CITINGS

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VELCADE® (bortezomib) Issue

The International Myeloma Foundation *(IMF) presents this special edition of CITINGS, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on VELCADE (bortezomib). This special edition corresponds with the 2009 annual meeting of the American Society of Clinical Oncology (ASCO). In this CITINGS, we have highlighted selected VELCADE data presentations from the ASCO meeting. We also provide references to the latest published journal articles on VELCADE from the second quarter of this year.*

It is our hope that CITINGS will help keep you abreast of the latest developments in myeloma treatment. As always, we welcome your feedback; you may contact the IMF at (800) 452-CURE (2873) or at our website www.myeloma.org.

– Susie Novis, President, IMF

American Society of Clinical Oncology Presentations 2009

Saturday, May 30th

A phase I MMRC clinical trial testing the combination of bortezomib and tipifarnib in relapsed/refractory multiple myeloma.

S. Lonial, D. Francis, C. Karanes, S. Trudel, A. Dollard, D. Harvey, J. Kaufman

J Clin Oncol 27:15s, 2009 (suppl; abstr 8597)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8597 **Session Type: General Poster**
Poster No.: T6
Time: 8:00 AM – 12:00 PM **Location: Level 2, West Hall C**

The authors conclude that the combination of bortezomib and tipifarnib is supported by preclinical rationale and has produced stable disease or better among 10 of 18 patients with refractory myeloma. Optimal dose of tipifarnib and bortezomib have yet to be defined.

Relationship of rapid M protein reduction to outcomes in a trial of pegylated liposomal doxorubicin (PLD) plus bortezomib (B) versus B alone in previously treated multiple myeloma (MM).

J. J. Shah, A. Londhe, K. C. Lantz, C. Lowery, R. Z. Orlowsk

J Clin Oncol 27:15s, 2009 (suppl; abstr 8591)

Lymphoma and Plasma Cell Disorders

Abstract No.: **8591** **Session Type: General Poster**
Poster No.: S21
Time: 8:00 AM – 12:00 PM **Location: Level 2, West Hall C**

The authors find that of pegylated liposomal doxorubicin + bortezomib has significant benefit over bortezomib alone in extending TTP in landmark analyses similar to the overall study. Also, a >50% reduction in M protein results in a significant risk reduction for progression—data which suggests that early reductions in M protein may provide better outcomes.

Role of autologous stem cell transplant after induction therapy with bortezomib-lenolidomide or bortezomib-thalidomide in newly diagnosed multiple myeloma patients.

N. Shah, D. Weber, R. Orlowski, M. Wang, S. K. Thomas, T. Richards, S. Giralt, M. Qazilbash, R. Alexanian, J. J. Shah

J Clin Oncol 27:15s, 2009 (suppl; abstr 8596)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8596 **Session Type: General Poster**
Poster No.: T5
Time: 8:00AM – 12:00PM **Location: Level 2, West Hall C**

The authors conduct a retrospective review of 95 newly diagnosed myeloma patients treated with induction bortezomib-lenolidomide-dexamethasone (BLD) or bortezomib-thalidomide-dexamethasone (BTD) prior to ASCT. They find there is a significant benefit of ASCT in these patients who initially demonstrate relative resistance to induction therapy with highly active regimens.

Sunday May 31st

Autologous and Allogeneic Transplant Management for Multiple Myeloma

Jean L. Harousseau

Leukemia, Myelodysplasia, and Transplantation, Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Education**
Time: 9:00AM **Location: Level 2, West Hall F3**

Myeloma

Robert Z. Orlowski, Ravi Vij

Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Oral**
Time: 9:00AM **Location: Level 2, West Hall F1**

Non-transplant regimens for treatment of myeloma

Donna Reece

Leukemia, Myelodysplasia, and Transplantation, Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Education**
Time: 9:00AM **Location: Level 2, West Hall F3**

Personalized care plan for treatment of myeloma

Morie A. Gertz

Leukemia, Myelodysplasia, and Transplantation, Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Education**
Time: 9:00AM **Location: Level 2, West Hall F3**

A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.

A. P. Palumbo, S. Bringhen, D. Rossi, S. Berretta, V. Montefusco, J. Peccatori, M. Galli, A. Carella, P. Omedè, M. Boccadoro

J Clin Oncol 27:15s, 2009 (suppl; abstr 8515)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8515 **Session Type: Oral**
Time: 9:00AM **Location: Level 2, West Hall F1**

The authors randomly assign 500 newly diagnosed myeloma patients ≥ 65 to receive bortezomib, melphalan, prednisone, and thalidomide (VMPT) or bortezomib, melphalan, prednisone (VMP). They find that VMPT is superior to VMP in terms of response rates, with longer follow-up is needed to assess their effects on PFS and OS. Both regimens appeared to overcome the poor prognosis of ISS and chromosomal abnormalities.

Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial.

S. Knop, P. Liebisch, H. Wandt, M. Kropff, W. Jung, N. Kroeger, O. Sezer, C. Straka, G. Fingerle-Rowson, H. Einsele

J Clin Oncol 27:15s, 2009 (suppl; abstr 8516)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8516 **Session Type: Oral**
Time: 9:15AM **Location: Level 2, West Hall F1**

This interim analysis demonstrates that bortezomib combined with dexamethasone and intravenous cyclophosphamide is a highly effective induction regimen for patients ≤ 60 years with newly diagnosed myeloma regardless of cytogenetic risk factors.

Lenalidomide, bortezomib, pegylated liposomal doxorubicin hydrochloride, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial.

A. J. Jakubowiak, C. C. Hofmeister, E. L. Campagnaro, T. M. Zimmerman, R. L. Schlossman, S. Lonial, D. E. Reece, M. S. Kaminski, K. C. Anderson, P. G. Richardson

J Clin Oncol 27:15s, 2009 (suppl; abstr 8517)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8517 **Session Type: Oral**
Time: 9:30AM **Location: Level 2, West Hall F1**

This phase I/II study was designed to determine the maximum tolerated dose of Revlimid, Velcade, Doxil, dexamethasone (RVDD), as well as assess safety and evaluate efficacy of this 4-drug regimen in newly diagnosed myeloma. The authors find RVDD is well tolerated in newly diagnosed myeloma and appears highly active with an overall response (> PR) of 95%.

Update on Induction Regimens for Multiple Myeloma

S. Vincent Rajkumar

Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Oral Discussion**
Time: 10:00AM **Location: Level 2, West Hall F1**

Bone marrow microenvironment (ME) associated genes identified prior to all altered 48 hours after bortexomib test-dose application and prognosis of multiple myeloma (MM) treated with total therapy 3 (TT3).

P. Qu, J. Haessler, B. Barlogie, J. Shaughnessy

J Clin Oncol 27:15s, 2009 (suppl; abstr 8520)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8520 **Session Type: Oral**
Time: 10:00AM **Location: Level 2, West Hall F1**

In this study, patients received a bortezomib test dose of 1mg/m2 to determine whether microenvironment (ME) alterations induced 48hr post-bortezomib could clarify the drug's in-vivo mechanism of action in the context of achieving myeloma control. This first report documenting a validated prognostic role of ME for cancer survival concludes that key genes shared by both studied models are involved in endothelial and mesenchymal stem-cell signaling.

New Prognostic Tools in Myeloma

Rafael Fonseca

Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Oral Discussion**
Time: 11:00AM **Location: Level 2, West Hall F1**

Monday June 1st

Adjuvant bortezomib and dexamethasone following risk-adapted melphalan and stem cell transplant in patients with light-chain amyloidosis (AL).

H. J. Landau, J. Hoffman, H. Hassoun, H. Elizabeth, E. Riedel, S. D. Nimer, A. Cohen, R. L. Comenzo

J Clin Oncol 27:15s, 2009 (suppl; abstr 8540)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8540 **Session Type: Poster Discussion**
Poster No.: 18
Time: 2:00PM – 6:00PM **Location: Level 2, W240A**
also
Time: 5:00PM – 6:00PM **Location: Level 2, West Hall F1**

This study finds that adjuvant bortezomib and dexamethasone effectively eradicates clonal plasma cell disease in patients with amyloidosis (AL) following SCT and results in an unprecedented CR rate at 12 months post-SCT; patients with cardiac AL continue to do poorly.

FDG PET/CT (FDG PET) in evaluation of response in patients with multiple myeloma (MM) treated with bortezomib, pegylated liposomal doxorubicin, and dexamethasone.

N. Pandit-Taskar, R. L. Comenzo, H. Hassoun, E. Hoover, S. Borkar, E. Reidel, A. Cohen, C. Surti, S. D. Nimer, H. J. Landau

J Clin Oncol 27:15s, 2009 (suppl; abstr 8533)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8533 **Session Type: Poster Discussion**
Poster No.: 11
Time: 2:00PM – 6:00PM **Location: Level 2, W240A**
also
Time: 5:00PM – 6:00PM **Location: Level 2, West Hall F1**

In this study, 40 patients with high-risk myeloma (defined as ISS II, ISS III or presence of extramedullary plasmacytoma) are treated using a combination of bortezomib, pegylated liposomal doxorubicin hydrochloride (Doxil), and dexamethasone (BDD) for 3 cycles followed by 2 cycles of thalidomide and dexamethasone for patients achieving at least PR. The authors find poor agreement between FDG PET response and myeloma disease response by International

Myeloma Working Group criteria. Serial FDG PET does not provide the authors with additional information for therapeutic response assessment in patients with newly diagnosed or primary refractory myeloma.

Lenalidomide, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma (MM): Encouraging outcomes and tolerability in a phase II study.

K. C. Anderson, S. Jagannath, A. Jakubowiak, S. Lonial, N. Raje, M. Alsina, I. Ghobrial, R. Knight, D. Esseltine, P. Richardson

J Clin Oncol 27:15s, 2009 (suppl; abstr 8536)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8536 **Session Type: Poster Discussion**
Poster No.: 14
Time: 2:00PM – 6:00PM **Location: Level 2, W240A**
also
Time: 5:00PM – 6:00PM **Location: Level 2, West Hall F1**

This multicenter phase 2 study evaluates lenalidomide, bortezomib, dexamethasone (RVD) efficacy and safety at the maximum tolerated dose and concludes that RVD is active and well tolerated in patients with relapsed/refractory myeloma, including patients who have received prior lenalidomide, bortezomib, thalidomide, and SCT. Durable responses are observed and appear independent of adverse cytogenetics and other recognized risk factors.

A phase I study of vorinostat in combination with bortezomib in refractory solid tumors.

J. A. Ninan, H. Bailey, J. Kolesar, R. Marnocha, J. Eickhoff, J. Wright, I. Espinoza-Delgado, D. Alberti, G. Wilding, W. Schelman

J Clin Oncol 27:15s, 2009 (suppl; abstr 2531)

Developmental Therapeutics: Cytotoxic Chemotherapy

Abstract No.: 2531 **Session Type: Poster Discussion**
Poster No.: 23
Time: 2:00PM – 6:00PM **Location: Level 3, W315A**
also
Time: 5:00PM – 6:00PM **Location: Level 3, W304A**

This study evaluates twice daily dosing of vorinostat during administration of bortezomib to determine safety and efficacy, pharmacokinetics, and activity this combination. A maximum tolerated dose is established.

Phase II trial of combination of bortezomib and rituximab in relapsed and/or refractory Waldenstrom macroglobulinemia.

I. M. Ghobrial, J. Matous, S. Padmanabhan, A. Badros, S. Chuma, R. Leduc, M. Rourke, J. Kunsman, B. Harris, D. Warren, P. Richardson

J Clin Oncol 27:15s, 2009 (suppl; abstr 8535)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8535 **Session Type: Poster Discussion**
Poster No.: 13
Time: 2:00PM – 6:00PM **Location: Level 2, W240A**
also
Time: 5:00PM – 6:00PM **Location: Level 2, West Hall F1**

The authors find that the combination of weekly bortezomib and rituximab is well tolerated and demonstrates encouraging activity, with CR+ PR + MR in 83% of evaluable patients with relapsed refractory Waldenstrom macroglobulinemia. They observe no significant peripheral neuropathy with this regimen.

Use of bortezomib (BOR) pharmacogenomics (PG) to identify mechanisms of drug resistance and predict survival in multiple myeloma (MM) treated with total therapy 3 (TT3).

J. D. Shaughnessy, P. Qu, J. Haessler, J. Crowley, B. Barlogie

J Clin Oncol 27:15s, 2009 (suppl; abstr 8538)

Lymphoma and Plasma Cell Disorders

Abstract No.: 8538 **Session Type: Poster Discussion**
Poster No.: 16
Time: 2:00PM – 6:00PM **Location: Level 2, W240A**
also
Time: 5:00PM – 6:00PM **Location: Level 2, West Hall F1**

The authors use pharmacogenomics to identify a powerful 80-gene post-bortezomib risk (PBR) model with unprecedented prognosis-discriminating power, dispelling baseline risk model (BLR) from multivariate analysis by altering BLR designation mainly from low to high risk. High PBR (18%) could be traced to up-regulation of proteasome genes, the target of bortezomib.

Current Use of Proteasome Inhibitors in Myeloma

Carol Ann Huff

Developmental Therapeutics, Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Clinical Science Symposium Discussion**
Time: 3:00PM **Location: Level 2, West Hall F1**

Tanespimycin plus bortezomib in patients with relapsed and refractory multiple myeloma: Final results of a phase I/II study.

P. G. Richardson, A. Chanan-Khan, S. Lonial, A. Krishnan, M. Carroll, M. Alsina, M. Albitar, D. Berman, S. Kaplita, K. Anderson

J Clin Oncol 27:15s, 2009 (suppl; abstr 8503)

Developmental Therapeutics, Lymphoma and Plasma Cell Disorders

Abstract No.: 8503 **Session Type: Clinical Science Symposium**
Time: 3:15PM **Location: Level 2, West Hall F1**

The authors find tanespimycin plus bortezomib is active and well tolerated in relapsed/refractory myeloma, with durable responses in bortezomib-naive, -pretreated and -refractory patients. Median duration of response for the combination compares favorably to bortezomib monotherapy and no severe peripheral neuropathy is observed.

Rational Combinations of Proteosome Inhibitors with Novel Therapeutics

Kapil N. Bhalla

Developmental Therapeutics, Lymphoma and Plasma Cell Disorders

Abstract No.: n/a **Session Type: Clinical Science Symposium Discussion**
Time: 3:30PM **Location: Level 2, West Hall F1**

Publication Only

Amplification and overexpression of the PSMB5 gene contributes to bortezomib resistance in retreatment of patients with multiple myeloma.

G. Altavilla, C. Arrigo, G. Marabello, G. Galletti, M. Santarpia, M. Sauta, V. Pitini

J Clin Oncol 27, 2009 (suppl; abstr e19500)

The authors conclude that amplification and overexpression of PSMB5 contributes to bortezomib resistance in clinical practice. These findings highlight the susceptibility of proteasome units to genetic modifications under constant selective pressure that occurs with continued treatment; furthermore, the drug resistance remains dormant but it rapidly revives upon re-exposure to bortezomib.

Current treatment (Tx) patterns in relapsed or refractory multiple myeloma (MM): A retrospective chart review study.

D. E. Reece, F. Zaman, B. L. Teixeira, K. Yoong, F. Camacho, R. K. Plante

J Clin Oncol 27, 2009 (suppl; abstr e19503)

This retrospective chart review includes all relapsed/refractory myeloma patient who initiated drug treatment, including with bortezomib, between Jul-06 and Jun-07 inclusive at Princess Margaret Hospital, Toronto, ON.

A phase II study of a 1-hour infusion of romidepsin combined with bortezomib for multiple myeloma (MM) patients with relapsed or refractory disease.

J. R. Berenson, O. Yellin, R. Mapes, B. Eades, C. D. Abaya, A. Strayer, D. Nix, R. A. Swift

J Clin Oncol 27, 2009 (suppl; abstr e19508)

Preliminary data from this study suggest that the 1-hr infusion of romidepsin combined with bortezomib is active for patients with myeloma relapsed or refractory to bortezomib. This study continues to enroll patients.

A phase II trial of sorafenib in patients with relapsing and resistant multiple myeloma (MM) previously treated with bortezomib (S0434).

G. Srkalovic, M. Hussein, V. Bolejack, A. Hoering, J. Zonder, B. Barlogie

J Clin Oncol 27, 2009 (suppl; abstr e19517)

The authors find that sorafenib might have a supportive role in combination therapy with bortezomib, lenalidomide or everolimus in relapsed/refractory myeloma.

A retrospective chart review study of relapsed or refractory multiple myeloma (MM) patients (Pts): A look into historical treatment (Tx) patterns.

F. Zaman, D. E. Reece, B. L. Teixeira, K. Yoong, F. Camacho, R. K. Plante

J Clin Oncol 27, 2009 (suppl; abstr e19535)

This retrospective analysis includes all relapsed/refractory myeloma patients who initiated drug treatment, including with thalidomide and lenalidomide, between Jul-06 and Jun-07 at Princess Margaret Hospital, Toronto, ON.

A retrospective review of pegylated liposomal doxorubicin (PLD), bortezomib, and dexamethasone (DVD) for relapsed or refractory (R/R) multiple myeloma (MM).

G. N. Waterman, O. Yellin, R. A. Swift, J. Hilger, J. R. Berenson

J Clin Oncol 27, 2009 (suppl; abstr e19523)

This retrospective analysis sought to evaluate the pegylated liposomal doxorubicin, bortezomib, and dexamethasone regimen for patients with relapsed/refractory myeloma. The authors conclude that patients treated with this regimen who had failed many prior regimens with progressive disease demonstrate a high response rate with few significant or drug-related adverse events.

VELCADE® Publications – 2nd Quarter, 2009

Emerging combination treatment strategies containing novel agents in newly diagnosed multiple myeloma.

Lonial S, Cavenagh J.

Br J Haematol. 2009 Mar 14. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19344388?ordinalpos=73&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review the improvements in response and outcome that are seen with novel agents, including bortezomib, both as induction therapy and in non-transplant patients, and highlight the latest data from key studies of various novel combinations. They also review data on response and outcomes in patients with poor prognostic characteristics that indicate that the adverse impact typically seen with these factors may be overcome using novel therapies.

Aminopeptidase inhibition as a targeted treatment strategy in myeloma.

Moore HE, Davenport EL, Smith EM, Muralikrishnan S, Dunlop AS, Walker BA, Krige D, Drummond AH, Hooftman L, Morgan GJ, Davies FE.

Mol Cancer Ther. 2009 Apr;8(4):762-70.

http://www.ncbi.nlm.nih.gov/pubmed/19372548?ordinalpos=62&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that CHR-2797, a novel aminopeptidase inhibitor, shows additive and synergistic effects with bortezomib, melphalan, and dexamethasone.

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

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

Leuk Res. 2009 Apr;33(4):584-6. [Epub 2008 Sep 30.]

http://www.ncbi.nlm.nih.gov/pubmed/18829108?ordinalpos=60&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Bortezomib in relapsed multiple myeloma: results of a non-interventional study by office-based haematologists.

Knauf WU, Otremba B, Overkamp F, Kornacker M.

Onkologie. 2009 Apr;32(4):175-80. [Epub 2009 Mar 13.]

http://www.ncbi.nlm.nih.gov/pubmed/19372712?ordinalpos=64&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In this German study, bortezomib is studied under routine conditions by office-based hematologists. The authors find that bortezomib's efficacy and tolerability in daily practice are consistent with the results obtained in large-scale clinical trials.

Bortezomib-induced neurogenic bladder in patients with multiple myeloma.

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

Ann Hematol. 2009 Apr;88(4):383-4. [Epub 2008 Oct 4.]

http://www.ncbi.nlm.nih.gov/pubmed/18836719?ordinalpos=48&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Curcumin circumvents chemoresistance in vitro and potentiates the effect of thalidomide and bortezomib against human multiple myeloma in nude mice model.

Sung B, Kunnumakkara AB, Sethi G, Anand P, Guha S, Aggarwal BB.

Mol Cancer Ther. 2009 Apr;8(4):959-70.

http://www.ncbi.nlm.nih.gov/pubmed/19372569?ordinalpos=61&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' findings suggest that curcumin overcomes chemoresistance and sensitizes multiple myeloma cells to thalidomide and bortezomib by down-regulating NF-kappaB and NF-kappaB-regulated gene products.

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. 2009 Apr;33(4):574-7. [Epub 2008 Oct 5.]

http://www.ncbi.nlm.nih.gov/pubmed/18838167?ordinalpos=59&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Frontline treatment in elderly patients with multiple myeloma.

Facon T, San Miguel J, Mateos MV, Hulin C.

Semin Hematol. 2009 Apr;46(2):133-42.

http://www.ncbi.nlm.nih.gov/pubmed/19389497?ordinalpos=68&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss melphalan-prednisone-thalidomide and melphalan-prednisone-bortezomib as new and emerging therapies providing multiple effective treatment options for myeloma patients and greatly enhanced treatment strategies for clinicians.

Front-line treatment in younger patients with multiple myeloma.

Rajkumar SV, Sonneveld P.

Semin Hematol. 2009 Apr;46(2):118-26.

http://www.ncbi.nlm.nih.gov/pubmed/19389495?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This review discusses the current status of front-line therapy in younger patients with myeloma who are candidates for stem cell transplantation.

Restoration of chemosensitivity by bortezomib: implications for refractory myeloma.

Chim CS, Hwang YY, Pang C, Shek TW; Medscape.

Nat Rev Clin Oncol. 2009 Apr;6(4):237-40.

http://www.ncbi.nlm.nih.gov/pubmed/19333230?ordinalpos=63&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors discuss salvage chemotherapy regimens including bortezomib plus steroid, bortezomib plus anthracycline and radiotherapy, and combined bortezomib, cyclophosphamide, melphalan and steroid therapy for a 59-year-old woman presented to the emergency department with a left rib fracture and diagnosed with IgA multiple myeloma; the patient underwent autologous bone-marrow transplantation, and 14 months later she developed obstructive jaundice.

A retrospective analysis of bortezomib therapy for Japanese patients with relapsed or refractory multiple myeloma: beta2-microglobulin associated with time to progression.

Ohguchi H, Sugawara T, Ishikawa I, Okuda M, Tomiya Y, Yamamoto J, Onishi Y, Fujiwara Yamada M, Ishizawa K, Kameoka J, Harigae H.

Int J Hematol. 2009 Apr;89(3):342-7. [Epub 2009 Mar 19.]

http://www.ncbi.nlm.nih.gov/pubmed/19296199?ordinalpos=56&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors retrospectively analyze 40 patients with relapsed or refractory myeloma who have received bortezomib at three collaborating centers in Miyagi prefecture in Japan. They find bortezomib is well tolerated and effective for Japanese patients with relapsed or refractory myeloma, with results suggesting that serum beta2-microglobulin level may be a marker of prognosis on bortezomib therapy for patients with relapsed or refractory myeloma— though further studies are needed.

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. 2009 Apr;33(4):577-8. [Epub 2008 Oct 7.]

http://www.ncbi.nlm.nih.gov/pubmed/18842298?ordinalpos=58&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

No abstract available.

Treatment of relapsed/refractory multiple myeloma.

Kastritis E, Palumbo A, Dimopoulos MA.

Semin Hematol. 2009 Apr;46(2):143-57.

http://www.ncbi.nlm.nih.gov/pubmed/19389498?ordinalpos=67&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review treatment of relapsed/refractory myeloma, including results of phase II trials finding lenalidomide and bortezomib have increased the post-relapse survival and are active in patients who have received prior novel agents.

Varicella-zoster virus prophylaxis with low-dose acyclovir in patients with multiple myeloma treated with bortezomib.

Pour L, Adam Z, Buresova L, Krejci M, Krivanova A, Sandecka V, Zahradova L, Buchler T, Vorlicek J, Hajek R.

Clin Lymphoma Myeloma. 2009 Apr;9(2):151-3.

http://www.ncbi.nlm.nih.gov/pubmed/19406726?ordinalpos=52&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors conclude that varicella-zoster virus (VZV) reactivation is a common and serious adverse effect of bortezomib treatment, but that acyclovir 400 mg once daily is sufficient to protect from VZV reactivation in patients with myeloma treated with bortezomib.

Combining milatuzumab with bortezomib, doxorubicin, or dexamethasone improves responses in multiple myeloma cell lines.

Stein R, Smith MR, Chen S, Zalath M, Goldenberg DM.

Clin Cancer Res. 2009 Apr 15;15(8):2808-17. [Epub 2009 Apr 7.]

http://www.ncbi.nlm.nih.gov/pubmed/19351768?ordinalpos=43&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that the therapeutic efficacies of bortezomib, doxorubicin, and dexamethasone are enhanced in myeloma cell lines when given in combination with milatuzumab, suggesting testing these combinations clinically.

Dysregulation of unfolded protein response partially underlies proapoptotic activity of bortezomib in multiple myeloma cells.

Dong H, Chen L, Chen X, Gu H, Gao G, Gao Y, Dong B.

Leuk Lymphoma. 2009 Apr 22:1-11. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19391038?ordinalpos=38&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors' data strongly suggest that dysregulated or disruptive unfolded protein response may, at least partly, underlie the antimyeloma activity of bortezomib.

Treatment of multicentric Castleman's Disease accompanying multiple myeloma with bortezomib: a case report.

Yuan ZG, Dun XY, Li YH, Hou J.

J Hematol Oncol. 2009 Apr 28;2(1):19. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19400935?ordinalpos=30&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors report a case of rare Multicentric Castleman's disease (MCD) complicated with myeloma; the patient received bortezomib and achieved very good remission. To the authors' knowledge, this is the first report on MCD in the setting of myeloma with good response to bortezomib.

CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells with the bone marrow microenvironment and enhances their sensitivity to therapy.

Azab AK, Runnels JM, Pitsillides C, Moreau AS, Azab F, Leleu X, Jia X, Wright R, Ospina B, Carlson AL, Alt C, Burwick N, Roccaro AM, Ngo HT, Farag M, Melhem MR, Sacco A, Munshi NC, Hideshima T, Rollins BJ, Anderson KC, Kung AL, Lin CP, Ghobrial IM.

Blood. 2009 Apr 30;113(18):4341-51. [Epub 2009 Jan 12.]

http://www.ncbi.nlm.nih.gov/pubmed/19139079?ordinalpos=28&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors find that AMD3100 enhances the tumor reduction induced by bortezomib.

Synergistic interaction of proteasome and topoisomerase II inhibition in multiple myeloma.

von Metzler I, Heider U, Mieth M, Lamottke B, Kaiser M, Jakob C, Sezer O.

Exp Cell Res. 2009 Apr 30. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19410573?ordinalpos=29&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

This study suggests that combining etoposide with bortezomib might be useful for cancer treatment, as bortezomib potentially inhibits counter-regulatory mechanisms of tumor cells, which are induced by topoisomerase II inhibition and which may contribute to acquired chemoresistance.

Hematology: Bortezomib in newly diagnosed multiple myeloma.

Berenson JR.

Nat Rev Clin Oncol. 2009 May;6(5):255-6.

http://www.ncbi.nlm.nih.gov/pubmed/19390550?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The author discusses bortezomib's role for myeloma patients undergoing chemotherapy, as well as for patients who are not chemotherapy candidates.

Myeloma cells exhibit an increase in proteasome activity and an enhanced response to proteasome inhibition in the bone marrow microenvironment in vivo.

Edwards CM, Lwin ST, Fowler JA, Oyajobi BO, Zhuang J, Bates AL, Mundy GR.

Am J Hematol. 2009 May;84(5):268-72.

http://www.ncbi.nlm.nih.gov/pubmed/19296472?ordinalpos=15&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors demonstrate that myeloma cells exhibit an increase in proteasome activity and an enhanced response to bortezomib treatment when located within the bone marrow microenvironment in vivo.

Multiple myeloma. [Article in Japanese]

Abe M.

Nippon Rinsho. 2009 May;67(5):991-5.

http://www.ncbi.nlm.nih.gov/pubmed/19432122?ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The author discusses the roles of bone-targeting agents, such as bortezomib, in the treatment of myeloma, by making the best use of them and eliminating underlying risk of their adverse effects.

Preclinical activity of P276-00, a novel small-molecule cyclin-dependent kinase inhibitor in the therapy of multiple myeloma.

Raje N, Hideshima T, Mukherjee S, Raab M, Vallet S, Chhetri S, Cirstea D, Pozzi S, Mitsiades C, Rooney M, Kiziltepe T, Podar K, Okawa Y, Ikeda H, Carrasco R, Richardson PG, Chauhan D, Munshi NC, Sharma S, Parikh H, Chabner B, Scadden D, Anderson KC.

Leukemia. 2009 May;23(5):961-970. [Epub 2009 Jan 8.]

http://www.ncbi.nlm.nih.gov/pubmed/19151776?ordinalpos=23&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors seek to identify the effects of targeting cyclin D in myeloma and find that because the cyclins are substrates of proteasome degradation, combination studies with bortezomib resulted in synergism.

Targeting the proteasome pathway.

Tsukamoto S, Yokosawa H.

Expert Opin Ther Targets. 2009 May;13(5):605-21.

http://www.ncbi.nlm.nih.gov/pubmed/19397479?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors review the current understanding of the ubiquitin-proteasome pathway and inhibitors targeting this pathway, including proteasome inhibitors (such as bortezomib), as candidate drugs for chemical therapy.

Does bortezomib induce de facto varicella zoster virus reactivation in patients with multiple myeloma?

Dasanu CA, Alexandrescu DT.

J Clin Oncol. 2009 May 1;27(13):2293-4; author reply 2294-6. [Epub 2009 Mar 23.]

http://www.ncbi.nlm.nih.gov/pubmed/19307496?ordinalpos=22&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Comment on: *J Clin Oncol. 2008 Oct 10;26(29):4784-90.*

Bortezomib induces canonical NF-{kappa}B activation in multiple myeloma cells.

Hideshima T, Ikeda H, Chauhan D, Okawa Y, Raje N, Podar K, Mitsiades C, Munshi NC, Richardson PG, Carrasco RD, Anderson KC.

Blood. 2009 May 12. [Epub ahead of print.]

http://www.ncbi.nlm.nih.gov/pubmed/19436050?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The authors demonstrate that bortezomib significantly downregulates IkappaBalpha expression and triggeres NF-kappaB activation in myeloma cell lines and primary tumor cells from myeloma patients, suggesting that bortezomib-induced cytotoxicity cannot be fully attributed to inhibition of canonical NF-kappaB activity in myeloma cells

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