



**POST-ASH** Issue 6, 2013

# Interim Results of a Phase II Study of Ibrutinib 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:

Brad S Kahl, MD  
Skoronski Chair of Lymphoma Research  
Associate Professor  
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Madison, Wisconsin

**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

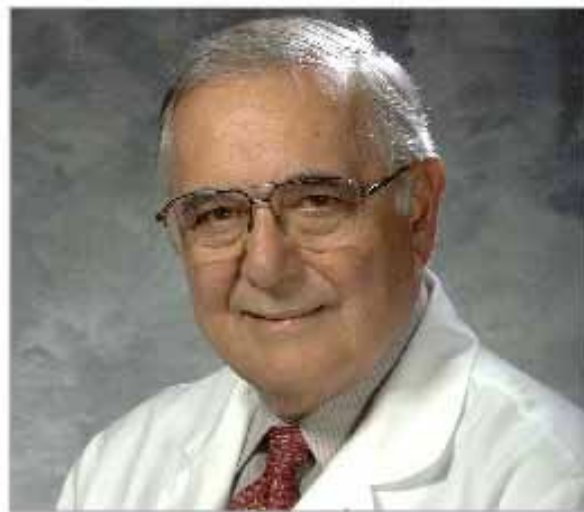
To go directly to slides and commentary for this issue, [click here](#).

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



# **Interim Results of a Phase II Study of Ibrutinib in Relapsed or Refractory MCL**

**Presentation discussed in this issue**

Wang M et al. **Interim results of an international, multicenter, Phase 2 study of Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), in relapsed or refractory mantle cell lymphoma (MCL): Durable efficacy and tolerability with longer follow-up.** *Proc ASH 2012*; **Abstract 904**.

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

## **Interim Results of an International, Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Relapsed or Refractory Mantle Cell Lymphoma (MCL): Durable Efficacy and Tolerability with Longer Follow-Up**

**Wang M et al.**

*Proc ASH 2012*; Abstract 904.

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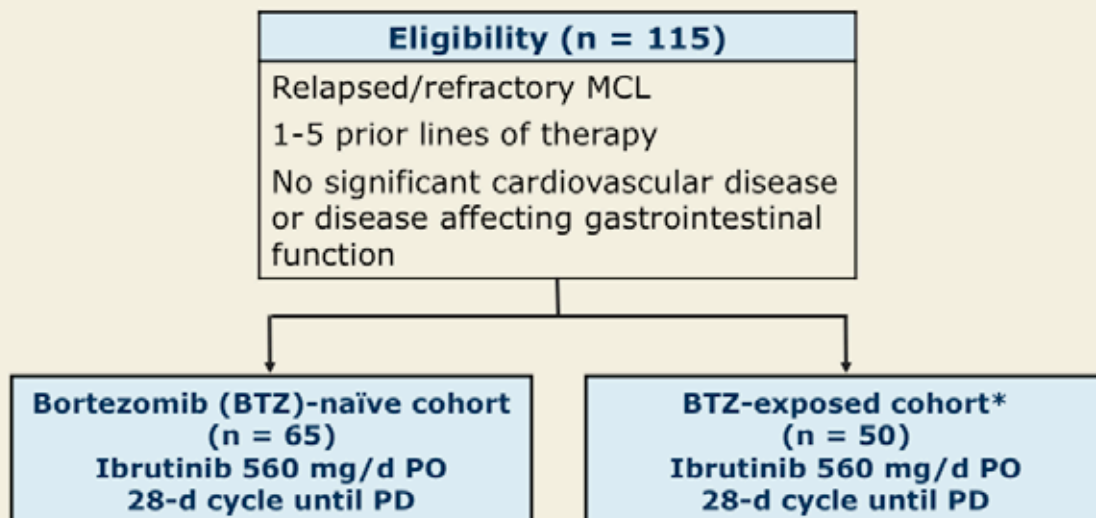
## Background

- Ibrutinib is an orally available BTK inhibitor that induces apoptosis and inhibits cellular migration and adhesion in malignant B cells.
- Preliminary results from the Phase II PCYC-1104-CA trial demonstrated that ibrutinib produced rapid nodal responses, including complete responses, in patients with relapsed or refractory MCL (*Proc ASH* 2011;Abstract 442).
- Treatment with ibrutinib was also associated with the inhibition of MCL cell chemotaxis and adherence (*Proc ASH* 2011;Abstract 954).
- **Study objective:** To provide updated PCYC-1104-CA interim analysis results of the efficacy and safety of single-agent ibrutinib in previously treated MCL.

Wang M et al. *Proc ASH* 2012;Abstract 904.

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## PCYC-1104-CA: Phase II Trial Design



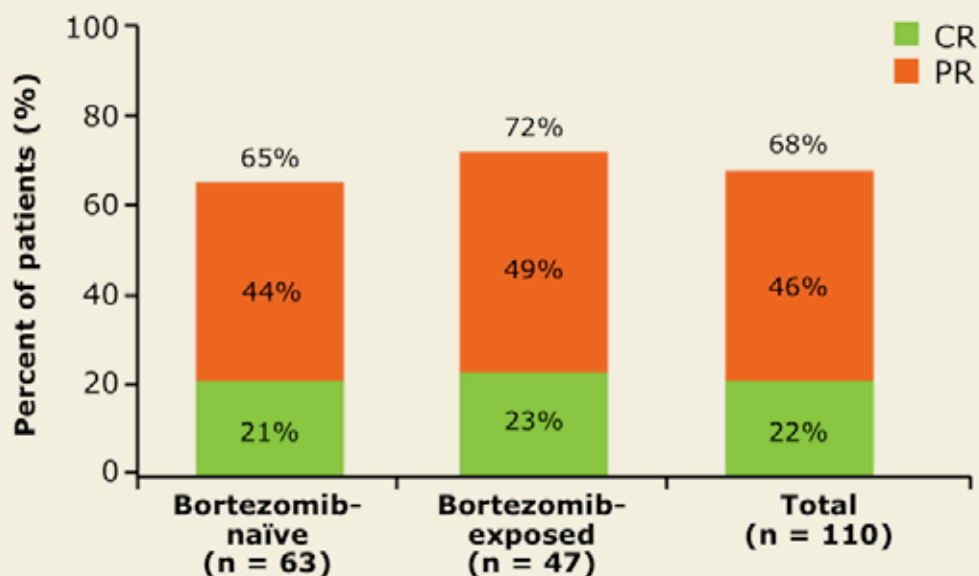
\* ≥2 cycles

Wang M et al. *Proc ASH* 2012;Abstract 904.

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## Best Response



Efficacy population, n = 110. Median follow-up: 9.2 mo

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## Time to Response (Phenomenon of Incremental Response)

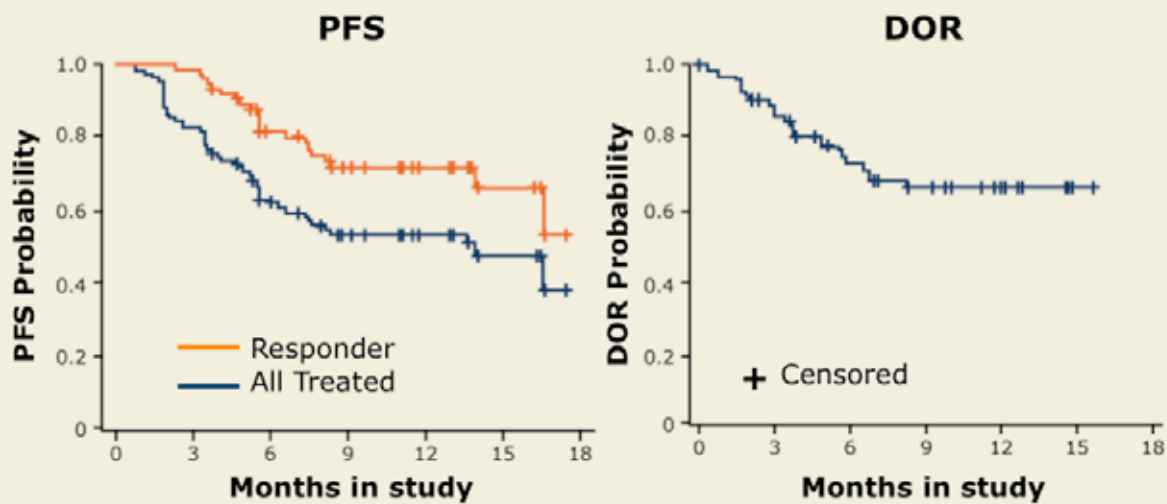
Response	Bortezomib naïve (n = 63)	Bortezomib exposed (n = 47)	Total (n = 110)
<b>Time to PR</b>			
N	37	31	68
Median	1.9 mo	1.8 mo	1.9 mo
Range	1.4-8.1 mo	1.5-9.1 mo	1.4-9.1 mo
<b>Time to CR</b>			
N	13	11	24
Median	5.6 mo	3.9 mo	5.5 mo
Range	1.7-16.4 mo	1.7-11.0 mo	1.7-16.4 mo

PR = partial response; CR = complete response

Wang M et al. *Proc ASH* 2012;Abstract 904.

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## Progression-Free Survival (PFS) and Duration of Response (DOR)

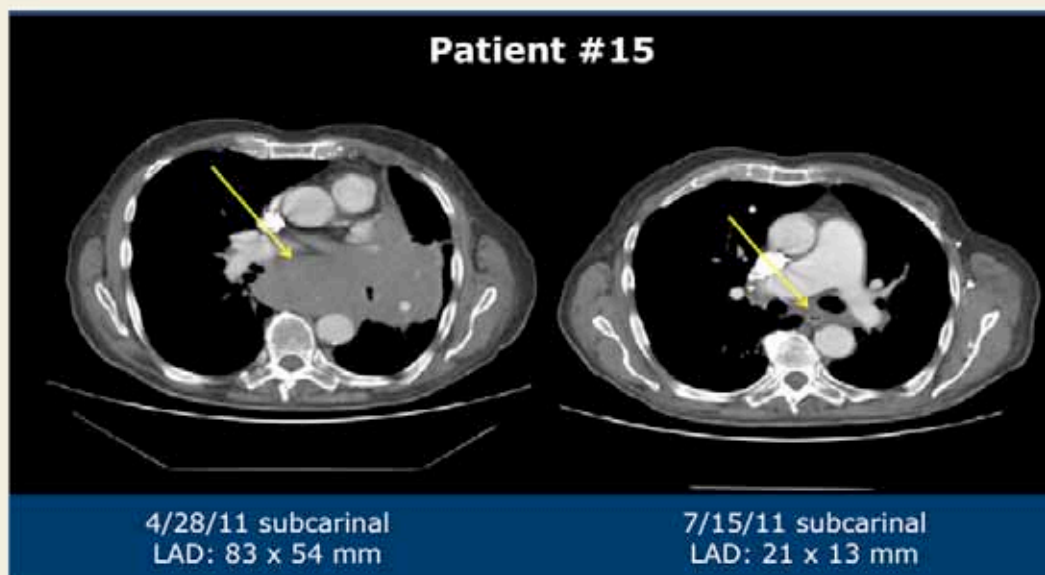


<b>All Treated Population</b>	<b>111</b>	<b>All Responded Population</b>	<b>75</b>
Median PFS (CI 95%) months	13.9 (6.64, NR)	Median DOR (CI 95%) months	NR (NR, NR)

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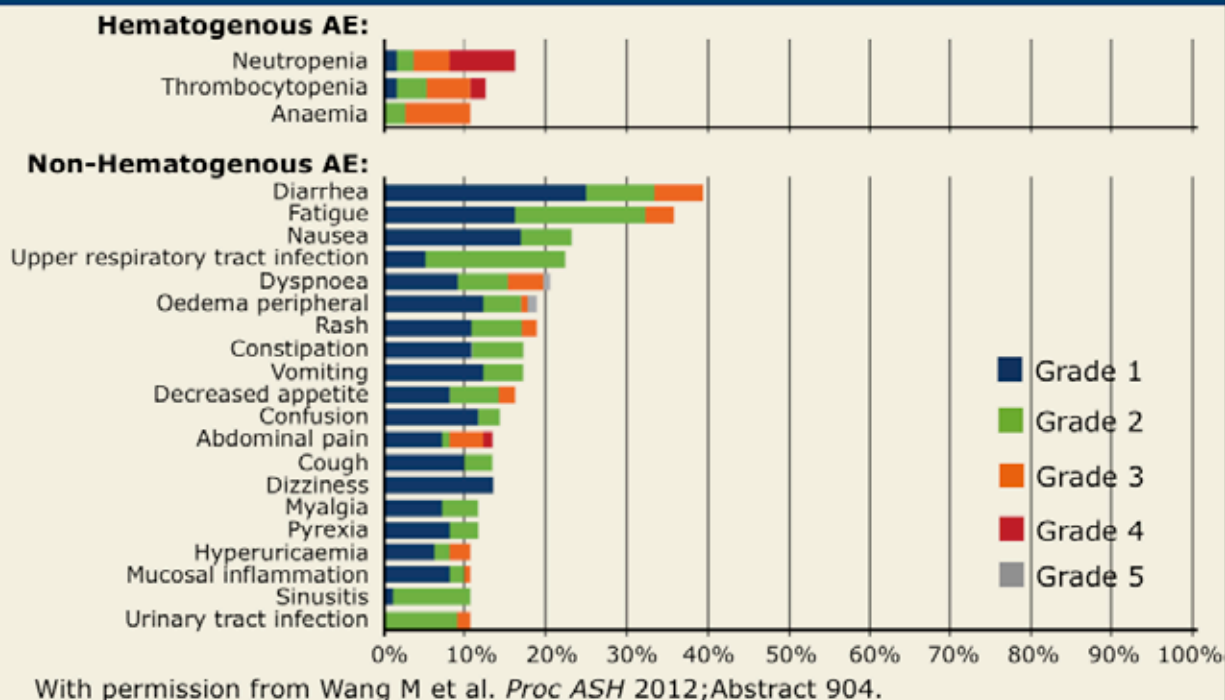
## Case Report: Response After 2 Cycles of Ibrutinib



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## Adverse Events (AEs) in >10% of Patients Regardless of Cause



## Author Conclusions

- Ibrutinib demonstrated an unprecedented single-agent overall response rate and a high complete response rate in relapsed/refractory MCL.
- Responses were durable: Median duration of response not reached, median PFS 13.9 months.
- Response improved with longer follow-up with the phenomenon of "incremental response."
- Ibrutinib has a favorable safety profile and is well tolerated. The treatment-emergent AEs were consistent with safety data previously reported.
- Additional studies have been initiated in multiple clinical settings in MCL.

Wang M et al. *Proc ASH 2012*;Abstract 904.

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### **Investigator Commentary: Interim Results of a Phase II Study of Ibrutinib in Relapsed or Refractory MCL**

This is a report of the results from a multicenter, Phase II study of single-agent ibrutinib for 115 patients with relapsed/refractory MCL. Similar to the data presented in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), ibrutinib produced fantastic responses in MCL. In this cohort of patients with MCL, the ORR was about 70%, and the durability of response was impressive. At 12 months, about 60% of patients were still experiencing disease remission.

In my opinion, the PFS curves across different disease histologies are interesting. The responses to ibrutinib appear to be most durable in CLL/SLL, with the PFS curves holding near the top. In MCL, however, the responses seem to be dropping off somewhat faster. Nonetheless, response to ibrutinib is impressive in MCL. I believe ibrutinib therapy yields better results in comparison to PI3-kinase inhibitors in MCL in terms of response rates and duration of response. Based on this study, it is fair to say that ibrutinib is an extremely impressive drug. Right now, bortezomib is the only agent approved for relapsed disease. About 7 years ago, we thought that the discovery of bortezomib was a tremendous breakthrough. Looking at ibrutinib today, it appears to be twice as effective as bortezomib in this patient population.

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