



POST-ASH Issue 2, 2016

**Venetoclax Alone and
in Combination with
Bendamustine/Rituximab for
Relapsed/Refractory NHL**

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. These events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unmatched and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the efficacy and safety of venetoclax alone or in combination for patients with CLL and FL.
- Compare the risks and benefits associated with the Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib for the treatment of CLL.
- Evaluate the activity and tolerability of obinutuzumab/bendamustine for patients with previously untreated CLL.
- Recall recent data on the activity of pembrolizumab in the treatment of relapsed/refractory CLL, including for patients with Richter's transformation.
- Assess the safety of idelalisib in the front-line treatment of CLL.

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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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Advisory Committee and Consulting Agreements: Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, Pharmacylics Inc; Contracted Research: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Gilead Sciences Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacylics Inc.

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This activity is supported by educational grants from Celgene Corporation, CTI BioPharma Corp/Baxalta Inc, Jazz Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Seattle Genetics and Takeda 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: March 2016

Expiration date: March 2017

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

Less than 2 weeks ago, in a historic act that will instantly affect the treatment of one of the most common hematologic cancers in general oncology practice, the FDA broadened the first-line indication of ibrutinib to now include patients both with and *without* 17p-deleted chronic lymphocytic leukemia (CLL). This landmark event is just part of an unprecedented explosion of new data and treatment options that have redefined the management of this disease over the past few years.

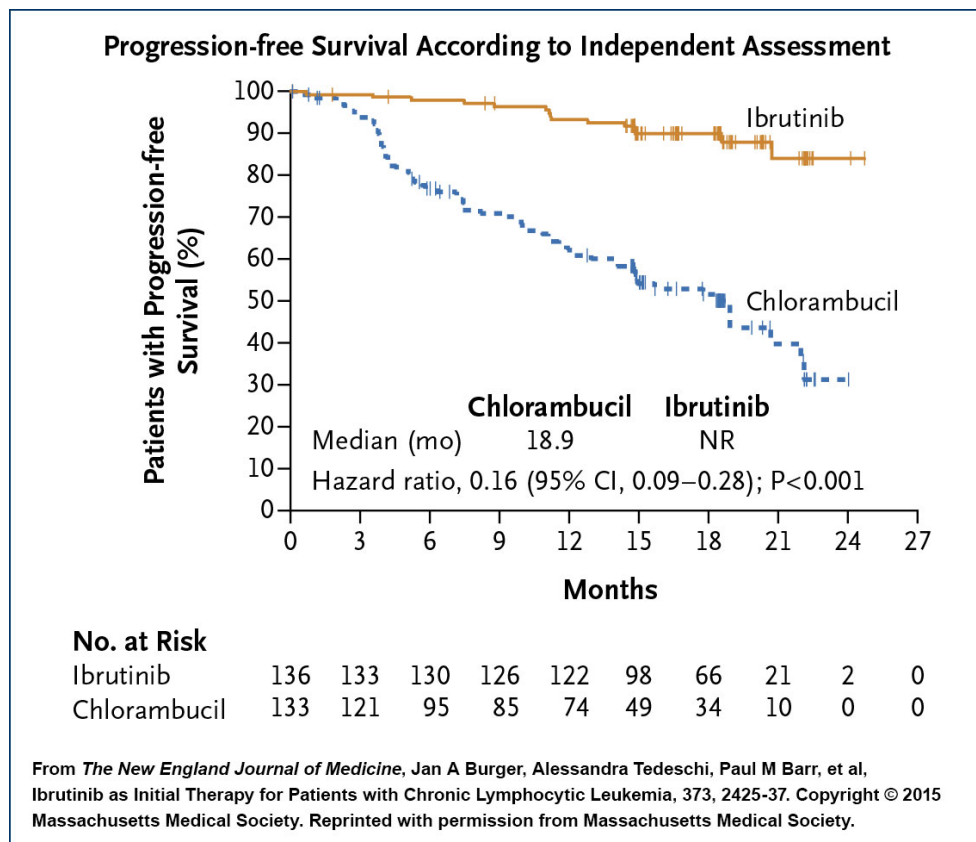


Jeff Sharman, MD

One of the many investigators in this worldwide effort is Dr Jeff Sharman, who first at Stanford and now in Springfield, Oregon has gained extensive practical experience working with many of the novel agents that are now part of current algorithms. I met with Jeff to learn about his perspectives — from both a clinical and a research standpoint — on relevant CLL and non-Hodgkin lymphoma data sets presented at the December ASH meeting and how these add to the rapidly evolving therapeutic paradigms in these cancers ([click for the interview](#)). Below find a summary of this conversation along with slides detailing the key findings from the ASH papers ([click to review](#)).

RESONATE-2: Ibrutinib versus chlorambucil in untreated CLL

In what might be compared to a matchup between the Green Bay Packers and my alma mater, Milford Mill High School, this randomized Phase III trial not surprisingly demonstrated the clear-cut superiority of the Bruton tyrosine kinase (BTK) inhibitor, with spectacular progression-free survival (PFS) and overall survival (OS) HRs of 0.16 for both endpoints. Although the trial focused on patients older than 65, the design and the results did not compel the FDA to tie an age stipulation to the recent approval expansion. In addition, ibrutinib had an acceptable safety profile, with the majority of adverse events being Grade 1 and a lower rate of treatment discontinuation due to toxicity compared to chlorambucil (9% versus 23%). As such, many, including Dr Sharman, believe ibrutinib will become the standard first-line treatment for most patients with CLL. He pointed out that the one exception might be younger patients with IgVH-mutated disease without high-risk FISH findings in whom a chemoimmunotherapy regimen like fludarabine/cyclophosphamide/rituximab (FCR) could potentially result in a prolonged remission or cure without the need for continuous treatment.



In discussing how the indefinite use of up-front ibrutinib may affect clinical practice, Dr Sharman focused on the need to pay even greater attention to the variety of treatment-related complications and potential adverse drug-drug interactions (discussed in another ASH report) that might lead to temporary discontinuation of this generally well-tolerated therapy. His concern in this regard stems from recent research demonstrating that treatment interruption for even 8 days has been associated with a reduction in PFS, a cautionary tale about the potential challenges of administering this or almost any agent indefinitely.

Acalabrutinib (acala-B): A better BTK inhibitor?

The extraordinary efficacy of acala-B might or might not exceed that of ibrutinib, but perhaps of equal importance is the hope that the safety profile may be superior, with early-onset headaches being the most common problem rather than the arthralgias, bruising, bleeding and atrial fibrillation observed with ibrutinib. In a Phase I/II trial of 60 evaluable patients with relapsed disease, responses were observed in 95% of patients, including all 18 with del(17p). A head-to-head Phase III trial will compare these relatively close cousins, but Dr Sharman believes this is another novel agent churning its way steadily toward approval.

Idelalisib in CLL

In one of the highlights of the late-breaking abstract session, Dr Andrew Zelenetz presented results of a Phase III trial evaluating bendamustine/rituximab (BR) alone or with idelalisib in relapsed/refractory (R/R) disease. The study, which was stopped early

based on “overwhelming efficacy,” demonstrated an impressive improvement in both PFS (HR 0.33) and OS (HR 0.55), and the findings were consistent for patients with or without high-risk features. Although Dr Sharman questions whether bendamustine really adds much to idelalisib/rituximab, he does consider BR/idelalisib a rational option in the R/R setting.

Importantly, another study at ASH — idelalisib up front combined with ofatumumab — revealed an overall response rate (ORR) of 100% among 24 patients but an excess of immune-related adverse events such as hepatitis, pneumonitis and colitis. Dr Sharman believes these toxicities are likely related to the drug’s inhibition of regulatory T cells and explained that the lower frequency of idelalisib-related immune toxicity in the R/R setting may be the result of what he calls “immuno-plegia” as a consequence of prior therapies such as FCR. As a direct result of these new toxicity findings, just yesterday the FDA announced that 6 ongoing combination trials involving idelalisib and a number of other anti-cancer agents had been stopped.

Venetoclax in CLL

Although it is still in clinical development, the emergence of this highly effective Bcl-2 inhibitor represents another gigantic recent CLL advancement, and in Orlando we saw more impressive data with this agent in del(17p) disease with an ORR of 79.4% among 107 patients with R/R disease. We were also treated to some encouraging findings with combination regimens that included bendamustine, rituximab and obinutuzumab (obin) administered prior to, after or with the Bcl-2 inhibitor.

The FDA has now bestowed not 1 but 2 breakthrough therapy designations upon the drug in CLL, and Dr Sharman believes that the overwhelming database supporting the useful clinical role of this agent will likely lead to its approval this year. However, he and others remain somewhat concerned about the potential for tumor lysis syndrome (TLS), which was observed in early trials, and would like to see specific recommendations emerge for how to prevent or manage this phenomenon. In that regard, he believes that we will likely be assessing pretreatment tumor burden and renal function to determine baseline risk for TLS and then aggressively monitoring or even hospitalizing select patients. With that being said, the availability of another profoundly effective agent with a totally different mechanism of action has the entire CLL investigator community wide eyed with excitement over the possibility of long-term or lifelong disease control.

Obinutuzumab in CLL

It will be interesting to see how the role of this novel anti-CD20 antibody evolves with ibrutinib rapidly moving in on its indicated turf and the current/emerging treatment roster loaded with other novel small agents. Regardless, many believe this drug has good activity in CLL (likely more than rituximab) and for that reason were excited to determine how it would fare in combination with bendamustine. At ASH we saw more

from the single-arm GREEN study of bendamustine/obin in untreated and R/R disease demonstrating encouraging efficacy and acceptable toxicity with some concerns about TLS and neutropenia. In the current analysis of 158 patients with previously untreated disease, the bendamustine/obin combination yielded a complete response rate of 32.3%, with minimal residual disease negativity in blood and bone marrow of 58.9% and 28.5%, respectively. Despite these data, Dr Sharman believes the regimen is not yet ready for clinical practice in CLL. It is worth noting that on February 26 of this year the FDA approved bendamustine/obin followed by obin maintenance for patients with *follicular lymphoma (FL)* who did not respond to a rituximab-containing regimen.

Pembrolizumab in CLL with Richter's transformation (RT)

RT occurs in approximately 2% to 10% of all CLL cases, and Dr Sharman commented that recently 2 patients in his practice died within 72 hours of diagnosis, in keeping with the often rapidly progressive course. In this preliminary ASH report of 5 patients with RT, 4 had mostly rapid and deep responses after receiving this anti-PD-1 antibody alone. Although it is clearly early days, Jeff found the findings so encouraging that he recently initiated treatment outside a trial setting with this agent in a patient with RT.

ASH disappointments in indolent lymphoma (ibrutinib, venetoclax)

With all the excitement in CLL, the ASH papers focused on indolent lymphomas were a bit underwhelming. In particular 2 studies in FL **combining ibrutinib with either rituximab or rituximab/lenalidomide** (R²) along with a **couple of Phase I trials** of venetoclax alone or with BR failed to inspire Dr Sharman, particularly when he considers how active idelalisib has been in this setting. He did find intriguing the significant activity observed with the Bcl-2 inhibitor in mantle-cell lymphoma, perhaps related to its biologic and therapeutic similarity to CLL.

Next on this series, Dr Michelle Fanale comments on other lymphoma papers from ASH, including more on the exciting findings now being reported with the use of checkpoint inhibitors in Hodgkin lymphoma.

Neil Love, MD

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Venetoclax Alone and in Combination with Bendamustine/Rituximab for Relapsed/Refractory NHL

Presentations discussed in this issue

Gerecitano JF et al. **A Phase 1 study of venetoclax (ABT-199/GDC-0199) monotherapy in patients with relapsed/refractory non-Hodgkin lymphoma.** *Proc ASH 2015*; **Abstract 254.**

de Vos S et al. **A dose-escalation study of venetoclax (ABT-199/GDC-0199) in combination with bendamustine and rituximab in patients with relapsed or refractory non-Hodgkin's lymphoma.** *Proc ASH 2015*; **Abstract 255.**

Slides from presentations at ASH 2015 and transcribed comments from a recent interview with Jeff Sharman, MD (2/9/16)

A Phase 1 Study of Venetoclax (ABT-199/GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma¹

A Dose-Escalation Study of Venetoclax (ABT-199/GDC-0199) in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Non-Hodgkin's Lymphoma²

¹ Gerecitano JF et al.
Proc ASH 2015; Abstract 254.

² de Vos S et al.
Proc ASH 2015; Abstract 255.

Venetoclax Monotherapy in Non-Hodgkin Lymphoma (NHL)

- Phase I, open-label, multicenter dose-escalation study of venetoclax, an orally bioavailable Bcl-2 inhibitor
- N = 106 patients with relapsed or refractory (R/R) NHL
 - Focus of current analysis: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle-cell lymphoma (MCL)
- **Primary endpoints:** Safety, maximum tolerated dose (MTD), Phase II dose, pharmacokinetics and preliminary efficacy

	All (N = 106)	MCL (n = 28)	FL (n = 29)	DLBCL (n = 34)
ORR	44%	75%	38%	18%
CR rate	13%	21%	14%	12%
Median PFS	17 mo	14 mo	11 mo	1 mo
12-mo OS rate	72%	82%	100%	34%

ORR = overall response rate; CR = complete response; PFS = progression-free survival; OS = overall survival
 Gerecitano JF et al. *Proc ASH* 2015;Abstract 254.

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Conclusions

- Venetoclax monotherapy demonstrated an acceptable safety profile in patients with R/R NHL.
- The MTD was not reached, with doses up to 1,200 mg explored.
- Laboratory tumor lysis syndrome was observed in 2 patients with high-risk disease and was managed effectively.
- ORR was 75% in MCL, 38% in FL and 18% in DLBCL:
 - The majority of responses were observed at higher dose levels in FL and DLBCL, whereas responses were reported at all dose levels in MCL.
 - CRs in patients with MCL and FCL were durable.
- Venetoclax is currently being evaluated with combination chemotherapy and targeted agents.

Gerecitano JF et al. *Proc ASH* 2015;Abstract 254.

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Investigator Commentary: Results from a Phase I Trial of Venetoclax Monotherapy for Patients with R/R NHL

This study evaluated the role of venetoclax in R/R NHL. This drug has remarkable activity in chronic lymphocytic leukemia (CLL) and will likely gain FDA approval in the first half of 2016 for this indication.

Unfortunately, the exquisite sensitivity of CLL to this agent has not been demonstrated in relapsed lymphoma.

This study included a variety of lymphoma histologies but reported results for DLBCL, MCL and FL. For patients with DLBCL the ORR was only 18%. The median time on therapy was only 5 months and the median duration of response was approximately 3 months, indicating that this agent lacks significant single-agent activity in R/R DLBCL. For those patients with relapsed FL the ORR was 38% and the median time on venetoclax was approximately 7 months.

Interestingly, high response rates were observed for patients with MCL. I believe this may be related to the biology of MCL, which is closest to CLL in terms of the cell of origin. In the future, when more mature data are available, a Bcl-2 inhibitor may be added to the armamentarium for MCL.

Continued

Investigator Commentary: Results from a Phase I Trial of Venetoclax Monotherapy for Patients with R/R NHL

These results compare less favorably to those with idelalisib in a similar patient population. A provocative signal was reported in Richter's transformation, for which the ORR was 43% and the response proved to be durable in at least 1 patient. However, this is a difficult population to evaluate prospectively, and venetoclax is unlikely to gain approval for this indication in the near term.

Interview with Jeff Sharman, MD, February 9, 2016

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Venetoclax in Combination with Bendamustine/Rituximab (BR) in NHL

- Phase I, open-label dose-escalation study with standard BR x 6 and venetoclax (10 cohorts: 50-800 mg with 3 dosing schedules, every 3, 7 and 28 days), which could be continued up to 2 years
- N = 48 patients with R/R NHL:
 - FL, DLBCL and marginal zone lymphoma (MZL)
- **Primary endpoints:** Safety, MTD, Phase II dose, pharmacokinetics and preliminary efficacy

	FL (n = 27)	DLBCL (n = 16)	MZL (n = 5)
ORR	78%	38%	80%
CR rate	30%	25%	20%

de Vos S et al. *Proc ASH* 2015;Abstract 255.

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Conclusions

- Combination therapy with venetoclax and BR demonstrated a tolerable safety profile:
 - Most common Grade ≥ 3 adverse events were cytopenias: Neutropenia (48%), lymphocyte count decrease (35%), leukopenia (17%), anemia (15%)
 - Most frequent serious adverse event: Febrile neutropenia (8%)
 - After dose-limiting toxicities in 4 patients, protocol amendment encouraged G-CSF prophylaxis during venetoclax administration
- Responses were observed across dose cohorts in this heavily pretreated population.
- The MTD has not been reached, and dose escalation (1,200 mg continuous dosing) is ongoing.

de Vos S et al. *Proc ASH* 2015;Abstract 255.

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Investigator Commentary: Results from a Phase I Trial of Venetoclax in Combination with BR for Patients with R/R NHL

Because venetoclax monotherapy is unlikely to be further developed in relapsed DLBCL or FL, it was also studied in a Phase I study combining it with BR. This study included both DLBCL and FL, in addition to some patients with MZL, but on the basis of the data presented, it is difficult to discern whether venetoclax added much to the activity of BR.

Venetoclax is known to cause neutropenia, and it appeared to adversely affect hematopoietic function in these patients. During the execution of this study a protocol amendment was added to encourage use of G-CSF.

This regimen requires further study before its proper use can be determined.

Interview with Jeff Sharman, MD, February 9, 2016

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