Relapsed Multiple Myeloma (MM): Results from a Binational, Multicenter Retrospective Survey
Irena Hrusovsky, Berthold Emmerich, Albert von Rohr, Monika Engelhardt, Jerome Voegeli, Christian Taverna, Robert Olie, Harold Pliskat, Claas Frohn and Georg Hess
Abstract No.: 2775 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-869**
Myeloma – Therapy, Excluding Transplantation Poster II

CCR1 Inhibition Targets Osteoclast-Myeloma Adhesion and Exerts in Vivo Anti-Osteoclast Activity
Sonia Vallet, Nileshwari Vaghela, Mariateresa Fulciniti, Petter Veiby, Teru Hideshima, Samantha Pozzi, Loredana Santo, Siddhartha Mukherjee, Diana Cirstea, David T. Scadden, Kenneth C. Anderson, and Noopur Raje
Abstract No.: 2757 **Location: Hall A (Moscone Center)**
Time: 6:00 PM - 8:00 PM **Poster Board: II-851**
Myeloma – Pathophysiology and Preclinical Studies Excluding Therapy Poster II

Characterization of Bortezomib Resistance in Multiple Myeloma Cell Lines
Silvia CW Ling, Angela M Nikolic, Ammira Al-Shabeeb, Edwin Lau, Phoebe Joy Ho, Douglas Joshua, and John D Allen
Abstract No.: 2639 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-733**
Molecular Pharmacology, Drug Resistance Poster II

Clinical Epidemiological Study on Multiple Myeloma in China: A 18-Year Retrospective Study in a Representative Center
Lugui Qiu, Yafei Wang, Peijing Qi, Dehui Zou, Yaozhong Zhao, and Junyuan Qi
Time: 6:00 PM – 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2723 **Poster Board: II-817**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster II

An Economic Evaluation of Bortezomib-Based Induction Therapy in Double Transplant Protocols for Newly Diagnosed Multiple Myeloma Patients
Si-Tien Wang, Mei Sheng Duh, Hui Huang, Leigh Ann White, Eva Chang, Dixie-Lee Esseltine, and Jing L. Marantz
Abstract No.: 2386 **Location: Hall A (Moscone Center)**
Time: 6:00 PM - 8:00PM **Poster Board: II-480**
Health Services and Outcomes Research Poster II

Expression Profile Signature to Predict Response to Bortezomib and Dexamethasone Combination Therapy in Newly-Diagnosed Myeloma: Moving towards Prospective Prediction
Nikhil C. Munshi, Cheng Li, Stephane Minvielle, Samir B Amin, Philippe Moreau, Florence Magrangeas, Kenneth C Anderson, and Hervé Avet-Loiseau
Abstract No.: 2746 **Location: Hall A (Moscone Center)**
Time: 6:00 PM - 8:00 PM **Poster Board: II-840**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster II

Indirect Comparison of the Efficacy of Melphalan-Prednisone-Bortezomib Relative to Melphalan-Prednisone-Thalidomide and Melphalan-Prednisone for the First Line Treatment of Multiple Myeloma
Yating Yeh, James Chambers, Sabine Gaugris, and Jeroen Jansen
Time: 6:00 PM - 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2367 **Poster Board: II-461**
Health Services and Outcomes Research Poster II

Inhibition of eIF2α Dephosphorylation Maximizes Bortezomib Efficiency and Eliminates Quiescent Multiple Myeloma Cells Surviving Therapy
Denis M Schewe and Julio A Aguirre-Ghiso
Abstract No.: 2762 **Location: Hall A (Moscone Center)**
Time: 6:00 PM - 8:00 PM **Poster Board: II-856**
Myeloma – Pathophysiology and Preclinical Studies Excluding Therapy Poster II

Interactions of the Mdm2/p53 and Proteasome Pathways: Implications for Combination Strategies to Enhance the Anti-Myeloma Activity of Bortezomib
Melissa G. Ooi, Patrick J. Hayden, Douglas W. McMillin, Joseph M. Negri, Jake Delmore, Noopur S Raje, Nikhil C. Munshi, Dharminder Chauhan, Teru Hideshima, Paul G. Richardson, Constantine S. Mitsiades, Kenneth C Anderson and Nicholas Mitsiades
Abstract No.: 2651 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-745**
Molecular Pharmacology, Drug Resistance Poster II

Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib
Shirin Arastu-Kapur, Kevin Shenk, Francesco Parlati and Mark K Bennett
Abstract No.: 2657 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-751**
Molecular Pharmacology, Drug Resistance Poster II

Novel Agents Overcome the Adverse Prognosis Imparted by Compromised Renal Function in Patients with Multiple Myeloma
Mehul Patel, Taimur Sher, Sikander Ailawadhi, Terry Mashtare Jr., Wei Tan, Pranay Soni, Gregory Wilding, Kena C Miller, Alice Mohr, Kelvin P. Lee and Asher Alban Chanan-Khan
Time: 6:00 PM – 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2726 **Poster Board: II-820**
Myeloma – Biology and Pathophysiology, Excluding Therapy Poster II

Parathyroid Hormones (PTH) Serum Variations Are Associated with Bortezomib Response in Multiple Myeloma Patients
Maurizio Zangari, Lisa Pappas, Fenghuang Zhan, Naveen Sanath kumar, Federica Cavallo, Larry J Suva, Guido Tricot, Dixie-Lee Esseltine, and Shmuel Yaccoby
Abstract No.: 2783 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-877**
Myeloma – Therapy, Excluding Transplantation Poster II

A Phase IB, Multicenter, Open-Label, Dose-Escalation Study of Oral Panobinostat (LBH589) and I.V. Bortezomib in Patients with Relapsed Multiple Myeloma
David Siegel, Orhan Sezer, Jesus F. San Miguel, Maria-Victoria Mateos, Ian Prosser, Michele Cavo, Muhammad Jalaluddin, Katharine Hazell, Priscille M. Bourquelot and Kenneth C. Anderson
Abstract No.: 2781 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board II-875**
Myeloma – Therapy, Excluding Transplantation Poster II

Results of a Phase II Open-Label Trial of Bortezomib in Patients with Multiple Myeloma Who Have Undergone High-Dose Melphalan Therapy Followed by Autologous Peripheral Blood Stem Cell Transplantation and Failed to Achieve a Complete Response
Robert M. Rifkin, Gary Spitzer, Andrew Greenspan, John F. Schwerkoske, Romeo A. Mandanas, Joe Stephenson, George T. Kannarkat, Feng Zhan, Lina Asmar, and Roy Beveridge
Abstract No.: 2780 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board: II-874**
Myeloma – Therapy, Excluding Transplantation Poster II

Salvage Therapy with Intravenous Liposomal Adryamicin (A), Bortezomib (B), Cyclophosphamide (C), and Dexamethasone (D) (ABCD) in Previously Treated Myeloma Patients
Francesco Di Raimondo, Alessandra Romano, Ausilia Gorgone, Annalisa Chiarenza, Maide Cavalli, Salvatore Berretta, Paolo Fiumara, Giovanna Motta and Giuseppe A. Palumbo
Abstract No.: 2779 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board II-873**
Myeloma – Therapy, Excluding Transplantation Poster II

Superior Outcomes Associated with Complete Response:
Analysis of the Phase III VISTA Study of Bortezomib Plus Melphalan–Prednisone Versus Melphalan–Prednisone
Jean-Luc Harousseau, Antonio Palumbo, Paul Richardson, Rudolf Schlag, Meletios A Dimopoulos, Ofer Shpilberg, Martin H Kropff, Michel Delforge, Rik Schots, Michele Cavo, Anatoly Golenkov, Mieczyslaw Komarnicki, Maria-Victoria Mateos, Andrew Cakana, Kevin Liu, William Deraedt, Helgi van de Velde and Jesus F San Miguel
Abstract No.: 2778 **Location: Hall A (Moscone Center)**
Time: 6:00 PM – 8:00 PM **Poster Board II-872**
Myeloma – Therapy, Excluding Transplantation Poster II

Thalidomide Versus Bortezomib-Based Regimens for Relapsed Myeloma: Meta-Analysis and Indirect Meta-Analysis
Ambuj Kumar, Iztok Hozo, and Benjamin Djulbegovic
Time: 6:00 PM – 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2362 **Poster Board: II-456**
Health Services and Outcomes Research Poster II

Treatment Patterns among Patients with Recently-Diagnosed Multiple Myeloma in a National Registry
Carla M. Van Bennekom, Noopur Raje, Kenneth C. Anderson, Theresa E. Anderson, and David W. Kaufman
Time: 6:00 PM – 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2374 **Poster Board: II-468**
Health Services and Outcomes Research Poster II

VELCADE®, Thalidomide, Dexamethasone (VTD) Followed by Melphalan, Prednisone, Thalidomide (MPT) Maintenance as a First Line Treatment Demonstrates High Response Rates for High-Risk Patients with Multiple Myeloma (MM) Who Are Non-Transplant Candidates: Updated Results of Phase II Trial
HyeonSeok Eom, Yeo-Kyeoung Kim, Joo-Seop Chung, Kihyun Kim, Hyo-Jung Kim, HoYoung Kim, Jong-Youl Jin, Young-Rok Do, Suk-Joong Oh, Cheolwon Suh, Chu-Myong Seong, Chul Soo Kim, Dong Soon Lee and Jae Hoon Lee
Time: 6:00 PM – 8:00 PM **Location: Hall A (Moscone Center)**
Abstract No.: 2785 **Poster Board: II-879**
Myeloma – Therapy, Excluding Transplantation Poster II

Monday, December 8, 2008

Bortezomib-Doxorubicin-Dexamethasone as Induction Prior to Reduced Intensity Autologous Transplantation Followed by Lenalidomide as Consolidation/Maintenance in Elderly Untreated Myeloma Patients
Antonio Palumbo, Patrizia Falco, Francesca Gay, Vittorio Montefusco, Claudia Crippa, Francesca Patriarca, Milena Gilestro, Anna M. Liberati, Fausto Rossini, Tommaso Caravita, Antonietta Falcone, Federica Cavallo, Paolo Corradini, Giuseppe Rossi, and Mario Boccadoro
Time: 7:30 AM **Location: 120-121-122-123-124-125 - North (Moscone Center)**
Abstract No.: 159
Autologous Transplantation: Myeloma, Amyloidosis and Autoimmune Diseases

Bortezomib (BOR) and High Dose Melphalan (HDM) as Conditioning Regimen Before Autologous Stem Cell Transplantation (ASCT) for De Novo Multiple Myeloma (MM): Final Results of the IFM Phase II Study VEL/MEL
Murielle Roussel, Anne Huynh, Philippe Moreau, Jean Luc Harousseau, Cyrille Hulin, Denis Caillot, Christophe Fruchart, Gerald Marit, Brigitte Pegourie and Michel Attal
Abstract No.: 160 **Location: 120-121-122-123-124-125 - North (Moscone Center)**
Time: 7:45 AM
Autologous Transplantation: Myeloma, Amyloidosis and Autoimmune Diseases

TNF-a Polymorphism Modulates the Outcome of Multiple Myeloma Patients Treated with Bortezomib Clinically Relevant Abstract
Gabriele Buda, Alessandro Martino, Valentina Maggini, Enrico Orciuolo, Sara Galimberti, Massimo Gentile, Marino Brunori, Fortunato Morabito, Anna Maria Rossi, and Mario Petrini
Abstract No.: 216 Location: Yerba Buena Ballroom Salon 8 (San Francisco Marriott)
Time: 7:45 AM
Genomic Pharmacology And Mechanisms of Drug Resistance

Ninety Percent Sustained Complete Response (CR) Rate Projected 4 Years after Onset of CR in Gene Expression Profiling (GEP)-Defined Low-Risk Multiple Myeloma (MM) Treated with Total Therapy 3 (TT3): Basis for GEP-Risk-Adapted TT4 and TT5
Bart Barlogie, Elias J. Anaissie, John D. Shaughnessy Jr., Frits van Rhee, Mauricio Pineda-Roman, Jeff Haessler, Klaus A. Hollmig, Yazan Alsayed, Sarah Waheed, Monica Graziutti, Elias Kiwan, and John Crowley
Time: 8:15 AM **Location: 120-121-122-123-124-125 - North (Moscone Center)**
Abstract No.: 162
Autologous Transplantation: Myeloma, Amyloidosis and Autoimmune Diseases

Preclinical Evaluation of CRx-501, a Potent Selective A2A Agonist as a Novel Drug Candidate for the Treatment of Multiple Myeloma
Richard J Rickles, Laura Pierce, Thomas Giordano, William Avery, Melissa Farwell, David Crowe, Winnie F. Tam, Mei Chen, Vikram Kansra, Douglas W. McMillin, Kenneth C Anderson, Constantine Mitsiades, and Margaret S. Lee
Abstract No.: 252 **Location: 2009-2011-2022-2024 - West (Moscone Center)**
Time: 8:45 AM
Pathophysiology and Translational Models

Updated Follow-up and Results of Subsequent Therapy in the Phase III VISTA Trial: Bortezomib Plus Melphalan–Prednisone Versus Melphalan–Prednisone in Newly Diagnosed Multiple Myeloma
Jesus F San Miguel, Rudolf Schlag, Nuriet K Khuageva, Meletios A Dimopoulos, Ofer Shpilberg, Martin H Kropff, Ivan Spicka, Maria Teresa Petrucci, Antonio Palumbo, Olga S Samoilova, Anna Dmoszynska, Kudrat M Abdulkadyrov, Rik Schots, Bin Jiang, Maria-Victoria Mateos, Kenneth C Anderson, Dixie-Lee Esseltine, Kevin Liu, Andrew Cakana, Helgi van de Velde and Paul Richardson
Abstract No.: 650 **Location: Halls B and C (Moscone Center)**
Time: 3:45 PM
Myeloma Therapy: Phase III Trials

Bortezomib (VELCADE®)-Melphalan-Prednisone (VMP) Versus VELCADE®-Thalidomide-Prednisone (VTP) in Elderly Untreated Multiple Myeloma Patients: Which Is the Best Partner for VELCADE®: An Alkylating or An Immunomodulator Agent?
Maria-Victoria Mateos, Albert Oriol, Joaquín Martínez, Mª Teresa Cibeira, Raquel de Paz, Mª José Terol, José García-Laraña, Enrique Bengoechea, Rafael Martínez, Alejandro Martin, Felipe de Arriba, Luis Palomera, José Hernández, Jose-Luis Bello, María-Luisa Martín, Yolanda González, Joan Bladé, Juan José Lahuerta and J.F. San Miguel
Time: 4:00 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 651
Myeloma Therapy: Phase III Trials

A Prospective, Randomized, Phase III Study of Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) Versus Bortezomib, Melphalan and Prednisone (VMP) in Elderly Newly Diagnosed Myeloma Patients
Antonio Palumbo, Sara Bringhen, Davide Rossi, Valeria Magarotto, Francesco Di Raimondo, Roberto Ria, Massimo Offidani, Chiara Nozzoli, Francesca Patriarca, Vincenzo Callea, Giulia Benevolo, Roberto Marasca, Tommasina Guglielmelli, Manuela Rizzo, Mariella Grasso, Maria Teresa Petrucci, Paola Omedè, Gianluca Gaidano, and Mario Boccadoro
Time: 4:15 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 652
Myeloma Therapy: Phase III Trials

First Analysis of HOVON-65/GMMG-HD4 Randomized Phase III Trial Comparing Bortezomib, Adriamycine, Dexamethasone (PAD) Vs VAD as Induction Treatment Prior to High Dose Melphalan (HDM) in Patients with Newly Diagnosed Multiple Myeloma (MM)
P. Sonneveld, B. van der Holt, I. G.H. Schmidt-Wolf, U. Bertsch, L. el Jarari, Hans-Jürgen Salwender, S. Zweegman, E. Vellenga, J. Schubert, I. W. Blau, GSK Jie, B. Beverloo, A. Jauch, D. Hose, R. Schaafsma, M. J. Kersten, M. Delforge, O. de Weerdt, R. van der Griend, P. W. Wijermans, Hans Martin, H. van der Velde, Henk M. Lokhorst and H. Goldschmidt
Abstract No.: 653 **Halls B and C (Moscone Center)**
Time: 4:30 PM
Myeloma Therapy: Phase III Trials

Thalidomide/Dexamethasone (TD) Vs. Bortezomib(VELCADE®)/Thalidomide / Dexamethasone (VTD) Vs. VBMCP/VBAD/VELCADE® As Induction Regimens Prior Autologous Stem Cell Transplantation (ASCT) in Younger Patients with Multiple Myeloma (MM): First Results of a Prospective Phase III PETHEMA/Gem Trial
Laura Rosinol, Mª Teresa Cibeira, Joaquin Martinez, Maria Victoria Mateos, Mª José Terol, Javier de la Rubia, Luis Palomera, Felipe de Arriba, Albert Oriol, Adrian Alegre, Juan Besalduch, Raquel de Paz, José Garcia-Laraña, Joaquín Díaz-Mediavilla, Anna Sureda, Juan José Lahuerta, J.F. San Miguel and Joan Bladé
Time: 4:45 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 654
Myeloma Therapy: Phase III Trials

Improved Survival of Patients with Multiple Myeloma after the Introduction of Novel Agents and the Applicability of the International Staging System (ISS) An Analysis of the Greek Myeloma Study Group (GMSG)
Efstathios Kastritis, Konstantinos Zervas, Argiris Symeonidis, Evangelos Terpos, Sossana Delimpassi, Nicolaos Anagnostopoulos, Evridiki Michali, Athanasios Zomas, Irini Katodritou, Dimitra Gika, Anastasia Pouli, Dimitrios Christoulas, Maria Roussou, Theofanis Economopoulos and Meletios A Dimopoulos
Time: 5:00 PM **Location: Halls B and C (Moscone Center)**
Abstract No.: 655
Myeloma Therapy: Phase III Trials

Bortezomib (VEL) Based Regimens in Multiple Myeloma (MM) Patients with Renal Impairment (RI): A Preliminary Retrospective Italian Multicenter Study
Massimo Gentile, Stefania Ciolli, Maria Teresa Petrucci, Sara Galimberti, Giuseppe Mele, Antonio Francesco Casulli, Donato Mannina, Eugenio Piro, Graziella Pinotti, Salvatore Palmieri, Lucio Catalano, Vincenzo Callea, Massimo Offidani, Pellegrino Musto, Sara Bringhen, Luca Baldini, Patrizia Tosi, Francesco Di Raimondo, Mario Boccadoro, Antonio Palumbo, Michele Cavo, and Fortunato Morabito
Abstract No.: 3681 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-763**
Myeloma – Therapy, Excluding Transplantation Poster III

Bortezomib-Doxorubicin-Dexamethasone (BDD) for Reversal of Acute Light Chain Induced Renal Failure (ARF) in Multiple Myeloma (MM). Results from a Phase II Study
Heinz Ludwig, Zdenek Adam, Roman Hajek, Richard Greil, Felix Keil, Niklas Zojer, Josef Thaler, Heinz Gisslinger and Alois Lang
Abstract No.: 3682 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-764**
Myeloma – Therapy, Excluding Transplantation Poster III

Bortezomib Plus Melphalan and Prednisone as Induction Prior to Transplant or as Frontline Therapy for Non-Transplant Candidates in Patients with Previously Untreated Multiple Myeloma
Cristina Gasparetto, Jon P Gockerman, Louis F Diehl, Carlos de Castro III, Joseph O Moore, Gwynn D Long, Mitchell Horwitz, John Chute, Keith M Sullivan, Rachel Neuwirth, Patricia H Davis, Linda M. Sutton, Russell D Anderson, Nelson Chao and David A. Rizzieri
Abstract No.: 3325 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-407**
Clinical Results – Autologous Transplantation Poster III

Clinical Efficacy of VEL-CTD (Bortezomib, Cyclophosphamide, Thalidomide, and Dexamethasone) Regimen in Patients with Relapsed or Refractory Multiple Myeloma: A Phase II Study
Yeo-Kyeoung Kim, Je-Jung Lee, Sang-Kyun Sohn, Ho-Jin Shin, Joo-Seop Chung, Young-Jin Choi, Joon-Ho Moon, Yee-Soo Chae, Jong-Gwang Kim, Jae-Sook Ahn, Deok-Hwan Yang, Hyeoung-Joon Kim and the Korean Multiple Myeloma Working Party (KMMWP).
Time: 5:30 PM – 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3693 **Poster Board: III-775**
Myeloma – Therapy, Excluding Transplantation Poster III

Combination of Vorinostat Plus Bortezomib for the Treatment of Patients with Multiple Myeloma Who Have Previously Received Bortezomib
Donna M. Weber, Sundar Jagannath, Ronald Sobecks, Gary Schiller, Lisa Chiacchierini, David Reiser, Carol Oerth, Jose Garcia-Vargas and Syed Rizvi
Abstract No.: 3711 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-793**
Myeloma – Therapy, Excluding Transplantation Poster III

Combined Autophagy and Proteasome Inhibition for Multiple Myeloma: Preliminary Results of a Phase 1/2 Trial of Hydroxychloroquine and Standard Dose Bortezomib for Relapsed or Refractory Myeloma
Dan T. Vogl, Edward A. Stadtmauer, James E. Bradner, Lisa Davis, Martin Carroll, Charles W. Nichols, Doris Shank, Mary Carberry, Cezary R. Swider, Patricia A. Mangan, Brenda K. Shelly, Craig B. Thompson and Ravi K. Amaravadi
Abstract No.: 3684 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-766**
Myeloma – Therapy, Excluding Transplantation Poster III

Dietary Supplement Vitamin C Significantly Abrogates Bortezomib-Induced Multiple Myeloma (MM) Cell Growth Inhibition
Giulia Perrone, Teru Hideshima, Hiroshi Ikeda, Yutaka Okawa, Diana Cristea, Loredana Santo, Gullu Gorgun, Elisabetta Calabrese, Noopur Raje, Michele Baccarani, Michele Cavo and Kenneth C. Anderson
Abstract No.: 3687 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-769**
Myeloma – Therapy, Excluding Transplantation Poster III

Dimethylaminoparthenolide (DMAPT) in Multiple Myeloma
Colin D. Crean, Genglin Zhang, Karen E. Pollok, Anthony L. Sinn, Peter A Crooks, Sherif Farag, Rafat Abonour and Attaya Suvannasankha
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3672 **Poster Board: III-754**
Myeloma – Pathophysiology and Preclinical Studies Excluding Therapy Poster III

Efficacy and Safety of Re-Treatment with Bortezomib (VELCADE®) in Patients with Multiple Myeloma: Results from a Prospective International Phase II Trial
Maria Teresa Petrucci, Igor W. Blau, Paolo Corradini, Meletios A. Dimopoulos, Johannes Drach, Pilar Giraldo, Adriana Teixeira, and Joan Bladé
Abstract No.: 3690 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-772**
Myeloma – Therapy, Excluding Transplantation Poster III

High Response Rates with the Combination of Bortezomib, Dexamethasone and the Pan-Histone Deacetylase Inhibitor Romidepsin in Patients with Relapsed or Refractory Multiple Myeloma in a Phase I/II Clinical Trial
Simon James Harrison, Hang Quach, Kally Yuen, Andrew Strayer, Michael C. Copeman, S. Peinert, M. Bishton, M. Wolf, H. Januszewicz, MK Kenealy, K. Herbert, David Westerman, D. Carney, J. F Seymour, R. W Johnstone, David Ritchie, and Miles Prince
Abstract No.: 3698 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-780**
Myeloma – Therapy, Excluding Transplantation Poster III

Inhibition of Autophagy Promotes Bortezomib-Mediated Cell Death in Myeloma Cells
Terry H. Landowski, Aluvia M Escalante, Andrew Jefferson, Robert T Dorr and Ronald Lynch
Abstract No.: 3677 **Location: Hall A (Moscone Center)**
Time: 5:30 PM - 7:30 PM **Poster Board: III-759**
Myeloma – Pathophysiology and Preclinical Studies Excluding Therapy Poster III

Initial Treatment with Bortezomib (VELCADE®), Doxil®, and Dexamethasone (VDD) Is Superior to Thalidomide and Dexamethasone (TD) as Initial Therapy Prior to Autologous Stem Cell Transplantation (ASCT) for Multiple Myeloma (MM)
Andrzej Jakubowiak, Tara Kendall, Ammar Al-Zoubi, Yasser Khaled, Shin Mineishi, Christine Brozo, Erica Campagnaro, Moshe Talpaz and Mark S. Kaminski
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3713 **Poster Board: III-795**
Myeloma – Therapy, Excluding Transplantation Poster III

Long-Term Outcomes of Autologous Transplantation in Multiple Myeloma: Benefit from the Newer Drugs Used in the Relapsed Setting
Roman Hajek, Marta Krejci, Vlastimil Scudla, Elena Tothova, Martin Mistrik, Jaroslav Bacovsky, Miroslava Schutzova, Vladimir Koza, Tomas Papajik, Libuse Novosadova, Hana Frankova, Yvetta Stavarova, Frantisek Lehanka, Milena Vranova, Petr Kessler, Marketa Zemanova, Ivana Meluzinova, Nadezda Seifertova, Elen Sumna, Ludek Pour, Vladimir Maisnar and Zdenek Adam
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3331 **Poster Board: III-413**
Clinical Results - Autologous Transplantation Poster III

Major Shrinking of Residual Tumor Cell Burden and Achievement of Molecular Remissions in Myeloma Patients Undergoing Post-Trasplant Consolidation with Bortezomib, Thalidomide and Dexamethasone: A Qualitative and Quantitative PCR Study
Marco Ladetto, Gloria Pagliano, Simone Ferrero, Federica Cavallo, Daniela Drandi, Michela Boi, Loredana Santo, Patrizia Pregno, Mariella Grasso, Anna Marina Liberati, Tommaso Caravita, Francesco Pisani, Claudia Crippa, Vincenzo Callea, Antonietta Falcone, Sergio Morandi, Mario Boccadoro, and Antonio Palumbo.
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3683 **Poster Board: III-765**
Myeloma – Therapy, Excluding Transplantation Poster III

A Phase I MMRC Clinical Trial Testing the Combination of Bortezomib and Tipifarnib in Relapsed/Refractory Multiple Myeloma
Sagar Lonial, Dixil Francis, Chatchada Karanes, Suzanne Trudel, Donna E. Reece, Amrita Krishnan, Marc Buacharern, Renee Smith, Faraz Zaman, Engin Gul, Akari M. Dollard, Donald Harvey and Jonathan Kaufman
Abstract No.: 3706 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-788**
Myeloma – Therapy, Excluding Transplantation Poster III

Phase I Trial of CCI-779 (Temsirolimus) and Weekly Bortezomib in Relapsed and/or Refractory Multiple Myeloma
Irene M. Ghobrial, Nikhil Munshi, Robert Schlossman, Stacey Chuma, Renee Leduc, Marybeth Nelson, Amy Sam, Kelly O'Connor, Brianna Harris, Diane Warren, Akari M. Dollard, Jacob Laubach, Ravi Vij, Erica Campagnaro, Ann Birner, Virginia Dixon-Lipscomb, Kenneth C. Anderson and Paul G. Richardson
Abstract No.: 3696 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-778**
Myeloma – Therapy, Excluding Transplantation Poster III

A Randomized Phase I Trial of Melphalan + Bortezomib as Conditioning for Autologous Transplant for Myeloma: The Effect of Sequence of Administration
Sagar Lonial, Jonathan Kaufman, Claire Torre, Amelia Langston, Mary J. Lechowicz, Christopher Flowers, Stephanie McMillan, Heather Renfroe, Leonard T Heffner and Edmund K Waller
Abstract No.: 3332 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-414**
Clinical Results – Autologous Transplantation Poster III

A Randomized Phase II Trial of High-Dose Melphalan, Ascorbic Acid and Arsenic Trioxide with or without Bortezomib in Multiple Myeloma
Muzaffar H. Qazilbash, Rima M. Saliba, Matteo Pelosini, Chitra M Hosing, Floralyn L Mendoza, Eric Han, Michael Wang, Donna M. Weber, Amin M. Alousi, Paolo Anderlini, Partow Kebriaei, Issa F. Khouri, Uday R Popat, Marcos De Lima, Robert Z. Orlowski, Richard E. Champlin and Sergio A. Giralt
Abstract No.: 3320 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-402**
Clinical Results – Autologous Transplantation Poster III

Sequential Administration of Bortezomib, Liposomal Doxorubicin and Dexamethasone (BDD) Followed by Thalidomide and Dexamethasone (TD) Results in Rapid Control of Untreated High-Risk Multiple Myeloma (MM) and Improves Depth of Response
Heather Landau, Hani Hassoun, Adam Cohen, Elizabeth Hoover, Tarun Kewalramani, Adam Boruchov, Virginia Klimek, Lillian Reich, Elyn Riedel, Neeta Pandit-Taskar, Stephen D. Nimer, and Raymond L. Comenzo
Time: 5:30 PM – 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3712 **Poster Board: III-794**
Myeloma – Therapy, Excluding Transplantation Poster III

Sequential VAD (Vincristine, Adriamycin, Dexamethasone) and VTD (Bortezomib, Thalidomide, Dexamethasone) Induction Followed by High-Dose Therapy with Autologous Stem Cell Transplantation and Maintenance Treatment with Bortezomib for Newly Diagnosed Multiple Myeloma: Final Analysis of Phase II Trial
Sung-Soo Yoon, Hye Jin Kim, Joo Seop Chung, HyeonSeok Eom, Jun-Ho Jang, Hye Jin Kang, Cheol Soo Kim, Kihyun Kim, Dongsoon Lee, Jae Hoon Lee, Junglim Lee, Sang Jae Lee, Yoo Hong Min, Chu-Myong Seong, Sang-Kyun Sohn, Cheolwon Suh and Jong-Ho Won
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3330 **Poster Board: III-412**
Clinical Results - Autologous Transplantation Poster III

Successful Harvesting of Peripheral Hematopoietic Stem Cells after Induction Treatment with Bortezomib, Adriamycin, Dexamethasone (PAD) in Patients with Newly Diagnosed Multiple Myeloma (MM)
Hartmut Goldschmidt, Henk M. Lokhorst, Uta Bertsch, Bronno van der Holt, Laila el Jarari, Hans-Jürgen Salwender, Sonja Zweegman, Edo Vellenga, Jörg Schubert, Igor W. Blau, Asiong Jie, Berna Beverloo, Dirk Hose, Helgi van de Velde, Martyn Ronald Schaafsma, Marie Jose Kersten, Michel Delforge, Okke de Weerdt, Rene Van der Griend, Pierre Wijermans, Hans Martin, Christof Scheid, Mathias Hänel, Ingo G.H. Schmidt-Wolf and Pieter Sonneveld for the HOVON and GMMG group
Abstract No.: 3470 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30PM **Poster Board: III-552**
Ex Vivo Expansion, Mobilization and Engraftment Poster II

Updated Results of a Phase I/II Trial of Autologous Peripheral Blood Progenitor Cell Transplantation with VELCADE® Maintenance as Treatment for Intermediate- and Advanced-Stage Multiple Myeloma
Mickey Liao, R Malone, K Bartoni, B Habtemariam, Ronald Paquette, Sven de Vos, Mary C Territo and Gary Schiller
Abstract No.: 3710 **Location: Hall A (Moscone Center)**
Time: 5:30 PM – 7:30 PM **Poster Board: III-792**
Myeloma – Therapy, Excluding Transplantation Poster III

VAMP/ThaCyDex: VELCADE® (Bortezomib), Adriamycin, Melphalan and Prednisone Alternating with Thalidomide, Cyclophosphamide and Dexametasone as a Salvage Regimen in Relapsed Multiple Myeloma Patients
Enrique Colado, Maria-Victoria Mateos, Maria-Jose Moreno, Felipe de Arriba, Javier de la Rubia, Juan José Lahuerta, Pastora Iniesta, Maria Cruz Viguria, Ana Pilar Gonzalez, Ramón García-Sanz, Juan Olazabal, and Jesús F San Miguel.
Time: 5:30 PM - 7:30 PM **Location: Hall A (Moscone Center)**
Abstract No.: 3694 **Poster Board: III-776**
Myeloma – Therapy, Excluding Transplantation Poster III

Changes in the Expression of Proteasome Genes in Tumor Cells Following Short-Term Proteasome Inhibitor Therapy Predicts Survival in Multiple Myeloma Treated with Bortezomib-Containing Multi-Agent Chemotherapy
John D. Shaughnessy Jr., Pingping Qu, Ricky Edmondson, Damir Herman, Yiming Zhou, Erming Tian, Frits van Rhee, Mauricio Pineda-Roman, Yazan Alsayed, Elias Anaissie, Ya-wei Qiang, Joshua Epstein, Shmuel Yaccoby, David Williams, Fenghuang Zhan, Owen Stephens, Antje Hoering, John Crowley, and Bart Barlogie
Abstract No.: 733 **Location: 2005-2007-2018-2020 - West (Moscone Center)**
Time: 6:00 PM
Molecular Targets and Biomarkers in Myeloma

Tuesday, December 9, 2008

Preliminary Results of CNTO 328, An Anti-Interleukin-6 Monoclonal Antibody, in Combination with Bortezomib in the Treatment of Relapsed or Refractory Multiple Myeloma
Jean-François Rossi, Robert F. Manges, Heather J. Sutherland, Sundar Jagannath, Peter Voorhees, Pieter Sonneveld, Michel Delforge, Brigitte Pegourie, Adrian Alegre, Javier de la Rubia, David La Police, Rajesh Bandekar, Hong Xie, and Robert Z. Orlowski
Abstract No.: 867 **Location: Gateway Ballroom 103 - South (Moscone Center)**
Time: 7:45 AM
Novel Therapies for Myeloma and Related Disorders

Significant Activity of Bortezomib-Based Therapy in Patients with Primary Systemic (AL) Amyloidosis
Efstathios Kastritis, Ashutosh D Wechalekar, Meletios A. Dimopoulos, Giampaolo Merlini, Philip N Hawkins, Vittorio Perfetti, Julian D Gillmore and Giovanni Palladini
Abstract No.: 869 **Location: Gateway Ballroom 103 - South (Moscone Center)**
Time: 8:15 AM
Novel Therapies for Myeloma and Related Disorders

Bortezomib Induces Osteoblast Differentiation Via Wnt-Independent Activation of Beta-catenin/TCF Signaling
Ya-wei Qiang, Bo Hu, Yu Chen, Ying Zhong, Bart Barlogie and John D. Shaughnessy Jr.
Abstract No.: 846 **Location: 2005-2007-2018-2020 - West (Moscone Center)**
Time: 8:30 AM
Molecular Pathology of Myeloma

Phase I/II Results of a Multicenter Trial of Perifosine (KRX-0401) + Bortezomib in Patients with Relapsed or Relapsed / Refractory Multiple Myeloma Who Were Previously Relapsed from or Refractory to Bortezomib
Paul Richardson, Jeffrey Wolf, Andrzej Jakubowiak, Jeffrey Zonder, Sagar Lonial, David H Irwin, John Densmore, Amrita Krishnan, Noopur Raje, Michael H. Bar, Jeffrey P. Allerton, Robert Schlossman, Irene M. Ghobrial, Nikhil C. Munshi, Thomas Martin, Jacob Laubach, Kathy Colson, Sarah Dean, Deanna Tocco, Elizabeth Steinfield, Tara Kendall, Kimberly O'Riley, Teru Hideshima, Peter Sportelli, Lesa Gardner, and Kenneth C. Anderson
Abstract No.: 870 **Location: Gateway Ballroom 103 - South (Moscone Center)**
Time: 8:30 AM
Novel Therapies for Myeloma and Related Disorders

Vorinostat Plus Bortezomib for the Treatment of Relapsed/Refractory Multiple Myeloma: Early Clinical Experience
Donna Weber, Ashraf Z. Badros, Sundar Jagannath, David Siegel, Victoria Richon, Syed Rizvi, Jose Garcia-Vargas, David Reiser and Kenneth C. Anderson
Abstract No.: 871 **Location: Gateway Ballroom 103 - South (Moscone Center)**
Time: 8:45 AM
Novel Therapies for Myeloma and Related Disorders

VELCADE® Publications – 4th Quarter, 2008

Blockage of interleukin-6 signaling with 6-amino-4-quinazoline synergistically induces the inhibitory effect of bortezomib in human U266 cells.

Park J, Ahn KS, Bae EK, Kim BS, Kim BK, Lee YY, Yoon SS.

Anticancer Drugs. 2008 Sep;19(8):777-82.

http://www.ncbi.nlm.nih.gov/pubmed/18690088?ordinalpos=54&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that combined treatment with bortezomib and 6-amino-4-quinazoline effectively inhibits the IL-6 and soluble IL-6R-induced activation of STAT3 and extracellular signal-regulated kinase phosphorylation.

The transcription factor nuclear factor-kappa B (NF-kappaB) regulates the transcription of a number of genes involved in a variety of cellular responses, including cell survival, inflammation, and differentiation. NF-kappaB is activated by a variety of stimuli, proinflammatory cytokines, mitogens, growth factors, and stress-inducing agents. Aberrant NF-kappaB expression is considered to be one of the oncogenic factors of cancer and the constitutive activation of NF-kappaB is observed in several hematologic disorders [classic Hodgkin's lymphoma, diffuse large B cell lymphoma, and multiple myeloma (MM)], and the modulation of NF-kappaB activation is emerging as a promising novel anticancer therapeutic strategy.Therefore, we focused on the regulation of NF-kappaB activation in MM. When U266 cells were treated with 6-amino-4-quinazoline, an NF-kappaB activation inhibitor, we determined that it most effectively blocked the interleukin (IL)-6-induced activation of MAPK and JAK/STAT pathways among different signaling inhibitors. The results of the luciferase assay indicated that 6-amino-4-quinazoline inhibited NF-kappaB activation with diminished NF-kappaB protein bound to NF-kappaB DNA binding sites. In addition, 6-amino-4-quinazoline suppressed the production of IL-6, which affected MM cell proliferation. Furthermore, combined treatment with bortezomib and 6-amino-4-quinazoline effectively inhibited the IL-6 and soluble IL-6R-induced activation of STAT3 and extracellular signal-regulated kinase phosphorylation. Our data showed that the inhibition of NF-kappaB activation abrogated MM cell proliferation induced by the IL-6 pathway, and might represent a promising therapeutic strategy for the treatment of MM.

The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma.

Niesvizky R, Richardson PG, Rajkumar SV, Coleman M, Rosiñol L, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Boral AL, Esseltine DL, Anderson KC, Bladé J.

Br J Haematol. 2008 Sep;143(1):46-53. [Epub 2008 Jul 31.]

http://www.ncbi.nlm.nih.gov/pubmed/18673366?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This cohort study within the phase 3 Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial of bortezomib versus dexamethasone in relapsed myeloma assesses the relationship between quality of response to bortezomib and clinical benefit. The authors conclude that bortezomib has substantial activity in relapsed myeloma patients and that complete response may be a surrogate marker for significant clinical benefit with bortezomib.

Quality of response is associated with prolonged overall survival (OS) in newly diagnosed multiple myeloma patients. This cohort study within the phase 3 Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial of bortezomib versus dexamethasone in relapsed myeloma assessed the relationship between quality of response to bortezomib (n = 315) and clinical benefit. Treatment-free interval (TFI), time to alternative therapy (TTAT), time to progression (TTP) and OS were assessed in response-evaluable patients in the bortezomib arm in cohorts defined by achievement of complete response (CR; n = 27), very good partial response (VGPR; n = 31), partial response (PR; n = 77), minimal response (MR; n = 21) or non-response (NR, including stable and progressive disease; n = 159). CR was associated with significantly longer median TFI (24.1 vs. 6.9/6.4 months) and TTAT (27.1 vs. 13.6/14 months) versus VGPR/PR. Median TTP was similar in CR, VGPR and PR cohorts; median OS was not reached. Patients achieving MR appeared to have prolonged median TFI (3.8 vs. 2.3 months), TTAT (8.7 vs. 6.2 months), TTP (4.9 vs. 2.8 months) and OS (24.9 vs. 18.7 months) versus NR. In conclusion, bortezomib had substantial activity in relapsed myeloma patients; CR may be a surrogate marker for significant clinical benefit with bortezomib. MR appeared to be valid as a separate response category in this setting.

The role of novel drugs in multiple myeloma.

Dimopoulos MA, Kastritis E.

Ann Oncol. 2008 Sep;19 Suppl 7:vii121-7.

http://www.ncbi.nlm.nih.gov/pubmed/18790953?ordinalpos=46&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Synergistic anti-proliferative and pro-apoptotic activity of combined therapy with bortezomib, a proteasome inhibitor, with anti-epidermal growth factor receptor (EGFR) drugs in human cancer cells.

Cascone T, Morelli MP, Morgillo F, Kim WY, Rodolico G, Pepe S, Tortora G, Berrino L, Lee HY, Heymach JV, Ciardiello F.

J Cell Physiol. 2008 Sep;216(3):698-707.

http://www.ncbi.nlm.nih.gov/pubmed/18381602?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the combined treatment with bortezomib and The epidermal growth factor receptor (EGFR) inhibitors has a synergistic growth inhibitory and pro-apoptotic activity in different human cancer cells which possess a functional EGFR-dependent autocrine growth pathway through to a more efficient and sustained inhibition of Akt.

The proteasome plays a pivotal role in the turnover of regulatory transduction proteins induced by activated cell membrane growth factor receptors. The epidermal growth factor receptor (EGFR) pathway is crucial in the development and progression of human epithelial cancers. Proteasome inhibition may sensitize human cancer cell lines to EGFR inhibitors. We investigated the growth inhibitory and pro-apoptotic effects of the proteasome inhibitor bortezomib in combination with anti-EGFR drugs, such as gefitinib, vandetanib, and cetuximab in EGFR-expressing human cancer cell lines. Bortezomib determined dose-dependent growth inhibition in a nine cancer cell line panel (IC(50) values, range 6-42 nM). A significant synergistic growth inhibitory effect was observed with the combination of bortezomib and each EGFR inhibitor in all cell lines (combination index, CI, range 0.10-0.55), which was accompanied by a significant induction in apoptosis by the combined treatment with bortezomib, cetuximab and vandetanib. In HCT-116 colon cancer and A549 lung adenocarcinoma cells, bortezomib plus EGFR inhibitor treatment induced a more effective inhibition of EGFR-activated down-stream signals, including a marked suppression in activated, phosphorylated Akt (P-Akt). In contrast, overexpression of a constitutively active P-Akt protected A549 cells by cell growth inhibition and apoptosis following treatment with bortezomib and EGFR inhibitors. The combined treatment with bortezomib and EGFR inhibitors has a synergistic growth inhibitory and pro-apoptotic activity in different human cancer cells which possess a functional EGFR-dependent autocrine growth pathway through to a more efficient and sustained inhibition of Akt. Erratum in: J Cell Physiol. 2008 Oct;217(1):290. Tortora, Giampaolo [added].

Update on recent developments for patients with newly diagnosed multiple myeloma.

Palumbo A, Magarotto V, Gay F, Falco P, Bringhen S, Boccadoro M.

Ann N Y Acad Sci. 2008 Sep;1138:19-21.

http://www.ncbi.nlm.nih.gov/pubmed/18837878?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss the use of bortezomib as a new standard of care in elderly patients with myeloma.

Recent studies have demonstrated that novel therapeutic combinations are challenging melphalan and prednisone (MP) as the standard of care in elderly patients with multiple myeloma. Combination regimens containing bortezomib or thalidomide can achieve response rates, especially complete response rates, which are superior to those seen with standard MP alone, and offer new possibilities for this patient population.

Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature.

Argyriou AA, Iconomou G, Kalofonos HP.

Blood. 2008 Sep 1;112(5):1593-9. [Epub 2008 Jun 23.]

http://www.ncbi.nlm.nih.gov/pubmed/18574024?ordinalpos=55&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review looks critically at the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of bortezomib-induced peripheral neuropathy, and highlights areas for future research.

Bortezomib has demonstrated significant activity in clinical trials, mainly against recurrent or newly diagnosed multiple myeloma (MM). Peripheral neuropathy is a significant toxicity of bortezomib, requiring dose modification and potential changes in the treatment plan when it occurs. The mechanism underlying bortezomib-induced peripheral neuropathy (BIPN) is unknown. Metabolic changes resulting from the accumulation of bortezomib in the dorsal root ganglia cells, mitochondrial-mediated disregulation of Ca(++) homeostasis, and disregulation of neurotrophins may contribute to the pathogenesis of BIPN. It is increasingly recognized that BIPN may be a proteasome inhibitor class effect, producing primarily a small fiber and painful, axonal, sensory distal neuropathy. Incidence of BIPN is mainly related to various risk factors, including cumulative dose and evidence of preexisting neuropathy. Assessment of BIPN is based primarily on neurologic clinical examination and neurophysiologic methods. To date, apart from the use of dose reduction and schedule change algorithm, there is no effective treatment with neuroprotective agents for BIPN. Analgesics, tricyclic antidepressants, anticonvulsants, and vitamin supplements have been used as symptomatic treatment against bortezomib-associated neuropathic pain with some success. This review looks critically at the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of BIPN, and highlights areas for future research.

Infiltration of the spinal cord in a patient with multiple myeloma.

Varettoni M, Corso A, Zappasodi P, Calliada F, Castagnola C, Mangiacavalli S, Lazzarino M.

J Clin Oncol. 2008 Sep 1;26(25):4207-9.

http://www.ncbi.nlm.nih.gov/pubmed/18757337?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Complete remission of psoriasis after autologous hematopoietic stem-cell transplantation for multiple myeloma.

Braiteh F, Hymes SR, Giralt SA, Jones R.

J Clin Oncol. 2008 Sep 20;26(27):4511-3.

http://www.ncbi.nlm.nih.gov/pubmed/18802165?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Bortezomib in combination with dexamethasone for a young multiple myeloma with t(8; 14).

Li JY, Wang LX, Shen WY, Lu SF, Chen LJ, Lu H.

Leuk Res. 2008 Sep 29. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18829108?ordinalpos=31&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report a case of a 23-year-old male with myeloma who is treated with a conditioning regimen of melphalan and bortezomib before a successful autologous peripheral hematopoietic stem cell transplantation.

Multiple myeloma (MM) is an age-related disorder usually occurring in older patients. Now, we report a case of a 23-year-old male suffering from this disease. The patient was admitted on account of pain in the left arm and a later fracture. Interphase fluorescence in situ hybridization (FISH) revealed the existence of t(8; 14) (q24; q32). Bortezomib in combination with dexamethasone was administered as the primary treatment and a complete response was achieved after five cycles of therapy. The conditioning regimen consisted of melphalan and bortezomib and the following autologous peripheral hematopoietic stem cell transplantation was successful.

Consolidation Therapy with Bortezomib/Lenalidomide/ Dexamethasone Versus Bortezomib/Dexamethasone After a Dexamethasone-Based Induction Regimen in Patients with Multiple Myeloma: A Randomized Phase III Trial.

Fonseca R, Rajkumar SV.

Clin Lymphoma Myeloma. 2008 Oct;8(5):315-7.

http://www.ncbi.nlm.nih.gov/pubmed/18854289?ordinalpos=37&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors introduce an upcoming clinical trial that will study the potential role of bortezomib and dexamethasone (VD) or VD plus lenalidomide as primary first-line therapy in the treatment of myeloma.

In recent years, we have seen tremendous progress in our ability to achieve durable responses in patients with multiple myeloma. At the center of this progress, we have the development of 2 unrelated classes of drugs: proteasome inhibitors such as bortezomib and immunomodulatory drugs such as thalidomide and lenalidomide. The depth and durability of responses attained with these agents in the first-line setting has raised the possibility that they may be considered primary therapy. The Eastern Cooperative Oncology Group E1A05 clinical trial addresses the potential role of bortezomib and dexamethasone (VD) or VD plus lenalidomide (VRD) as primary first-line therapy. This clinical trial enrolls patients who have completed a dexamethasone-based induction (excluding patients using bortezomib). Assuming that most patients entering this clinical trial have been previously treated with thalidomide or lenalidomide, the trial will test whether switching to a proteasome inhibitor (VD arm) versus adding a proteasome inhibitor (VRD) results in superior longterm disease control. Patients entering this clinical trial will have deferred stem cell transplantation until the time of relapse. The primary endpoint of the trial is progression-free survival. By using an alkylator-free consolidation and reserving stem cell transplantation until the time of relapse, we hope that these treatment strategies will further prolong the survival of patients with myeloma.

Homoharringtonine inhibits the AKT pathway and induces in vitro and in vivo cytotoxicity in human multiple myeloma cells.

Meng H, Yang C, Jin J, Zhou Y, Qian W.

Leuk Lymphoma. 2008 Oct;49(10):1954-62.

http://www.ncbi.nlm.nih.gov/pubmed/18949618?ordinalpos=51&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study demonstrates that homoharringtonine (HHT), an antileukemic drug first isolated from the Chinese evergreen Cephalotaxus harringtonia, induces significant cytotoxicity in dexamethasone-sensitive and -resistant and chemotherapy-sensitive multiple myeloma cell lines in a time and dose-dependent manner. The authors also find an additive antitumor effect in the myeloma cells treated with HHT and bortezomib concomitantly.

Involvement of phosphatidylinositol 3-kinase/Akt-1 in cell survival and proliferation of multiple myeloma (MM) has been well established. In this study, we demonstrate that homoharringtonine (HHT), an antileukemic drug first isolated from the Chinese evergreen Cephalotaxus harringtonia, induces significant cytotoxicity in dexamethasone-sensitive and -resistant and chemotherapy-sensitive MM cell lines in a time and dose-dependent manner. HHT also triggers apoptosis in chemotherapy-resistant patient's myeloma cells. Contrary to dexamethasone, the cytotoxicity of HHT on myeloma is independent of interleukin-6. The mechanism of HHT cytotoxicity is related to down-regulation of Akt phosphorylation/activation and various target genes of Akt including nuclear factor kappa B, XIAP, cIAP and cyclin D1. Moreover, in vivo antitumor activity of HHT is demonstrated in RPMI8226 myeloma xenograft model. Importantly, an additive effect of antitumor is confirmed in the myeloma cells treated with HHT and bortezomib concomitantly with inhibition of phosphorylated Akt. Together, these findings obtained with HHT should give useful insights into a novel antimyeloma chemotherapy.

Lenalidomide inhibits osteoclastogenesis, survival factors and bone-remodeling markers in multiple myeloma.

Breitkreutz I, Raab MS, Vallet S, Hideshima T, Raje N, Mitsiades C, Chauhan D, Okawa Y, Munshi NC, Richardson PG, Anderson KC.

Leukemia. 2008 Oct;22(10):1925-32. [Epub 2008 Jul 3.]

http://www.ncbi.nlm.nih.gov/pubmed/18596740?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors investigate the effect of lenalidomide on osteoclast (OCL) formation and osteoclastogenesis in comparison with bortezomib and conclude that both agents specifically target key factors in osteoclastogenesis, and could directly affect the myeloma-OCL- bone marrow stromal cells activation loop in osteolytic bone disease.

Osteolytic bone disease in multiple myeloma (MM) is caused by enhanced osteoclast (OCL) activation and inhibition of osteoblast function. Lenalidomide and bortezomib have shown promising response rates in relapsed and newly diagnosed MM, and bortezomib has recently been reported to inhibit OCLs. We here investigated the effect of lenalidomide on OCL formation and osteoclastogenesis in comparison with bortezomib. Both drugs decreased alpha V beta 3-integrin, tartrate-resistant acid phosphatase-positive cells and bone resorption on dentin disks. In addition, both agents decreased receptor activator of nuclear factor-kappaB ligand (RANKL) secretion of bone marrow stromal cells (BMSCs) derived from MM patients. We identified PU.1 and pERK as major targets of lenalidomide, and nuclear factor of activated T cells of bortezomib, resulting in inhibition of osteoclastogenesis. Furthermore, downregulation of cathepsin K, essential for resorption of the bone collagen matrix, was observed. We demonstrated a significant decrease of growth and survival factors including macrophage inflammatory protein-alpha, B-cell activating factor and a proliferation-inducing ligand. Importantly, in serum from MM patients treated with lenalidomide, the essential bone-remodeling factor RANKL, as well as the RANKL/OPG ratio, were significantly reduced, whereas osteoprotegerin (OPG) was increased. We conclude that both agents specifically target key factors in osteoclastogenesis, and could directly affect the MM-OCL-BMSCs activation loop in osteolytic bone disease.

Role of thalidomide in previously untreated patients with multiple myeloma.

Musto P, D'Auria F, Pietrantuono G, Bringhen S, Morabito F, Di Raimondo F, Pozzi S, Sacchi S, Boccadoro M, Palumbo A; Gruppo Italiano Malatte Ematologiche dell'Adulto Multiple Myeloma Working Party; Italian Myeloma Network and Gruppo Italiano Studio Linfomi.

Expert Rev Anticancer Ther. 2008 Oct;8(10):1569-80.

http://www.ncbi.nlm.nih.gov/pubmed/18925849?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report and discuss the clinical results achieved with thalidomide, including in combination with bortezomib, in previously untreated myeloma patients.

Thalidomide represents one of the most relevant therapeutic advances for patients with multiple myeloma over the last 10 years. Despite some toxicities, it has demonstrated significant efficacy in elderly patients, as well as in the setting of younger subjects receiving autologous stem cell transplantation. Here, we report and discuss the clinical results achieved with thalidomide alone or in combination with dexamethasone or other drugs, such as melphalan, cyclophosphamide, doxorubicin and bortezomib, in previously untreated myeloma patients.

Treatment for multiple myeloma: current status and future strategy in Japan. [Article in Japanese]

Iida S.

Rinsho Ketsueki. 2008 Oct;49(10):1368-73.

http://www.ncbi.nlm.nih.gov/pubmed/18833921?ordinalpos=50&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Triptolide overcomes dexamethasone resistance and enhanced PS-341-induced apoptosis via PI3k/Akt/NF-kappaB pathways in human multiple myeloma cells.

Yang M, Huang J, Pan HZ, Jin J.

Int J Mol Med. 2008 Oct;22(4):489-96.

http://www.ncbi.nlm.nih.gov/pubmed/18813856?ordinalpos=47&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that triptolide is able to enhance the activities of bortezomib in multiple myeloma cell lines.

Human multiple myeloma is a presently incurable hematological malignancy and novel biologically based therapies are urgently needed. Triptolide (TPL) is a purified diterpenod isolated from the Chinese herb, Tripterygium wilfordii Hook. F that has shown antitumor activities in various cancer cell types. But its activity in Dex-resistant multiple myeloma cell lines and the main upstream signaling pathway has not been reported. Here we show that TPL induces apoptosis in dexamethasone-sensitive (MM.1S) and dexamethasone-resistant (MM.1R) cells, most importantly its main upstream signaling pathway is through the PI3k/Akt/NF-kappaB pathway and is also associated with MAPK pathway, via mitochondrial apoptotic signaling and is also associated with the caspase and Bcl-2 family members. Moreover, TPL was able to enhance the activities of dexamethasone or bortezomib/PS-341 in multiple myeloma cell lines. Collectively, these findings provide the framework for a clinical evaluation of TPL, either alone or in combination with dexamethasone or bortezomib/PS-341, to overcome drug resistance and improve outcome for patients with this universally fatal hematological malignancy.

Multiple myeloma: diagnosis and treatment.

Nau KC, Lewis WD.

Am Fam Physician. 2008 Oct 1;78(7):853-9.

http://www.ncbi.nlm.nih.gov/pubmed/18841734?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors provide an overview of myeloma and its treatment, including discussion of bortezomib.

Multiple myeloma, the most common bone malignancy, is occurring with increasing frequency in older persons. Typical symptoms are bone pain, malaise, anemia, renal insufficiency, and hypercalcemia. Incidental discovery on comprehensive laboratory panels is common. The disease is diagnosed with serum or urine protein electrophoresis or immunofixation and bone marrow aspirate analysis. Skeletal radiographs are important in staging multiple myeloma and revealing lytic lesions, vertebral compression fractures, and osteoporosis. Magnetic resonance imaging and positron emission tomography or computed tomography are emerging as useful tools in the evaluation of patients with myeloma; magnetic resonance imaging is preferred for evaluating acute spinal compression. Nuclear bone scans and dual energy x-ray absorptiometry have no role in the diagnosis and staging of myeloma. The differential diagnosis of monoclonal gammopathies includes monoclonal gammopathy of uncertain significance, smoldering (asymptomatic) and symptomatic multiple myeloma, amyloidosis, B-cell non-Hodgkin lymphoma, Waldenström macroglobulinemia, and rare plasma cell leukemia and heavy chain diseases. Patients with monoclonal gammopathy of uncertain significance or smoldering multiple myeloma should be followed closely, but not treated. Symptomatic multiple myeloma is treated with chemotherapy followed by autologous stem cell transplantation, if possible. Melphalan, prednisolone, dexamethasone, vincristine, doxorubicin, bortezomib, and thalidomide and its analogue lenalidomide have been used successfully. It is important that family physicians recognize and appropriately treat multiple myeloma complications. Bone pain is treated with opiates, bisphosphonates, radiotherapy, vertebroplasty, or kyphoplasty; nephrotoxic nonsteroidal anti-inflammatory drugs should be avoided. Hypercalcemia is treated with isotonic saline infusions, steroids, furosemide, or bisphosphonates. Because of susceptibility to infections, patients require broad-spectrum antibiotics for febrile illness and immunization against influenza, pneumococcus, and Haemophilus influenzae B. Five-year survival rates approach 33 percent, and the median survival rate is 33 months.

Bortezomib-induced neurogenic bladder in patients with multiple myeloma.

Shimura K, Shimazaki C, Taniguchi K, Inaba T, Horiike S, Taniwaki M.

Ann Hematol. 2008 Oct 4. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18836719?ordinalpos=33&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Drug-induced hypersensitivity syndrome after bortezomib treatment for refractory multiple myeloma.

Hattori N, Adachi D, Nakashima H, Saito B, Nakamaki T, Tomoyasu S.

Leuk Res. 2008 Oct 4. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18838167?ordinalpos=34&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

A striking response to bortezomib in a patient with pleural localization of multiple myeloma.

Mangiacavalli S, Varettoni M, Zappasodi P, Pica G, Lazzarino M, Corso A.

Leuk Res. 2008 Oct 6. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18842298?ordinalpos=32&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Bone marrow microenvironment and the identification of new targets for myeloma therapy.

Podar K, Chauhan D, Anderson KC.

Leukemia. 2008 Oct 9. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18843284?ordinalpos=24&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss new agents, including bortezomib, which mediate myeloma tumor cytotoxicity in the bone marrow milieu.

The development of multiple myeloma (MM) is a complex multi-step process involving both early and late genetic changes in the tumor cell as well as selective supportive conditions by the bone marrow (BM) microenvironment. Indeed, it is now well established that MM cell-induced disruption of the BM homeostasis between the highly organized cellular and extracellular compartments supports MM cell proliferation, survival, migration and drug resistance through activation of various signaling (for example, PI3K/Akt, JAK/Stat-, Raf/MEK/MAPK-, NFkappaB- and Wnt-) pathways. Based on our enhanced understanding of the functional importance of the MM BM microenvironment and its inter-relation with the MM cell resulting in homing, seeding, proliferation and survival, new molecular targets have been identified and derived treatment regimens in MM have already changed fundamentally during recent years. These agents include thalidomide, its immunomodulatory derivative lenalidomide and the proteasome inhibitor bortezomib, which mediate tumor cytotoxicity in the BM milieu. Ongoing studies are further delineating MM pathogenesis in the BM to enhance cytotoxicity, avoid drug resistance and improve patient outcome.

Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study.

Chanan-Khan A, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Neuwirth R, Anderson KC, Richardson PG.

J Clin Oncol. 2008 Oct 10;26(29):4784-90. [Epub 2008 Aug 18.]

http://www.ncbi.nlm.nih.gov/pubmed/18711175?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The study aims to determine if bortezomib treatment is associated with increased incidence of varicella-zoster virus (VZV) reactivation in patients with relapsed multiple myeloma and concludes that though further studies are needed, for patients treated with bortezomib or bortezomib-containing regimens, the risk of VZV reactivation should be monitored and routine use of antiviral prophylaxis considered.

PURPOSE: The aim of this subset analysis was to determine if bortezomib treatment is associated with increased incidence of varicella-zoster virus (VZV) reactivation in patients with relapsed multiple myeloma (MM). PATIENTS AND METHODS: Incidence of herpes zoster was evaluated in 663 patients with relapsed MM from the phase III APEX trial comparing single-agent bortezomib with high-dose dexamethasone. RESULTS: Bortezomib was associated with a significantly higher incidence of herpes zoster compared with dexamethasone treatment (13%, 42 of 331 v 5%, 15 of 332; P = .0002). Most herpes zoster infections were grade 1/2; incidences of grade 3/4 events (1.8% v 1.5%) and infections considered serious adverse events (1.5% v 0.9%) were similar between treatment arms, and no herpes zoster-related deaths occurred. Neither the time to onset of the herpes event nor the patients' absolute lymphocyte counts at baseline differed significantly between arms. VZV reactivation was the only herpes viral event noted to be significantly elevated in the bortezomib treatment group compared with the dexamethasone treatment group (P = .0002). The incidence of non-VZV-related herpes viral infections was comparable between arms. No additional risk factors for herpes zoster reactivation were identified. CONCLUSION: Further studies are needed to explain these observations and their implications; however, for patients treated with bortezomib or bortezomib-containing regimens, the risk of VZV reactivation should be monitored and routine use of antiviral prophylaxis considered.

Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma.

Reece DE, Rodriguez GP, Chen C, Trudel S, Kukreti V, Mikhael J, Pantoja M, Xu W, Stewart AK.

J Clin Oncol. 2008 Oct 10;26(29):4777-83. [Epub 2008 Jul 21.]

http://www.ncbi.nlm.nih.gov/pubmed/18645194?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to improve the efficacy of the combination of oral weekly cyclophosphamide and alternate day prednisone in relapsed/refractory myeloma by adding bortezomib to the regimen. They find that weekly bortezomib 1.5 mg/m(2) plus oral cyclophosphamide and prednisone produces an unprecedented response rate and encouraging 1-year survival in relapsed/refractory patients with myeloma and conclude that further evaluation of this promising regimen is warranted both in relapsed and newly diagnosed disease.

PURPOSE: The combination of oral weekly cyclophosphamide and alternate day prednisone is a convenient regimen for relapsed/refractory multiple myeloma (MM), and we sought to improve its efficacy by adding bortezomib, a proteasome inhibitor with proven antimyeloma activity. PATIENTS AND METHODS: We conducted a phase I-II trial evaluating six dose levels to define the maximum tolerated dose (MTD) of this combination in relapsed/refractory MM. An additional 10 patients were evaluated at the highest dose level reached. RESULTS: Thirty-seven patients were treated on this study. The MTD was not defined. Both of the highest dose levels of bortezomib tested (1.3 mg/m(2) on days 1, 4, 8, and 11 and 1.5 mg/m(2) on days 1, 8, and 15, each on a 28-day cycle) could be safely given with cyclophosphamide 300 mg/m(2) per week and prednisone. At these dose levels, the overall response rate was 95% (complete responses [CR] plus partial response plus minimal response), with CR observed in more than 50% of patients. The weekly bortezomib regimen resulted in fewer instances of grade 3 thrombocytopenia and grade 1 to 2 peripheral neuropathy; the 1-year progression-free and overall survival probabilities with this dose level were 83% (95% CI, 73% to 96%) and 100%, respectively. CONCLUSION: Weekly bortezomib 1.5 mg/m(2) plus oral cyclophosphamide and prednisone produces an unprecedented response rate and encouraging 1-year survival in relapsed/refractory patients with MM. Further evaluation of this promising regimen is warranted both in relapsed and newly diagnosed disease.

Bortezomib overcomes cell adhesion-mediated drug resistance through downregulation of VLA-4 expression in multiple myeloma.

Hatano K, Kikuchi J, Takatoku M, Shimizu R, Wada T, Ueda M, Nobuyoshi M, Oh I, Sato K, Suzuki T, Ozaki K, Mori M, Nagai T, Muroi K, Kano Y, Furukawa Y, Ozawa K.

Oncogene. 2008 Oct 13. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/18850009?ordinalpos=27&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors perform functional screening using short hairpin RNA (shRNA) to define the molecule(s) responsible for CAM-DR of myeloma. They find that bortezomib is relatively resistant to CAM-DR because of its ability to specifically downregulate CD49d expression and that the combination of bortezomib with conventional anti-myeloma drugs may be effective in overcoming CAM-DR of myeloma.

Multiple myeloma (MM) is incurable, mainly because of cell adhesion-mediated drug resistance (CAM-DR). In this study, we performed functional screening using short hairpin RNA (shRNA) to define the molecule(s) responsible for CAM-DR of MM. Using four bona fide myeloma cell lines (KHM-1B, KMS12-BM, RPMI8226 and U266) and primary myeloma cells, we identified CD29 (beta1-integrin), CD44, CD49d (alpha4-integrin, a subunit of VLA-4), CD54 (intercellular adhesion molecule-1 (ICAM-1)), CD138 (syndecan-1) and CD184 (CXC chemokine receptor-4 (CXCR4)) as major adhesion molecules expressed on MM. shRNA-mediated knockdown of CD49d but not CD44, CD54, CD138 and CD184 significantly reversed CAM-DR of myeloma cells to bortezomib, vincristine, doxorubicin and dexamethasone. Experiments using blocking antibodies yielded almost identical results. Bortezomib was relatively resistant to CAM-DR because of its ability to specifically downregulate CD49d expression. This property was unique to bortezomib and was not observed in other anti-myeloma drugs. Pretreatment with bortezomib was able to ameliorate CAM-DR of myeloma cells to vincristine and dexamethasone. These results suggest that VLA-4 plays a critical role in CAM-DR of MM cells. The combination of bortezomib with conventional anti-myeloma drugs may be effective in overcoming CAM-DR of MM.

Advances in therapy of multiple myeloma.

Bladé J, Rosiñol L.

Curr Opin Oncol. 2008 Nov;20(6):697-704.

http://www.ncbi.nlm.nih.gov/pubmed/18841053?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This article summarizes the results of treatment of multiple myeloma in the era of novel agents, including the combination of bortezomib with melphalan-prednisone or with dexamethasone as highly effective regimens for patients not eligible for high-dose therapy/stem cell transplantation.

PURPOSE OF REVIEW: To summarize the results of treatment of multiple myeloma in the era of novel agents. RECENT FINDINGS: Recent publications comparing autologous stem cell transplantation (ASCT) with conventional chemotherapy in the era of 'old' drugs have shown that the contribution of ASCT in the treatment of multiple myeloma has been modest. Five trials comparing single vs. double ASCT showed an increased progression-free survival in three of them, whereas the overall survival was significantly prolonged in one. The benefit would be only for patients failing to achieve very good partial response with the first transplant. The results of allogeneic transplantation with reduced-intensity conditioning, particularly after debulking with an ASCT, are encouraging. On the contrary, the impact of pretransplant induction regimens with novel agents (thalidomide, bortezomib and lenalidomide) on the posttransplant outcome is being investigated in several large phase III trials. For elderly patients, the combination of 'old' therapies with thalidomide, bortezomib or lenalidomide has resulted in the melphalan-prednisone-thalidomide, melphalan-prednisone-Velcade, melphalan-prednisone-Revlimid and lenalidomide/dexamethasone regimens, which are highly effective. SUMMARY: ASCT has resulted in a modest contribution in the treatment of multiple myeloma. Hopefully, its impact will be increased with the incorporation of novel agents in the pretransplant induction regimens. The combination of thalidomide, bortezomib or lenalidomide with melphalan-prednisone or with dexamethasone has resulted in highly effective regimens for patients not eligible for high-dose therapy/stem cell transplantation.

Arsenic trioxide and 2-methoxyestradiol reduce beta-catenin accumulation after proteasome inhibition and enhance the sensitivity of myeloma cells to Bortezomib.

Zhou L, Hou J, Fu W, Wang D, Yuan Z, Jiang H.

Leuk Res. 2008 Nov;32(11):1674-83. [Epub 2008 May 15.]

http://www.ncbi.nlm.nih.gov/pubmed/18485479?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study shows that beta-catenin protein levels are negatively associated with myeloma cells' sensitivity to bortezomib. As(2)O(3)/2ME2 can reduce cytoplasmic beta-catenin accumulation after proteasome inhibition and enhance myeloma cells' sensitivity to bortezomib. This finding can preliminarily help to optimize the new therapeutic regimens for myeloma treatment in the future.

Beta-catenin, the key protein in canonical Wingless/int (Wnt) pathway, degrades via ubiquitin-proteasome pathway. Recently, it proved important roles in the proliferation of myeloma cells. But little is known about whether cytoplasmic beta-catenin content is associated with myeloma cell's sensitivity to Bortezomib. We examined the constitutive expression of beta-catenin in five myeloma cell lines and primary cells from patients. Meanwhile, the effect of Bortezomib combined with arsenic trioxide (As(2)O(3))/2-methoxyestradiol (2ME2) on beta-catenin accumulation, myeloma cells' survival, apoptosis and their sensitivity to Bortezomib were also investigated. Our study proved that beta-catenin protein levels are negatively associated with myeloma cells' sensitivity to Bortezomib. As(2)O(3)/2ME2 can reduce cytoplasmic beta-catenin accumulation after proteasome inhibition and enhance myeloma cells' sensitivity to Bortezomib. This will preliminarily help to optimize the new therapeutic regimens for MM treatment in the future.

Bortezomib directly inhibits osteoclast function in multiple myeloma: implications into the management of myeloma bone disease.

Terpos E.

Leuk Res. 2008 Nov;32(11):1646-7. [Epub 2008 Jul 9.]

http://www.ncbi.nlm.nih.gov/pubmed/18614229?ordinalpos=15&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: Leuk Res. 2008 Nov;32(11):1661-8.

Frontline treatment of multiple myeloma in elderly patients.

Moreau P, Hulin C, Facon T.

Blood Rev. 2008 Nov;22(6):303-9. [Epub 2008 Jun 11.]

http://www.ncbi.nlm.nih.gov/pubmed/18550234?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss highly active new treatment options available to treat elderly patients with myeloma, including melphalan and prednisone in combination with bortezomib.

Until 2007, frontline chemotherapy with melphalan and prednisone (MP) was considered as the standard of care in the treatment of elderly patients with multiple myeloma (MM). Recently, several prospective randomized studies comparing MP with the same combination plus new agents such as thalidomide (MPT) or bortezomib (MPV) clearly showed that MPT and MPV were superior to MP in terms of progression-free and overall survival. Melphalan-prednisone-lenalidomide (MPR) is currently compared to MP in one prospective trial and will also probably be superior to MP. Lenalidomide plus low-dose dexamethasone is a promising combination. Thus, at least four highly active new treatment options are now available to treat elderly patients with MM. The goal of future trials will be to determine the best treatment strategy in this group of patients.

Immune-mediated neuropathies in myeloma patients treated with bortezomib.

Ravaglia S, Corso A, Piccolo G, Lozza A, Alfonsi E, Mangiacavalli S, Varettoni M, Zappasodi P, Moglia A, Lazzarino M, Costa A.

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The authors report a series of patients treated with bortezomib who develop a peripheral damage possibly related to immuno-mediated, rather than toxic, mechanisms. They conclude that, in some instances, the peripheral damage associated with bortezomib may recognize immuno-mediated mechanisms and that this form of bortezomib-associated neuropathy needs to be recognized as treatable condition, as it may respond to immune therapies.

OBJECTIVE: Bortezomib is a new chemotherapeutic drug available for the treatment of lymphoid disorders, including multiple myeloma. Although its primary mechanism of action is proteasome inhibition, other mechanisms can contribute to the therapeutic effects, including modulation of inflammatory cytokines and immune response. One of the main toxic effects of bortezomib is peripheral neuropathy, usually occurring in the form of a painful, sensory axonal neuropathy. The mechanisms of peripheral damage, however, are still unclear. We here report a series of patients treated with bortezomib, who developed a peripheral damage possibly related to immuno-mediated, rather than toxic, mechanisms. METHODS: Five patients who developed a peripheral neuropathy with severe motor involvement under bortezomib treatment underwent CSF, electrophysiological, and spinal cord MRI examinations. RESULTS: Peripheral damage was characterized by: demyelinating or mixed axonal-demyelinating neuropathy, with prominent motor involvement; albumin-cytological dissociation; lumbar root enhancement on MRI in 2/5 patients; favourable outcome in 4/5 patients after immune treatments, either steroids (2 patients) or IVIg (2 patients). CONCLUSIONS: In some instances, the peripheral damage associated with bortezomib may recognize immuno-mediated mechanisms. SIGNIFICANCE: This form of bortezomib-associated neuropathy needs to be recognized as treatable condition, as it may respond to immune therapies. Unexplained worsening of neurological dysfunction despite bortezomib discontinuation, with prominent motor involvement and CSF signs of inflammation, may be the clues to this complication.

Multiple myeloma--an update on diagnosis and treatment.

Caers J, Vande broek I, De Raeve H, Michaux L, Trullemans F, Schots R, Van Camp B, Vanderkerken K.

Eur J Haematol. 2008 Nov;81(5):329-43. [Epub 2008 Sep 13.]

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This myeloma treatment update addresses the optimalization of different treatment options and schedules, including the use of bortezomib.

Multiple myeloma is a plasma cell (PC) malignancy characterized by the accumulation of monoclonal PCs in the bone marrow and the production of large amounts of a monoclonal immunoglobulin or paraprotein. In the past years, new approaches in the diagnosis and treatment were introduced aiming to identify high-risk patients who need proper anti-myeloma treatment. Intensive therapy including autologous hematopoietic stem cell transplantation and the new agents bortezomib, thalidomide, and lenalidomide have improved patients' responses. Further optimalization of the different treatment schedules in well-defined patient groups may prolong their survival. Patient stratification is currently based on patient characteristics, extent of myeloma disease, and associated cytogenetic and laboratory anomalies. More and more gene expression studies are introduced to stratify patients and to individualize therapy.

Novel targets for myeloma bone disease.

Roodman GD.

Expert Opin Ther Targets. 2008 Nov;12(11):1377-87.

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This article reviews the pathophysiology underlying bone remodeling and discusses potential new strategies to treat myeloma bone disease, including the use of bortezomib.

BACKGROUND: Multiple myeloma (MM) is a plasma cell malignancy in which osteolytic bone lesions develop in over 80% of patients. The increased bone destruction results from increased osteoclast formation and activity, which occurs adjacent to marrow sites involved with MM cells. This is accompanied by suppressed or absent osteoblast differentiation and activity, resulting in severely impaired bone formation and development of purely osteolytic lesions. OBJECTIVE: The pathophysiology underlying this bone remodeling is reviewed, and potential new strategies to treat MM bone disease are discussed. RESULTS: Recent advances in our understanding of factors involved in pathogenesis of MM bone disease have identified novel therapeutic targets. Several of these are or will be in clinical trials soon. CONCLUSION: Agents which target the tumor and bone-destructive process, such as the immunomodulatory drugs (IMiDs) or bortezomib, in combination with novel anti-resorptives should be effective. These combinations should be in clinical trials in the next few years. It is unclear if these treatments will be able to 'heal' bone lesions in MM patients.

Pulse treatment with the proteasome inhibitor bortezomib inhibits osteoclast resorptive activity in clinically relevant conditions.

Boissy P, Andersen TL, Lund T, Kupisiewicz K, Plesner T, Delaissé JM.

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The authors test bortezomib on cultured osteoclasts in conditions mimicking the pulse treatment used in the clinic, thereby avoiding continuous proteasome inhibition and unselective toxicity. Their study demonstrates a direct inhibition of osteoclasts by bortezomib in conditions relevant to treatment of myeloma.

Myeloma bone disease is due to bone degradation by osteoclasts, and absence of repair by bone forming osteoblasts. Recent observations suggest that the anti-myeloma drug bortezomib, a proteasome inhibitor, stimulates bone formation and may inhibit bone resorption. Here, we tested bortezomib on cultured osteoclasts in conditions mimicking the pulse treatment used in the clinic, thereby avoiding continuous proteasome inhibition and unselective toxicity. A 3 h pulse with 25 nM bortezomib followed by a 3-day culture in its absence markedly inhibited osteoclast activity as evaluated through bone resorption, TRAcP release, and RANKL-induced NF-kappaB translocation into nuclei, an event dependent on proteasomes and critical for osteoclast function. The effect on TRAcP was maximal during the first 24 h post-pulse, and then tended to subside. Importantly, applying this pulse treatment to cultured myeloma cells drastically reduced their survival. We measured next the levels of two bone resorption markers in patients during the 3 days following five and seven therapeutic bortezomib administrations, respectively. These levels decreased significantly already 1-2 days after injection, and then increased, showing temporary inhibition of osteoclast activity and paralleling the in vitro effect on TRAcP. Our study demonstrates a direct inhibition of osteoclasts by bortezomib in conditions relevant to treatment of myeloma.

Dietary flavonoids inhibit the anticancer effects of the proteasome inhibitor bortezomib.

Liu FT, Agrawal SG, Movasaghi Z, Wyatt PB, Rehman IU, Gribben JG, Newland AC, Jia L.

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The authors review the data that indicate dietary flavonoids limit the efficacy of bortezomib, whereas supplemental inorganic boric acid is able to reverse this. They conclude that the complex interactions between quercetin, tumor cells, and bortezomib mean caution is required when giving dietary advice to patients.

Dietary flavonoids have many health-promoting actions, including anticancer activity via proteasome inhibition. Bortezomib is a dipeptide boronate proteasome inhibitor that has activity in the treatment of multiple myeloma but is not effective in chronic lymphocytic leukemia (CLL). Although CLL cells are sensitive in vitro to bortezomib-induced apoptosis when cultured in medium, the killing activity was blocked when cultured in 50% fresh autologous plasma. Dietary flavonoids, quercetin and myricetin, which are abundant in plasma, inhibited bortezomib-induced apoptosis of primary CLL and malignant B-cell lines in a dose-dependent manner. This inhibitory effect was associated with chemical reactions between quercetin and the boronic acid group, -RB(OH)2, in bortezomib. The addition of boric acid diminished the inhibitory effect of both quercetin and plasma on bortezomib-induced apoptosis. The protective effect was also reduced when myeloma cell lines, but not B-cell lines, were preincubated with quercetin, indicating a direct effect of quercetin on myeloma cells. At high doses, quercetin itself induced tumor cell death. These data indicate that dietary flavonoids limit the efficacy of bortezomib, whereas supplemental inorganic boric acid is able to reverse this. The complex interactions between quercetin, tumor cells, and bortezomib mean caution is required when giving dietary advice to patients.

A phase I and pharmacologic study of the combination of bortezomib and pegylated liposomal doxorubicin in patients with refractory solid tumors.

Dees EC, O'Neil BH, Lindley CM, Collichio F, Carey LA, Collins J, Riordan WJ, Ivanova A, Esseltine D, Orlowski RZ.

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The authors conduct a phase I trial of bortezomib and pegylated liposomal doxorubicin (PLD) in patients with refractory solid tumors and conclude that a regimen of bortezomib, 1.3 mg/m(2) on days 1, 4, 8, and 11 with PLD, 30 mg/m(2), on day 4 of a 21-day cycle, is safe in this study, and merits further investigation.

PURPOSE: Pre-clinical studies combining the proteasome inhibitor bortezomib with anthracyclines have shown enhanced anti-tumor activity. We conducted a phase I trial of bortezomib and pegylated liposomal doxorubicin (PLD) in patients with refractory solid tumors. METHODS: Patients received bortezomib, 0.9-1.5 mg/m(2), on days 1, 4, 8, and 11 of every 21-day cycle, along with PLD, 30 mg/m(2), on day 4. The goals were to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD), and to investigate pharmacokinetic and pharmacodynamic interactions of the combination. RESULTS: A total of 37 patients with four median prior therapies were treated. Frequent grade 1-2 toxicities included fatigue, nausea, thrombocytopenia, anemia, neutropenia, constipation, myalgias, and peripheral neuropathy. DLTs included grade 3 nausea and vomiting in 1 of 6 patients receiving bortezomib at 1.2 mg/m(2), and grade 3 nausea, vomiting, and diarrhea in 1 of 6 patients receiving bortezomib at 1.5 mg/m(2). Grade 3 toxicities in later cycles included hand-foot syndrome, thrombocytopenia, anemia, neutropenia, nausea, diarrhea, and abdominal pain. Because of frequent dose-delays, dose-reductions, and gastrointestinal toxicity at the 1.4 and 1.5 mg/m(2) levels, bortezomib at 1.3 mg/m(2) and PLD at 30 mg/m(2) are recommended for further testing. Among 19 patients with breast cancer, four had evidence of a clinical benefit. Pharmacokinetic and pharmacodynamic studies did not show any significant interactions between the two drugs. CONCLUSIONS: A regimen of bortezomib, 1.3 mg/m(2) on days 1, 4, 8, and 11 with PLD, 30 mg/m(2), on day 4 of a 21-day cycle, was safe in this study, and merits further investigation.

A phase I pharmacodynamic trial of bortezomib in combination with doxorubicin in patients with advanced cancer.

Loconte NK, Thomas JP, Alberti D, Heideman J, Binger K, Marnocha R, Utecht K, Geiger P, Eickhoff J, Wilding G, Kolesar J.

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This phase I trial seeks to define the toxicity, maximally tolerated dose and pharmacodynamics of a combination of bortezomib and doxorubicin in patients with advanced malignancies, and concludes that bortezomib and doxorubicin can be administered safely. This combination may be of special interest in multiple myeloma, given the activity of both drugs in that disease.

PURPOSE: This phase I trial sought to define the toxicity, maximally tolerated dose (MTD) and pharmacodynamics of a combination of bortezomib and doxorubicin in patients with advanced malignancies. PATIENTS AND METHODS: Twenty-six patients were treated with bortezomib intravenously on days 1, 4, 8 and 11, with doxorubicin also administered intravenously on days 1 and 8, both in a 21-day cycle. Dosing ranged from 1.0 mg/m(2) of bortezomib with 15 mg/m(2) of doxorubicin to 1.5 mg/m(2) of bortezomib with 20 mg/m(2) of doxorubicin. Pharmacodynamic studies performed included assessment of levels of 20S proteasome activity and ubiquitin-protein conjugates. RESULTS: The combination of bortezomib and doxorubicin was generally well tolerated. There were two dose limiting toxicities (DLT) at dose cohort 3 (1.3 mg/m(2) bortezomib, 20 mg/m(2) doxorubicin) and 2 DLT at dose cohort 3a (1.5 mg/m(2) bortezomib, 15 mg/m(2) doxorubicin). DLT seen included neutropenia, thrombocytopenia, and neuropathy. In addition, one patient developed grade 3 central nervous system toxicity in cycle 2 (not a DLT). One patient with hormone refractory prostate cancer had a partial response. Proteasome inhibition in whole blood was demonstrated and an increase in ubiquitin-protein conjugates was observed in peripheral blood mononuclear cells of most patients. CONCLUSIONS: Bortezomib and doxorubicin can be administered safely. The recommended phase II dose for this 21-day cycle is bortezomib 1.3 mg/m(2)intravenously on days 1, 4, 8 and 11, and doxorubicin 20 mg/m(2) intravenously on days 1 and 8. This combination may be of special interest in multiple myeloma, given the activity of both drugs in that disease.

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