

# Beyond the Guidelines:

## Clinical Investigators Provide Their Perspectives on the Management of Multiple Myeloma

### CME Information

#### TARGET AUDIENCE

This activity is intended for hematologists, medical oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of hematologic cancers.

#### OVERVIEW OF ACTIVITY

It is estimated that approximately 24,050 new cases of multiple myeloma (MM) were identified in the United States in the year 2014, and 11,090 individuals died from the disease. Of importance, currently more than 60 drug products are labeled for use in the management of hematologic malignancies, comprising more than 70 distinct FDA-approved indications. Although the extensive list of available treatment options is reassuring for patients and oncology healthcare professionals, it poses a challenge to the practicing clinician who must maintain up-to-date knowledge of appropriate clinical management strategies.

These proceedings from a CME symposium during the 56<sup>th</sup> ASH Annual Meeting use the perspectives of renowned experts in the field of hematologic oncology to frame a relevant discussion of the optimal management of MM. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist hematologists, medical oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for MM.

#### LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in multiple myeloma (MM), and integrate this information, as appropriate, into current clinical care.
- Develop a treatment algorithm for symptomatic Waldenström macroglobulinemia incorporating newly approved agents.
- Compare and contrast the benefits and risks of immunomodulatory agents, proteasome inhibitors or both as systemic treatment for active MM.
- Customize the use of maintenance therapeutic approaches in the post-transplant and nontransplant settings on the basis of patient- and disease-related factors, including cytogenetic profile.

- Effectively integrate the recently FDA-approved agents carfilzomib and pomalidomide into the nonresearch care of patients with MM.
- Assess the ongoing clinical trials evaluating innovative investigational approaches for MM, and refer appropriate patients for study participation.

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**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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**Contracted Research:** Amgen Inc, Celgene Corporation.

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**Consulting Agreements:** Celgene Corporation, Takeda Oncology; **Contracted Research:** Celgene Corporation;  
**Speakers Bureau:** Novartis Pharmaceuticals Corporation.

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**Hardware/Software Requirements:**

A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later  
Adobe Flash Player 10.2 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

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## Select Publications

### Rafael Fonseca, MD

Attal M et al. **Lenalidomide maintenance after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366:1782-91.

Avet-Loiseau H et al. **Long-term maintenance with lenalidomide improves progression free survival in myeloma patients with high-risk cytogenetics: An IFM study.** *Proc ASH 2010;Abstract 1944.*

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906-17.

Cavo M et al. **Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma.** *Blood* 2012;120(1):9-19.

Martinez-Lopez J et al. **Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma.** *Blood* 2014;123:3073-9.

McCarthy PL et al. **Lenalidomide after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366(19):1770-81.

Morgan GJ et al. **Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: The Medical Research Council Myeloma IX trial.** *Blood* 2012;119(23):7-15.

Neben K et al. **Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p.** *Blood* 2012;119(4):940-8.

Palumbo A et al. **Continuous lenalidomide treatment for newly diagnosed multiple myeloma.** *N Engl J Med* 2012;366(19):1759-69.

Stewart AK et al. **A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: The National Cancer Institute of Canada Clinical Trials Group Myeloma 10 trial.** *Blood* 2013;121(9):1517-23.

### Morie A Gertz, MD, MACP

**A safety and efficacy study of carfilzomib and pomalidomide with dexamethasone in patients with relapsed or refractory multiple myeloma.** [NCT01464034](#)

**A study of oral ixazomib citrate (MLN9708) maintenance therapy in patients with multiple myeloma following autologous stem cell transplant.** [NCT02181413](#)

**Carfilzomib, pomalidomide, and dexamethasone in treating patients with relapsed or refractory multiple myeloma.** [NCT01665794](#)

Chauhan D et al. **A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma.** *Blood* 2010;116(23):4906-15.

Ghobrial IM et al. **Clinical profile of single-agent modified-release oprozomib tablets in patients (pts) with hematologic malignancies: Updated results from a multicenter, open-label, dose escalation phase 1b/2 study.** *Proc ASH 2013;Abstract 3184.*

**Ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma.** [NCT01850524](#)

Kumar SK et al. **Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma.** *Blood* 2014;124(7):1047-55.

Mothy M et al. **Myeloma: Therapy, excluding transplantation I.** *Proc ASH 2014;Abstract 653.*

Ocio EM et al. **New drugs and novel mechanisms of action in multiple myeloma in 2013: A report from the International Myeloma Working Group (IMWG).** *Leukemia* 2014;28(3):525-42.

Richardson PG et al. **Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients.** *Blood* 2014;124(7):1038-46.

Rosenthal AC et al. **The cardiovascular impact of carfilzomib in multiple myeloma.** *Proc ASH 2014;Abstract 4748.*

Shah JJ et al. **Phase II study of the combination of MLN 9708 with lenalidomide as maintenance therapy post autologous stem cell transplant in patients with multiple myeloma.** *Proc ASH 2013;Abstract 1983.*

Siegel D et al. **Integrated safety profile of single-agent carfilzomib: Experience from 526 patients enrolled in 4 phase II clinical studies.** *Haematologica* 2013;98(11):1753-61.

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Vij R et al. **Clinical profile of single-agent oprozomib in patients (pts) with multiple myeloma (MM): Updated results from a multicenter, open-label, dose escalation phase 1b/2 study.** *Proc ASH* 2014;Abstract 34.

### Sagar Lonial, MD

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Catley L et al. **Aggresome induction by proteasome inhibitor bortezomib and  $\alpha$ -tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells.** *Blood* 2006;108(10):3441-9.

Collins SM et al. **Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: Evidence for augmented NK cell function complementing ADCC.** *Cancer Immunol Immunother* 2013;62(12):1841-9.

Guo H et al. **Immune cell inhibition by SLAMF7 is mediated by a mechanism requiring src kinases, CD45, and SHIP-1 that is defective in multiple myeloma cells.** *Mol Cell Biol* 2015;35(1):41-51.

Hideshima T et al. **Intracellular protein degradation and its therapeutic implications.** *Clin Cancer Res* 2005;11(24):8530-3.

Hsi ED et al. **CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma.** *Clin Cancer Res* 2008;14(9):2775-84.

Lonial S et al. **Phase I/II study of elotuzumab plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma: Updated Phase II results and Phase I/II long term safety.** *Proc ASCO* 2013;Abstract 8542.

**Panobinostat or placebo with bortezomib and dexamethasone in patients with relapsed multiple myeloma (PANORAMA-1). NCT01023308**

Richardson PG et al. **A phase 2 study of bortezomib in relapsed, refractory myeloma.** *N Engl J Med* 2003;348(26):2609-17.

Tai YT, Anderson KC. **Antibody-based therapies in multiple myeloma.** *Bone Marrow Res* 2011;924058.

### Gareth John Morgan, PhD

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**A study of siltuximab (anti-IL 6 monoclonal antibody) in patients with high-risk smoldering multiple myeloma. NCT01484275**

**Biomarker study of elotuzumab in high risk smoldering myeloma. NCT01441973**

Bianchi G et al. **High levels of peripheral blood circulating plasma cells as a specific risk factor for progression of smoldering multiple myeloma.** *Leukemia* 2013;27(3):680-5.

**Carfilzomib, lenalidomide, and dexamethasone for smoldering multiple myeloma. NCT01572480**

Dhodapkar MV et al. **Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120).** *Blood* 2014;123(1):78-85.

Dispenzieri A et al. **Smoldering multiple myeloma requiring treatment: Time for a new definition?** *Blood* 2013;122(26):4172-81.

Dispenzieri A et al. **Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma.** *Blood* 2008;111(2):785-9.

Facon T et al. **Prognostic factors in low tumour mass asymptomatic multiple myeloma: A report on 91 patients. The Groupe d'Etudes et de Recherche sur le Myélome (GERM).** *Am J Hematol* 1995;48(2):71-5.

Hanamura I et al. **Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: Incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation.** *Blood* 2006;108(5):1724-32.

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Hillengass J et al. **Lumbar bone marrow microcirculation measurements from dynamic contrast-enhanced magnetic resonance imaging is a predictor of event-free survival in progressive multiple myeloma.** *Clin Cancer Res* 2007;13(2):475-81.

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Kyle RA et al. **Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma.** *N Engl J Med* 2007;356(25):2582-90.

Kyle RA, Greipp PR. **Smoldering multiple myeloma.** *N Engl J Med* 1980;302(24):1347-9.

Madan S et al. **Plasma cell labeling index in the evaluation of smoldering (asymptomatic) multiple myeloma.** *Proc Mayo Clinic* 2010;85(3):300.

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Neben K et al. **Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load.** *J Clin Oncol* 2013;31(34):4325-32.

Pérez-Persona E et al. **New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells.** *Blood* 2007;110(7).

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**Study of BHQ880 in patients with high risk smoldering multiple myeloma. NCT01302886**

**Treatment optimization in patients with untreated multiple myeloma (GERMAIN). NCT02145598**

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### Noopur Raje, MD

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906-17.

Bensinger W. **Stem-cell transplantation for multiple myeloma in the era of novel drugs.** *J Clin Oncol* 2008;26(3):480-92.

**Bortezomib or carfilzomib with lenalidomide and dexamethasone in treating patients with newly diagnosed multiple myeloma. NCT01863550**

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Fayers PM et al. **Thalidomide for previously untreated elderly patients with multiple myeloma: Meta-analysis of 1685 individual patient data from 6 randomized clinical trials.** *Blood* 2011;118(5):1239-47.

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801-9.

Korde N et al. **Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients.** *Proc ASH* 2013;Abstract 538.

Kumar S et al. **Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma.** *Blood* 2012;119(19):4375-82.

Kumar S et al. **Novel three- and four-drug combination regimens of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for previously untreated multiple myeloma: Results from the multi-center, randomized, phase 2 EVOLUTION study.** *Proc ASH* 2010;Abstract 621.

Kumar SK et al. **Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: An open-label phase 1/2 study.** *Lancet Oncol* 2014;15(13):1503-12.

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## Select Publications

- O'Donnell E et al. **A phase II study of modified lenalidomide, bortezomib, and dexamethasone (RVD lite) for transplant-ineligible patients with newly diagnosed multiple myeloma.** *Proc ASH* 2014;Abstract 3454.
- Palumbo A. **Continuous lenalidomide treatment for newly diagnosed multiple myeloma.** *N Engl J Med* 2012;366(19):1759-69.
- Rawstron AC et al. **Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: Impact on outcome in the Medical Research Council Myeloma IX study.** *J Clin Oncol* 2013;31(20):2540-7.
- Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.
- San Miguel JF et al. **Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma.** *J Clin Oncol* 2013;31(4):448-55.
- San Miguel JF et al. **Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.** *N Engl J Med* 2008;359(9):906-17.
- Stewart AK et al. **How I treat multiple myeloma in younger patients.** *Blood* 2009;114(27):5436-43.
- Study comparing conventional dose combination RVD to high-dose treatment with ASCT in the initial myeloma up to 65 years (IFM/DFCI2009). NCT01191060**
- Study to compare VMP with HDM followed by VRD consolidation and lenalidomide maintenance in patients with newly diagnosed multiple myeloma (HO95). NCT01208766**