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 (AL).

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 56,100 individuals will die from these diseases. Importantly, nearly 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 myeloma, 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 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 this disease. 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 AL 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 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 R/R MM.
- Design and implement a plan of care to recognize and manage side effects and toxicities associated with the use of existing and recently approved systemic therapies to support quality of life and continuation of treatment.
- Develop an evidence-based algorithm for the use of stem cell transplant, chemotherapy and/or novel targeted agents for the management of primary AL.
- 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 AL, and obtain consent from appropriate patients for study participation.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM) — MAINTENANCE OF CERTIFICATION (MOC)

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.75 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed

for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

Personal information and data sharing: Research To Practice aggregates deidentified user data for program-use analysis, program development, activity planning and site improvement. We may provide aggregate and deidentified data to third parties, including commercial supporters. We do not share or sell personally identifiable information to any unaffiliated third parties or commercial supporters. Please see our privacy policy at **ResearchToPractice.com/Privacy-Policy** for more information.

HOW TO USE THIS CME ACTIVITY

This CME activity consists of a video component. To receive credit, the participant should review the CME information, watch the video, complete the Post-test with a score of 80% or better and fill out the Educational Assessment and Credit Form located at **ResearchToPractice.com/ASHMM2017/CME**.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess conflicts of interest with faculty, planners and managers of CME activities. Conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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

Meletios A Dimopoulos, MD
Chairman, Department of Medical Therapeutics
University of Athens School of Medicine
Athens, Greece

Advisory Committee: Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Novartis, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology.

Sagar Lonial, MD
Professor and Executive Vice Chair
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University
Atlanta, Georgia

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Merck, Novartis, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology; **Consulting Agreements:** Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Merck, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology.

Nikhil C Munshi, MD
Professor of Medicine, Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Consulting Agreements: Celgene Corporation, Janssen Biotech Inc, Merck, OncoPep, Pfizer Inc, Takeda Oncology; **Ownership Interest:** OncoPep.

Robert Z Orlowski, MD, PhD
Florence Maude Thomas Cancer Research Professor
Chair Ad Interim, Department of Lymphoma and Myeloma
Professor, Department of Experimental Therapeutics
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Advisory Committee and Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Takeda Oncology; **Contracted Research:** Bristol-Myers Squibb Company, Celgene Corporation, Forma Therapeutics, Karus Therapeutics, Onyx Pharmaceuticals, an Amgen subsidiary, Spectrum Pharmaceuticals Inc, Takeda Oncology.

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Consulting Agreements: Amgen Inc, Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Oncology; **Contracted Research:** Acetylon Pharmaceuticals Inc, Lilly.

MODERATOR — **Dr Love** is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite Pharma Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceu-

ticals Inc, Sanofi Genzyme, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology and Tokai Pharmaceuticals Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from AbbVie Inc, Adaptive Biotechnologies, AstraZeneca Pharmaceuticals LP/Acerta Pharma, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Genentech BioOncology, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Pharmacyclics LLC, an AbbVie Company, Seattle Genetics and Takeda Oncology.

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

Last review date: March 2018

Expiration date: March 2019

Select Publications

Sagar Lonial, MD

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.

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.

Laubach JP et al. **A pilot study of eltrombopag plus G-CSF for human CD34+ cell mobilization in patients with multiple myeloma undergoing autologous stem cell transplant.** *Proc ASH* 2016;**Abstract 5815**.

Mateos MV et al. **Phase 3 randomized study of daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) in newly diagnosed multiple myeloma (NDMM) patients (Pts) ineligible for transplant (ALCYONE).** *Proc ASH* 2017;**Abstract LBA-4**.

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

Robert Z Orlowski, MD, PhD

Attal M et al. **Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma.** *N Engl J Med* 2017;376(14):1311-20.

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

de Tute RM et al. **Minimal residual disease in the maintenance setting in myeloma: Prognostic significance and impact of lenalidomide.** *Proc ASH* 2017;**Abstract 904**.

Dimopoulos MA et al. **Efficacy and safety of long-term ixazomib maintenance therapy in patients (Pts) with newly diagnosed multiple myeloma (NDMM) not undergoing transplant: An integrated analysis of four phase 1/2 studies.** *Proc ASH* 2017;**Abstract 902**.

Facon T et al. **Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma.** *Blood* 2017;131(3):301-10.

Holstein SA et al. **Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: A randomised, double-blind, phase 3 trial.** *Lancet Hematol* 2017;4(9):e431-42.

Jackson G et al. **Lenalidomide maintenance significantly improves outcomes compared to observation irrespective of cytogenetic risk: Results of the Myeloma XI trial.** *Proc ASH* 2017;**Abstract 436**.

Patel KK et al. **Update on a phase II study of ixazomib with lenalidomide as maintenance therapy following autologous stem cell transplant in patients with multiple myeloma.** *Proc ASH* 2017;**Abstract 437**.

Stadtmauer EA et al. **Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (len) and dexamethasone (RVD) consolidation with len maintenance (ACM), tandem autohct with len maintenance (TAM) and autohct with len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM): Primary results from the randomized phase III trial of the blood and marrow transplant clinical trials network (BMT CTN 0702 - StaMINA trial).** *Proc ASH* 2016;**Abstract LBA-1**.

Nikhil C Munshi, MD

Avet-Loiseau H et al. **Evaluation of minimal residual disease (MRD) in relapsed/refractory multiple myeloma (RRMM) patients treated with daratumumab in combination with lenalidomide plus dexamethasone or bortezomib plus dexamethasone.** *Proc ASH* 2016;**Abstract 246**.

Chari A et al. **Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma.** *Blood* 2017;130(8):974-81.

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.

Jakubowiak A et al. **Randomized phase 2 study: Elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM.** *Blood* 2016;127(23):2833-40.

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.

Nooka AK et al. **Treatment options for relapsed and refractory multiple myeloma.** *Blood* 2015;125(20):3085-99.

Orlowski RZ, Lonial S. **Integration of novel agents into the care of patients with multiple myeloma.** *Clin Cancer Res* 2016;22(22):5443-52.

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

Palumbo A, Anderson K. **Multiple myeloma.** *N Engl J Med* 2011;364(11):1046-60.

Palumbo A et al. **Personalized therapy in multiple myeloma according to patient age and vulnerability: A report of the European Myeloma Network (EMN).** *Blood* 2011;118(17):4519-29.

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 Oncology* 2014;5(11):1195-206.

Usmani SZ et al. **Open-label, multicenter, dose escalation phase 1b study to assess the subcutaneous delivery of daratumumab in patients (pts) with relapsed or refractory multiple myeloma (PAVO).** *Proc ASH* 2016;**Abstract 1149**.

Noopur Raje, MD

Berdeja JG et al. **First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results.** *Proc ASCO* 2017;**Abstract 3010**.

Kumar S et al. **Venetoclax monotherapy for relapsed/refractory multiple myeloma: Safety and efficacy results from a phase I study.** *Proc ASH* 2016;**Abstract 488**.

Moreau P et al. **Venetoclax combined with bortezomib and dexamethasone for patients with relapsed/refractory multiple myeloma.** *Proc ASH* 2016;**Abstract 975**.

Raje NS et al. **Impact of denosumab (DMB) compared with zoledronic acid (ZA) on renal function in the treatment of myeloma bone disease.** *Proc ASCO* 2017;**Abstract 8005**.

Meletios A Dimopoulos, MD

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):1327-37.

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):758-9.

Gonsalves WI et al. **Quantification of circulating clonal plasma cells via multiparametric flow cytometry identifies patients with smoldering multiple myeloma at high risk of progression.** *Leukemia* 2017;31(1):130-5.

Gustine J et al. **Ibrutinib discontinuation in Waldenström macroglobulinemia: Etiologies, outcomes, and IgM rebound.** *Proc ASH* 2017;**Abstract 802**.

Hillengass J et al. **Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma.** *J Clin Oncol* 2010;28(9):1606-10.

Kastritis E et al. **Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease.** *Leukemia* 2013;27(4):947-53.

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

Keane N et al. **MYC translocations identified by sequencing panel in smoldering multiple myeloma strongly predict for rapid progression to multiple myeloma.** *Proc ASH* 2017;**Abstract 393**.

Select Publications

Korde N et al. **Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma.** *JAMA Oncol* 2015;1(6):746-54.

Kyle R et al. **Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma.** *N Engl J Med* 2007;356(25):2582-60.

Leblond V et al. **Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia.** *Blood* 2016;128(10):1321-8.

Manier S et al. **Genomic complexity of multiple myeloma and its clinical implications.** *Nat Rev Clin Oncol* 2016;14(2):100-13.

Mateos MV et al. **Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): Long-term follow-up of a randomised, controlled, phase 3 trial.** *Lancet Oncol* 2016;17(8):1127-36.

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

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):2586-92.

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

Ravi P et al. **Evolving changes in disease biomarkers and risk of early progression in smoldering multiple myeloma.** *Blood Cancer J* 2016;6(7):e454.

Rosiñol L et al. **Smoldering multiple myeloma: Natural history and recognition of an evolving type.** *Br J Haematol* 2003;123(4):631-6.

Siontis B et al. **Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: Identification of patients needing therapy.** *Blood Cancer J* 2015;5(10):e364.

Treon SP et al. **Ibrutinib is highly active as first line therapy in symptomatic Waldenstrom's macroglobulinemia.** *Proc ASH* 2017;**Abstract 2767**.

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