"Until There is a Cure… There is the IMF."

# CITINGS

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## Novel Therapies Issue

**The International Myeloma Foundation** *(IMF) presents this edition of Citings, our premiere publication featuring the most up-to-date information on myeloma treatment, focused on the novel therapies currently under study and in use. This edition corresponds with articles published between December 2009 and March 2010.*

*It is our hope that CITINGS will be a valuable tool in keeping you informed on the latest developments in myeloma treatment. Please feel free to contact us at (800) 452-CURE (2873) or visit us on the web at www.myeloma.org.*

*– Susie Novis, President, IMF*

## Novel Therapies Publications

### MARCH 2010

***High incidence of arterial thrombosis in young patients treated for multiple myeloma: results of a prospective cohort study.***
Libourel EJ, Sonneveld P, van der Holt B, de Maat MP, Leebeek FW.

*Blood. 2010 Mar 25. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20339094

This prospective study evaluates the risk of arterial thrombosis in 195 consecutive patients aged 18-65 years with newly diagnosed myeloma, finding that patients have an increased risk for arterial thrombotic events during and following induction chemotherapy with either vincristine, doxorubicin and dexamethasone (VAD); thalidomide-AD; or bortezomib-AD . Hypertension, smoking and high factor VIII levels, possibly reflecting disease activity, contribute to the risk of arterial thrombosis.

***Bortezomib and donor lymphocyte infusion in multiple myeloma relapsed after allo-SCT does not result in durable remissions.***
Hoevenaren A, van Vulpen LF, Levenga H, Minnema MC, Raymakers R.

*Bone Marrow Transplant. 2010 Mar 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20305701

No abstract available.

***Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma.***
Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L, Crippa C, De Rosa L, Pregno P, Grasso M, Liberati AM, Caravita T, Pisani F, Guglielmelli T, Callea V, Musto P, Cangialosi C, Passera R, Boccadoro M, Palumbo A.

*J Clin Oncol. 2010 Mar 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20308672

The authors investigate the effect on minimal residual disease, by qualitative and real-time quantitative polymerase chain reaction (RQ-PCR), of a consolidation regimen that includes bortezomib, thalidomide, and dexamethasone (VTD) in patients with myeloma responding to autologous stem-cell transplantation (auto-SCT), becoming the first study to document the occurrence of persistent molecular remissions in a proportion of myeloma patients treated without allogeneic transplantation. The authors also find that a major reduction in tumor load recorded by RQ-PCR after VTD suggests that unprecedented levels of tumor cell reduction can be achieved in myeloma thanks to new nonchemotherapeutic drugs.



*Funded by unrestricted educational grants from Celgene Corporation and Millennium: The Takeda Oncology Company.*

***Pharmacological Properties of Thalidomide and Its Analogues.***

De Sanctis JB, Mijares M, Suárez A, Compagnone R, Garmendia J, Moreno D, Salazar-Bookaman M.

*Recent Pat Inflamm Allergy Drug Discov. 2010 Mar 22. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20307255

In this review, the authors explore the current trend of the different structures, the new patents, and the possible new applications in different pathologies of novel agents including thalidomide and lenalidomide.

***Pharmacokinetic and pharmacodynamic study of two doses of bortezomib in patients with relapsed multiple myeloma.***

Reece DE, Sullivan D, Lonial S, Mohrbacher AF, Chatta G, Shustik C, Burris H 3rd, Venkatakrishnan K, Neuwirth R, Riordan WJ, Karol M, von Moltke LL, Acharya M, Zannikos P, Keith Stewart A.

*Cancer Chemother Pharmacol. 2010 Mar 20. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20306195

The authors find that bortezomib pharmacokinetics change with repeat dose administration, characterized by a reduction in plasma clearance and associated increase in systemic exposure. Their findings support the current clinical dosing regimen.

***Consensus guidelines for the optimal management of adverse events in newly diagnosed, transplant-ineligible patients receiving melphalan and prednisone in combination with thalidomide (MPT) for the treatment of multiple myeloma.***

Palumbo A, Davies F, Kropff M, Bladé J, Delforge M, Leal da Costa F, Garcia Sanz R, Schey S, Facon T, Morgan G, Moreau P.

*Ann Hematol. 2010 Mar 16. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20232066

This article outlines both evidence- and consensus-based recommendations discussed by a panel of experts in order to provide a practical guide for physicians addressing the effective management of newly diagnosed, transplant-ineligible myeloma patients receiving thalidomide therapy.

***THADD Plus High Dose Therapy And Autologous Stem Cell Transplantation Does Not Appear Superior To THADD Plus Maintenance In Elderly Patietns With De Novo Multiple Myeloma.***

Offidani M, Leoni P, Corvatta L, Polloni C, Gentili S, Savini A, Alesiani F, Brunori M, Catarini M, Visani G, Samori A, Burattini M, Centurioni R, Montanari M, Fraticelli P, Ruggieri M, Falcioni S, Galieni P.

*Eur J Haematol. 2010 Mar 11. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20331733

With the aim to address the issue whether high dose therapy (HDT) is required after new drug combinations to improve outcome of elderly newly diagnosed myeloma patients, the authors compare the toxicity and the outcome of ThaDD plus maintenance to those of ThaDD plus HDT-ASCT. Their results suggest that in elderly myeloma patients ThaDD plus HDT, though it significantly increases complete response rate, seems to be equivalent to ThaDD plus maintenance in terms of time to progression, progression free survival, and overall survival.

***Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenström macroglobulinemia.***

Ghobrial IM, Hong F, Padmanabhan S, Badros A, Rourke M, Leduc R, Chuma S, Kunsman J, Warren D, Harris B, Sam A, Anderson KC, Richardson PG, Treon SP, Weller E, Matous J.

*J Clin Oncol. 2010 Mar 10;28(8):1422-8. [Epub 2010 Feb 8.]*

http://www.ncbi.nlm.nih.gov/pubmed/20142586

This study aims to determine activity and safety of weekly bortezomib and rituximab in patients with relapsed/refractory Waldenström macroglobulinemia (WM). The authors conclude that the combination shows significant activity and minimal neurologic toxicity in this patient group.

***Advances in treatment for relapses and refractory multiple myeloma.***

Richards T, Weber D.

*Med Oncol. 2010 Mar 6. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20213220

This article reviews the current role for thalidomide, lenalidomide, and bortezomib-based combinations for patients with relapsed and/or refractory myeloma.

***Hematopoietic stem cell transplantation for multiple myeloma beyond 2010.***
Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E.

*Blood. 2010 Mar 4. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20203260

The authors discuss the development of novel reduced-intensity preparative regimens (including use of bortezomib) and peri- and -post-transplant strategies aimed at minimizing graft-versus-host disease and enhancing the graft-versus-myeloma effect as key issues in the future treatment of myeloma.

***Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences.***
Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, Durie BG, Harousseau JL.

*J Clin Oncol. 2010 Mar 1;28(7):1209-14. [Epub 2010 Jan 19.]*

http://www.ncbi.nlm.nih.gov/pubmed/20085933

These long-term follow-up data of transplantation trials provide a crucial framework of reference for outcome reporting of novel agent-based trials (including thalidomide and bortezomib) reportedly exhibiting remarkable short-term efficacy approaching high-dose therapy results.

***The novel inhibitor of histone deacetylase resminostat (RAS2410) inhibits proliferation and induces apoptosis in multiple myeloma (MM) cells.***
Mandl-Weber S, Meinel F, Jankowsky R, Oduncu F, Schmidmaier R, Baumann P.

*Br J Haematol. 2010 Mar 1. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20201941

The authors observe synergistic effects for combinations of resminostat with melphalan and the proteasome inhibitors bortezomib and S-2209.

***Bortezomib restores stroma-mediated APO2L/TRAIL apoptosis resistance in multiple myeloma.***
Perez LE, Parquet N, Meads M, Anasetti C, Dalton W.

*Eur J Haematol. 2010 Mar;84(3):212-22. [Epub 2009 Nov 17.]*

http://www.ncbi.nlm.nih.gov/pubmed/19922463

The authors test whether bortezomib can reverse the APO2L/TRAIL environmental mediated-immune resistance. Their findings provide the rationale to combine bortezomib and APO2L/TRAIL to disrupt the influence of the stroma microenvironment on myeloma cells.

***Differential activities of thalidomide and isoprenoid biosynthetic pathway inhibitors in multiple myeloma cells.***
Holstein SA, Tong H, Hohl RJ.

*Leuk Res. 2010 Mar;34(3):344-51. [Epub 2009 Jul 30.]*

http://www.ncbi.nlm.nih.gov/pubmed/19646757

The authors evaluate the interactions between thalidomide and the isoprenoid biosynthetic pathway (IBP) inhibitors in myeloma cells, with findings that provide a mechanism for the differential sensitivity of myeloma cells to pharmacologic manipulation of the IBP.

***DKK1 correlates with response and predicts rapid relapse after autologous stem cell transplantation in multiple myeloma.***
Lemaire O, Attal M, Bourin P, Laroche M.

*Eur J Haematol. 2010 Mar;84(3):276-7. [Epub 2009 Nov 5.]*

http://www.ncbi.nlm.nih.gov/pubmed/19891699

No abstract available.

***Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexaméthasone.***

Avet-Loiseau H, Soulier J, Fermand JP, Yakoub-Agha I, Attal M, Hulin C, Garderet L, Belhadj K, Dorvaux V, Minvielle S, Moreau P; IFM and MAG groups.

*Leukemia. 2010 Mar;24(3):623-8. [Epub 2010 Jan 14.]*

http://www.ncbi.nlm.nih.gov/pubmed/20072152

This retrospective analysis investigates the prognostic value of del(13) and t(4;14) abnormalities and the impact of prior treatment on outcomes in heavily pretreated patients with relapsed or refractory myeloma treated with lenalidomide plus dexamethasone.

***Lenalidomide for the treatment of cryoglobulinemia and undifferentiated spondyloarthropathy in a patient with multiple myeloma.***

Lin RJ, Curran JJ, Zimmerman TM, Song J, Niewold TB, Sweiss NJ.

*J Clin Rheumatol. 2010 Mar;16(2):90-1.*

http://www.ncbi.nlm.nih.gov/pubmed/20130475

No abstract available.

***Reversal of dialysis-dependent renal failure in patients with advanced multiple myeloma: single institutional experiences over 8 years.***

Matsue K, Fujiwara H, Iwama K, Kimura S, Yamakura M, Takeuchi M.

*Ann Hematol. 2010 Mar;89(3):291-7. [Epub 2009 Aug 20.]*

http://www.ncbi.nlm.nih.gov/pubmed/19693498

The authors study the impact on the reversibility of high-dose dexamethasone and/or thalidomide-containing regimen in 12 newly diagnosed myeloma patients and find that dialysis-dependent renal failure is reversible in most myeloma patients, even if the patient is in advanced age.

***Safety and efficacy of bortezomib-based regimens for multiple myeloma patients with renal impairment: a retrospective study of Italian Myeloma Network GIMEMA.***

Morabito F, Gentile M, Ciolli S, Petrucci MT, Galimberti S, Mele G, Casulli AF, Mannina D, Piro E, Pinotti G, Palmieri S, Catalano L, Callea V, Offidani M, Musto P, Bringhen S, Baldini L, Tosi P, Di Raimondo F, Boccadoro M, Palumbo A, Cavo M.

*Eur J Haematol. 2010 Mar;84(3):223-8. [Epub 2009 Nov 23.]*

http://www.ncbi.nlm.nih.gov/pubmed/19930441

This retrospective analysis investigates the safety and efficacy of bortezomib-based therapy in myeloma patients with renal impairment (RI). The authors conclude that bortezomib-based regimens are safe and effective and should be considered as appropriate treatment options for myeloma patients with any degree of RI.

***Severe pulmonary complications after bortezomib treatment in multiple myeloma.***

Dun X, Yuan Z, Fu W, Zhang C, Hou J.

*Hematol Oncol. 2010 Mar;28(1):49-52.*

http://www.ncbi.nlm.nih.gov/pubmed/19728395

No abstract available.

***Vorinostat enhances the antimyeloma effects of melphalan and bortezomib.***

Campbell RA, Sanchez E, Steinberg J, Shalitin D, Li ZW, Chen H, Berenson JR.

*Eur J Haematol. 2010 Mar;84(3):201-11. [Epub 2009 Nov 18.]*

http://www.ncbi.nlm.nih.gov/pubmed/19929977

The authors find that vorinostat enhances the anti-myeloma activity of melphalan and bortezomib in vitro and in vivo, providing rationale for further evaluation of vorinostat in combination with chemotherapeutic agents and bortezomib for the treatment of myeloma.

# FEBRUARY 2010

***Thalidomide-Dexamethasone As Induction Therapy Prior To Autologous Stem-Cell Transplantation In Patients With Newly Diagnosed Multiple Myeloma And Renal Insufficiency.***

Tosi P, Zamagni E, Tacchetti P, Ceccolini M, Perrone G, Brioli A, Pallotti MC, Pantani L, Petrucci A, Baccarani M, Cavo M.

*Biol Blood Marrow Transplant. 2010 Feb 27. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20197100

The authors evaluate the efficacy and the toxicity of thalidomide-dexamethasone (thal-dex) as induction therapy prior to autologous peripheral blood stem-cell (PBSC) transplantation in newly diagnosed myeloma patients with renal insufficiency. They find that thal-dex is effective and safe in patients with newly diagnosed myeloma and renal insufficiency; given the relationship between recovery of renal function and response to induction treatment, more intensive thal+bortezomib regimens could be explored in order to rescue a higher number of patients.

***Thalidomide-Dexamethasone As Up-Front Therapy For Newly Diagnosed Multiple Myeloma Patients: Thrombophilic Alterations, Thrombotic Complications And Thromboprophylaxis With Low-Dose Warafin.***

Cini M, Zamagni E, Valdré L, Palareti G, Patriarca F, Tacchetti P, Legnani C, Catalano L, Masini L, Tosi P, Gozzetti A, Cavo M.

*Eur J Haematol. 2010 Feb 23. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20192986

The authors address the issue of pathogenesis of thalidomide-induced VTE as not well recognized and the role of prothrombotic factors, especially of thrombophilic abnormalities, as not yet determined. On the basis of their data, they do not recommend a baseline thrombophilic work up in myeloma patients receiving up-front thalidomide-dexamethasone. For these patients, fixed low-dose warfarin may be a valuable prophylaxis against VTE.

***Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment.***

Dimopoulos MA, Christoulas D, Roussou M, Kastritis E, Migkou M, Gavriatopoulou M, Matsouka C, Mparmparoussi D, Psimenou E, Grapsa I, Efstathiou E, Terpos E.

*Eur J Haematol. 2010 Feb 20. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20192988

The authors study the effect of the lenalidomide and dexamethasone regimen (LenDex) on renal impairment (RI) and renal reversibility. They find that with dosing of lenalidomide according to renal function, LenDex can be administered to patients with RI (who may not have other treatment options) without excessive toxicity. Furthermore, LenDex may improve the renal function in approximately 40% of patients with RI.

***The evolution and impact of therapy in multiple myeloma.***

Laubach JP, Richardson PG, Anderson KC.

*Med Oncol. 2010 Feb 19. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20169425

This review highlights important historic landmarks as well as more recent events that have played an important role in the evolution of myeloma therapy, including the use of thalidomide, lenalidomide, and bortezomib.

***Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients.***

Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S, Dispenzieri A, Mikhael JR, Bergsagel PL, Dingli D, Reeder CB, Lust JA, Russell SJ, Roy V, Zeldenrust SR, Witzig TE, Fonseca R, Kyle RA, Greipp PR, Stewart AK, Rajkumar SV.

*Blood. 2010 Feb 18;115(7):1343-50. [Epub 2009 Dec 11.]*

http://www.ncbi.nlm.nih.gov/pubmed/20008302

This retrospective study compares the efficacy and toxicity of lenalidomide plus dexamethasone (len/dex) versus thalidomide plus dexamethasone (thal/dex) as initial therapy for newly diagnosed myeloma. The authors conclude that len/dex appears well-tolerated and more effective than thal/dex.

***A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma.***

Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, von dem Borne P, Wijermans P, Schaafsma R, de Weerdt O, Wittebol S, Delforge M, Berenschot H, Bos GM, Jie KS, Sinnige H, van Marwijk-Kooy M, Joosten P, Minnema MC, van Ammerlaan R, Sonneveld P; Dutch-Belgian Hemato-Oncology Group (HOVON).

*Blood. 2010 Feb 11;115(6):1113-20. [Epub 2009 Oct 30.]*

http://www.ncbi.nlm.nih.gov/pubmed/19880501

The phase III trial evaluates the effect of thalidomide during induction treatment and as maintenance in myeloma patients who are transplant candidates and finds that patients randomized to thalidomide had strongly reduced survival after relapse.

***A TAD better for myeloma therapy?***

Giralt S.

*Blood. 2010 Feb 11;115(6):1109-10.*

http://www.ncbi.nlm.nih.gov/pubmed/20150417

The author reports on the results of HOVON-50, a phase 3 randomized trial, that together with other randomized and nonrandomized trials establishes a definitive role for thalidomide as induction therapy in conjunction with dexamethasone, anthracyclines, and alkylating agents.

***Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients.***

Palumbo A, Gay F, Falco P, Crippa C, Montefusco V, Patriarca F, Rossini F, Caltagirone S, Benevolo G, Pescosta N, Guglielmelli T, Bringhen S, Offidani M, Giuliani N, Petrucci MT, Musto P, Liberati AM, Rossi G, Corradini P, Boccadoro M.

*J Clin Oncol. 2010 Feb 10;28(5):800-7. [Epub 2010 Jan 4.]*

http://www.ncbi.nlm.nih.gov/pubmed/20048187

The authors evaluate the effect of bortezomib as induction therapy before autologous transplantation, followed by lenalidomide as consolidation-maintenance in myeloma patients. They find it to be an effective regimen.

***Enhancing activity and overcoming chemoresistance in hematologic malignancies with bortezomib: preclinical mechanistic studies.***

Reddy N, Czuczman MS.

*Ann Oncol. 2010 Feb 4. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20133382

This review indicates the potential utility of proteasome inhibition, explains the mechanisms responsible for the observed clinical activity of bortezomib-based regimens, and elucidates novel therapeutic approaches through identification of combinations of agents with complimentary mechanisms of action.

***Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with bortezomib, lenalidomide and dexamethasone (VRD) maintenance.***

Nair B, van Rhee F, Shaughnessy JD Jr, Anaissie E, Szymonifka J, Hoering A, Alsayed Y, Waheed S, Crowley J, Barlogie B.

*Blood. 2010 Feb 2. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20124509

The authors report here on the results of successor trial 2006-66, employing bortezomib-lenalidomide-dexamethasone maintenance for 3 years, versus bortezomib-thalidomide-dexamethasone in year 1 and thalidomide-dexamethasone in years 2 and 3. They conclude that robustness of the gene expression profiling risk model should be exploited in clinical trials aimed at improving the notoriously poor outcome in high-risk myeloma.

***Bortezomib plus dexamethasone can improve stem cell collection and overcome the need for additional chemotherapy before autologous transplant in patients with myeloma.***

Corso A, Barbarano L, Mangiacavalli S, Spriano M, Alessandrino EP, Cafro AM, Pascutto C, Varettoni M, Bernasconi P, Grillo G, Carella AM, Montalbetti L, Lazzarino M, Morra E.

*Leuk Lymphoma. 2010 Feb;51(2):236-42.*

http://www.ncbi.nlm.nih.gov/pubmed/20001242

This phase II trial investigates the efficacy of bortezomib plus dexamethasone (Vel-Dex) as induction therapy in patients with myeloma and seeks to define the role of intensification before transplantation. The authors conclude that Vel-Dex produces high response rates, improves stem cell collection, and overcomes the need for intensification before autologous transplantation.

***Complications of multiple myeloma therapy, part 2: risk reduction and management of venous thromboembolism, osteonecrosis of the jaw, renal complications, and anemia.***

Niesvizky R, Badros AZ.

*J Natl Compr Canc Netw. 2010 Feb;8 Suppl 1:S13-20.*

http://www.ncbi.nlm.nih.gov/pubmed/20141670

This article discusses the common myeloma treatment complications— venous thromboembolism, osteonecrosis of the jaw, renal failure, and anemia— in detail, and provides strategies for health care providers to best prevent, identify, and manage them.

***Constitutive down-regulation of Osterix in osteoblasts from myeloma patients: in vitro effect of Bortezomib and Lenalidomide.***

De Matteo M, Brunetti AE, Maiorano E, Cafforio P, Dammacco F, Silvestris F.

*Leuk Res. 2010 Feb;34(2):243-9. [Epub 2009 Aug 4.]*

http://www.ncbi.nlm.nih.gov/pubmed/19656567

The authors' findings provide additional evidence suggesting that, at least in vitro, bortezomib promotes osteoblast maturation.

***The current status and future of multiple myeloma in the clinic.***

Jagannath S, Kyle RA, Palumbo A, Siegel DS, Cunningham S, Berenson J.

*Clin Lymphoma Myeloma Leuk. 2010 Feb;10(1):28-43.*

http://www.ncbi.nlm.nih.gov/pubmed/20223727

This review highlights challenges in the clinic and newer approaches under evaluation for the treatment and/or management of patients with MGUS, smoldering myeloma, and myeloma, including the use of thalidomide, lenalidomide, and bortezomib.

***Effects of induction with novel agents versus conventional chemotherapy on mobilization and autologous stem cell transplant outcomes in multiple myeloma.***

Benson DM Jr, Panzner K, Hamadani M, Hofmeister CC, Bakan CE, Smith MK, Elder P, Krugh D, O'Donnell L, Devine SM.

*Leuk Lymphoma. 2010 Feb;51(2):243-51.*

http://www.ncbi.nlm.nih.gov/pubmed/20038230

The authors compare conventional induction regimens with novel agent-based induction strategies (including use of thalidomide, lenalidomide, and bortezomib) and the associated effects on stem cell mobilization and HDC/SCT outcome in 224 patients. They find that an improvement in overall survival after HDC/SCT may be related to induction therapy with novel agents as opposed to chemotherapy.

***In the age of novel therapies, what defines high-risk multiple myeloma?***

Badros AZ.

*J Natl Compr Canc Netw. 2010 Feb;8 Suppl 1:S28-34.*

http://www.ncbi.nlm.nih.gov/pubmed/20141672

The author discusses the advent of risk-based therapy in the treatment of myeloma, and the role of novel agents, such as bortezomib, thalidomide, and lenalidomide, within this new treatment model.

***Induction Treatment With Cyclophosphamide, Thalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma: A Phase II Study.***

Yang DH, Kim YK, Sohn SK, Chung JS, Joo YD, Lee JH, Lee JL, Ahn JS, Moon JH, Shin HJ, Choi YJ, Lee WS, Kim HJ, Lee JJ.

*Clin Lymphoma Myeloma Leuk. 2010 Feb;10(1):62-7.*

http://www.ncbi.nlm.nih.gov/pubmed/20223731

This study finds that an induction therapy of cyclophosphamide, thalidomide, and dexamethasone results in favorable response with tolerable toxicity in patients with newly diagnosed myeloma, and does not affect the yield of stem cell collection.

***Lenalidomide as salvage therapy after allo-SCT for multiple myeloma is effective and leads to an increase of activated NK (NKp44(+)) and T (HLA-DR(+)) cells.***

Lioznov M, El-Cheikh J Jr, Hoffmann F, Hildebrandt Y, Ayuk F, Wolschke C, Atanackovic D, Schilling G, Badbaran A, Bacher U, Fehse B, Zander AR, Blaise D, Mohty M, Kröger N.

*Bone Marrow Transplant. 2010 Feb;45(2):349-53. [Epub 2009 Jul 6.]*

http://www.ncbi.nlm.nih.gov/pubmed/19584825

The authors investigate efficacy and toxicity of lenalidomide in 24 heavily pretreated myeloma patients with a median age of 59 years and relapse after allo-SCT. In their study, response is achieved in 66% of patients, and they find that immunomonitoring after lenalidomide shows significant increase of activated NK (NKp44(+)) and T (HLA-DR(+)) cells, as well as regulatory T cells (CD4(+), CD25(+), CD127(lo)), supporting an immunomodulating anti-myeloma effect of lenalidomide.

***Osteoblastogenesis and tumor growth in myeloma.***

Yaccoby S.

*Leuk Lymphoma. 2010 Feb;51(2):213-20.*

http://www.ncbi.nlm.nih.gov/pubmed/20038269

The author reviews the role of osteoblastogenesis suppression in the treatment of myeloma and concludes that increased osteoblast activity (including the use of bortezomib) is a promising approach to treat myeloma bone disease and simultaneously control myeloma development and progression.

***Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations.***

Mohty B, El-Cheikh J, Yakoub-Agha I, Moreau P, Harousseau JL, Mohty M.

*Haematologica. 2010 Feb;95(2):311-9.*

http://www.ncbi.nlm.nih.gov/pubmed/20139393

This review discusses the pathogenesis, incidence, risk factors, diagnosis, characteristics, and management of peripheral neuropathy related to new myeloma drugs, primarily bortezomib and thalidomide.

***Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre.***

Haynes RJ, Read S, Collins GP, Darby SC, Winearls CG.

*Nephrol Dial Transplant. 2010 Feb;25(2):419-26. [Epub 2009 Sep 19.]*

http://www.ncbi.nlm.nih.gov/pubmed/19767634

The authors document the natural history of 107 myeloma patients referred to a large regional renal unit over a 20-year period and investigate factors associated with survival over a long period of time. Their analysis highlights the need for clinical trials of novel chemotherapy regimens in this complicated group of patients; the advent of efficacious low toxicity chemotherapy (such as thalidomide) and new dialysis techniques may radically alter the outcome of this group of patients.

***The role of maintenance therapy in the treatment of multiple myeloma.***

Badros AZ.

*J Natl Compr Canc Netw. 2010 Feb;8 Suppl 1:S21-7.*

http://www.ncbi.nlm.nih.gov/pubmed/20141671

The author discusses the emerging role of the novel agents thalidomide, lenalidomide, and bortezomib as maintenance therapy in the treatment of myeloma.

***Weekly bortezomib, pegylated liposomal doxorubicin, and dexamethasone is a safe and effective therapy for elderly patients with relapsed/refractory multiple myeloma.***

Gozzetti A, Fabbri A, Oliva S, Marchini E, Bocchia M, Defina M, Lauria F.

*Clin Lymphoma Myeloma Leuk. 2010 Feb;10(1):68-72.*

http://www.ncbi.nlm.nih.gov/pubmed/20223732

The authors pursue the first-ever evaluation of the synergic, additive effect of bortezomib and pegylated liposomal doxorubicin (PLD) in an elderly group of patients with relapsed/refractory myeloma. They conclude that PLD is safe and effective in elderly patients with resistant-relapsing myeloma.

## JANUARY 2010

***Role of the TNF-alpha promoter polymorphisms for development of multiple myeloma and clinical outcome in thalidomide plus dexamethasone.***

Du J, Yuan Z, Zhang C, Fu W, Jiang H, Chen B, Hou J.

*Leuk Res. 2010 Jan 30. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20122728

The authors study the role of TNF-alpha promoter polymorphisms in the development of myeloma, evaluating patients treated with a thalidomide-dexamethasone regimen.

***Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vitro and in vivo synergistic cytotoxicity in multiple myeloma.***

Chauhan D, Singh AV, Ciccarelli B, Richardson PG, Palladino MA, Anderson KC.

*Blood. 2010 Jan 28;115(4):834-45. [Epub 2009 Nov 13.]*

http://www.ncbi.nlm.nih.gov/pubmed/19965674

The authors demonstrate that combining NPI-0052 and lenalidomide induces synergistic anti-myeloma activity in vitro using myeloma-cell lines or patient myeloma cells.

***Stem cell transplant in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction.***

Gertz MA, Kumar S, Lacy MQ, Dispenzieri A, Dingli D, Hayman SR, Buadi FK, Hogan WJ.

*Blood. 2010 Jan 20. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20089967

This retrospective study analyzes progression-free survival and overall survival in patients who do not have a partial response after induction therapy with a regimen that contains thalidomide or lenalidomide.

***Bortezomib down-regulates the osterix expression by osteoblasts in the myeloma microenvironment: Implications into osteoblast function in myeloma bone disease.***

Terpos E.

*Leuk Res. 2010 Jan 12. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20074800

No abstract available.

***Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM).***

Roussel M, Moreau P, Huynh A, Mary JY, Danho C, Caillot D, Hulin C, Fruchart C, Marit G, Pégourié B, Lenain P, Araujo C, Kolb B, Randriamalala E, Royer B, Stoppa AM, Dib M, Dorvaux V, Garderet L, Mathiot C, Avet-Loiseau H, Harousseau JL, Attal M; Intergroupe Francophone du Myélome (IFM).

*Blood. 2010 Jan 7;115(1):32-7. [Epub 2009 Nov 2.]*

http://www.ncbi.nlm.nih.gov/pubmed/19884643

This phase II study finds that bortezomib-HDM is a safe and promising conditioning regimen. Randomized studies are needed to assess whether this conditioning regimen is superior to HDM alone.

***Melphalan, prednisone, thalidomide and defibrotide in relapsed/refractory multiple myeloma: results of multicenter phase I/II trial.***

Palumbo A, Larocca A, Genuardi M, Kotwica K, Gay F, Rossi D, Benevolo G, Magarotto V, Cavallo F, Bringhen S, Rus C, Masini L, Iacobelli M, Gaidano G, Mitsiades C, Anderson K, Boccadoro M, Richardson P; for the Italian Multiple Myeloma Network, GIMEMA.

*Haematologica. 2010 Jan 6. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20053869

This phase I/II trial concludes that the combination of oral melphalan, thalidomide, and defibrotide shows anti-tumor activity with favorable tolerability.

***Dexamethasone Synergizes with Lenalidomide to Inhibit Multiple Myeloma Tumor Growth, But Reduces Lenalidomide-Induced Immunomodulation of T and NK Cell Function.***

Gandhi AK, Kang J, Capone L, Parton A, Wu L, Zhang LH, Mendy D, Lopez-Girona A, Tran T, Sapinoso L, Fang W, Xu S, Hampton G, Bartlett JB, Schafer P.

*Curr Cancer Drug Targets. 2010 Jan 1. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20088798

To determine the effect of dexamethasone on the antimyeloma effects of lenalidomide, the authors test in vitro proliferation, tumor suppressor gene expression, caspase activity, cell cycling, and apoptosis levels in a series of myeloma and plasma cell leukemia cell lines treated with lenalidomide and dexamethasone, alone or in combination. Their findings further elucidate the mechanism of action of lenalidomide and dexamethasone in myeloma, and suggest that use of low-dose dexamethasone with lenalidomide may retain the antiproliferative effect of lenalidomide while permitting greater immunomodulatory effects of this combination regimen.

***Survival effect of venous thromboembolism in patients with multiple myeloma treated with lenalidomide and high-dose dexamethasone.***

Zangari M, Tricot G, Polavaram L, Zhan F, Finlayson A, Knight R, Fu T, Weber D, Dimopoulos MA, Niesvizky R, Fink L.

*J Clin Oncol. 2010 Jan 1;28(1):132-5. [Epub 2009 Nov 9.]*

http://www.ncbi.nlm.nih.gov/pubmed/19901114

The authors conduct a retrospective analysis of the survival effect of venous thromboembolism (VTE) development in patients with multiple myeloma and find that myeloma patients treated with lenalidomide and high-dose dexamethasone who developed a VTE do not experience shorter overall survival or time to progression.

***Bortezomib and zoledronic acid on angiogenic and vasculogenic activities of bone marrow macrophages in patients with multiple myeloma.***

Moschetta M, Di Pietro G, Ria R, Gnoni A, Mangialardi G, Guarini A, Ditonno P, Musto P, D'Auria F, Ricciardi MR, Dammacco F, Ribatti D, Vacca A.

*Eur J Cancer. 2010 Jan;46(2):420-9. [Epub 2009 Nov 13.]*

http://www.ncbi.nlm.nih.gov/pubmed/19914061

This study provides evidence that the exposure of bone marrow macrophages in myelomaduring the treatment with zoledronic acid and bortezomib, alone and or in combination, impacts their angiogenic and vasculogenic properties, suggesting that these cells may be considered as a target of both drugs in myeloma patients.

***Enhanced antimyeloma cytotoxicity by the combination of arsenic trioxide and bortezomib is further potentiated by p38 MAPK inhibition.***

Wen J, Feng Y, Huang W, Chen H, Liao B, Rice L, Preti HA, Kamble RT, Zu Y, Ballon DJ, Chang CC.

*Leuk Res. 2010 Jan;34(1):85-92. [Epub 2009 Jul 15.]*

http://www.ncbi.nlm.nih.gov/pubmed/19608275

The authors study the cytotoxicity of bortezomib, ATO, and ATO+bortezomib with or without inhibiting p38 MAPK, along with associated molecular changes in myeloma cells. Their results suggest the opportunity for using p38 MAPK inhibition to enhance the efficacy of ATO+bortezomib in myeloma.

***Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial.***

Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, Abonour R, Siegel DS, Katz M, Greipp PR; Eastern Cooperative Oncology Group.

*Lancet Oncol. 2010 Jan;11(1):29-37. [Epub 2009 Oct 21.]*

http://www.ncbi.nlm.nih.gov/pubmed/19853510

The authors study whether low-dose dexamethasone in combination with lenalidomide is non-inferior to and has lower toxicity than high-dose dexamethasone plus lenalidomide. They find that in newly diagnosed myeloma patients, lenalidomide plus low-dose dexamethasone is associated with better short-term overall survival and with lower toxicity than lenalidomide plus high-dose dexamethasone.

***Lenalidomide (Revlimid) combined with continuous oral cyclophosphamide (endoxan) and prednisone (REP) is effective in lenalidomide/dexamethasone-refractory myeloma.***

van de Donk NW, Wittebol S, Minnema MC, Lokhorst HM.

*Br J Haematol. 2010 Jan;148(2):335-7.*

http://www.ncbi.nlm.nih.gov/pubmed/20085583

No abstract available.

***Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma.***

Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, Prince HM.

*Leukemia. 2010 Jan;24(1):22-32. [Epub 2009 Nov 12.]*

http://www.ncbi.nlm.nih.gov/pubmed/19907437

The authors discuss the nature of immunomodulatory drugs (IMiDs) and conclude that much is yet to be elucidated regarding the complex interplay of immunomodulatory cytokines that occurs in vivo, which ultimately dictates the net effects of IMiDs in myeloma – the understanding of which is necessary to facilitate optimal manipulation of these drugs in future myeloma management.

***New developments in the treatment of patients with multiple myeloma.***

Minnema MC, van der Spek E, van de Donk NW, Lokhorst HM.

*Neth J Med. 2010 Jan;68(1):24-32.*

http://www.ncbi.nlm.nih.gov/pubmed/20103818

This review focuses on the studies of thalidomide, bortezomib, and lenalidomide that have changed the treatment guidelines for patients with myeloma.

***New treatments for myeloma.***

Azaïs I, Brault R, Debiais F.

*Joint Bone Spine. 2010 Jan;77(1):20-6. [Epub 2009 Dec 23.]*

http://www.ncbi.nlm.nih.gov/pubmed/20031467

The authors discuss how the management of myeloma has benefited substantially from the introduction of bortezomib, thalidomide, and lenalidomide.

***Rapid improvement in renal function in patients with multiple myeloma and renal failure treated with bortezomib.***

Qayum A, Aleem A, Al Diab AR, Niaz F, Al Momen AK.

*Saudi J Kidney Dis Transpl. 2010 Jan;21(1):63-8.*

http://www.ncbi.nlm.nih.gov/pubmed/20061695

The authors report six cases of renal failure secondary to myeloma treated with bortezomib. They find that bortezomib may have an effect on the kidneys in reversal of renal failure, other than its anti-myeloma effect, and conclude that bortezomib appears to be an effective treatment for patients with advanced myeloma and renal failure irrespective of performance status and age.

***"Short course" bortezomib plus melphalan and prednisone as induction prior to transplant or as frontline therapy for nontransplant candidates in patients with previously untreated multiple myeloma.***

Gasparetto C, Gockerman JP, Diehl LF, de Castro CM, Moore JO, Long GD, Horwitz ME, Keogh G, Chute JP, Sullivan KM, Neuwirth R, Davis PH, Sutton LM, Anderson RD, Chao NJ, Rizzieri D.

*Biol Blood Marrow Transplant. 2010 Jan;16(1):70-7. [Epub 2009 Sep 3.]*

http://www.ncbi.nlm.nih.gov/pubmed/19733251

The authors find that short-course course bortezomib, melphalan, prednisone (VMP) is highly effective and generally well tolerated, both as initial treatment in non-ASCT patients and induction prior to ASCT, and that VMP does not negatively affect stem cell collection.

***Towards a new standard of care for patients with myeloma?***

Palumbo A, Gay F.

*Lancet Oncol. 2010 Jan;11(1):3-4. [Epub 2009 Oct 21.]*

http://www.ncbi.nlm.nih.gov/pubmed/19853511

Comment on: Lancet Oncol. 2010 Jan;11(1):29-37.

***Treatment outcome of thalidomide based regimens in newly diagnosed and relapsed/refractory non-transplant multiple myeloma patients: a single center experience from Thailand.***

Niparuck P, Sorakhunpipitkul L, Atichartakarn V, Chuncharunee S, Ungkanont A, Aungchaisuksiri P, Puavilai T, Jootar S.

*J Hematol Oncol. 2010 Jan 5;3:1.*

http://www.ncbi.nlm.nih.gov/pubmed/20051128

The authors conduct a retrospective study of 42 consecutive patients with newly diagnosed and relapsed/refractory myeloma treated with thalidomide-based induction regimens followed by thalidomide maintenance therapy. They find that prolonged thalidomide therapy enhances survival rate and less frequently leads to serious toxicity in non-transplant myeloma patients.

***Bortezomib.***

Einsele H.

*Recent Results Cancer Res. 2010;184:173-87.*

http://www.ncbi.nlm.nih.gov/pubmed/20072838

The author discusses bortezomib's role in the treatment of newly diagnosed as well as relapsed/progressive myeloma, and the major impact it has had on improvement in the treatment of myeloma in the last few years.

***Current multiple myeloma treatment strategies with novel agents: a European perspective.***

Ludwig H, Beksac M, Bladé J, Boccadoro M, Cavenagh J, Cavo M, Dimopoulos M, Drach J, Einsele H, Facon T, Goldschmidt H, Harousseau JL, Hess U, Ketterer N, Kropff M, Mendeleeva L, Morgan G, Palumbo A, Plesner T, San Miguel J, Shpilberg O, Sondergeld P, Sonneveld P, Zweegman S.

*Oncologist. 2010;15(1):6-25. [Epub 2010 Jan 19.]*

http://www.ncbi.nlm.nih.gov/pubmed/20086168

This review presents an overview of the most recent data with thalidomide, lenalidomide, and bortezomib, and summarizes European treatment practices incorporating these novel agents.

***Resolving a double standard for risk management of thalidomide: an evaluation of two different risk management programmes in Japan.***

Ooba N, Sato T, Watanabe H, Kubota K.

*Drug Saf. 2010;33(1):35-45.*

http://www.ncbi.nlm.nih.gov/pubmed/20000865

The authors evaluate the difference between the Thalidomide Education and Risk Management System and the Safety Management System for Unapproved Drugs (SMUD) in order to establish a way to resolve the "double standard" for risk management of thalidomide treatment in Japan. They conclude that SMUD should be improved so that all patients are monitored in a way that results in a similar level of risk management.

***Thalidomide and bortezomib overcome the prognostic significance of proliferative index in multiple myeloma.***
Minarik J, Scudla V, Bacovsky J, Zemanova M, Pika T, Ordeltova M, Langova K.

*Neoplasma. 2010;57(1):8-14.*

http://www.ncbi.nlm.nih.gov/pubmed/19895166

The authors analyze proliferative index of myeloma plasmocytes (PC-PI) in a cohort of 217 patients with myeloma treated with conventional chemotherapy and novel agents thalidomide and bortezomib. Their results suggest that the treatment of myeloma with novel agents overcomes the prognostic significance of PC-PI and should be used in all myeloma patients.

## DECEMBER 2009

***How I treat multiple myeloma in younger patients.***
Stewart AK, Richardson PG, San-Miguel JF.

*Blood. 2009 Dec 24;114(27):5436-43. [Epub 2009 Oct 27.]*

http://www.ncbi.nlm.nih.gov/pubmed/19861683

The authors discuss induction therapy, including the use of bortezomib, lenalidomide, and thalidomide, as part of their treatment goal with younger myeloma patients to target a durable complete remission.

***VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study.***
Dimopoulos MA, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, Kastritis E, Kropff M, Petrucci MT, Delforge M, Alexeeva J, Schots R, Masszi T, Mateos MV, Deraedt W, Liu K, Cakana A, van de Velde H, San Miguel JF.

*J Clin Oncol. 2009 Dec 20;27(36):6086-93. [Epub 2009 Oct 26.]*

http://www.ncbi.nlm.nih.gov/pubmed/19858394

This study finds that bortezomib plus melphalan and prednisone is a feasible, active, and well-tolerated treatment option for previously untreated myeloma patients with moderate renal impairment, resulting in 44% renal impairment reversal.

***Inhibition of mTORC1 activity by REDD1 induction in myeloma cells resistant to bortezomib cytotoxicity.***
Decaux O, Clément M, Magrangeas F, Gouraud W, Charbonnel C, Campion L, Loiseau HA, Minvielle S.

*Cancer Sci. 2009 Dec 11. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20100206

The authors use gene expression profiling to identify early responsive genes induced by bortezomib in resistant myeloma cells. Their results identify a possible novel mechanism of bortezomib resistance in myeloma patients mediated by REDD1 overexpression involving inhibition of mTORC1 activity, and suggest that the use of mammalian target of rapamycin inhibitors in myeloma patients could be deleterious.

***Future directions in immunomodulatory therapy.***
Lonial S.

*Med Oncol. 2009 Dec 11. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20012563

The author discusses the roles of thalidomide, lenalidomide, and bortezomib in the management of patients with myeloma in all phases of their disease.

***Bortezomib, thalidomide, dexamethasone induction therapy followed by melphalan, prednisolone, thalidomide consolidation therapy as a first line of treatment for patients with multiple myeloma who are non-transplant candidates: results of the Korean Multiple Myeloma Working Party (KMMWP).***
Eom HS, Kim YK, Chung JS, Kim K, Kim HJ, Kim HY, Jin JY, Do YR, Oh SJ, Suh C, Seong CM, Kim CS, Lee DS, Lee JH.

*Ann Hematol. 2009 Dec 10. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20012045

The authors find that as first-line therapy, bortezomib-thalidomide-dexamethasone followed by melphalan-prednisolone-thalidomide has the potential to provide high-quality responses with durable remission among elderly and high-risk myeloma patients.

***Treatment response to bortezomib in multiple myeloma correlates with plasma hepatocyte growth factor concentration and bone marrow thrombospondin concentration.***

Ludek P, Hana S, Zdenek A, Martina A, Dana K, Tomas B, Lucie K, Marta K, Jaroslav M, Miroslav P, Jiri V, Roman H.

*Eur J Haematol. 2009 Dec 10. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/20015241

The authors evaluate association between therapeutic response to bortezomib and thrombospondin and hepatocyte growth factor (HGF) levels. They find that high pretreatment thrombospondin and low pretreatment HGF concentrations are associated with therapeutic response to bortezomib in patients with myeloma.

***Researchers debate best use of stem cell transplants in patients with multiple myeloma.***

Rowan K.

*J Natl Cancer Inst. 2009 Dec 2;101(23):1608-11. [Epub 2009 Nov 12.]*

http://www.ncbi.nlm.nih.gov/pubmed/19910555

Comment on: J Natl Cancer Inst. 2009 Dec 2;101(23):1610.

***A high-affinity fully human anti-IL-6 mAb, 1339, for the treatment of multiple myeloma.***

Fulciniti M, Hideshima T, Vermot-Desroches C, Pozzi S, Nanjappa P, Shen Z, Patel N, Smith ES, Wang W, Prabhala R, Tai YT, Tassone P, Anderson KC, Munshi NC.

*Clin Cancer Res. 2009 Dec 1;15(23):7144-52. [Epub 2009 Nov 24.]*

http://www.ncbi.nlm.nih.gov/pubmed/19934301

The authors' data confirm in vitro and in vivo anti-multiple myeloma activity of, as well as inhibition of bone turnover by, fully humanized mAb 1339, as a single agent and in combination with conventional and novel agents (including bortezomib and lenalidomide), providing a rationale for its clinical evaluation in myeloma.

***Interactions of the Hdm2/p53 and proteasome pathways may enhance the antitumor activity of bortezomib.***

Ooi MG, Hayden PJ, Kotoula V, McMillin DW, Charalambous E, Daskalaki E, Raje NS, Munshi NC, Chauhan D, Hideshima T, Buon L, Clynes M, O'Gorman P, Richardson PG, Mitsiades CS, Anderson KC, Mitsiades N.

*Clin Cancer Res. 2009 Dec 1;15(23):7153-60. [Epub 2009 Nov 24.]*

http://www.ncbi.nlm.nih.gov/pubmed/19934289

The authors find that a differential response of myeloma versus epithelial carcinomas to combination of nutlin-3 with bortezomib sheds new light on the role of p53 in bortezomib-induced apoptosis. Concurrent Hdm2 inhibition with bortezomib may extend the spectrum of bortezomib applications to malignancies with currently limited sensitivity to single-agent bortezomib or, in the future, to myeloma patients with decreased clinical responsiveness to bortezomib-based therapy.

***Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma.***

Richardson PG, Weller E, Jagannath S, Avigan DE, Alsina M, Schlossman RL, Mazumder A, Munshi NC, Ghobrial IM, Doss D, Warren DL, Lunde LE, McKenney M, Delaney C, Mitsiades CS, Hideshima T, Dalton W, Knight R, Esseltine DL, Anderson KC.

*J Clin Oncol. 2009 Dec 1;27(34):5713-9. [Epub 2009 Sep 28.]*

http://www.ncbi.nlm.nih.gov/pubmed/19786667

This phase I, dose-escalation study evaluates safety and determines the maximum-tolerated dose of lenalidomide plus bortezomib in patients with relapsed or with relapsed and refractory myeloma.

***Prognostic significance of apoptotic index in multiple myeloma patients treated by conventional therapy and novel agents, thalidomide and bortezomib.***

Minarik J, Scudla V, Ordeltova M, Bacovsky J, Pika T, Langova K.

*Eur J Haematol. 2009 Dec 1;83(6):528-34. [Epub 2009 Jul 18.]*

http://www.ncbi.nlm.nih.gov/pubmed/19624720

The authors seek to assess the outcome of the measurement of apoptotic index in myeloma patients treated by conventional chemotherapy and novel drugs (including thalidomide and bortezomib). Their results suggest the use of apoptotic index by flow cytometry measurement as a fast and accessible method for prognostic stratification of myeloma patients in routine practice.

***The proteasome inhibitor CEP-18770 enhances the anti-myeloma activity of bortezomib and melphalan.***
Sanchez E, Li M, Steinberg JA, Wang C, Shen J, Bonavida B, Li ZW, Chen H, Berenson JR.

*Br J Haematol. 2009 Dec 1. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/19958357

These studies provide strong preclinical rationale for further development of the proteasome inhibitor CEP-18770 in the treatment of myeloma as a monotherapy, as well as combined with either melphalan or bortezomib.

***Relapse/Refractory myeloma patient: potential treatment guidelines.***
San Miguel JF.

*J Clin Oncol. 2009 Dec 1;27(34):5676-7. [Epub 2009 Sep 28.]*

http://www.ncbi.nlm.nih.gov/pubmed/19786652

Comment on: J Clin Oncol. 2009 Dec 1;27(34):5713-9.

***Bortezomib-based therapy as induction regimen of an autograft program in front-line treatment of multiple myeloma with end-stage renal disease.***
Siniscalchi A, Dentamaro T, Perrotti A, Tatangelo P, de Fabritiis P, Caravita T.

*Ann Hematol. 2009 Dec 2. [Epub ahead of print.]*

http://www.ncbi.nlm.nih.gov/pubmed/19953253

No abstract available.

***Bortezomib in combination with dexamethasone and subsequent thalidomide for newly-diagnosed multiple myeloma: a Chinese experience.***
Zheng W, Wei G, Ye X, He J, Li L, Wu W, Shi J, Zhang J, Huang W, Xie W, Luo Y, Xue X, Lin M, Huang H, Cai Z.

*Leuk Res. 2009 Dec;33(12):1615-8.*

http://www.ncbi.nlm.nih.gov/pubmed/19773080

The authors' preliminary experience in Chinese patients indicates that bortezomib-dexamethasone-thalidomide is highly effective in newly-diagnosed myeloma. The relative lower rates of neuropathy and DVT/PE in the Chinese patients with myeloma are being cautiously observed.

***Combined effects of bortezomib and daunorubicin on multiple myeloma cell KM3 in vitro.***
Ouyang GF, Lin MF.

*Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Dec;17(6):1468-71.*

http://www.ncbi.nlm.nih.gov/pubmed/20030928

This study finds that bortezomib has synergistic inhibitory effect with daunorubicin on the growth of human myeloma cell line KM3 cell in vitro.

***Hematology: first-line bortezomib benefits patients with multiple myeloma.***
Dimopoulos MA, Terpos E.

*Nat Rev Clin Oncol. 2009 Dec;6(12):683-5.*

http://www.ncbi.nlm.nih.gov/pubmed/19942924

Comment on: J Clin Oncol. 2009 Jul 20;27(21):3518-25.

***In vitro anti-myeloma activity of the Aurora kinase inhibitor VE-465.***
Negri JM, McMillin DW, Delmore J, Mitsiades N, Hayden P, Klippel S, Hideshima T, Chauhan D, Munshi NC, Buser CA, Pollard J, Richardson PG, Anderson KC, Mitsiades CS.

*Br J Haematol. 2009 Dec;147(5):672-6. [Epub 2009 Sep 14.]*

http://www.ncbi.nlm.nih.gov/pubmed/19751238

This study characterizes the preclinical anti-myeloma activity of VE465 and finds that combination with bortezomib finds no antagonism.

***Long-term outcomes of autologous transplantation in multiple myeloma: significant survival benefit of novel drugs in post-transplantation relapse.***

Krejci M, Scudla V, Tothova E, Schutzova M, Koza V, Adam Z, Krivanova A, Pour L, Buchler T, Sandecka V, Kralova D, Zahradova L, Vorlicek J, Mayer J, Hajek R.

*Clin Lymphoma Myeloma. 2009 Dec;9(6):436-42.*

http://www.ncbi.nlm.nih.gov/pubmed/19951883

The authors find that the achievement of complete response after transplantation, ISS stage other than III, and administration of thalidomide or bortezomib in posttransplantation relapse are significant parameters favoring long-term posttransplantation survival for newly diagnosed myeloma patients.

***Regulatory effect of thalidomide on the expression of constimulatory molecules in patients with multiple myeloma. [Article in Chinese]***

Yang Y, Zhang WG, He AL, Yang HY, Wang Y, Tian W.

*Nan Fang Yi Ke Da Xue Xue Bao. 2009 Dec;29(12):2470-2.*

http://www.ncbi.nlm.nih.gov/pubmed/20034904

This study finds that thalidomide can up-regulate the expression of B7-1 molecules on myeloma cells, which the authors conclude is probably one of the therapeutic mechanisms of thalidomide.

***The relationship among tumor architecture, pharmacokinetics, pharmacodynamics, and efficacy of bortezomib in mouse xenograft models.***

Williamson MJ, Silva MD, Terkelsen J, Robertson R, Yu L, Xia C, Hatsis P, Bannerman B, Babcock T, Cao Y, Kupperman E.

Mol Cancer Ther. 2009 Dec;8(12):3234-43.

http://www.ncbi.nlm.nih.gov/pubmed/19934276

The authors compare and contrast the differences between a bortezomib-responsive and a bortezomib-resistant models and establish a relationship among tumor perfusion, drug exposure, pharmacodynamic response and efficacy, and provide an explanation for why some solid tumor models do not respond to bortezomib treatment.

***Retrospective analysis of 71 cases of multiple myeloma. [Article in Chinese]***

Yang P, Zhang WJ, Jing HM, Ke XY.

*Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009 Dec;17(6):1573-6.*

http://www.ncbi.nlm.nih.gov/pubmed/20030950

The authors find that a bortezomib-combined regimen may be considered as a new and effective regimen for myeloma patients.

***Treatment of multiple myeloma: 2009 update.***

No authors listed.

*Prescrire Int. 2009 Dec;18(104):263-6.*

http://www.ncbi.nlm.nih.gov/pubmed/20025098

This review updates discussions of the use of bortezomib and thalidomide for myeloma patients pre- and post- autologous stem cell transplantation, as well as the use of lenalidomide in patients who relapse or who are refractory to initial treatment.

***Update in multiple myeloma: international criteria for treatment response and renal complications. [Article in French]***

Decaux O, Karras A.

*Rev Med Interne. 2009 Dec;30(12):1080-3. [Epub 2009 Oct 14.]*

http://www.ncbi.nlm.nih.gov/pubmed/19833418

No abstract available.

***The use of novel agents in the treatment of relapsed and refractory multiple myeloma.***

Laubach JP, Mahindra A, Mitsiades CS, Schlossman RL, Munshi NC, Ghobrial IM, Carreau N, Hideshima T, Anderson KC, Richardson PG.

*Leukemia. 2009 Dec;23(12):2222-32. [Epub 2009 Sep 10.]*

http://www.ncbi.nlm.nih.gov/pubmed/19741729

This review focuses on the role of thalidomide, lenalidomide, and bortezomib in relapsed and refractory myeloma.


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