

Beyond the Guidelines:

Clinical Investigators Provide Their Perspectives on the Management of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

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

Taken together, it is estimated that approximately 86,520 new non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) cases were identified in the United States in the year 2014, and 23,590 individuals died from these diseases. Of importance, currently more than 60 drug products are labeled for use in the management of hematologic cancers, comprising more than 70 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.

These proceedings from a CME symposium during the 56th 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 various forms of NHL. 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 NHL.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in the non-Hodgkin lymphomas, including chronic lymphocytic leukemia (CLL), and integrate this information, as appropriate, into current clinical care.
- Develop an algorithm for the risk-stratified induction treatment of follicular lymphoma, diffuse large B-cell lymphoma and mantle-cell lymphoma.
- Customize the selection of systemic therapy for patients with newly diagnosed and progressive mantle-cell lymphoma, recognizing the addition of recently FDA-endorsed options for these patients.

- Appreciate the recent FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed/refractory CLL, and discern how these treatments can be appropriately integrated into clinical practice.
- Compare and contrast completed and ongoing clinical trials evaluating novel investigational approaches for B-cell lymphomas and CLL, and use this information to refer appropriate patients for study participation and/or available expanded access programs.
- Recognize the role of novel agents in the management of peripheral T-cell lymphoma and/or advanced-stage cutaneous T-cell lymphoma, and ensure appropriate supportive care measures to minimize side effects.

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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, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Myriad Genetic Laboratories Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

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This activity is supported by educational grants from AbbVie Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Onyx Pharmaceuticals, an Amgen subsidiary and Takeda Oncology.

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

Last review date: March 2015

Expiration date: March 2016

Select Publications

Stephen M Ansell, MD, PhD

- Armand P et al. **Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: Results of an international phase II trial.** *J Clin Oncol* 2013;31(33):4199-206.
- Chitta KS et al. **Inhibition of the deubiquitinating enzymes UCHL5 and USP14 is lethal to Waldenström's macroglobulinemia cells.** *Blood* 2013;122(21):1823.
- Dunleavy K et al. **Using biologic predictive factors to direct therapy of diffuse large B-cell lymphoma.** *Ther Adv Hematol* 2013;4(1):43-57.
- Hu S et al. **MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: A report from the international DLBCL rituximab-CHOP consortium program.** *Blood* 2013;121:4021-31.
- Lenz G et al. **Stromal gene signatures in large-B-cell lymphomas.** *N Engl J Med* 2008;359(22):2313-23.
- Maurer MJ et al. **Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy.** *J Clin Oncol* 2014;32(10):1066-73.
- 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* 2014;5714.
- Okazaki T et al. **A rheostat for immune responses: The unique properties of PD-1 and their advantages for clinical application.** *Nat Immunol* 2013;14(12):1212-8.
- Phase 3 randomized, double-blind, placebo controlled, multicenter study to compare the efficacy and safety of lenalidomide (CC-5013) plus R-CHOP chemotherapy (R2-CHOP) versus placebo plus R-CHOP chemotherapy in subjects with previously untreated activated B-cell type diffuse large B-cell lymphoma. NCT02285062**
- Randomized phase II open label study of lenalidomide R-CHOP (R2CHOP) vs RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) in patients with newly diagnosed diffuse large B-cell lymphoma. NCT01856192**
- Scott DW et al. **Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue.** *Blood* 2014;123(8):1214-7.
- Steensma DP, Stone RM. **Lenalidomide in AML: Del(5q) or who?** *Blood* 2011;118:481-2.
- Vitolo U et al. **Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: Results of the REAL07 open-label, multicentre, phase 2 trial.** *Lancet Oncol* 2014;15(7):730-7.
- Westin JR et al. **Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: A single group, open-label, phase 2 trial.** *Lancet Oncol* 2014;15(1):69-77.

Brad S Kahl, MD

- Brown JR et al. **Safety and efficacy of obinutuzumab (GA101) with fludarabine/cyclophosphamide (G-FC) or bendamustine (G-B) in the initial therapy of patients with chronic lymphocytic leukemia (CLL): Results from the phase 1b GALTON trial (GAO4779g).** *Proc ASH* 2013;Abstract 523.
- Byrd JC et al. **Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.** *N Engl J Med* 2014;371(3):213-23.
- Eichhorst B et al. **Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study).** *Proc ASH* 2014;Abstract 19.
- Furman RR et al. **Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.** *N Engl J Med* 2014;370(11):997-1007.
- Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.
- Greil R et al. **Rituximab maintenance after chemoimmunotherapy induction in 1st and 2nd line improves progression free survival: Planned interim analysis of the international randomized AGMT-CLL8/a Maintenance trial.** *Proc ASH* 2014;Abstract 20.
- Maintenance: International, multicentre, randomized phase III study of rituximab as maintenance treatment versus observation alone in patients with chronic lymphocytic leukemia. NCT01118234**

Select Publications

O'Brien SM et al. **Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease.** *Proc ASCO* 2014;Abstract 7014.

Phase III trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) versus bendamustine and rituximab (BR) in patients with previously untreated chronic lymphocytic leukaemia. NCT00769522

Porter DL et al. **Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL.** *Proc ASH* 2014;Abstract 1982.

Seymour JF et al. **Bcl-2 inhibitor ABT-199 (GDC-0199) monotherapy shows anti-tumor activity including complete remissions in high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).** *Proc ASH* 2013;Abstract 872.

Shanafelt T. **Treatment of older patients with chronic lymphocytic leukemia: Key questions and current answers.** *Hematology Am Soc Hematol Educ Program* 2013;2013:158-67.

Sharman JP et al. **Second interim analysis of a phase 3 study of idelalisib (ZYDELIG®) plus rituximab (R) for relapsed chronic lymphocytic leukemia (CLL): Efficacy analysis in patient subpopulations with del(17p) and other adverse prognostic factors.** *Proc ASH* 2014;Abstract 330.

van Oers MHJ et al. **Ofatumumab (OFA) maintenance prolongs PFS in relapsed CLL: Prolong study interim analysis results.** *Proc ASH* 2014;Abstract 21.

John P Leonard, MD

A randomized, double-blind, placebo-controlled phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma. NCT01776840

Cavalli F et al. **Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT).** *Proc ASCO* 2014;Abstract 8500.

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.

Rituximab, bendamustine hydrochloride, and bortezomib followed by rituximab and lenalidomide in treating older patients with previously untreated mantle cell lymphoma. NCT01415752

Wang ML et al. **Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.** *N Engl J Med* 2013;369(6):507-16.

Gilles A Salles, MD, PhD

A phase 3 open label randomized study to compare the efficacy and safety of rituximab plus lenalidomide (CC-5013) versus rituximab plus chemotherapy followed by rituximab in subjects with previously untreated follicular lymphoma (RELEVANCE). NCT01650701

A study of obinutuzumab (RO5072759) plus chemotherapy in comparison with MabThera/rituxan (rituximab) plus chemotherapy followed by GA101 or MabThera/rituxan maintenance in patients with untreated advanced indolent non-Hodgkin's lymphoma (GALLIUM). NCT01332968

Efficacy and safety study of idelalisib in subjects with indolent B-cell non-Hodgkin lymphoma (DELTA). NCT01282424

Flinn IW et al. **Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study.** *Blood* 2014;123(19):2944-52.

Fowler NH et al. **Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: An open-label, phase 2 trial.** *Lancet Oncol* 2014;15(12):1311-8.

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Gopal AK et al. **PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma.** *N Engl J Med* 2014;370(11):1008-18.

Kahl BS et al. **Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: Eastern Cooperative Oncology Group protocol E4402.** *J Clin Oncol* 2014;32(28):3096-102.

Leonard J et al. **CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma.** *Proc ASCO* 2012;Abstract 8000.

Prospective randomised multicenter study for therapy optimization (first line) of advanced progredient, low malignant non-Hodgkin lymphomas and mantle cell lymphomas. NCT00991211

Rummel MJ et al. **Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL) — 7 year updated results from the StiL NHL1 study.** *Proc ASH* 2014;Abstract 4407.

Rummel MJ et al. **Bendamustine plus rituximab followed by rituximab maintenance for patients with untreated advanced follicular lymphomas. Results from the StiL NHL 7-2008 trial (MAINTAIN trial).** *Proc ASH* 2014;Abstract 3052.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial.** *Lancet* 2013;381(9873):1203-10.

Significance of duration of maintenance therapy with rituximab in non-Hodgkin lymphomas (MAINTAIN). NCT00877214

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Julie M Vose, MD, MBA

Coiffier B et al. **Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.** *J Clin Oncol* 2012;30(6):631-6.

ECHELON-2: A comparison of brentuximab vedotin and CHP with standard-of-care CHOP in the treatment of patients with CD30-positive mature T-cell lymphomas. NCT01777152

Ellin F et al. **Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: A study from the Swedish Lymphoma Registry.** *Blood* 2014;124(10):1570-7.

Friedberg JW et al. **Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas.** *J Clin Oncol* 2014;32(1):44-50.

Horwitz S et al. **Belinostat in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL) subtype angioimmunoblastic T-cell lymphoma (AITL): Results from the pivotal BELIEF trial.** *Proc ICML* 2013;Abstract 153.

Horwitz SM et al. **Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin.** *Blood* 2014;123:3095-100.

Mak V et al. **Survival of patients with peripheral T-cell lymphoma after first relapse or progression: Spectrum of disease and rare long-term survivors.** *J Clin Oncol* 2013;31(16):1970-6.

O'Connor OA et al. **Phase III trial of brentuximab vedotin and CHP versus CHOP in the frontline treatment of patients (pts) with CD30+ mature T-cell lymphomas (MTCL).** *Proc ASCO* 2013;Abstract TPS8611.

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Odejide O et al. **A targeted mutational landscape of angioimmunoblastic T-cell lymphoma.** *Blood* 2014;123:1293-6.

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Pro B et al. **Three-year survival results from an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2013;Abstract 1809.

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Pro B et al. **Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study.** *J Clin Oncol* 2012;30:2190-6.

Savage KJ et al. **Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification.** *Ann Oncol* 2004;15(10):1467-75.

Schatz JH et al. **Targeted mutational profiling of peripheral T-cell lymphoma not otherwise specified highlights new mechanisms in a heterogeneous pathogenesis.** *Leukemia* 2015;29(1):237-41.

Vose J et al. **International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes.** *J Clin Oncol* 2008;26:4124-30.