Prospective Study of the Efficacy and Safety of $^{90}$Y-Ibritumomab Tiuxetan for Elderly Patients with CD20-Positive B-Cell NHL
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 ⁹⁰Y-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 (R² 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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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:

Andrew M Evens, DO, MSc
Professor of Medicine
Chief, Division of Hematology/Oncology
Tufts University School of Medicine
Director, Lymphoma Program
Leader, Clinical Sciences Program
Tufts Cancer Center
Boston, Massachusetts

Advisory Committee: Millennium: The Takeda Oncology Company, Seattle Genetics, Spectrum Pharmaceuticals Inc; Contracted Research: Millennium: The Takeda Oncology Company, ZIOPHARM Oncology Inc.

Ian W Flinn, MD, PhD
Director of Blood Cancer Research
Sarah Cannon Research Institute
Nashville, Tennessee

Contracted Research: AstraZeneca Pharmaceuticals LP, Celgene Corporation, Cephalon Inc, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Infinity Pharmaceuticals Inc, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc.

Christopher Flowers, MD, MS
Associate Professor of Hematology and Medical Oncology
Emory School of Medicine Winship Cancer Institute
Atlanta, Georgia
Consulting Agreements: Celgene Corporation, Genentech BioOncology; Contracted Research: Abbott Laboratories, Janssen Pharmaceuticals Inc, Millennium: The Takeda Oncology Company, Sanofi, Spectrum Pharmaceuticals Inc.

Jonathan W Friedberg, MD, MMSc
Samuel Durand Professor of Medicine
Director, Wilmot Cancer Center
University of Rochester
Rochester, New York

Advisory Committee: Genentech BioOncology; Data and Safety Monitoring Board: Lilly.


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This activity is supported by educational grants from Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc and Spectrum Pharmaceuticals Inc.

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
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.
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
Research To Practice
Miami, Florida
Prospective Study of the Efficacy and Safety of 90Y-Ibritumomab Tiuxetan for Elderly Patients with CD20-Positive B-Cell NHL

Presentation discussed in this issue


Slides from a presentation at EHA 2013 and transcribed comments from a recent interview with Andrew M Evens, DO, MSc (10/28/13)
Background

- $^{90}$Y-ibritumomab tiuxetan ($^{90}$Y-IT) is an immunoconjugate of the monoclonal antibody ibritumomab that is linked to the radioisotope yttrium-90 ($^{90}$Y) and targets the CD20 antigen on B-cell surfaces.

- The radioimmunotherapeutic agent $^{90}$Y-IT is an effective therapeutic option for patients with B-cell non-Hodgkin lymphoma (NHL) (Cancer Biother Radiopharm 2013;28 (5):370-9).

- **Study objective:** To determine the safety and efficacy of $^{90}$Y-IT in a prospective study for elderly patients with CD20-positive B-cell NHL.


Trial Design

<table>
<thead>
<tr>
<th>Eligibility (n = 39)</th>
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<tbody>
<tr>
<td>CD20-positive, B-cell NHL</td>
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<tr>
<td>Age &gt;65 years</td>
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<tr>
<td>Neutrophils: $\geq 1.5 \times 10^9$/L; platelets: $\geq 100 \times 10^9$/L</td>
</tr>
<tr>
<td>Bone marrow lymphocytes CD20-positive: $\leq 25%$</td>
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$^{90}$Y-IT
0.3 or 0.4 mCi/kg (IV)
Response evaluation performed after 12 weeks

- $^{90}$Y-IT administered as consolidation of first-line therapy (rituximab alone, R-COP or R-CHOP21; n = 13) or in the R/R setting (n = 26)
- Endpoints included: Objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and safety

### Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 39)</th>
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<tbody>
<tr>
<td>Mean age (range)</td>
<td>72.8 years (65-87)</td>
</tr>
<tr>
<td>Male</td>
<td>46%</td>
</tr>
<tr>
<td>ECOG PS 0-1</td>
<td>92.3%</td>
</tr>
<tr>
<td>NHL-follicular</td>
<td>69.2%</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>17.9%</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>10.3%</td>
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<tr>
<td>Mucosa-associated lymphoid tissue lymphoma</td>
<td>2.6%</td>
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Campos M et al. *Proc EHA* 2013; Abstract B2009. (Abstract only)

### Response Rates

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients (n = 39)</th>
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<tbody>
<tr>
<td>ORR</td>
<td>84.6%</td>
</tr>
<tr>
<td>Complete response</td>
<td>74.3%</td>
</tr>
<tr>
<td>Partial response</td>
<td>10.2%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15.4%*</td>
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</tbody>
</table>

* Patients had relapsed or refractory disease.
  - Study period: September 2005 to February 2013
  - Deaths at the end of the study: 10 patients

Campos M et al. *Proc EHA* 2013; Abstract B2009. (Abstract only)
## Survival Outcomes

<table>
<thead>
<tr>
<th></th>
<th>n = 39</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
</tr>
<tr>
<td>Mean PFS</td>
<td>39.5 months</td>
</tr>
<tr>
<td>Median PFS</td>
<td>Not reached</td>
</tr>
<tr>
<td>Estimated mean OS since ⁹⁰Y-IT</td>
<td>63.1 months</td>
</tr>
<tr>
<td>Estimated mean OS since diagnosis</td>
<td>158 months</td>
</tr>
<tr>
<td><strong>Patients who received ⁹⁰Y-IT as consolidation of first-line therapy</strong></td>
<td>n = 13</td>
</tr>
<tr>
<td>Mean PFS</td>
<td>52.1 months</td>
</tr>
</tbody>
</table>

* Patients with NHL-follicular (n = 11) experienced either relapse or death
  - Median follow-up time: 46.0 months

Campos M et al. *Proc EHA* 2013;Abstract B2009. (Abstract only)

## Adverse Events

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<thead>
<tr>
<th>Adverse event (AE)</th>
<th>n = 39</th>
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<tbody>
<tr>
<td>Neutropenia* (Grade 3/4)</td>
<td>41.0%</td>
</tr>
<tr>
<td>Thrombocytopenia† (Grade 3/4)</td>
<td>35.9%</td>
</tr>
<tr>
<td>Severe mucositis</td>
<td>2.6%</td>
</tr>
<tr>
<td>Concomitant associated tumors (breast, colon, lung, prostate)</td>
<td>10.3%</td>
</tr>
<tr>
<td>Rectal carcinoma after 18 months of Tx (age &gt;77 y)</td>
<td>5.1%</td>
</tr>
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* Median time to recovery from AE: 2.6 wk
† Median time to development of AE: 4 wk; median time to recovery: 4.2 wk
  - Red blood cell transfusion was required by 5 patients.
  - Platelet transfusion was required by 10 patients.
  - The most common nonhematologic AE was asthenia.

Campos M et al. *Proc EHA* 2013;Abstract B2009. (Abstract only)
Author Conclusions

- $^{90}\text{Y}$-IT is a safe and effective therapy for elderly patients, >65 years old, with NHL.

- Based on the PFS results from this study, it appears that the inclusion of this kind of therapy in early therapy offers good and maintained response rates with lower toxicity in this fragile patient population.

- The overall survival result in this elderly patient population was not inferior to that observed in younger patients with NHL.

Campos M et al. Proc EHA 2013;Abstract B2009. (Abstract only)

Investigator Commentary: Efficacy and Safety of $^{90}\text{Y}$-IT for Elderly Patients with B-Cell NHL

These data show that $^{90}\text{Y}$-IT is safe and easy to administer. I often consider this agent in the second- or third-line setting for patients with relapsed follicular lymphoma, and it is a highly active drug in this setting. I’m excited about several studies investigating how to make $^{90}\text{Y}$-IT or other radioimmunoconjugates better, including studies combining them with other agents.

It is important to be cautious about the use of $^{90}\text{Y}$-IT in that it should not be administered to patients with a certain level of bone-marrow lymphoma. This level must be lower than 25%, otherwise too much of the drug will end up in the bone marrow. Also, the patient should have received a limited level of radiation therapy so that the bone marrow is not “beat-up” before the administration of $^{90}\text{Y}$-IT. Most physicians know that even though treatment-associated cytopenias are not as severe as they are with chemotherapy, the effect is delayed. The platelet and white blood cell counts drop about 6 to 9 weeks after treatment initiation, but the change is modest and less significant than that observed with chemotherapy.

Interview with Andrew M Evens, DO, MSc, October 26, 2013