



Key ASH Presentations

Issue 6, 2012

**Phase II Trial of Lenalidomide/Rituximab
+/- Dexamethasone in Relapsed/
Refractory B-Cell Lymphomas or MCL
Resistant to Rituximab**

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Consider the inclusion of single-agent romidepsin in the treatment algorithm for relapsed or refractory peripheral T-cell lymphoma.
- Integrate new and existing therapeutic strategies into the best-practice management of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with relapsed/refractory mantle-cell lymphoma.
- Recall new data with investigational agents demonstrating promising activity in non-Hodgkin lymphomas.

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 1.25 *AMA PRA Category 1 Credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2012/6/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 potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent 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 real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Steven M Horwitz, MD
Assistant Attending
Lymphoma Service
Division of Hematologic Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Advisory Committee: Allos Therapeutics, Celgene Corporation;
Consulting Agreements: Allos Therapeutics, Bristol-Myers Squibb Company, Celgene Corporation, Kyowa Hakko Kirin Co Ltd, Seattle Genetics, Spectrum Pharmaceuticals Inc; Paid Research: Allos Therapeutics, Celgene Corporation, Kyowa Hakko Kirin Co Ltd, Millennium: The Takeda Oncology Company, Seattle Genetics, Spectrum Pharmaceuticals Inc.

Brad S Kahl, MD
Associate Professor
Director, Lymphoma Service
University of Wisconsin School of
Medicine and Public Health
Associate Director for Clinical Research
UW Carbone Cancer Center
Madison, Wisconsin

Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology, GlaxoSmithKline, Millennium: The Takeda Oncology Company.

Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

Advisory Committee: Cephalon Inc, Genentech BioOncology, Seattle Genetics; Paid Research: Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

Owen A O'Connor, MD, PhD
Professor of Medicine and Developmental Therapeutics
Director, Center for Lymphoid Malignancies
Columbia University Medical Center
College of Physicians and Surgeons
NewYork-Presbyterian Hospital
New York, New York

Advisory Committee: Allos Therapeutics, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Onyx Pharmaceuticals Inc, Spectrum Pharmaceuticals Inc; Consulting Agreements: Allos Therapeutics, Celgene Corporation, Millennium: The Takeda Oncology Company; Paid Research: Millennium: The Takeda Oncology Company.

EDITOR — 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: Abbott Laboratories, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent 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 Allos Therapeutics, Celgene Corporation, Genentech BioOncology/ Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Last review date: March 2012
Expiration date: March 2013

To go directly to slides and commentary for this issue, [click here](#).

This past Friday 8 clinical investigators ventured to Miami for our annual post-ASH lymphoma Think Tank. Over the course of more than 6 fascinating hours together we focused on a multitude of topics and as always recorded the proceedings, which will be available as an enduring activity in the coming months. While our engineers are busy de-umming (our little secret) and editing the audio, we thought we would hold you over with a taste of some of the new ASH NHL papers that were fodder for discussion and debate during Friday's lymphoma extravaganza.

1. [Lenalidomide/rituximab](#)

The so-called R-squared regimen of the immunomodulatory agent lenalidomide (len) and rituximab (R) has generated considerable excitement among investigators, and at ASH we saw the results from a Phase II trial evaluating this combination alone or with dexamethasone for patients with relapsed indolent NHL or mantle-cell lymphoma (MCL) considered to be resistant to R. Of the 48 patients treated on the trial more than a third had a response, and the median progression-free survival was 18 months. These findings have raised hopes that len might help overcome R resistance and that in select populations such as the elderly this combination might become an alternative to aggressive treatment of relapsed disease — for example, with autologous stem cell transplant (ASCT).

2. [Two papers on MCL](#)

Another ASH NHL highlight was the presentation of a Phase II study of PCI-32765, an oral irreversible Bruton's tyrosine kinase inhibitor, as a single agent in relapsed/refractory MCL. The results are compelling, as two thirds of the 39 patients in the study had objective responses and 35 remain on treatment. Importantly, none stopped therapy due to toxicity. Many investigators now have patients in their practices on trials who have experienced obvious prolonged benefit with this agent, and as a result significant excitement surrounds it and other small molecules, like the PI3 kinase inhibitor CAL-101 that is also under active investigation in a variety of NHL subtypes.

The rarity of MCL has made the definition of treatment benefits a challenge, and another important study reported at ASH attempted to better establish the effects of R in this disease. This effort from the UK evaluated the combination of fludarabine and cyclophosphamide with or without R, and while a high rate of infection was observed in these patients receiving fludarabine, substantial improvements in response rate and an almost doubling of progression-free survival reinforced the value of adding the CD20 antibody, which is now used routinely up front and often as maintenance treatment.

3. Two studies of diffuse large B-cell lymphoma (DLBCL)

Previous research with dose-adjusted EPOCH with R has shown promising results in untreated DLBCL, and this [Phase IV trial](#) of 81 patients with poor-prognosis disease (age-adjusted IPI of 1 or higher) reported an encouraging 62% 5-year progression-free survival rate. An ongoing Phase III Intergroup trial is comparing EPOCH-R to R-CHOP.

One of the biggest disappointments at ASH came from the much-awaited [Phase III SWOG study](#) comparing conditioning R/BEAM (carmustine, etoposide, cytarabine, melphalan) to ¹³¹I-tositumomab/BEAM for patients with DLBCL about to undergo ASCT. The trial results were flat-out negative, confounding the positive findings observed in the Phase II setting and forcing investigators back to the drawing board to look at higher doses of radioimmunotherapy as pretransplant conditioning.

4. [Two papers on T-cell lymphoma](#)

At ASH Dr Bertrand Coiffier presented an update of the Phase II pivotal study evaluating the selective inhibitor of histone deacetylase romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL). This trial, which led to the FDA approval in this setting, evaluated 130 patients across PTCL subgroups, and these findings reveal higher response rates among individuals with the most common forms of the disease. This suggests that romidepsin may perhaps have more activity in common PTCL subtypes than initial data suggested.

In cutaneous T-cell lymphoma we saw the results of a Phase II trial investigating the interesting sequence of pegylated liposomal doxorubicin (PLD) — which has been shown to have high response rates and is known to concentrate in the skin — followed by the synthetic retinoid bexarotene (Bex). Perhaps because the study selected for patients with more aggressive disease, a 41% response rate (lower than reported in other trials) was observed with PLD and Bex did not increase the rate or duration of response. With the current shortage of PLD, not many patients are being treated with this agent.

Next up on this ASH series we go back to multiple myeloma and new reports on effective long-term disease control in older patients on continuing therapy.

Neil Love, MD

[Research To Practice](#)

Miami, Florida

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

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

This email was sent to you by Dr Neil Love and Research To Practice. To unsubscribe from future emails in this series, [click here](#). To unsubscribe from all email communications, including CME/CNE activities sent by Research To Practice, [click here](#).

To update your information on our current distribution lists, [click here](#).

Phase II Trial of Lenalidomide/Rituximab +/- Dexamethasone in Relapsed/Refractory B-Cell Lymphomas or MCL Resistant to Rituximab

Presentations discussed in this issue

Ahmadi T et al. **Phase II trial of lenalidomide - rituximab +/- dexamethasone in relapsed or refractory indolent B-cell or mantle cell lymphomas resistant to rituximab.** *Proc ASH 2011*; **Abstract 266**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Owen A O'Connor, MD, PhD (2/3/12)

Phase II Trial of Lenalidomide- Rituximab +/- Dexamethasone in Relapsed or Refractory Indolent B-Cell or Mantle Cell Lymphomas Resistant to Rituximab

Ahmadi T et al.

Proc ASH 2011; Abstract 266.

Research
To Practice®

Background

- Single-agent rituximab has demonstrated activity in patients with relapsed low-grade or follicular lymphoma (*JCO* 1998;16:2825).
- However, approximately 50% of patients may not respond to initial rituximab treatment and most will become resistant to rituximab.
- Preclinical studies suggest that lenalidomide may act synergistically with rituximab to overcome clinical resistance to rituximab.
- **Objective:**
 - Test the efficacy of lenalidomide combined with rituximab in patients with relapsed or refractory indolent B-cell or mantle-cell lymphoma (MCL).

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

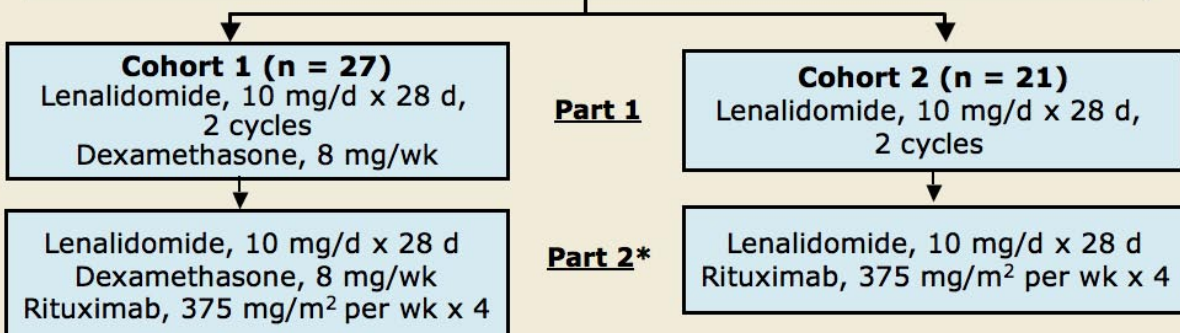
Research
To Practice®

Trial Design

Eligibility (n = 48)

Relapsed/refractory indolent B-cell lymphoma or MCL

Rituximab refractory: Lack of response or progression ≤ 6 months of standard course of rituximab monotherapy or rituximab-based regimen



* Only patients with stable or responsive disease after Part 2 continued with treatment of lenalidomide +/- dexamethasone until disease progression.

- Response assessments were performed after Part 1 and after Part 2.

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Research
To Practice®

Response Rates (Evaluable Patients, n = 40)

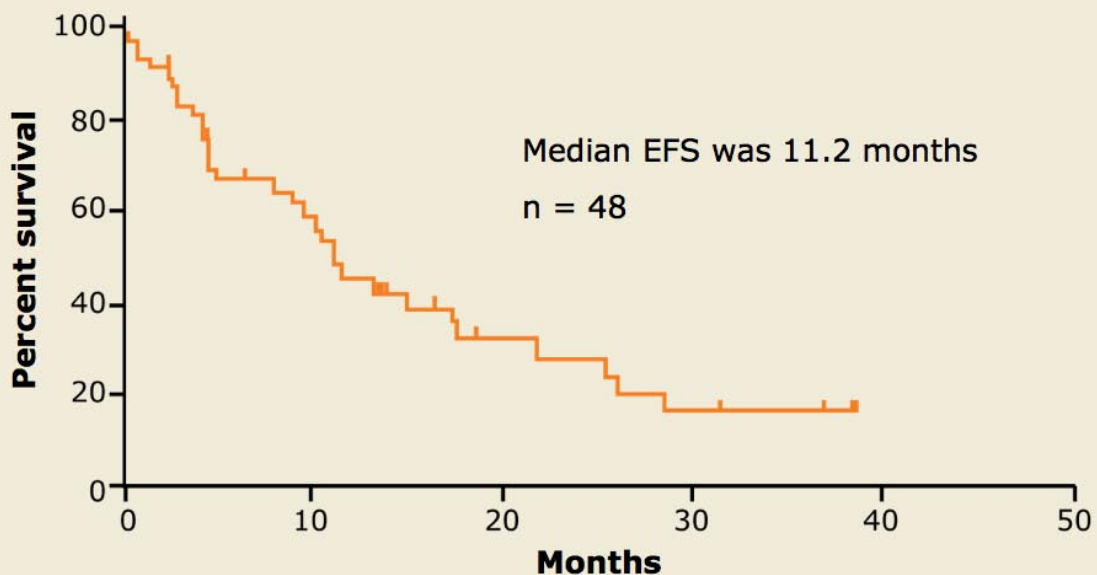
Response	Cohort 1 (n = 24)		Cohort 2 (n = 16)	
	Part 1	Part 2	Part 1	Part 2
Complete response (CR)	17%	33%	19%	50%
Partial response (PR)	13%	25%	19%	25%
Stable disease (SD)	63%	33%	44%	19%
Progressive disease (PD)	8%	8%	19%	6%
Overall response rate (ORR)	29%	58%	37%	75%

- For all evaluable patients (n = 40), ORR was 33% (Part 1) and 65% (Part 2).
- ORR by histology (after completion of Part 2): 67% (FL, n = 24); 60% (MCL, n = 10); 75% (SLL, n = 4); 50% (MZL, n = 50).

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Research
To Practice®

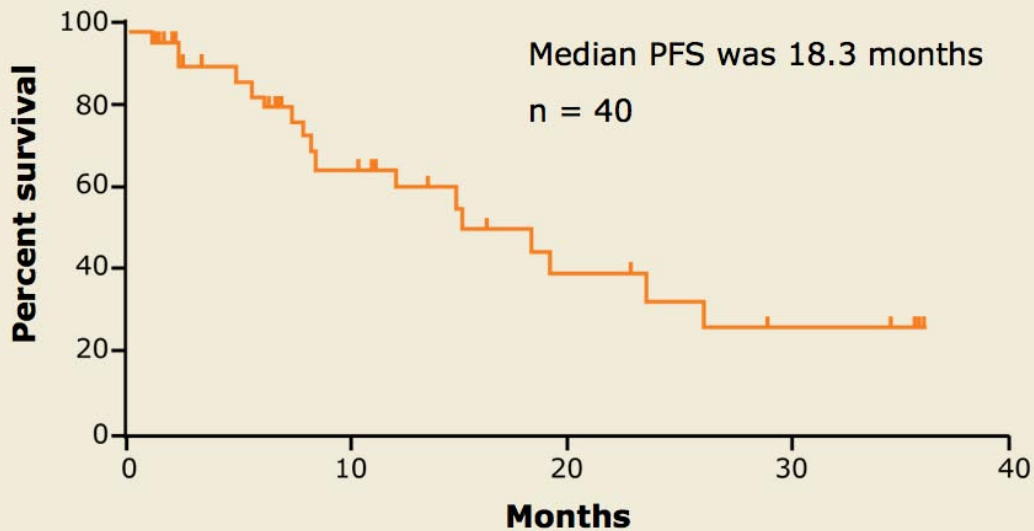
Event-Free Survival (EFS) Intent to Treat



With permission from Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Research
To Practice®

Progression-Free Survival (PFS) from Last Dose of Rituximab



With permission from Ahmadi T et al. *Proc ASH 2011*;Abstract 266.

Research
To Practice®

Selected Adverse Events

Event, n	Cohort 1 (n = 27)	Cohort 2 (n = 18)
Fatigue	10	3
GI complaint	8	6
Tumor flare	5	6
Rash	4	6
Neutropenia	4	2
Neuropathy	3	3
Anemia	2	—
Leukopenia	2	—
Weight loss	2	—
Periorbital edema	—	2

Patients with dose interruptions: 14.8% (cohort 1); 50% (cohort 2), $p = 0.02$.

Ahmadi T et al. *Proc ASH 2011*;Abstract 266.

Research
To Practice®

Author Conclusions

- The combination of lenalidomide with low-dose dexamethasone and a 4-week course of rituximab produced a high ORR with durable responses (data not shown) in patients with rituximab-resistant small B-cell lymphoma.
- The response rate appears to improve following the addition of rituximab to lenalidomide-dexamethasone, although a delayed response to lenalidomide-dexamethasone is possible for some patients.
- It is possible that the “immunomodulatory” effects of lenalidomide may overcome resistance to rituximab in some patients.

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Research
To Practice®

Investigator Commentary: Phase II Trial of Lenalidomide-Rituximab with or without Dexamethasone in B-Cell Lymphoma or MCL

Lenalidomide has emerged as a promising drug for different types of non-Hodgkin lymphoma, including follicular lymphoma and MCL, especially in combination with rituximab. A registration-directed study is evaluating the potential approval of lenalidomide for patients with MCL. This study uses an interesting regimen. Presently, I use lenalidomide for patients, including a fair number of elderly patients, with relapsed or refractory MCL. Some have been receiving lenalidomide (10 mg/d, without breaks) for 1 to 2 or more years, and the drug is well tolerated. When administered at 25 mg/d for shorter periods, we find that lenalidomide is not as well tolerated in many of the elderly patients with MCL. Therefore, combinations such as lenalidomide with rituximab and dexamethasone may be particularly good for elderly patients with MCL who may not be great candidates for other combination therapies, let alone autologous stem cell transplant.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

Research
To Practice®