5 Minute JournalClub

Hematologic Oncology
Issue 4, 2013

Results from the BRIGHT Trial of First-Line Bendamustine/Rituximab versus R-CHOP/R-CVP in Advanced Indolent NHL or MCL

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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 Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings and the International Conference on Malignant Lymphoma (ICML), to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, 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 unprecedented 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 are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, 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 treatment approaches and novel agents in non-Hodgkin lymphoma (NHL) from the latest ASCO, EHA and ICML meetings, including expert perspectives on how these new evidence-based concepts may 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

- Appraise recent clinical research findings on the efficacy and safety of radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan for elderly patients with CD20-positive B-cell NHL.
- Compare and contrast the differences in patterns of care and treatment outcomes in older versus younger patients with follicular lymphoma based on data from the US National LymphoCare Study database.
- Evaluate the benefits and risks of novel therapeutic approaches with lenalidomide as a single agent in relapsed or refractory mantle-cell lymphoma (MCL) after bortezomib treatment or in combination with rituximab (R^2 regimen) for patients with previously untreated follicular lymphoma.
- Assess the effectiveness and tolerability of up-front combination therapy with bendamustine and rituximab versus standard rituximab-based chemotherapy in advanced indolent NHL compared to in MCL.
- Consider the clinical impact of rituximab maintenance versus observation after induction chemotherapy on the risk of relapse for patients with aggressive B-cell lymphoma.
- Recall the utility of post-therapy surveillance imaging approaches for earlier detection of relapses in patients with diffuse large B-cell lymphoma.

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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: November 2013
Expiration date: November 2014

5 Minute Journal Club

Hematologic Oncology
Issue 4, 2013

To go directly to slides and commentary for this issue, **click here**.

This fourth and final issue of *5-Minute Journal Club* walks through a number of interesting lymphoma presentations from ASCO, EHA and ICML at Lugano, but as we were putting the final touches on the program last Friday, a white-hot email came through announcing the FDA approval of yet another novel anticancer agent, in this case the glycoengineered type II anti-CD20 monoclonal antibody (MoAb) obinutuzumab (O) combined with chlorambucil (Clb) in previously untreated CLL. To add to the critical nature of this moment, just yesterday ASH posted abstracts from the annual meeting coming up next month, and among these are definitive findings from a Phase III up-front trial in CLL of 663 older patients (median age 73) first reported preliminarily at ASCO evaluating Clb alone or with O or with rituximab (R).

The world will see these landmark data and begin the debate at ASH, but the bottom line is that OClb resulted in a statistically significant and clinically meaningful prolongation of progression-free survival (PFS) and higher rates of complete response (CR) and minimal residual disease negativity compared to RClb. However, in terms of tolerability, infusion-related reactions and neutropenia without an increase in infections were more common with OClb.

We immediately sought help in figuring out what this means to physicians in practice, and for the bonus finale of this series check out the thoughts of Dr Michael Williams about obinutuzumab, trogocytosis and where we are in CLL at the moment. Meanwhile, here are our picks for the best summer lymphoma papers:

1. R squared (again)

At ASH in December Dr Nathan Fowler presented more mature data from his pathfinding Phase II trial evaluating lenalidomide (Len)/rituximab (R squared) up front in indolent lymphomas, including follicular lymphoma (FL), and at Lugano we saw **a CALGB study** with similar stellar results (72% CRs). An ongoing Phase III trial compares this nonchemotherapy regimen to R-chemotherapy, but where this will fit in with O and the new small-molecule B-cell receptor inhibitors such as ibrutinib and idelalisib is unclear.

In another interesting Lugano paper, the US-based prospective "LymphoCare" registry reported the largest ever series of patients with FL older than age 80 (n = 209) and not surprisingly demonstrated less use of R-chemotherapy and more R monotherapy, but of interest, response rates were only slightly lower than those in younger patients.

2. Radioimmunotherapy (RIT) consolidation after R-chemotherapy as an alternative to R maintenance

During our recent (and soon to be published) lymphoma/CLL think tank, Dr Julie Vose commented that she sometimes uses RIT rather than R maintenance after R-chemotherapy in older patients with indolent lymphomas, particularly when transportation to and from clinic for R infusions is problematic. In this regard, **a Phase II Polish study** presented in Lugano looked at RIT consolidation in 46 patients with mantle-cell lymphoma (MCL) ineligible for autologous stem cell transplantation or after chemosensitive relapse and reported an encouraging median PFS of 3.5 years. **Another paper from EHA** documented excellent outcomes in 39 patients with a variety of lymphomas, using RIT either as consolidation or monotherapy for relapsed/refractory disease with 74% CRs.

3. Bendamustine + R (BR) in indolent lymphoma

At ASCO and Lugano we saw more data from **the Phase III BRIGHT study** demonstrating at least equivalent efficacy between BR and R-CHOP/R-CVP in patients with NHL and perhaps an advantage in MCL with BR, which is now commonly used first line in indolent lymphomas primarily due to its tolerability profile, including the lack of alopecia.

4. Len in MCL

The 134-patient **EMERGE study** that led to the recent FDA indication of Len in MCL was updated at EHA and recently published in the *JCO* demonstrating a 28% overall response rate in patients with heavily pretreated disease (median of 4 prior therapies). The hope is that greater efficacy will be seen if this agent is administered earlier, although the current indication restricts its use to patients who have received 2 prior treatments, including bortezomib.

5. Post-therapy surveillance scans in diffuse large B-cell lymphoma (DLBCL); R maintenance in DLBCL

An ASCO oral presentation was one of a number of recent retrospective lymphoma series documenting the rare likelihood of surveillance scans detecting recurrence in an asymptomatic patient with normal laboratory data, but many oncologists continue to employ this practice, likely due to the potential curability of relapsed disease.

This summer we also saw more generally unimpressive results with **R maintenance in DLBCL**, and not surprisingly, investigators do not endorse this strategy. Perhaps better outcomes will be seen with the new generation of anti-CD20 MoAbs like O.

Speaking of O, as promised here are a few initial thoughts and comments from Dr Williams on questions that will be discussed a great deal starting at 4:15 PM on Sunday, December 8 in New Orleans:

Aren't all anti-CD20 MoAbs the same?

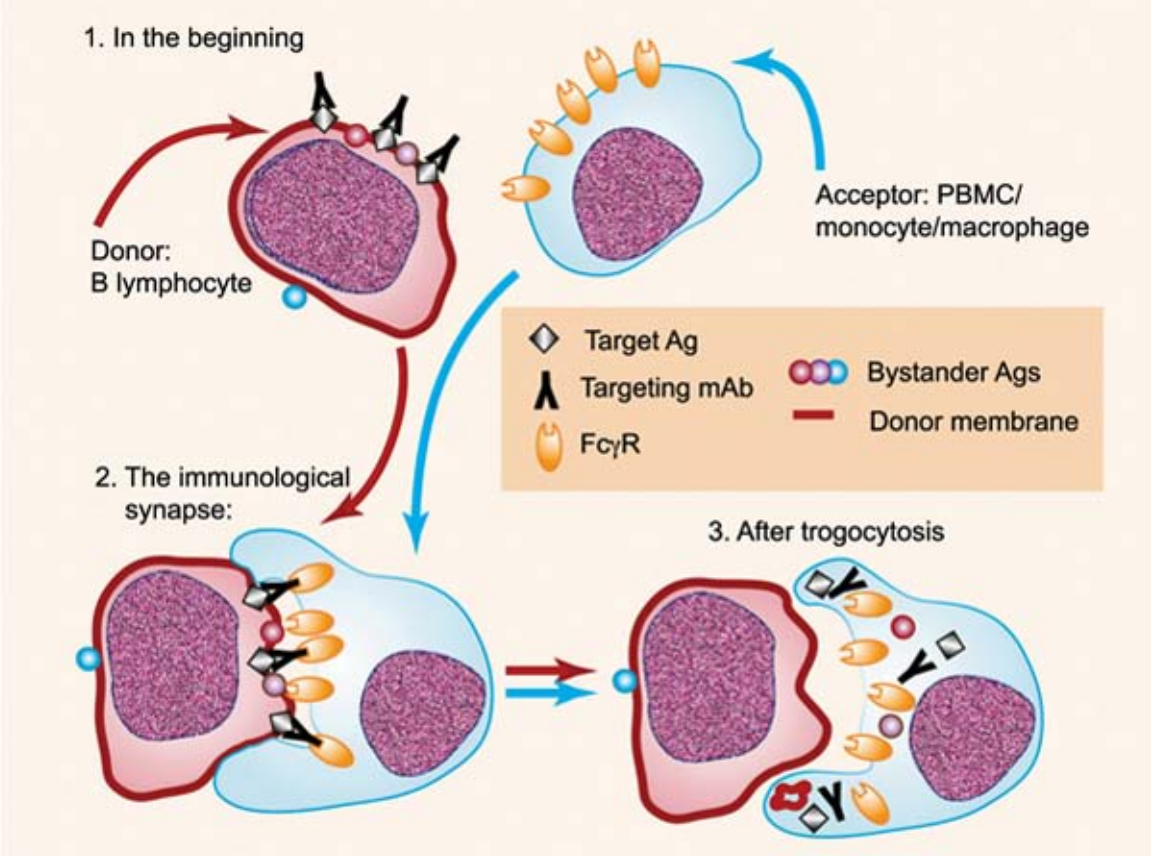
Until maybe yesterday most lymphoma investigators have been generally unexcited about the possibility that a whole lot more could be squeezed out of new anti-CD20 agents compared to R in B-cell neoplasia, but the new O data are likely to result in a lot more interest in exactly how MoAbs improve cancer outcomes (trastuzumab, for example, in breast cancer). Dr Williams notes that the enhanced efficacy of O compared to R may relate to its much greater binding affinity to CD20 and increased stimulation of antibody-dependent cell-mediated cytotoxicity — factors that may be more important in CLL than lymphomas because of the lower CD20 density on CLL cells.

When should O be considered right now in practice?

Dr Williams, like many lymphoma investigators, not uncommonly uses the venerable Clb alone or with R mainly in older, frail patients with lower-risk disease, and based on the new FDA indication he is ready to selectively combine O with Clb as soon as it's available on his formulary. He also often uses the type I MoAb ofatumumab as monotherapy in patients with CLL who have received prior R but will now be inclined to try O instead. However, until more data are available, Dr Williams will not combine O with other chemotherapies either in CLL or lymphomas, but he is interested in seeing data emerge from Phase II combination studies, particularly those testing O with bendamustine.

What is the basis for the apparent improved outcomes with O compared to R?

The dosing with O is greater than with R, and some have suggested this was a factor in the trial results. Dr Williams, however, is convinced that the fundamental differences in mechanisms of action of O and R explain the advantage observed, at least in CLL, and he is particularly interested to see data with O related to a phenomenon called "shaving" that he and collaborators reported on, in which the CD20/R complex on the cell surface is removed by the spleen and reticuloendothelial system, allowing leukemic cells to survive. This process is also known as trogocytosis (from the ancient Greek "to nibble"), and Dr Williams is curious to study whether a variation in how the O/CD20 complex is "nibbled" might explain the improved outcomes.



Trogocytosis of IgG bound to targeted antigens is mediated by Fcγ receptors on acceptor cells. Interaction of IgG bound to target antigens on the donor cell (1) with Fcγ receptors on the acceptor cell leads to formation of an immunologic synapse (2). The acceptor cell then ingests the immune complex and portions of the donor cell membrane, along with the participating Fcγ receptors (3). Other surface antigens in close proximity to the target immune complex are also taken up by the acceptor cell. Ag, antigen; PBMC, peripheral blood mononuclear cell. Professional illustration by Paulette Dennis.

That does it for this short review series. Stay tuned for our upcoming audio and video highlights of the aforementioned lymphoma/CLL think tank as Dr Vose, Dr Williams and their colleagues tackle many other key questions of the day.

Neil Love, MD
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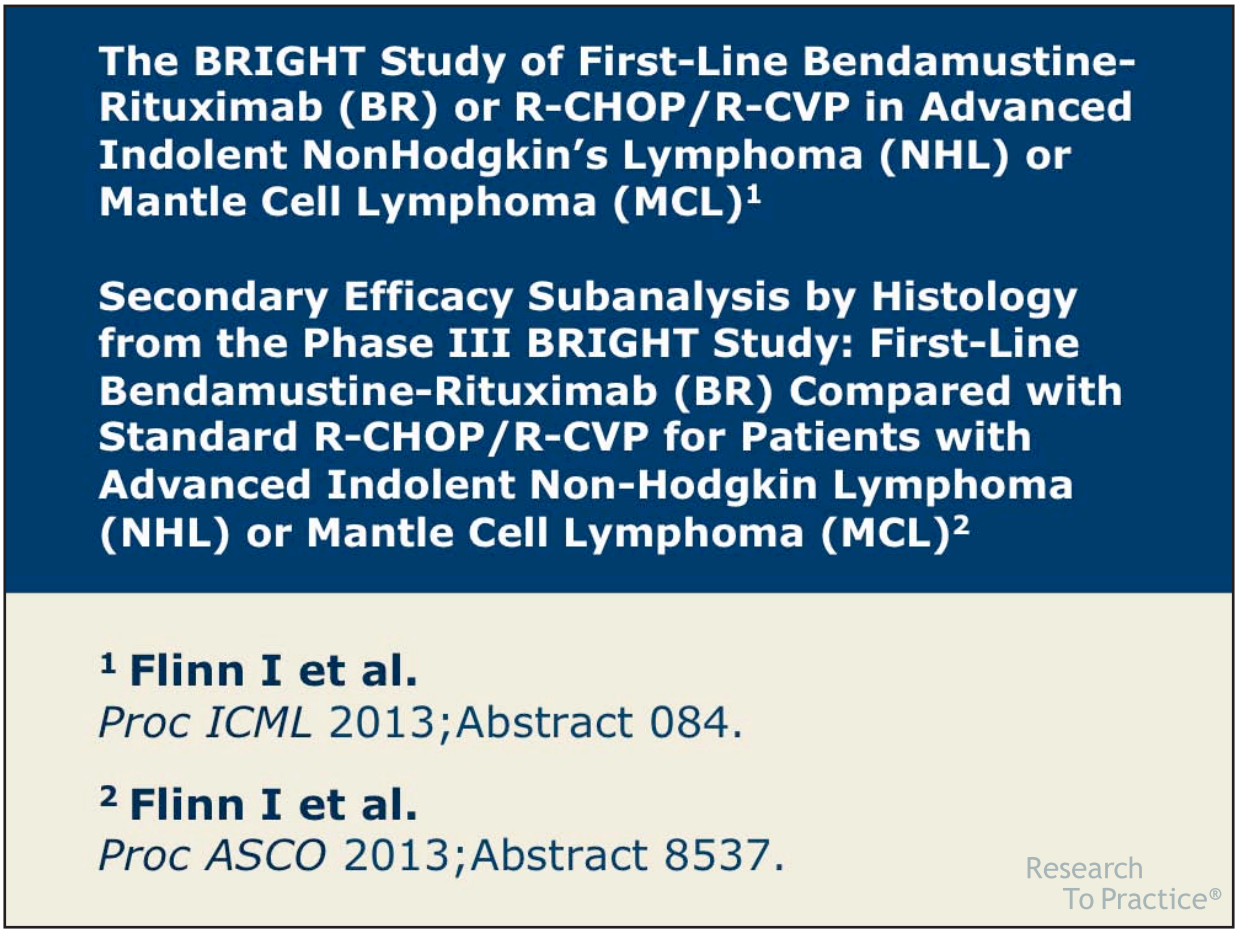
Results from the BRIGHT Trial of First-Line Bendamustine/ Rituximab versus R-CHOP/R-CVP in Advanced Indolent NHL or MCL

Presentations discussed in this issue

Flinn I et al. **The BRIGHT study of first-line bendamustine-rituximab (BR) or R-CHOP/R-CVP in advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL).** *Proc ICML* 2013;**Abstract 084**.

Flinn I et al. **Secondary efficacy subanalysis by histology from the Phase III BRIGHT study: First-line bendamustine-rituximab (BR) compared with standard R-CHOP/R-CVP for patients with advanced indolent non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL).** *Proc ASCO* 2013;**Abstract 8537**.

Slides from presentations at ICML 2013/ASCO 2013 and transcribed comments from recent interviews with Jonathan W Friedberg, MD, MMSc (7/19/13) and Ian W Flinn, MD, PhD (10/5/13)



The BRIGHT Study of First-Line Bendamustine-Rituximab (BR) or R-CHOP/R-CVP in Advanced Indolent NonHodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL)

Flinn I et al.

Proc ICML 2013;Abstract 084.

Background

- The combination of rituximab (R) with chemotherapy, commonly CHOP, is the first-line standard treatment for patients with advanced indolent lymphoma.
- Bendamustine is a cytotoxic alkylating agent with a favorable safety profile and is highly effective as a single agent or when combined with R (BR) for patients with relapsed or refractory lymphoid malignancies (*JCO* 2008;26:4473).
- Recently, the Phase III StiL trial demonstrated that first-line BR increased progression-free survival (PFS) and had fewer toxic effects compared to R-CHOP for patients with untreated indolent lymphoma (*Lancet* 2013;381:1203).
- **Study objective:** To compare the efficacy and safety of first-line BR to those of standard R-CHOP or R-CVP for patients with indolent NHL or MCL.

Flinn I et al. *Proc ICML* 2013;Abstract 084.

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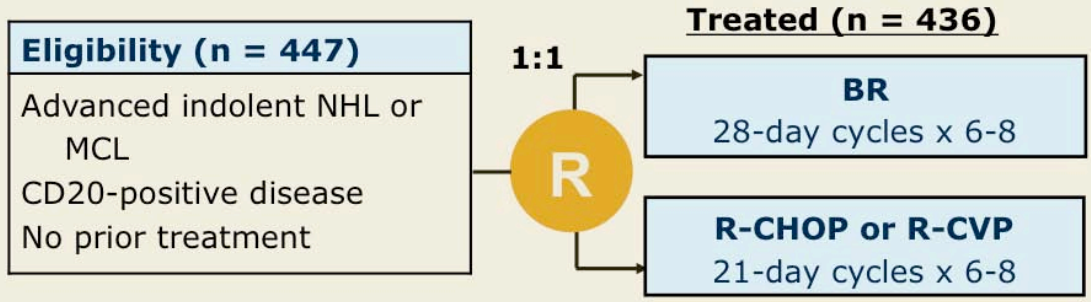
Phase III BRIGHT Trial Design



Bendamustine: 90 mg/m^2 (IV), d1,2

- **Primary endpoint:** Noninferiority of complete response (CR) rate
- **Secondary endpoints include:** Overall response rate (ORR), PFS, safety and quality of life
- Antiemetic use was similar between groups except that aprepitant use was higher with R-CHOP (23%) than BR (9%) or R-CVP (3%).
- Colony-stimulating factors were administered (per institutional standards) to 29% of patients for BR and 43% for R-CHOP/R-CVP.

Flinn I et al. *Proc ICML* 2013;Abstract 084.

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CR Rates

All patients	BR	R-CHOP/R-CVP	CR ratio	*p*-value
Evaluable pts	31%	25%	1.26	0.0225*
Randomized pts	31%	23%	1.34	0.0084*
Pts with NHL				
Evaluable pts	28%	25%	1.11	0.1903*
Randomized pts	27%	23%	1.16	0.1289*
Pts with MCL				
Evaluable pts	50%	27%	1.76	0.0586†
Randomized pts	51%	24%	1.95	0.0180†

* Noninferior (margin of 0.88); † Superior

- Evaluable pts (n = 419): BR (n = 213), R-CHOP/R-CVP (n = 206)

Flinn I et al. *Proc ICML* 2013;Abstract 084. (Abstract only)

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Outcomes

Response*	BR	R-CHOP/R-CVP
Progressive/relapsed disease	8%	4%
Deaths	8%	11%

* By committee or investigator assessment of available data at cut-off

Flinn I et al. *Proc ICML* 2013;Abstract 084. (Abstract only)

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Adverse Events

All grades	BR	R-CHOP/R-CVP	
Nausea	63%	48%	
Fatigue	51%	50%	
Neutropenia	34%	40%	
Grades 3/4	**BR**	**R-CHOP/R-CVP**	
Lymphopenia	62%	30%	
Neutropenia	44%	70%	
Leukopenia	38%	54%	
Grades 3/4	**BR**	**R-CHOP**	**R-CVP**
Hematologic	56%	69%	50%

Flinn I et al. *Proc ICML* 2013;Abstract 084. (Abstract only)

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Author Conclusions

- In patients with advanced indolent NHL and MCL, the CR rate of BR is noninferior to that of R-CHOP/R-CVP.
- In the small group of patients with MCL, the CR rate is 2-fold higher with BR.
- BR and R-CHOP/R-CVP have distinct profiles of adverse events.

Flinn I et al. *Proc ICML* 2013;Abstract 084. (Abstract only)

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Investigator Commentary: Efficacy and Safety Results from the Phase III BRIGHT Study of BR versus R-CHOP/R-CVP

The BRIGHT study was designed to demonstrate whether similar results to those from the German StiL trial of BR versus R-CHOP would be obtained. BRIGHT had a smaller patient population of 447 patients. It compared R-CHOP and R-CVP to BR. Although BRIGHT is still premature as far as assessing PFS data, the response rates were lower than those in the StiL trial. Importantly, the CR rate in the StiL study was better with BR than with R-CHOP, but that was not the case in BRIGHT for the entire study population. Whereas the CR rate in the StiL study was 40% with BR, a CR rate of 31% was reported in the BRIGHT study. It is important to emphasize that BRIGHT did not suggest that BR was inferior. It just didn't demonstrate the degree of superiority. In terms of the tolerability and toxicity of BR, the BRIGHT trial probably more accurately reflects what physicians observe. For instance, nausea wasn't described as an issue in the StiL trial. However, in my experience of administering BR to many patients, it is an issue for which you must administer antiemetics. I believe the BRIGHT study captured adverse events in a more rigorous way than StiL. It is hard to argue that BR isn't better tolerated by most patients. The lack of alopecia, the decreased rate of infections, the lack of significant neutropenia and the ability to save the anthracycline for later lines of therapy are all appealing.

Interview with Jonathan W Friedberg, MD, MMSc, July 19, 2013

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Secondary Efficacy Subanalysis by Histology from the Phase III BRIGHT Study: First-Line Bendamustine-Rituximab (BR) Compared with Standard R-CHOP/R-CVP for Patients with Advanced Indolent Non-Hodgkin Lymphoma (NHL) or Mantle Cell Lymphoma (MCL)

Flinn I et al.

Proc ASCO 2013;Abstract 8537.

Background

- NHL has a wide variety of histologic subtypes ranging from slow, indolent to aggressive disease.
- In the Phase III StiL trial, bendamustine/rituximab (BR) demonstrated efficacy when compared to R-CHOP for patients with previously untreated indolent NHL and MCL (*Lancet* 2013;381:1203).
- Previously, the primary measure of the BRIGHT study showed that BR was noninferior to R-CHOP or R-CVP in terms of the CR rate (*Proc ASH* 2012;Abstract 902).
  - CR: BR (31%) vs R-CHOP/R-CVP (25%)
    - CR ratio = 1.26; $p = 0.0225$
- **Study objective:** To perform a subanalysis of efficacy and safety by histologic subtype of BR versus R-CHOP/R-CVP for patients with untreated advanced indolent NHL or MCL.

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

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Baseline Characteristics

	BR (n = 224)	R-CHOP/R-CVP (n = 223)
Median age (range)	60 years (28-84)	58 years (25-86)
Male	61%	59%
Lymphoplasmacytic	2%	3%
Marginal zone	12%	8%
MCL	16%	17%
Follicular lymphoma, Grade I	38%	31%
Follicular lymphoma, Grade II	31%	40%
Missing	n = 1	n = 1
Median time from diagnosis	1.5 months	1.4 months

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

Complete Response Rate Ratios

Histologic classification	BR vs R-CHOP/R-CVP *p*-value (superiority)	
	Rate ratio	*p*-value (superiority)
Indolent NHL (n = 352)	>1	N/A
Lymphoplasmacytic (n = 11)	<1*	0.3613
Marginal zone (n = 42)	<1	0.7665
Follicular lymphoma (n = 297)	>1	0.2851
MCL (n = 67)	>1	0.0586

- Rate ratio >1 favors BR

N/A = not available/calculated

* Very wide 95% CI

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

Response Rates by Histologic Subtypes

Histologic classification	BR		R-CHOP/R-CVP	
	ORR	CR	ORR	CR
Indolent NHL (n = 178, 174)	97%	28%	92%	25%
Follicular lymphoma (n = 148, 149)	99.3%	30%	94%	25%
Marginal zone (n = 25, 17)	92%	20%	71%	24%
Lymphoplasmacytic (n = 5, 6)	60%	0%	100%	17%
MCL (n = 34, 33)	94%	50%	85%*	27%*

* R-CHOP (n = 22)

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

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Adverse Events

	Preselected for R-CHOP		Preselected for R-CVP	
	BR (n = 103)	R-CHOP (n = 98)	BR (n = 118)	R-CVP (n = 116)
Nausea	63%	58%	63%	39%*
Vomiting	29%	13%*	25%	13%*
Constipation	32%	40%	27%	44%*
Infection†	55%	57%	53%	50%
PN/paresthesia†	9%	44%*	14%	47%*
Rash/urticaria†	20%	12%	24%	16%
Alopecia	4%	51%*	3%	21%*

* $p < 0.05$; † Composed of multiple preferred terms

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

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Author Conclusions

- Among all patients (all histologic subtypes), BR achieved the primary endpoint of noninferior CR rate compared to R-CHOP or R-CVP.
- The findings from the histologic subanalysis should be interpreted with caution. The size of some of the subtypes, such as lymphoplasmacytic NHL, was small with a wide confidence interval.
- There were no differences in tolerability by histologic subtypes (data not shown).
- There was a trend for a greater CR ratio with BR versus R-CHOP/R-CVP for patients with MCL compared to other histologic subgroups, although none was statistically significant.

Flinn I et al. *Proc ASCO* 2013;Abstract 8537.

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Investigator Commentary: Subanalysis of Efficacy and Safety by Histologic Subtype in the Phase III BRIGHT Study

In the BRIGHT study, patients were preassigned by the treating physician to receive either R-CHOP or R-CVP standard chemotherapy prior to the randomization to receive BR versus chemotherapy. In the overall population, the CR rate was 31% with BR versus 25% with R-CHOP or R-CVP, with a CR ratio of 1.26. This was clearly statistically noninferior but did not meet the level of superiority.

In the subanalysis of data by histologic subtype all subcategories of patients seemed to benefit from BR in the sense that it was equivalent to R-CHOP or R-CVP. Analysis of CR rates suggested that in MCL, BR was superior, with a hazard ratio of 1.76 based on the evaluable population as judged by the independent review committee. It appeared that BR holds up well for patients with MCL and low-grade lymphoma, perhaps a little better in MCL. In terms of toxicity, I was surprised that the incidence of nausea was higher with BR. In reality, BR caused as much nausea as R-CHOP. Because patients on the BR arm did not receive vincristine, neuropathy was reduced. This was a clear difference. These results were relatively short in follow-up, so we have yet to see the long-term consequences of anthracyclines and cardiotoxicity.

Interview with Ian W Flinn, MD, PhD, October 5, 2013

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