



POST-ASH Issue 6, 2013

EMERGE: A Phase II Study of Single-Agent Lenalidomide in Relapsed or Refractory MCL

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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

- Recall emerging clinical research data on the efficacy and safety of lenalidomide in combination with R-CHOP for the treatment of diffuse large B-cell lymphoma (DLBCL) or as single-agent therapy for bortezomib-refractory mantle-cell lymphoma (MCL).
- Compare and contrast the benefits and risks of bendamustine/rituximab versus R-CHOP and R-CVP in the first-line treatment of advanced indolent non-Hodgkin lymphoma or MCL.
- Evaluate the efficacy and safety of the novel agent ibrutinib in relapsed/refractory DLBCL and MCL.

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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:

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Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; **Contracted Research:** Abbott Laboratories, Cephalon Inc, Genentech BioOncology.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva 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: May 2013

Expiration date: May 2014

More ASH lymphoma papers... and another perspective on the disease from a very unusual patient

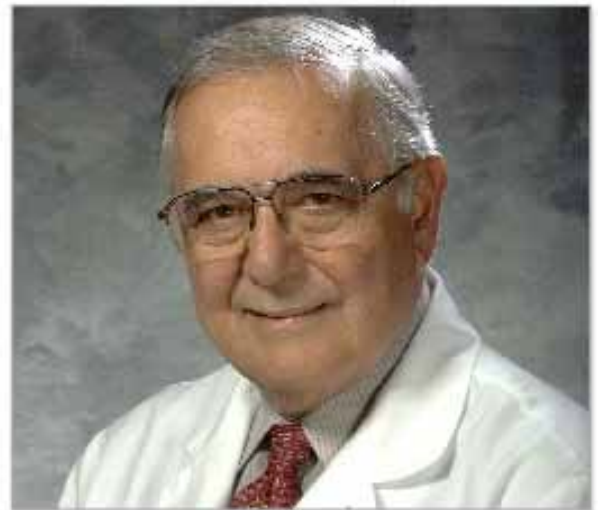
To go directly to slides and commentary for this issue, [click here](#).

In-depth interviews with clinical investigators occasionally veer into unexpected territory, and this was the case last fall during a fascinating conversation I had with lung cancer researcher Dr David Carbone. Like many similar sessions, our discussion focused in part on reviewing instructive personal cases, and during one in particular in which the patient required a laparoscopic thoracotomy, Dr Carbone casually mentioned that he himself had once undergone that procedure. My ears twitched to attention and in an instant we were deep inside an amazing and profound story.



David Carbone, MD, PhD

David's father was the late Dr Paul Carbone, the legendary founder of the Eastern Cooperative Oncology Group and a former pioneering clinical investigator who along with others at the NCI and then the University of Wisconsin helped develop new chemotherapy regimens for breast cancer, Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL). Following in his father's inspiring footsteps, David tracked through Johns Hopkins Medical School and then the NCI, after which he joined the medical oncology faculty at Vanderbilt. In 1999, at the age of 40, while shaving he noticed that the veins in his neck were markedly distended, which he self-diagnosed as superior vena cava syndrome. The cause he soon



Paul Carbone, MD

learned was mediastinal large cell lymphoma, and with 4 children under the age of 14 the younger Dr Carbone accelerated into action. Fortunately, the regimen developed in part by his father, CHOP (rituximab was not quite on board then), along with radiation therapy did the trick and he remains free of recurrence to this day (and recently joined the faculty of the Ohio State Buckeyes).

However, while the end result was a positive one, the experience affected him deeply. After hearing about chemotherapy all his life and prescribing it for many years, David was shocked by its debilitating effects, including “end-to-end” mucositis along with profound fatigue and nausea mixed in with an uncomfortable postop recovery. This eloquent man becomes virtually speechless in trying to describe the suffering and despair engendered by CHOP, although like others who have traveled this difficult path, the experience instantly rearranged his priorities, and one of his fondest memories took place a year after finishing treatment when this former workaholic took off for 2 weeks to visit Sicily with his dad, mom and sister. ([Click here for more of this story.](#))

Thinking back on this conversation and Dr David Carbone’s real-life perspectives, one could expect that he and CHOP survivors everywhere will welcome the day that chemotherapy becomes an afterthought in lymphoma management, and while we may not yet be there, the current evolution of systemic treatment toward selective novel biologic agents — some of which are noteworthy for impressive efficacy and a relative lack of side effects — is in full swing and offering more promise than ever before. Here are a few of the most compelling ASH reports in that regard:

1. “R-squared CHOP” in DLBCL and more on lenalidomide (len) alone in mantle-cell lymphoma (MCL)

The R-squared regimen of len/rituximab (lenR) has generated considerable excitement in early trials of chronic lymphocytic leukemia and follicular lymphoma (FL), and the known single-agent activity of len in DLBCL led to a natural interest in partnering this immunomodulatory agent with standard R-CHOP. At ASH we saw **2 important Phase II trials** demonstrating impressive overall response rates (95 of 100 patients combined) with this regimen. Of perhaps greater interest, when the results were analyzed by cell of origin, the addition of len appeared to be more effective for patients with activating B-cell (ABC) versus germinal center B-cell-like DLBCL.

While these 2 major DLBCL molecular subtypes were identified more than 10 years ago, up until now this information has been more theoretical than practical. However, a new Intergroup trial (ECOG-E1412) randomly assigning patients with previously untreated DLBCL to R-CHOP or R-squared CHOP will mandate that all patients have their tumors genotyped for cell of origin. The results will be analyzed to definitely assess whether cell of origin is a useful predictive factor.

Another related ASH paper by Dr Andre Goy helped to expand our knowledge base by confirming the activity of len monotherapy in relapsed/refractory MCL. These results from the Phase II EMERGE trial documented a 28% objective response rate for heavily pretreated patients and may help pave the way for this useful agent to be approved in this setting where more options are sorely needed.

2. More on ibrutinib in DLBCL and MCL

A presentation by the NCI's Dr Wyndham Wilson revealed impressive response rates in relapsed/refractory DLBCL with this Bruton tyrosine kinase inhibitor as monotherapy. Importantly, and further strengthening the case for genotyping, benefit was generally confined to patients with the ABC subtype, of whom partial responses were seen in 12 of 29 compared to only 1 of 20 patients with the germinal center B-cell-like subtype of DLBCL. While these findings clearly do not yet have implications for clinical practice, it seems certain that they will play a significant role in informing future research paradigms.

Similarly, in MCL we saw an **update from a Phase II study** originally presented at ASH 2011 further confirming the unprecedented objective response rate (68%) with ibrutinib monotherapy in relapsed/refractory disease. Needless to say, there is extensive enthusiasm for this agent, which has recently been designated as a **"breakthrough therapy"** by the FDA.

3. Bendamustine/rituximab (BR) as induction therapy in FL and MCL

As reflected by the central role of the BR backbone in current Phase III FL and MCL cooperative group trials, it can be surmised that this novel regimen has largely replaced R-CHOP and R-CVP in the minds of many. This trend got started at ASH 2009 when we were treated to the first results from the German StiL trial in which BR outperformed R-CHOP, and at ASH 2012 Dr Ian Flinn presented **data from the Bright study**, another major related Phase III effort comparing BR to R-CHOP or R-CVP as first-line therapy for FL and MCL. In this instance BR was found to be roughly equivalent in FL, with a modest advantage observed for patients with MCL, and while these results are not likely to shift practice one way or the other, they do confirm that BR is at least as effective as R-CHOP and provide additional perspectives on the relative tradeoffs of these regimens.

Related to the choice of induction treatment, **an interesting Phase II ECOG report** in MCL focused on the VcR-CVAD regimen, which incorporates bortezomib, cyclophosphamide and rituximab (VcR) with the modified hyper-CVAD chemotherapy backbone without methotrexate/cytarabine. Overall the treatment was well tolerated with high response rates (94%). However, it seems more likely that the role of bortezomib as part of up-front therapy will be defined by the ongoing Phase II

ECOG-E1411 trial of BR alone or with bortezomib followed by R maintenance alone or with len for patients with previously untreated MCL.

Next, on the final issue of this series, we check out ASH papers in chronic myelogenous leukemia, for which the never-ending avalanche of new data sets has resulted in 3 newly approved agents in the past year.

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EMERGE: A Phase II Study of Single-Agent Lenalidomide in Relapsed or Refractory MCL

Presentation discussed in this issue

Goy A et al. **Phase II multicenter study of single-agent lenalidomide in subjects with mantle cell lymphoma who relapsed or progressed after or were refractory to bortezomib: The MCL-001 "EMERGE" study.** *Proc ASH 2012*; **Abstract 905**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Brad S Kahl, MD (1/17/13)

Phase II Multicenter Study of Single-Agent Lenalidomide in Subjects with Mantle Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: The MCL-001 Study (EMERGE™ Trial)

Goy A et al.

Proc ASH 2012; Abstract 905.

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Background

- Relapsed/refractory mantle-cell lymphoma (MCL) is characterized by frequent chemoresistance and limited treatment options.
- There is no standard therapy for patients for whom bortezomib (BTZ) has failed.
- Phase II studies have shown activity and tolerability with single-agent lenalidomide in relapsed/refractory aggressive non-Hodgkin lymphomas, including MCL (*Ann Oncol* 2011;22:1622, *Br J Haematol* 2009;145:344).
- **Study objective:** To assess the safety and efficacy of single-agent lenalidomide in patients with MCL that has relapsed or is refractory to BTZ.

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Phase II EMERGE Study Design

Eligibility (N = 134)

- MCL diagnosis reviewed by central pathology
- Disease progression on prior anthracycline (or mitoxantrone), cyclophosphamide, rituximab, BTZ
- BTZ failure: Relapsed/progressed ≤ 12 mo from last dose after CR/PR or refractory with $< PR$ after ≥ 2 cycles

Lenalidomide:
25 mg, d1-21, q28d*

* Until disease progression or unacceptable toxicity, CT every 2 cycles; follow-up CT every 90 d

Aspirin or low-molecular-weight heparin prophylaxis for patients at high risk

Primary endpoints: Overall response rate and duration of response

Secondary endpoints: CR, PFS, TTP, OS and safety

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Response to Lenalidomide

Response (n = 134)	Central review	Investigator review
Overall response rate*	28%	32%
CR/CRu	8%	16%
PR	20%	16%
Stable disease	29%	27%
Progressive disease	26%	32%
Median DOR	16.6 mo	18.5 mo
Median DOR for CR/CRu	16.6 mo	26.7 mo

* No response assessments available for 23 pts (central review) and 12 pts (investigator review)

- Maximum DOR was 29+ months at data cutoff

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Efficacy of Lenalidomide

Efficacy parameter (n = 134)	Central review	Investigator review
Median time to response	2.2 mo	2.0 mo
Median time to CR/CRu	3.7 mo	5.6 mo
Median PFS	4.0 mo	3.8 mo
Median OS*	19.0 mo	

* Median follow-up = 9.9 months

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Efficacy Subgroup Analysis (Central Review)

Characteristics	ORR	Median DOR
High MIPI (n = 39)	26%	7.7 mo
High tumor burden* (n = 77)	29%	14.8 mo
Bulky disease [†] (n = 44)	30%	14.8 mo
Refractory to BTZ (n = 81)	27%	20.5 mo
Refractory to last prior therapy (n = 74)	27%	26.7 mo
Prior high-dose or high-intensity treatment (n = 44)	27%	16.7 mo

* At least 1 lesion ≥ 5 cm in diameter or at least 3 lesions ≥ 3 cm in diameter by central radiology review

[†] At least 1 lesion ≥ 7 cm by central radiology review

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Select Adverse Events

Adverse event (n = 134)	Overall	Grade 3/4
Hematologic		
Neutropenia	49%	43%
Thrombocytopenia	36%	27%
Anemia	31%	11%
Leukopenia	15%	7%
Febrile neutropenia	6%	7%
Nonhematologic		
Fatigue	34%	7%
Diarrhea	31%	6%

Overall incidence of other AEs: Tumor flare reaction (Grade 1/2): 10%; deep vein thrombosis: 4%; pulmonary embolism: 2%; second primary malignancy: 5%

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Author Conclusions

- The EMERGE trial confirmed lenalidomide efficacy with an ORR of 28% (CR/CRu 8%); median DOR 16.6 months.
- These results were obtained in a population with heavily pretreated MCL: Median 4 prior therapies (range, 2-10), two thirds refractory to BTZ, more than half with high tumor burden, one third with bulky disease and one third received prior transplant (data not shown).
- Safety profile was manageable and consistent with other studies of lenalidomide in non-Hodgkin lymphoma.
- Lenalidomide demonstrated rapid (median time to response, 2 months) and durable efficacy in patients with MCL for whom prior therapies that included BTZ had failed.

Goy A et al. *Proc ASH* 2012;Abstract 905.

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Investigator Commentary: Phase II EMERGE Study of Lenalidomide in Relapsed/Refractory MCL

EMERGE is a multicenter, registration trial investigating single-agent lenalidomide in relapsed/refractory MCL. The results of this study will determine whether lenalidomide receives FDA approval in MCL.

The overall response rate to single-agent lenalidomide was 28%, which is respectable. The response rates are not as exciting in the ibrutinib era where responses in the 50% to 70% range are being observed in relapsed MCL. The progression-free survival of 4 months is not impressive, but the median duration of response was approximately 17 months, which suggests that in patients who do respond, the responses are durable.

Toxicities were similar to what had been previously observed with lenalidomide and included neutropenia, thrombocytopenia and a low rate of venous thromboembolic disease.

My hope is that lenalidomide does receive approval in this setting. MCL is incurable, and we need more treatment options for patients with this disease.

Interview with Brad S Kahl, MD, January 17, 2013