5 Minute JournalClub

POST-ASH Issue 6, 2013

Ibrutinib Activity in the ABC Subtype of Relapsed/Refractory De Novo DLBCL: Interim Results of a Phase II Study

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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
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, 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

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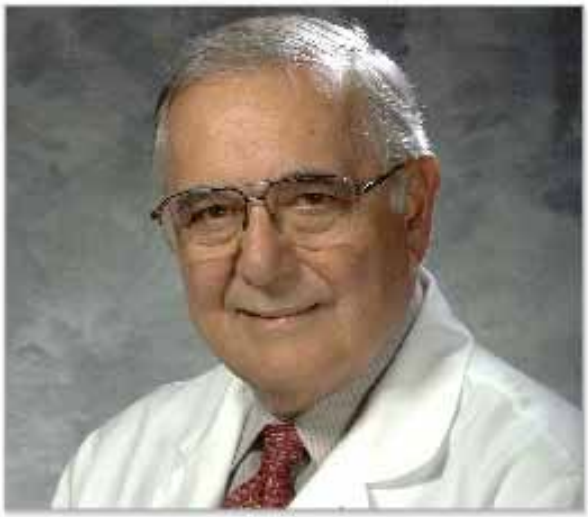
POST-ASH Issue 6, 2013

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**.

David Carbone, MD, PhD

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.



Paul Carbone, MD

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

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.

Neil Love, MD
Research To Practice
Miami, Florida

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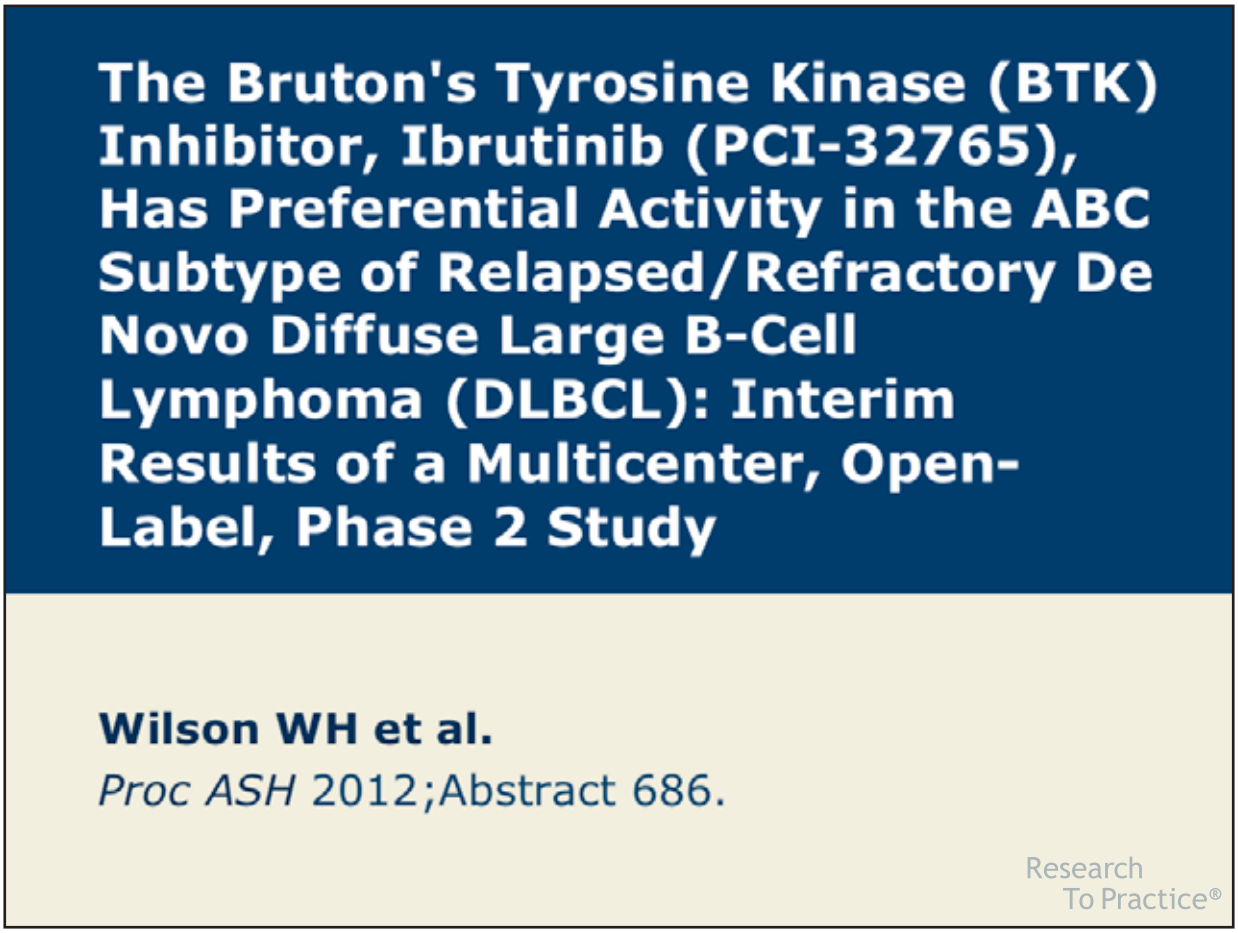
Ibrutinib Activity in the ABC Subtype of Relapsed/Refractory De Novo DLBCL: Interim Results of a Phase II Study

Presentation discussed in this issue

Wilson WH et al. **The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): Interim results of a multicenter, open-label, Phase 2 study.** *Proc ASH* 2012;**Abstract 686**.

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



Background

- Survival of activated B-cell-like (ABC) but not germinal center B-cell-like (GCB) DLBCL cell lines is sustained by "chronic active" B-cell receptor (BCR) signaling.
- Constitutive activation of NFκB leads to activation of a prosurvival program in ABC DLBCL.
- Mutations in the BCR subunit CD79B and in the adaptor protein for toll-like receptors, MYD88, occur more frequently in ABC than GCB DLBCL and could lead to the activation of NFκB and chronic BCR signaling in ABC DLBCL.
- Ibrutinib is a first-in-class oral inhibitor of Bruton tyrosine kinase (BTK), a kinase in the BCR pathway.
- **Study objective:** Evaluate the efficacy and safety of ibrutinib in relapsed/refractory DLBCL.

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

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Phase II Study Design

Eligibility (N = 70)

- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

→ Ibrutinib: 560 mg/d, PO

ASCT = autologous stem cell transplant

- Gene expression profiling of biopsy tissues using Affymetrix arrays to identify DLBCL subtype (ABC, GCB, unclassifiable)
- Mutations in tumor samples analyzed by PCR and DNA sequencing
- ABC DLBCL tumors analyzed for mutations in CD79B, MYD88 and CARD11 genes

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

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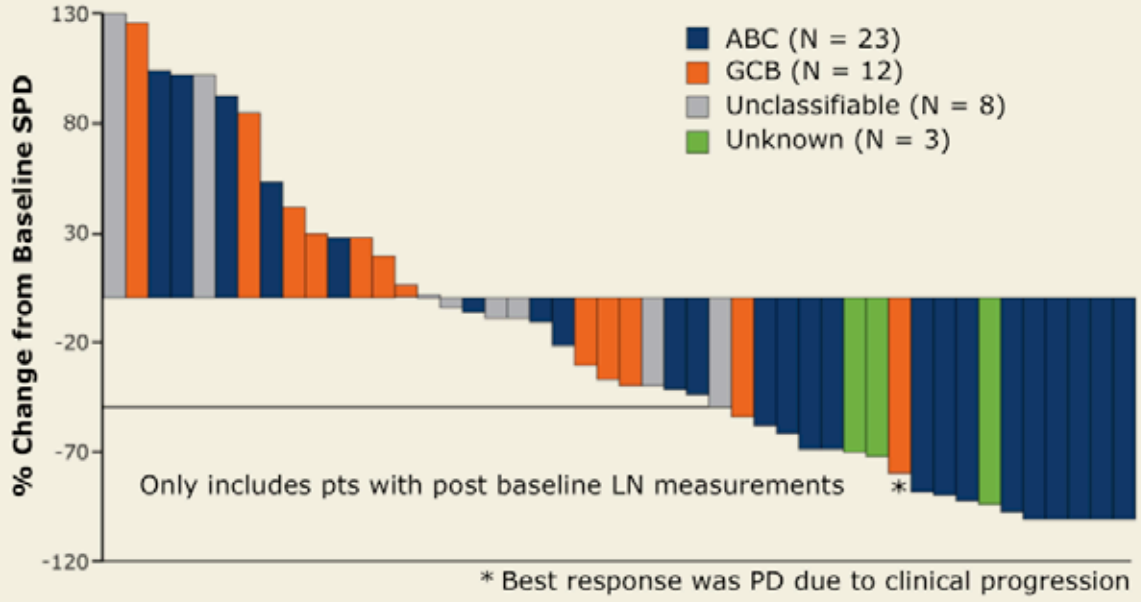
Waterfall Plot of Maximum Decrease in Bidimensional Measurements



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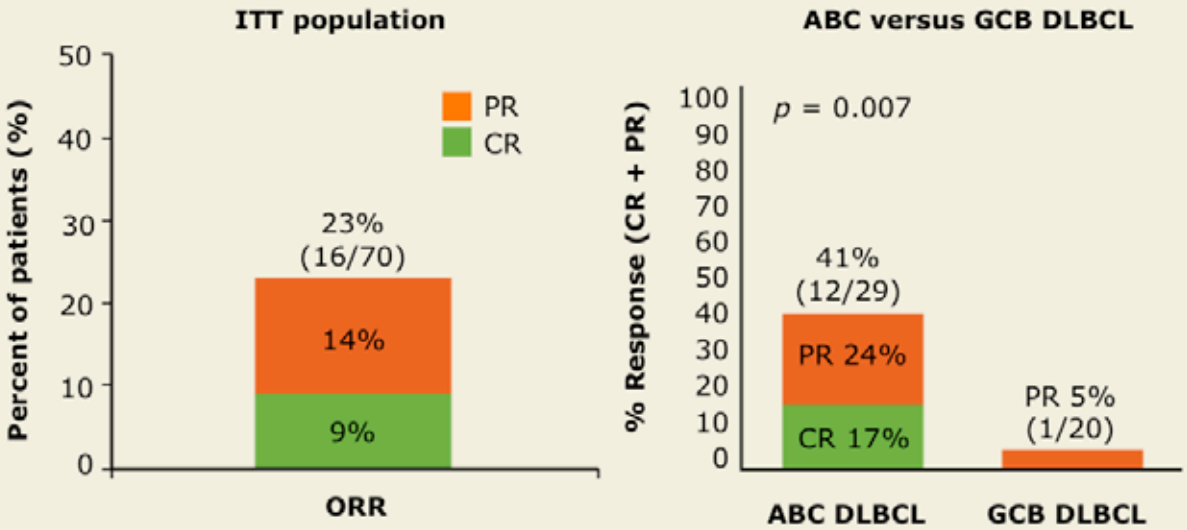
Response to Ibrutinib



ORR = overall response rate; PR = partial response; CR = complete response

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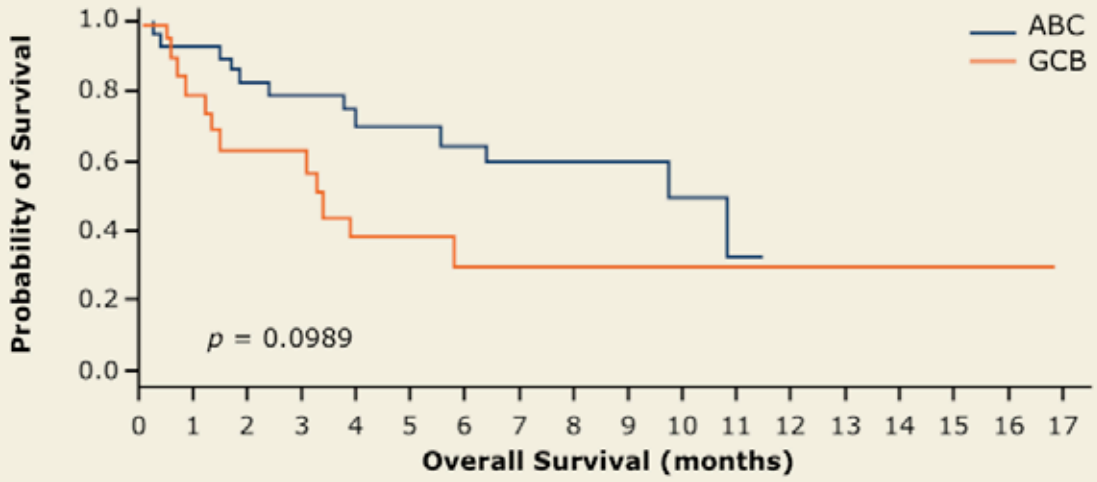
Overall Survival in ABC and GCB DLBCL



	ABC (n = 29)	GCB (n = 20)
Median OS	9.76 mo	3.35 mo

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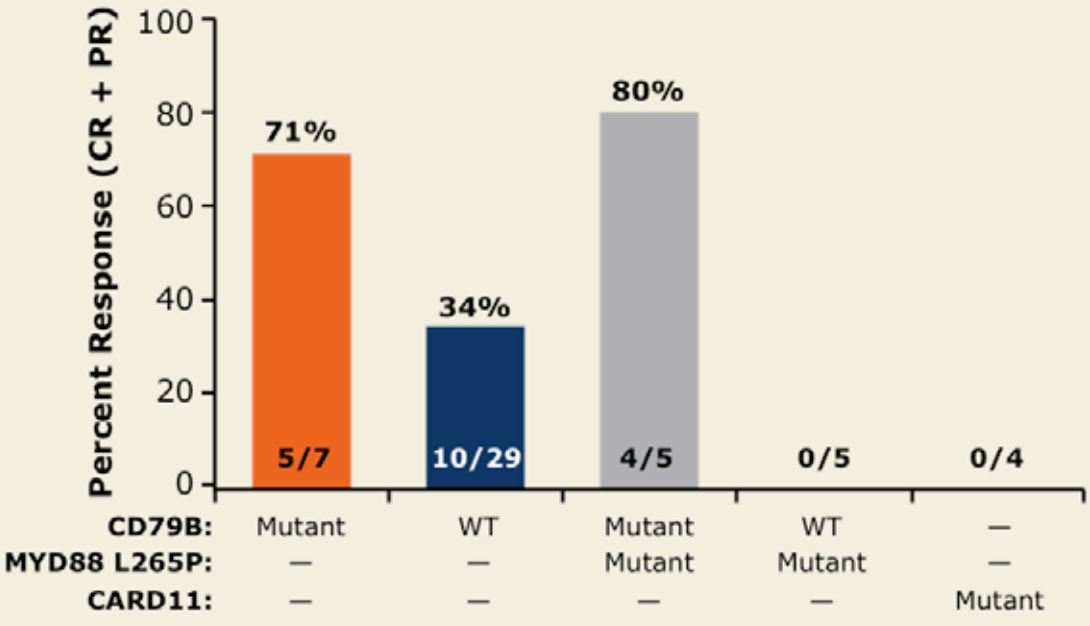
Response of CD79B-, MYD88- and CARD11-Mutant ABC DLBCL to Ibrutinib



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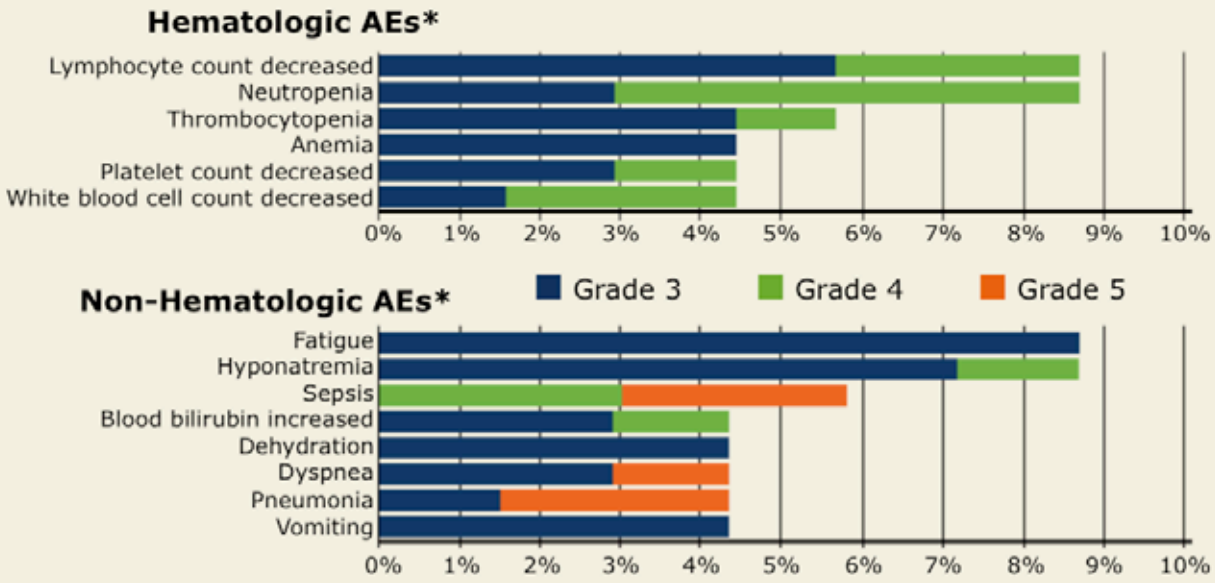
Grade ≥3 Adverse Events



* >3% incidence (unrelated and related to ibrutinib)

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Author Conclusions

- Ibrutinib induced a high response rate in relapsed/refractory ABC DLBCL.
- Ibrutinib had marginal activity in GCB DLBCL, supporting the ABC DLBCL molecular subtype as a biomarker for activity.
- CD79B-mutant tumors responded frequently to ibrutinib, suggesting that it inhibits "chronic active" BCR signaling in ABC DLBCL.
- Ibrutinib response did not require CD79B mutation, suggesting that BCR pathway addiction can occur by other means in ABC DLBCL.
- CARD11-mutant tumors were resistant, suggesting that ibrutinib response requires upstream BCR signaling.
- Tumors harboring only MYD88 L265P mutation were resistant to ibrutinib, suggesting a BCR-independent pathway to ABC DLBCL.
- Ibrutinib was associated with a favorable safety profile.

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

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Investigator Commentary: Phase II Study of Ibrutinib in the ABC Subtype of Relapsed/Refractory DLBCL

The oral BTK inhibitor ibrutinib is one of the most dynamite drugs in lymphoid cancers. The drug is active in chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle-cell lymphoma. Its activity in follicular lymphoma is less well defined.

In DLBCL, the activity of ibrutinib is selective based on the cell of origin. The overall activity of ibrutinib in an unselected population in this study was not impressive. However, when patients were classified according to the cell of origin subtype, the overall response rate (ORR) for those with the ABC subtype was approximately 40%, whereas the ORR for those with the GCB subtype was 5%.

This is an example of how a better understanding of the biology of the disease can lead to a more rational selection of patients for treatment with targeted agents. The preferential activity of ibrutinib in ABC DLBCL has implications not only for relapsed/refractory disease but also for the design of trials that may be initiated with ibrutinib in the front-line treatment of the disease.

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

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