

The logo features a white stopwatch icon with a large number '5' inside the circular face. To the right of the icon, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

# 5 Minute Journal Club

*Hematologic Oncology*  
Issue 4, 2013

## Study of the Utility of Post-Therapy Surveillance Scans in DLBCL

For more visit [ResearchToPractice.com/5MJCHEM2013](http://ResearchToPractice.com/5MJCHEM2013)

Research  
To Practice®

## 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 <sup>90</sup>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<sup>2</sup> 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.

### ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

### CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at [ResearchToPractice.com/5MJCHEM2013/4/CME](http://ResearchToPractice.com/5MJCHEM2013/4/CME).

### CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

**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  
Tennessee Oncology  
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.

EDITOR —Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Exelixis Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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?**

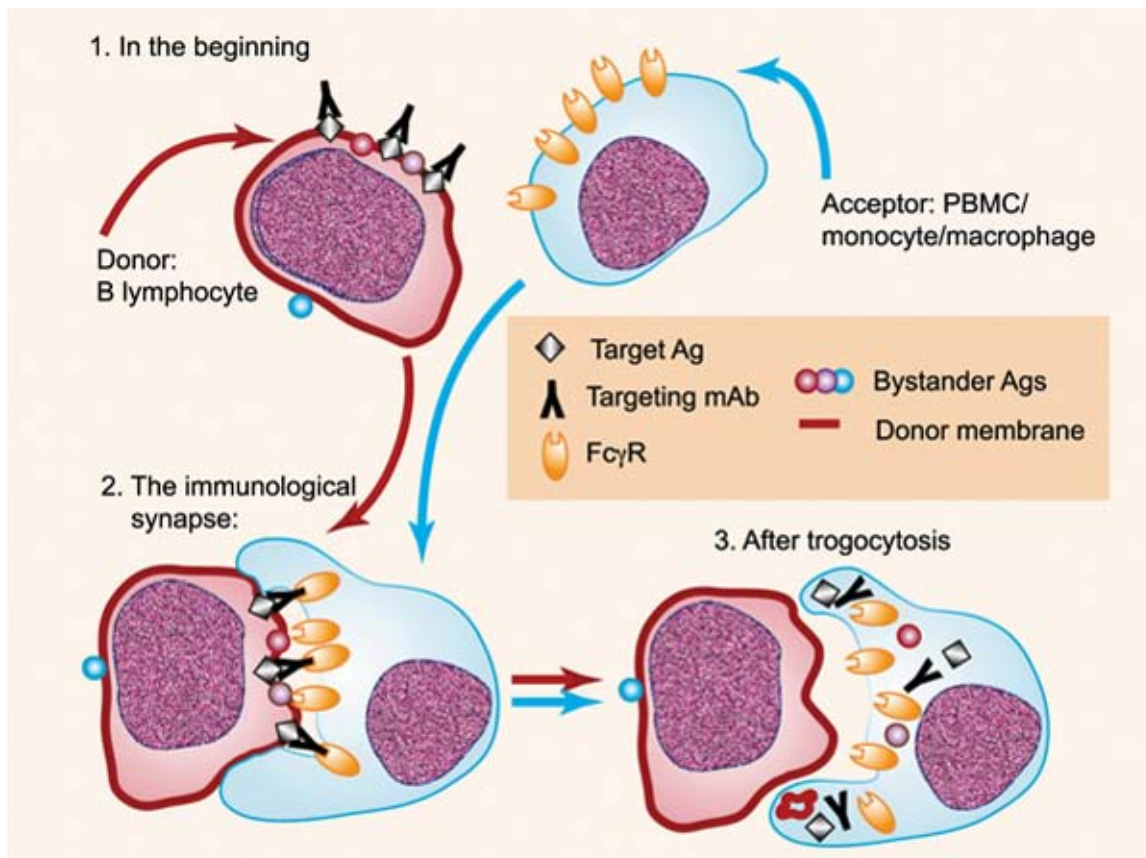
Until maybe yesterday most lymphoma investigators have been generally unexcited about the possibility that a whole lot more could be squeezed out of new anti-CD20 agents compared to R in B-cell neoplasia, but the new O data are likely to result in a lot more interest in exactly how MoAbs improve cancer 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.



Trogocytosis of IgG bound to targeted antigens is mediated by Fc $\gamma$  receptors on acceptor cells. Interaction of IgG bound to target antigens on the donor cell (1) with Fc $\gamma$  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 Fc $\gamma$  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.

Used with permission of *Blood*, from **Gnawing at Metchnikoff's paradigm**, Ronald P Taylor, 122:17, 2013; permission conveyed through Copyright Clearance Center, Inc.

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

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*<sup>SM</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

# Study of the Utility of Post-Therapy Surveillance Scans in DLBCL

Presentation discussed in this issue

Thompson CA et al. **Utility of post-therapy surveillance scans in DLBCL.** *Proc ASCO 2013*; **Abstract 8504.**

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

## Utility of Post-Therapy Surveillance Scans in Diffuse Large B-Cell Lymphoma

**Thompson C et al.**

*Proc ASCO 2013*; Abstract 8504.

Research  
To Practice®

## Background

- Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma that is potentially curable even after relapse.
- The optimal follow-up strategy for patients in remission is not clear.
- The NCCN guidelines suggest:
  - Evaluation every 3 to 6 months for 5 years
  - CT scan no more often than every 6 months for first 2 years after completion of treatment and then only as clinically indicated
- **Study objective:** To assess the utility of surveillance scans in a large, prospective, multi-institutional cohort of patients in remission from DLBCL.

Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

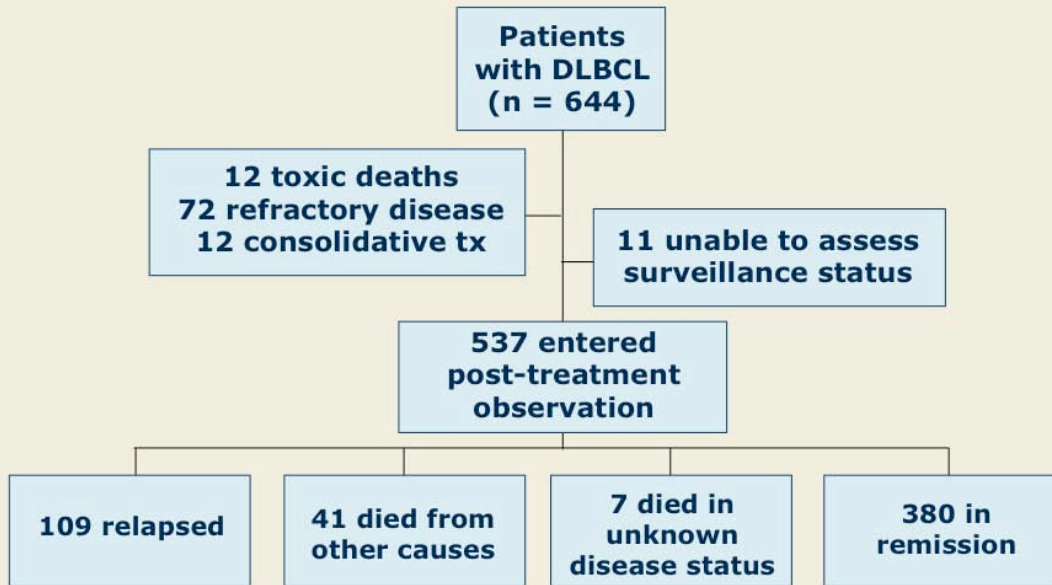
## Study Methods

- The study population consisted of a prospective cohort of patients (n = 644) with newly diagnosed, biopsy-proven DLBCL treated with anthracycline-based immunochemotherapy who were enrolled at University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource.
- Patients were followed for events, including relapse, re-treatment and death, with events verified by medical records.
- Management, including treatment and surveillance strategy, was per treating physician.
- Medical records were re-reviewed in patients with events for clinical details at relapse.
  - Timing: Routine versus nonroutine visit
  - Clinical features of relapse: Physical examination, symptoms, LDH

Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

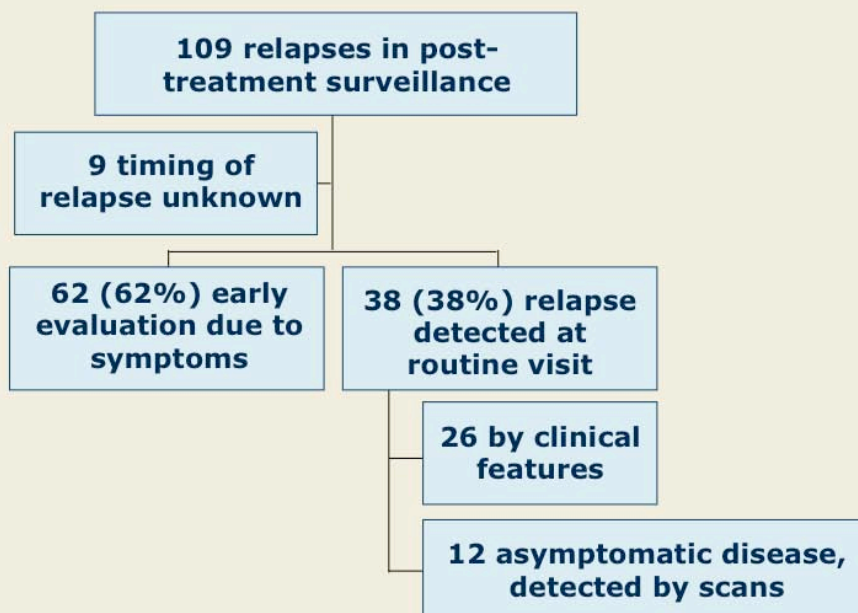
# Enrollment and Outcomes



With permission from Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

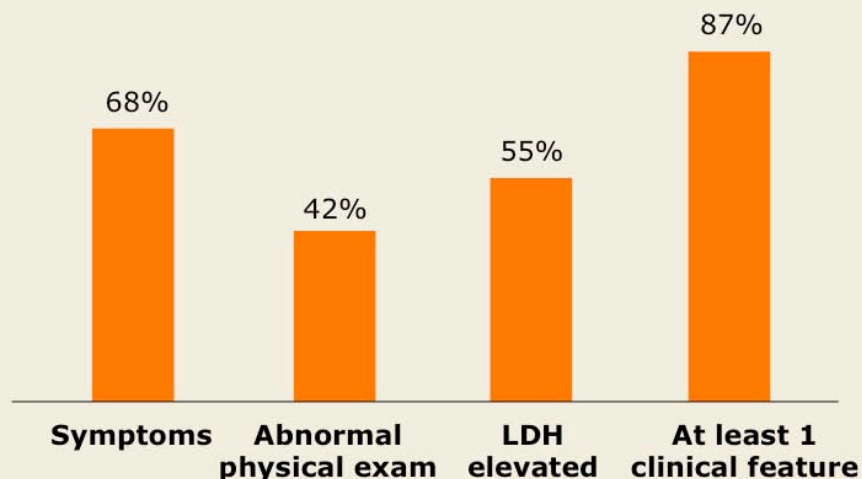
# Detection of Relapses



With permission from Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

## Clinical Features of Relapse in 109 Patients



With permission from Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

## Relapse in 12 Patients with Asymptomatic Disease Detected by Imaging

- Four patients had relapse of low-grade or other NHL subtype.
- Eight patients had asymptomatic DLBCL detected via surveillance scans.
  - On re-review, 4 patients had equivocal or positive PET scans reported at the end of treatment.
- Of 537 patients being observed after therapy, surveillance scans detected DLBCL relapse prior to clinical manifestations in 8 patients (1.5%).

Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

## Study Limitations

- This study was a retrospective review of medical records from a prospective cohort of patients with newly diagnosed DLBCL.
- Surveillance scans were frequently performed in conjunction with planned visits:
  - Reporting of clinical features of relapse may be biased by the treating physician's knowledge of scan results.
- Some of the data were missing.

Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

## Author Conclusions

- The majority of DLBCL relapses are detected outside of planned follow-up.
- Relapses are generally accompanied by symptoms, physical examination or laboratory abnormalities.
- Routine surveillance scans after therapy add little to the detection of DLBCL relapse in patients with no symptoms, examination or LDH abnormalities.
- A randomized prospective trial would be ideal to determine the optimal strategy for scanning.

Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

Research  
To Practice®

## **Investigator Commentary: Utility of Post-Therapy Surveillance Scans in DLBCL**

The question exists whether patients with DLBCL need to be tracked with scans after they have obtained a complete remission, which is the current standard. This retrospective evaluation of whether routine post-therapy surveillance scans added to detection of DLBCL relapse in patients in complete remission beyond what was provided by clinical follow-up concluded that routine scans did not improve upon the ability to detect DLBCL relapse. Only a small percentage of relapses were detected earlier by scans than by physical exams, laboratory analysis or presentation of symptoms. The critical question to ask is, does it matter? Does the ability to detect relapses earlier make a difference in the survival of these patients? We don't have data from a prospective analysis to answer that question.

This issue remains an important one, and I believe that we need a randomized trial to prove whether scans are needed to detect DLBCL relapses earlier. For the time being, I will continue with my practice of following my patients with CAT scans every 6 months for 2 years from time of diagnosis. I do not recommend the use of PET scans because a high false positive rate is associated with them.

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