Dissecting the Decision:

Documenting and Discussing the Clinical Practice Patterns of Hematologic Oncology Investigators in the Management of 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 chronic lymphocytic leukemia (CLL).

OVERVIEW OF ACTIVITY

An estimated 20,940 new cases of CLL will be diagnosed in the United States in 2018, with 4,510 deaths attributed to the disease. The clinical course of the disease and outcomes for patients vary widely, largely based on individual predictive and other risk factors. In recent years, the identification of cytogenetic abnormalities and their subsequent incorporation into traditional clinical staging systems has further refined clinicians' ability to determine patient prognosis. While risk stratification plays an important role in treatment decision-making, the disease remains incurable. Thus, despite the availability of numerous effective agents and regimens, the inevitable mortality has led many to seek new and better management approaches. To this end, and based on an improved understanding of the biology of CLL, a number of novel agents and strategies have proven successful and are already available for use in the clinic. However, with the many exciting advances that are rapidly occurring, a number of vexing questions and clinical challenges are simultaneously emerging.

These proceedings from a CME/CNE symposium held during the 2018 Pan Pacific Lymphoma Conference use an innovative strategy to formally document and present the perspectives, experiences and preferred treatment approaches of 25 lymphoma-specific investigators. 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 CLL with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recognize the incidence, prognostic significance and potential clinical implications of select biomarkers and chromosomal abnormalities (eg, del[17p], del[11q], TP53 and IGHV gene mutations) associated with a diagnosis of CLL, and use this information to develop evidence-based testing algorithms in general oncology practice.
- Individualize the selection of systemic therapy for patients with newly diagnosed CLL considering the patient's clinical presentation (eg, performance status, comorbidities), biomarker profile (eg, cytogenetics) and psychosocial status (eg, desire for active treatment).
- Appreciate the frequency with which biomarker transformation has been observed in patients with relapsed/refractory (R/R) CLL, and consider this information when developing care strategies for individuals experiencing disease progression.
- Review recent therapeutic advances and related FDA authorizations for patients with R/R CLL, and use this information to counsel patients regarding protocol and clinical therapy.
- Design a plan of care to recognize and manage side effects and toxicities associated with the use of existing and recently approved systemic therapies in the management of CLL to support quality of life and continuation of therapy.
- Assess the ongoing clinical trials evaluating novel investigational agents/regimens for CLL, and where applicable, refer eligible patients for trial participation or expanded access programs.

CME/CNE ACCREDITATION AND CREDIT DESIGNATION STATEMENTS

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the University of Nebraska Medical Center, Center for Continuing Education (UNMC CCE), University of Nebraska Medical Center College of Nursing Continuing Nursing Education (UNMC CON CNE) and Research To Practice.

PHYSICIANS: The University of Nebraska Medical Center, Center for Continuing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The University of Nebraska Medical Center, Center for Continuing Education designates this live activity for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NURSES: The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited with distinction as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is provided for 2.25 contact hours under ANCC criteria.

FOR SUCCESSFUL COMPLETION

CME: 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/Lymphomas18/CLL/CME**.

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CONTENT VALIDATION AND DISCLOSURES

It is the policy of the UNMC CCE and UNMC CON CNE to ensure balance, independence, objectivity and scientific rigor in all their educational symposia. All faculty, planners and managers participating in these activities are required to disclose any relevant financial relationship(s) they (or spouse/partner) have with a commercial interest that benefits the individual in any financial amount that has occurred within the past 12 months; and the opportunity to affect the content of CME/CNE about the products or services of the commercial interest. UNMC CCE, UNMC CON CNE and Research To Practice ensured that any conflicts of interest were resolved before the educational activity occurred.

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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MODERATOR — **Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, 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, Genomic Health Inc, Gilead Sciences Inc, Guardant Health, 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,

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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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Expiration date: August 2019

Select Publications

Neil Love, MD

Love N et al. **A biomarker-driven algorithm for sequencing of systemic therapy for metastatic NSCLC: A survey of 25 investigators.** Chicago Multidisciplinary Symposium in Thoracic Oncology 2017;**Abstract PS02.17**.

Matthew S Davids, MD, MMSc

Byrd JC et al. **The Bruton tyrosine kinase (Btk) Inhibitor ACP-196: Marked activity in relapsed/refractory CLL with a favorable safety profile.** *Blood* 2015;126(23):831.

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.

Fischer K et al. **Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: Updated results of the CLL8 trial.** *Blood* 2016;127(2):208-15.

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.

Landau DA et al. **Mutations driving CLL and their evolution in progression and relapse.** *Nature* 2015;526(7574):525-30.

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.

Rasi S et al. **Analysis of NOTCH1 mutations in monoclonal B-cell lymphocytosis.** *Haematologica* 2012;97(1):153-4.

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.

Rossi D et al. **Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia.** *Blood* 2014; 123(14):2139-47.

Rossi D et al. **Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia.** *Blood* 2013;121(8):1403-12.

Thompson PA et al. **Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia.** *Blood* 2016;127(3):303-9.

Zainuddin N et al. **TP53 mutations are infrequent in newly diagnosed chronic lymphocytic leukemia.** *Leuk Res* 2011;35(2):272-4.

Zenz T et al. **TP53 mutation and survival in chronic lymphocytic leukemia.** *J Clin Oncol* 2010;28(29):4473-9.

Prof John G Gribben, MD, DSc, FMedSci

Burger JA et al. **Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia.** *N Engl J Med* 2015;373(25):2425-37.

Eichhorst B et al. **First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): An international, open-label, randomised, phase 3, non-inferiority trial.** *Lancet Oncol* 2016;17(7):928-42.

Eichhorst B et al. **Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Ann Oncol* 2011;22(Suppl 6):vi50-vi54.

Fischer K et al. **Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: Updated results of the CLL8 trial.** *Blood* 2016;127(2):208-15.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.

Gribben JG. **How and when I do allogeneic transplant in CLL.** *Blood* 2018;132(1):31-9.

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.

Select Publications

Thompson PA et al. **Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia.** *Blood* 2016;127(3):303-9.

Thurmes P et al. **Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia.** *Leuk Lymphoma* 2008;49(1):49-56.

Jonathan W Friedberg, MD, MMSc

Anderson MA et al. **Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax.** *Blood* 2017;129(25):3362-70.

Byrd JC et al. **Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: Updated results from the phase 1/2 ACE-CL-001 study.** *Blood* 2017;130(Suppl 1):498.

Cheson BD et al. **Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia.** *J Clin Oncol* 2012;30(23):2820-2.

Hallek M et al. **Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines.** *Blood* 2008;111(12):5446-56.

Roberts AW et al. **Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia.** *N Engl J Med* 2016; 374(4):311-22.

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

Thomas J Kipps, MD, PhD

Burger JA et al. **Randomized trial of ibrutinib versus ibrutinib plus rituximab (Ib+R) in patients with chronic lymphocytic leukemia (CLL).** *Blood* 2017;130(Suppl 1):427.

Choi MY et al. **Phase I trial: Cirmtuzumab inhibits ROR1 signaling and stemness signatures in patients with chronic lymphocytic leukemia.** *Cell Stem Cell* 2018;22(6):951-9.

Choi M et al. **Durable and specific inhibition of ROR1 signaling associates with prolonged progression free survival in patients with chronic lymphocytic leukemia treated with cirmtuzumab.** *Blood* 2017;130(Suppl 1):829.

Flinn I et al. **Safety, efficacy and MRD negativity of a combination of venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia — Results from a phase 1b study (GP28331).** *Blood* 2017;130(Suppl 1):430.

Jain N et al. **Combined venetoclax and ibrutinib for patients with previously untreated high-risk CLL, and relapsed/refractory CLL: A phase II trial.** *Blood* 2017;130(Suppl 1):429.

Kipps TJ et al. **Chronic lymphocytic leukaemia.** *Nat Rev Dis Primers* 2017;3:16096.

Malta TM et al. **Machine learning identifies stemness features associated with oncogenic dedifferentiation.** *Cell* 2018;173(2):338-54.

Michallet A et al. **Phase II, multicenter trial, exploring "Chemo-Sparing" strategy associating obinutuzumab+ibrutinib followed by a MRD driven strategy, in previously untreated symptomatic medically fit chronic lymphocytic leukemia patients (CLL): Preliminary results of the induction phase of the Icll-07 Filo study.** *Blood* 2017;130(Suppl 1):497.

Wierda WG et al. **Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL).** *Proc ASCO* 2018;**Abstract 7502**.

Woyach J et al. **Acalabrutinib with obinutuzumab in relapsed/refractory and treatment-naïve patients with chronic lymphocytic leukemia: The phase 1b/2 ACE-CL-003 study.** *Blood* 2017;130(Suppl 1):432.

Yu J et al. **Cirmtuzumab inhibits Wnt5a-induced Rac1 activation in chronic lymphocytic leukemia treated with ibrutinib.** *Leukemia* 2017;31(6):1333-9.