Addressing Current Questions and Controversies in the Management of Multiple Myeloma, Waldenström Macroglobulinemia and Amyloidosis

CME Information

TARGET AUDIENCE

This activity is intended for hematologists, medical oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of multiple myeloma (MM), Waldenström macroglobulinemia (WM) and amyloidosis.

OVERVIEW OF ACTIVITY

Hematologic cancers include the lymphomas, the leukemias, MM and other related disorders stemming from lymphoid and myeloid progenitor cell lines. Taken together, it is estimated that approximately 174,250 new lymphoid, myeloid and leukemic cancer cases will be identified in the United States in the year 2018, and 58,100 individuals will die from these diseases. Importantly, more than 70 drug products are currently labeled for use in the management of hematologic cancers with more than 120 distinct FDA-approved indications. Although this 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 their appropriate application across a vast spectrum of tumor types. This is particularly true within the realm of MM, WM and amyloidosis, where the past several years have yielded a staggering number of important clinical and research advances.

These proceedings from a CME symposium during the ASH Annual Meeting use the perspectives of a group of community oncologists/hematologists gathered during a daylong working group to establish and subsequently address some of the most frequently encountered questions and controversies facing clinicians involved in the management of these diseases. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist hematologists, medical oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of MM, WM and amyloidosis with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Customize the use of induction, consolidation and maintenance therapeutic approaches for patients with MM in the post-transplant and nontransplant settings, considering patient- and disease-related factors, including cytogenetic profile.
- Consider published research data and other clinical factors in the best-practice selection, sequencing or combining of available therapies in the nonresearch care of patients with relapsed/refractory (R/R) MM.
- Appreciate the mechanisms of action of, supportive research database with and FDA-endorsed indications for monoclonal antibodies directed at CD38 and SLAMF7, and effectively identify where and how these agents should be integrated into the clinical management of newly diagnosed and R/R MM.
- Design and implement a plan of care for patients with smoldering myeloma, considering the applicability of existing and emerging clinical trial data.
- Develop an evidence-based algorithm for the use of stem cell transplant, chemotherapy and/or novel targeted agents in the management of primary amyloidosis.
- Consider clinical and other patient-related factors in the sequence and selection of systemic therapy for patients with WM requiring active treatment.
- Assess the ongoing clinical trials evaluating novel investigational approaches for MM, WM and amyloidosis, and obtain consent from appropriate patients for study participation.

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No relevant conflicts of interest to disclose.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 11 or later, Firefox 56 or later, Chrome 61 or later, Safari 11 or later, Opera 48 or later
Adobe Flash Player 27 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Select Publications

Sagar Lonial, MD

Anderson KC. **Should minimal residual disease negativity be the end point of myeloma therapy?** *Blood Adv* 2017;1(8):517-21.

Davies FE. **Is molecular remission the goal of multiple myeloma therapy?** *Hematology Am Soc Hematol Educ Program* 2017;2017(1):205-11.

Durie BG et al. **Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial.** *Lancet* 2017;389(10068):519-27.

Mailankody S et al. **Minimal residual disease in multiple myeloma: Bringing the bench to the bedside.** *Nat Rev Clin Oncol* 2015;12(5):286-95.

Nooka AK et al. **Managing infusion reactions to new monoclonal antibodies in multiple myeloma: Daratumumab and elotuzumab.** *J Oncol Pract* 2018;14(7):414-22.

Voorhees PM et al. **Efficacy and updated safety analysis of a safety run-in cohort from Griffin, a phase 2 randomized study of daratumumab (Dara), bortezomib (V), lenalidomide (R), and dexamethasone (D; Dara-Vrd) vs Vrd in patients (Pts) with newly diagnosed (ND) multiple myeloma (MM) eligible for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT).** *Proc ASH* 2018;**Abstract 151**.

Rafael Fonseca, MD

Cavo M et al; GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. **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.

Chakraborty R et al. **Outcomes of maintenance therapy with lenalidomide or bortezomib in multiple myeloma in the setting of early autologous stem cell transplantation.** *Leukemia* 2018;32(3):712-8.

Dimopoulos MA et al. **Maintenance therapy with the oral proteasome inhibitor (PI) ixazomib significantly prolongs progression-free survival (PFS) following autologous stem cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma (NDMM): Phase 3 Tourmaline-MM3 trial.** *Proc ASH* 2018;**Abstract 301**.

Fonseca R et al. **Trends in overall survival and costs of multiple myeloma, 2000-2014.** *Leukemia* 2017;31(9):1915-21.

McCarthy PL et al. **Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: A meta-analysis.** *J Clin Oncol* 2017;35(28):3279-89.

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.

Nooka AK et al. **Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients.** *Leukemia* 2014;28(3):690-3.

Sivaraj D et al. **Outcomes of maintenance therapy with bortezomib after autologous stem cell transplantation for patients with multiple myeloma.** *Biol Blood Marrow Transplant* 2017;23(2):262-8.

Yong K et al. **Multiple myeloma: Patient outcomes in real-world practice.** *Br J Haematol* 2016;175(2):252-64.

Professor Katja Weisel, MD

Dimopoulos MA et al. **Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: Updated analysis of POLLUX.** *Haematologica* 2018;[Epub ahead of print].

Dimopoulos MA et al. **Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial.** *Cancer* 2018;124(20):4032-43.

Dimopoulos M et al. **Response and progression-free survival according to planned treatment duration in patients with relapsed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in the phase III ASPIRE study.** *J Hematol Oncol* 2018;11(1):49.

Dimopoulos MA et al. **Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): An interim overall survival analysis of an open-label, randomised, phase 3 trial.** *Lancet Oncol* 2017;18(10):1327-73.

Dimopoulos MA et al; ENDEAVOR Investigators. **Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomised, phase 3, open-label, multicentre study.** *Lancet Oncol* 2016;17(1):27-38.

Select Publications

Dimopoulos MA et al; POLLUX Investigators. **Daratumumab, lenalidomide, and dexamethasone for multiple myeloma.** *N Engl J Med* 2016;375(14):1319-31.

Laubach JP et al. **Management of relapsed multiple myeloma: Recommendations of the International Myeloma Working Group.** *Leukemia* 2016;30(5):1005-17.

Lonial S et al; ELOQUENT-2 Investigators. **Elotuzumab therapy for relapsed or refractory multiple myeloma.** *N Engl J Med* 2015;373(7):621-31.

Ludwig H et al. **Prevention and management of adverse events of novel agents in multiple myeloma: A consensus of the European Myeloma Network.** *Leukemia* 2018;32(7):1542-60.

Moreau P et al; TOURMALINE-MM1 Study Group. **Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma.** *N Engl J Med* 2016;374(17):1621-34.

Palumbo A et al; CASTOR Investigators. **Daratumumab, bortezomib, and dexamethasone for multiple myeloma.** *N Engl J Med* 2016;375(8):754-66.

San-Miguel JF et al. **Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): A randomised, placebo-controlled, phase 3 trial.** *Lancet Haematol* 2016;3(11):e506-15.

San-Miguel JF et al. **Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial.** *Lancet Oncol* 2014;15(11):1195-2067.

Siegel DS et al. **Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma.** *J Clin Oncol* 2018;36(8):728-34.

Stewart AK et al; ASPIRE Investigators. **Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.** *N Engl J Med* 2015;372(2):142-52.

Richardson PG et al. **Pomalidomide (POM), bortezomib, and low- dose dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients (pts) with relapsed or refractory multiple myeloma (RRMM): Phase 3 OPTIMISMM trial.** *Proc ASCO* 2018;**Abstract 8001**.

Noopur Raje, MD

Certo M et al. **Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members.** *Cancer Cell* 2006;9(5):351-65.

Costa LJ et al. **Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma.** *Proc ASCO* 2018;**Abstract 8004**.

Czabotar PE et al. **Control of apoptosis by the BCL-2 protein family: Implications for physiology and therapy.** *Nat Rev Mol Cell Biol* 2014;15(1):49-63.

Del Gaizo Moore V et al. **Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737.** *J Clin Invest* 2007;117(1):112-21.

Kumar S et al. **Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma.** *Blood* 2017;130(22):2401-9.

Lee DW et al. **Current concepts in the diagnosis and management of cytokine release syndrome.** *Blood* 2014;124(2):188-95.

Leverson JD et al. **Exploiting selective BCL-2 family inhibitors to dissect cell survival dependencies and define improved strategies for cancer therapy.** *Sci Transl Med* 2015;7(279):279ra40.

Matulis SM et al. **Dexamethasone treatment promotes Bcl-2 dependence in multiple myeloma resulting in sensitivity to venetoclax.** *Leukemia* 2016;30(5):1086-93.

Plati J et al. **Apoptotic cell signaling in cancer progression and therapy.** *Integ Biol (Camb)* 2011;3(4):279-96.

Punnoose EA et al. **Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models.** *Mol Cancer Ther* 2016;15(5):1132-44.

Raje NS et al. **bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study.** *Proc ASCO* 2018;**Abstract 8007**.

Souers AJ et al. **ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets.** *Nat Med* 2013;19(2):202-8.

Select Publications

Robert Z Orlowski, MD, PhD

Dimopoulos MA et al. **Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia.** *N Engl J Med* 2018;378(25):2399-410.

Kaufman GP et al. **Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis.** *Blood* 2017;130(7):900-2.

Kumar S et al. **Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements.** *J Clin Oncol* 2012;30(9):989-95.

Lakshman A et al. **Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria.** *Blood Cancer* 2018;8(6):59.

Mateos MV et al. **Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma.** *N Engl J Med* 2013;369(5):438-47.

Nuvolone M, Merlini G. **Systemic amyloidosis: Novel therapies and role of biomarkers.** *Nephrol Dial Transplant* 2017;32(5):770-80.

Owen R et al. **Acalabrutinib in patients (pts) with Waldenström macroglobulinemia (WM).** *Proc ASCO* 2018;**Abstract 7501**.

Rajkumar SV et al. **International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma.** *Lancet Oncol* 2014;15(12):e538-48.

Sanchorawala V et al. **A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis.** *Blood* 2017;130(5):597-605.

Treon SP et al. **Ibrutinib in previously treated Waldenström's macroglobulinemia.** *N Engl J Med* 2015;372(15):1430-40.

Treon SP et al. **MYD88 L265P somatic mutation in Waldenström's macroglobulinemia.** *N Engl J Med* 2012;367(9):826-33.

Treon SP. **How I treat Waldenström macroglobulinemia.** *Blood* 2009;114(12):2375-85.