# **BEYOND THE GUIDELINES**

Investigator Perspectives on Current Clinical Issues and Ongoing Research in the Management of Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma

# **CME** Information

## TARGET AUDIENCE

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

## **OVERVIEW OF ACTIVITY**

Hematologic cancers include the lymphomas, the leukemias, multiple myeloma (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 appropriate clinical management strategies across a vast spectrum of liquid and solid tumors. This is particularly true, however, within the realm of Hodgkin and non-Hodgkin lymphoma (including chronic lymphocytic leukemia [CLL]) and MM, where the past several years have seen a staggering number of important clinical and research advances.

Several consensus- and evidence-based treatment guidelines are available and aim to assist clinicians with making management decisions in this dynamic clinical and research environment. However, in situations where multiple acceptable therapeutic options exist, such guidelines may not be particularly helpful at the time of decision-making. By exploring the perspectives of leading investigators regarding a number of clinical scenarios and reviewing key data sets, this activity will assist medical oncologists, hematologists, hematologyoncology fellows and other allied healthcare professionals in the development of evidence-based strategies for the treatment of hematologic cancers.

## LEARNING OBJECTIVES

 Individualize the selection and sequence of systemic therapy for patients with newly diagnosed and relapsed/ refractory (R/R) CLL, considering clinical presentation, biomarker profile and psychosocial status.

- Consider existing and emerging clinical research data in the formulation of therapeutic recommendations for patients with newly diagnosed and R/R diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma.
- Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and R/R Hodgkin lymphoma (HL).
- 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 therapeutic agents in the nonresearch care of patients with R/R MM.
- Compare and contrast the mechanisms of action, efficacy and safety of approved and investigational immunotherapeutic approaches (eg, immune checkpoint inhibitors, chimeric antigen receptor-directed T-cell therapy) for the treatment of HL, non-Hodgkin lymphoma (NHL), CLL and MM to determine the current and/or potential utility of each in clinical practice.
- Design and implement a plan of care to recognize and manage side effects and toxicities associated with existing and recently approved systemic therapies in the management of HL, NHL, CLL and MM to support quality of life and continuation of treatment.
- Assess the ongoing clinical trials evaluating other novel investigational approaches for HL, NHL, CLL and MM, and obtain consent from appropriate patients for study participation.

## **ACCREDITATION STATEMENT**

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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**.

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

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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**

### Rafael Fonseca, MD

Cavo M et al. Daratumumab plus bortezomib-melphalan-prednisone (VMP) in elderly (≥75 y) patients (Pts) with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE). ASCO 2018; Abstract 8031.

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

Lahuerta JJ et al. Depth of response in multiple myeloma: A pooled analysis of three PETHEMA/GEM clinical trials. *J Clin Oncol* 2017;35(25):2900-10.

Martinez-Lopez J et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. *Blood* 2011;118(3):529-34.

Mateos MV et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med* 2018;378(6):518-28.

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

#### Paul G Richardson, MD

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

Czabotar PE et al. Structural insights into the degradation of McI-1 induced by BH3 domains. *Proc Natl Acad Sci USA* 2007;104(15):6217-22.

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.

Qin J-Z et al. Proteasome inhibitors trigger NOXA-mediated apoptosis in melanoma and myeloma cells. *Cancer Res* 2005;65(14):6282-93.

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. ASCO 2018; Abstract 8007.

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. ASCO 2018;Abstract 8001.

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Touzeau C et al. The Bcl-2 specific BH3 mimetic ABT-199: A promising targeted therapy for t(11;14) multiple myeloma. *Leukemia* 2014;28(1):210-2.

### Matthew S Davids, MD, MMSc

Damle RN et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood* 1999;94(6):1840-7.

Döhner H et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343(26):1910-6.

Hallek M et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. *Lancet* 2010;376(9747):1164-74.

Hamblin TJ et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood* 1999;94(6):1848-54.

Kovacs G et al. Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: Comprehensive analysis of two phase III studies of the German CLL study group. *J Clin Oncol* 2016;34(31):3758-65.

O'Brien S et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: A 5-year experience. *Blood* 2018;131(17):1910-9.

Rossi D et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood* 2015;126(16):1921-4.

Seymour JF et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* 2018;378(12):1107-20.

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#### Anas Younes, MD

Gordon LI et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: An intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2013;31(6):684-91.

Johnson P et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med 2016;374(25):2419-29.

Moskowitz CH et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;385(9980):1853-62.

Stathis A, Younes A. The new therapeutical scenario of Hodgkin lymphoma. Ann Oncol 2015;26(10):2026-33.

Younes A, Ansell SM. Novel agents in the treatment of Hodgkin lymphoma: Biological basis and clinical results. *Semin Hematol* 2016;53(3):186-9.

#### Stephen Maxted Ansell, MD, PhD

Bonifant CL et al. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics 2016;3:16011.

Castellino A et al. Long term follow-up (FU) of lenalidomide plus R-CHOP therapy in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL): Combined analysis from two phase 2 trials. ASCO 2018; Abstract 7562.

Crump M et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood* 2017;130(16):1800-8.

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Neelapu SS et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017;377(26):2531-44.

Nowakowski GS et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: A phase II study. *J Clin Oncol* 2015;33(3):251-7.

Schuster SJ et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med 2017;377(26):2545-54.

Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. Nat Rev Cancer 2014;14(8):517-34.

Thieblemont C et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2017;35(22):2473-81.

Wilson WH et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med* 2015;21(8):922-6.

Younes A et al. Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naïve patients with CD20-positive B-cell non-Hodgkin lymphoma: A non-randomised, phase 1b study. *Lancet* Oncol 2014;15(9):1019-26.

#### Laurie H Sehn, MD, MPH

Brice P et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: A randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 1997;15(3):1110-7.

Cheson BD et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *J Clin Oncol* 2014;32(27):3059-68.

Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-86.

# Select Publications

Davids MS et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol* 2017;35(8):826-33.

Dreyling M et al. **Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma.** *J Clin Oncol* 2017;35(35):3898-905.

Dreyling M et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: An international, randomised, open-label, phase 3 study. *Lancet* 2016;387(10020):770-8.

Fisher RI et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2006;24(30):4867-74.

Fowler N et al. **RELEVANCE:** Phase III randomized study of lenalidomide plus rituximab (R2) versus chemotherapy plus rituximab, followed by rituximab maintenance, in patients with previously untreated follicular lymphoma. ASCO 2018;Abstract 7500.

Goy A et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study. *J Clin Oncol* 2013;31(29):3688-95.

Kahl BS et al. A phase 1 study of the PI3Kδ inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood* 2014;123(22):3398-405.

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Wang M et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: A phase 1/2 clinical trial. *Lancet Oncol* 2012;13(7):716-23.