# 5 Minute JournalClub

## *Hematologic Oncology*

Issue 4, 2013

For more visit ResearchToPractice.com/5MJCHEM2013

Research To Practice®

# CME Information

**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.

# CME Information (Continued)

**LEARNING OBJECTIVES**

- 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.

**CREDIT DESIGNATION STATEMENT**

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

# CME Information (Continued)

**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.

**FACULTY DISCLOSURES**

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

# CME Information (Continued)

*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.

# CME Information (Continued)

**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.

5 MinuteJournalClub

Hematologic Oncology
Issue 4, 2013

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.

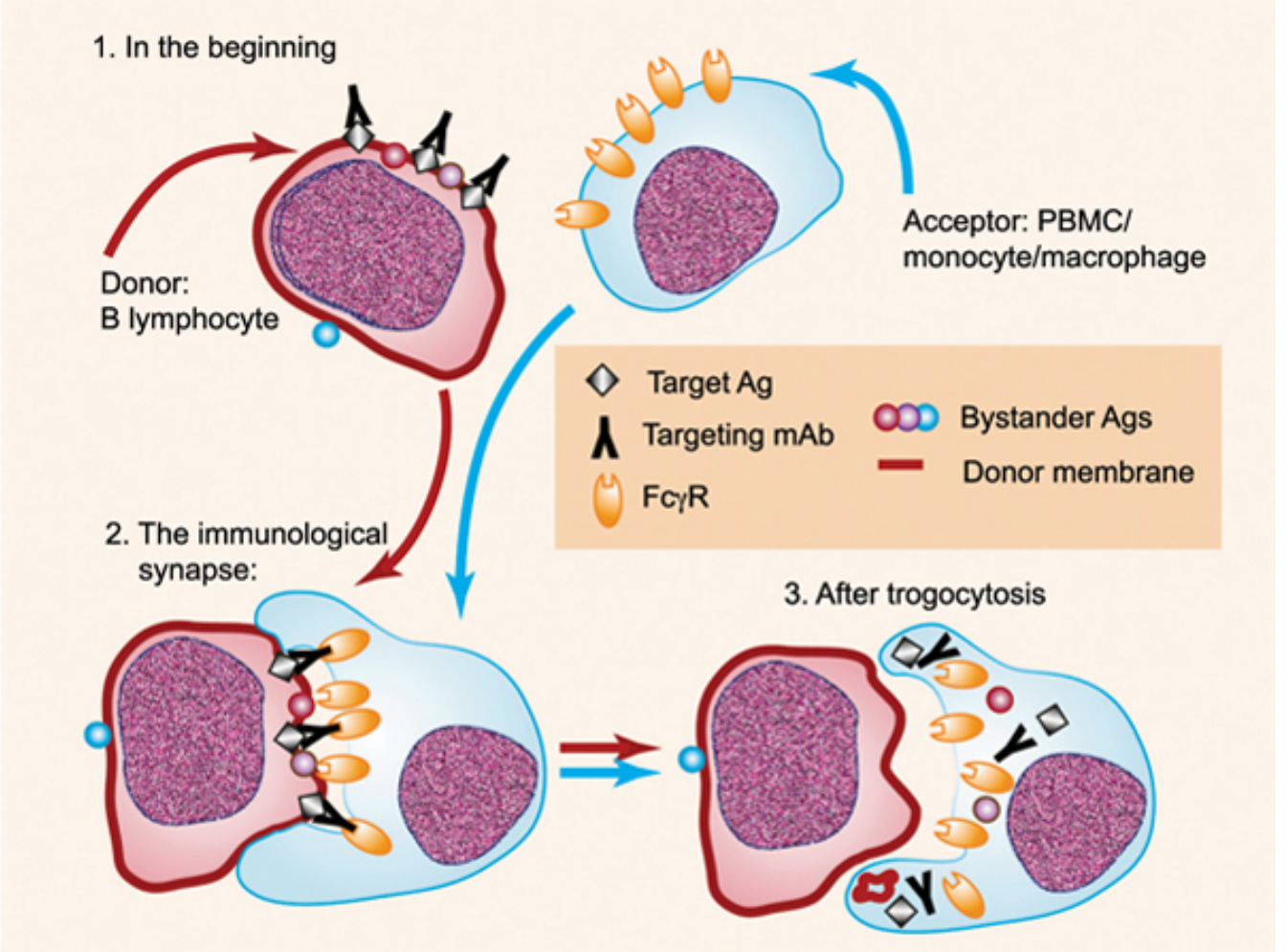
**When should O be considered right now in practice?**

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




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.

"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**

**Alliance/CALGB 50803: A Phase 2 Trial of Lenalidomide plus Rituximab in Patients with Previously Untreated Follicular Lymphoma[1]**

**The 'RELEVANCE' Trial: A LYSA-Sponsored Phase 3 Randomized Study to Compare the Efficacy and Safety of Rituximab plus Lenalidomide versus Rituximab plus Any Chemotherapy in Subjects with Previously Untreated Advanced Follicular Lymphoma[2]**


**[1]Martin P et al.**

*Proc ICML* 2013;Abstract 063.

**[2]Morschhauser F et al.**

*Proc ICML* 2013;Abstract 136.

# Alliance/CALGB 50803: A Phase 2 Trial of Lenalidomide plus Rituximab in Patients with Previously Untreated Follicular Lymphoma

**Martin P et al.**

*Proc ICML* 2013;Abstract 063.

# Background

- The SAKK trial demonstrated that rituximab is active as a single agent for the treatment of follicular lymphoma (FL).
- Two Phase II studies demonstrated that rituximab in combination with galiximab or epratuzumab is effective in patients with previously untreated FL and a low FLIPI score (*Ann Oncol* 2012;23:2356; *Cancer* 2013;119(21):3797-804).
- Also, the Phase II CALGB-50401 study showed that lenalidomide in combination with rituximab ($R^2$) demonstrated activity in patients with recurrent FL.
- **Study objective:** To determine the efficacy and safety of lenalidomide in combination with rituximab for patients with previously untreated FL.

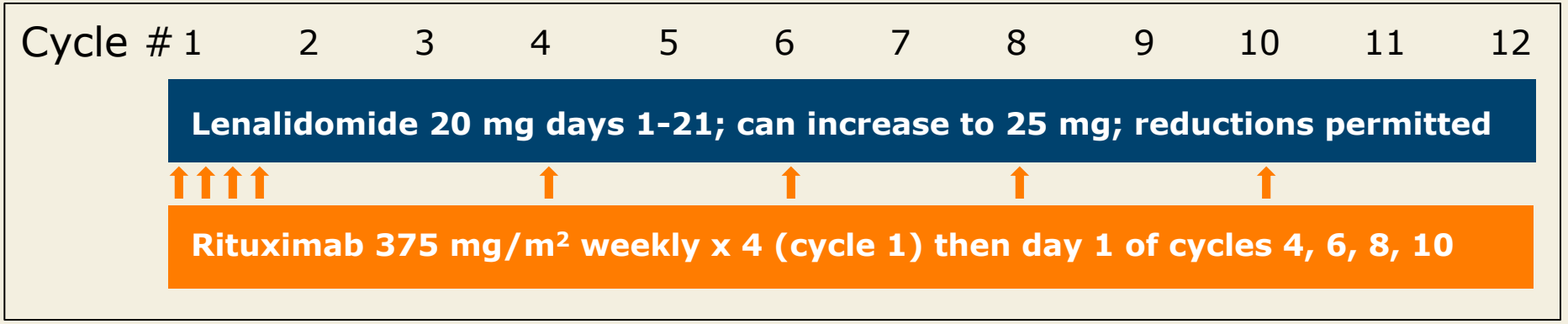
Martin P et al. *Proc ICML* 2013;Abstract 063.

# Phase II CALGB-50803 Trial Design

**Eligibility (n = 65)**

Bulky Stage 2 or Stage 3, 4 follicular NHL
Previously untreated, Grade 1, 2 or 3a disease
FLIPI 0-2 risk factors

1 cycle = 28 days, 12 cycles planned




- PET/CT scan performed at baseline, weeks 10, 24 and 52
- CT/MRI chest/abdomen/pelvis every 4 mo x 2 y, then every 6 mo until PD up to 10 y
- **Primary endpoints:** Response rate, time to progression

Martin P et al. *Proc ICML* 2013;Abstract 063.

# Baseline Characteristics

| | All FLIPI (n = 65) | FLIPI 0-1 (n = 20) | FLIPI 2 (n = 41) |
|---|---|---|---|
| Median age | 53 years | 53 years | 53 years |
| ≥60 years | 19% | 5% | 22% |
| Male | 48% | 65% | 41% |
| >4 nodal sites | 49% | 5% | 71% |
| Grade 1-2 disease | 95% | 100% | 95% |
| Bulky (≥7 cm) disease | 23% | 35% | 18% |
| Stage 3-4 disease | 92% | 75% | 100% |

Martin P et al. *Proc ICML* 2013;Abstract 063.

# Best Response

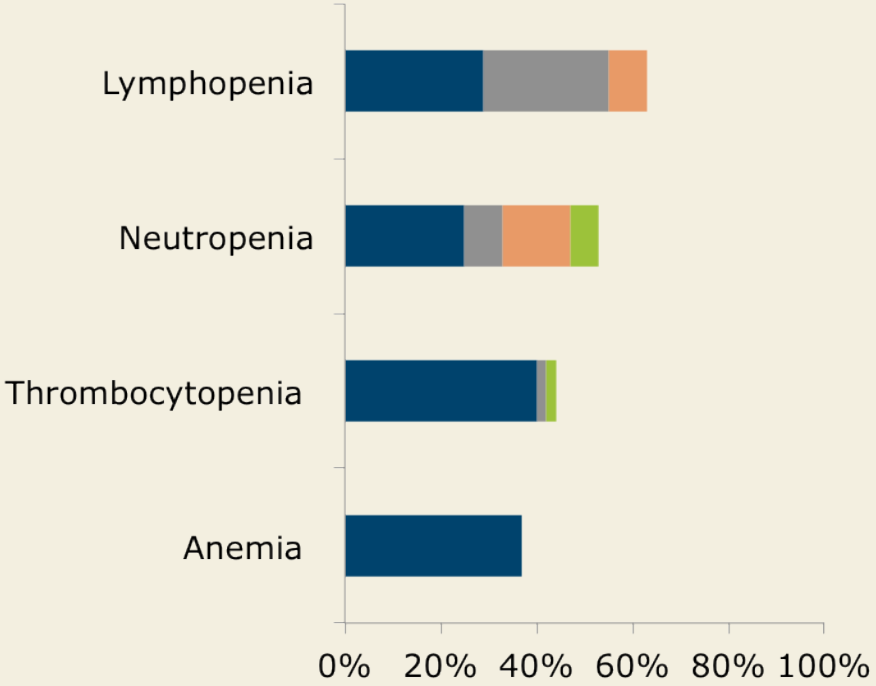
| Response | Overall (n = 57) | FLIPI 0-1 (n = 17) | FLIPI 2 (n = 36) | FLIPI 3 (n = 2) |
|---|---|---|---|---|
| ORR | 93% | 94% | 92% | 100% |
| Complete response (CR) | 72% | 77% | 70% | 100% |
| Partial response | 21% | 18% | 22% | 0% |
| Stable disease | 4% | 0% | 6% | 0% |
| Not evaluable | 4% | 6% | 3% | 0% |

- 4 additional patients in PET CR but not confirmed by bone marrow biopsy
- No significant association was found between CR rate and FLIPI score, presence of bulky disease or grade.
- Median time to first response: 10 weeks
- Progressive disease: 7/57 (12%)

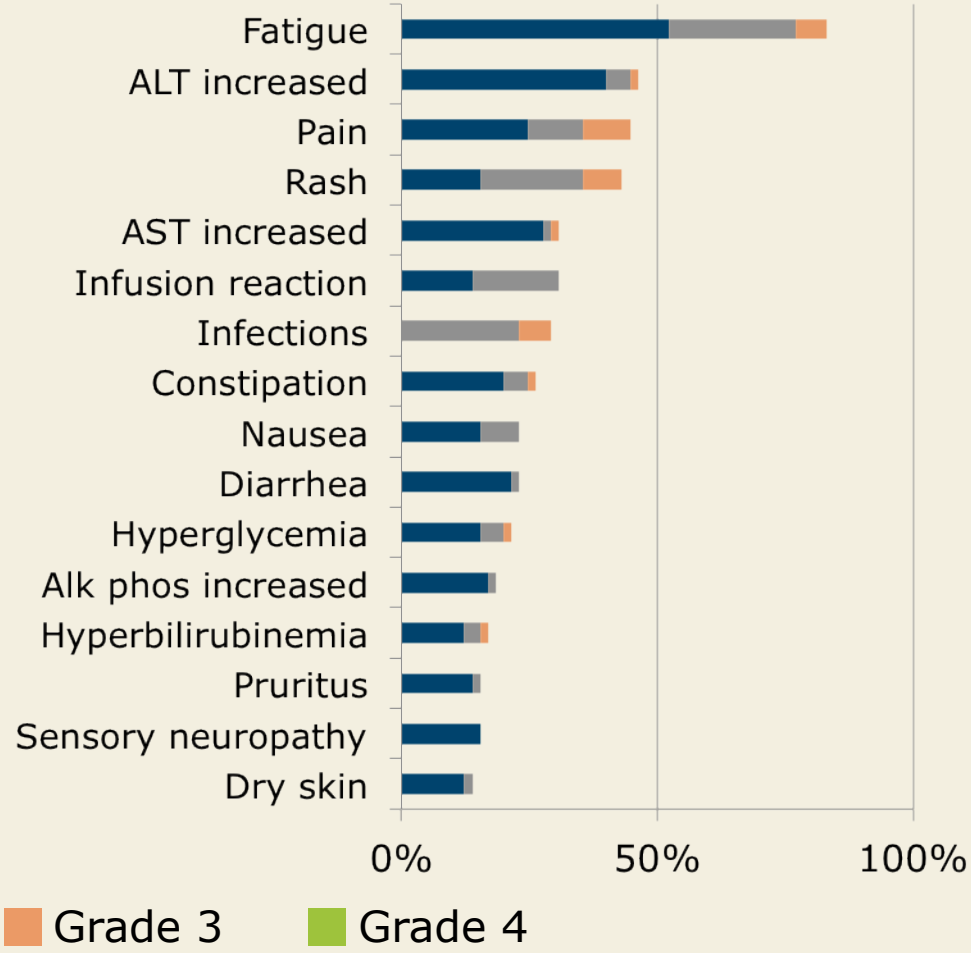
Martin P et al. *Proc ICML* 2013;Abstract 063.

# Adverse Events

## Hematologic




## Nonhematologic




Grade 1 Grade 2 Grade 3 Grade 4

With permission from Martin P et al. *Proc ICML* 2013;Abstract 063.

# Comparison to Other Phase II CALGB Trials of Rituximab

| Characteristic | 50803 (n = 65) | 50701* (n = 59) | 50402† (n = 61) |
|---|---|---|---|
| Regimen | $R^2$ | Epratuzumab/R | Galiximab/R |
| Median age | 53 y | 54 y | 57 y |
| Median follow-up | 1.6 y | 2.7 y | 4.3 y |
| Completed Tx | 81% | 93% | 82% |
| ORR | 93% | 88% | 72.1% |
| CR/CRu (overall)<br>FLIPI 0-1/2 | 72%<br>77%/70% | 42%<br>31%/44% | 48%<br>75%/52% |
| Median PFS | Not reached | 3.5 y | 2.9 y |

* Grant et al. *Cancer* 2013;119(21):3797-804.

† Czuczman et al. *Ann Oncol* 2012;23(9):2356-62.

Martin P et al. *Proc ICML* 2013;Abstract 063.

# Author Conclusions

- Lenalidomide in combination with rituximab is highly active as front-line therapy for patients with low- and intermediate-risk FLIPI scores.
  - Overall response rate: 93%; CR: 72%
  - No association between FLIPI score and CR
- A longer follow-up time is required to evaluate PFS.
- The regimen was well tolerated.
  - Grade 3/4 neutropenia occurred in 20% of patients
  - Febrile neutropenia was reported in only 1 patient
  - Fatigue was common with Grade 1/2 intensity occurring in 77% of patients

Martin P et al. *Proc ICML* 2013;Abstract 063.

## Investigator Commentary: CALGB-50803 Phase II Trial of Lenalidomide/Rituximab ($R^2$) in Previously Untreated FL

This CALGB single-arm Phase II study of $R^2$ for patients with previously untreated FL yielded similar results to those previously reported by Nathan Fowler and colleagues (*Proc ASH* 2012;Abstract 901). The combination regimen in the CALGB trial was administered in a slightly different manner than that used in the Fowler study but still resulted in an extremely high response rate. Based on Phase II data, the Phase III RELEVANCE trial will evaluate the $R^2$ regimen versus R/chemotherapy (see Morschhauser et al. *Proc ICML* 2013;Abstract 136).

The question persists as to how lenalidomide and rituximab work together to produce these responses. Some of my earlier clinical research studied how to potentiate rituximab by stimulating the immune system. To the degree that lenalidomide acts as an immunomodulator, it may stimulate some components of the immune system and it may help an antibody work better. The bottom line is that there is no question from the data that for an indolent lymphoma $R^2$ is better than lenalidomide alone, and this CALGB study demonstrated that.

***Interview with Jonathan W Friedberg, MD, MMSc, July 18, 2013***

# The 'RELEVANCE' Trial: A LYSA-Sponsored Phase 3 Randomized Study to Compare the Efficacy and Safety of Rituximab plus Lenalidomide versus Rituximab plus Any Chemotherapy in Subjects with Previously Untreated Advanced Follicular Lymphoma

**Morschhauser F et al.**

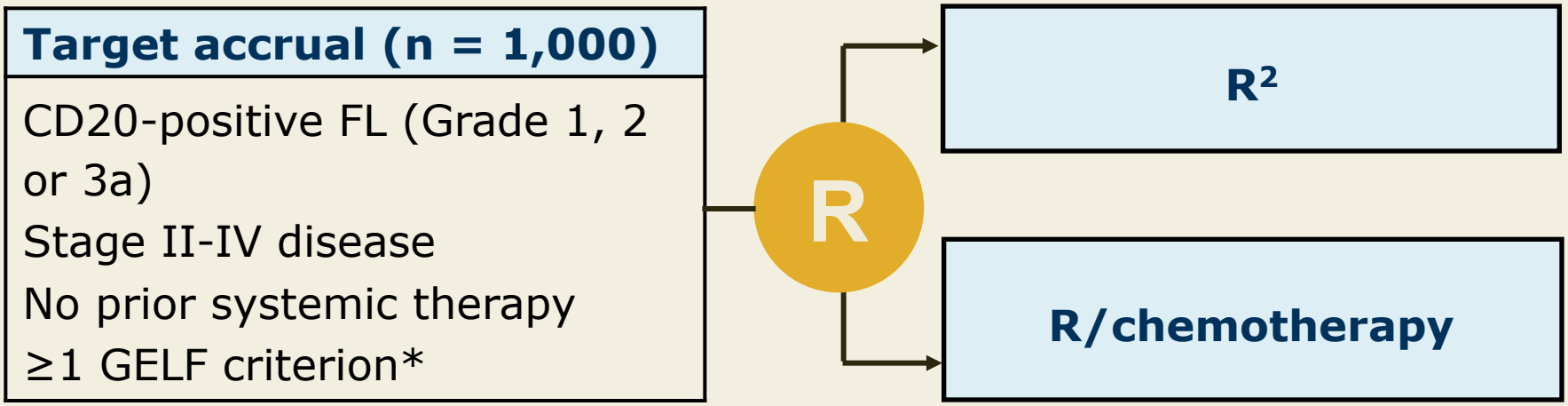
*Proc ICML* 2013;Abstract 136.

# Background

- Rituximab (R) in combination with chemotherapy followed by R maintenance is a standard treatment for patients with previously untreated follicular lymphoma (FL) (*Lancet* 2011;377:42-51).
- A Phase II trial demonstrated that the combination of lenalidomide with rituximab ($R^2$) is active and tolerable in patients with untreated FL (*Proc ASH* 2012;Abstract 901):
  - 3-year progression-free survival (PFS): 81%
  - Overall response rate: 98%
    - Complete response (CR)/unconfirmed CR (CRu): 87%
- **Study objective:** To compare the efficacy and safety of $R^2$ to R/chemotherapy for patients with previously untreated FL.

Morschhauser F et al. *Proc ICML* 2013;Abstract 136.

# Ongoing Phase III RELEVANCE Trial Design (NCT01650701)




Study start date: February 2012

Estimated study completion date: July 2024

* 1 lesion >7 cm; 3 nodes ≥3 cm; symptomatic splenomegaly; organ compression, pleural or peritoneal effusion; elevated LDH or β2-microglobulin; B-symptoms

- **Primary endpoints:** CR/CRu rate at 120 weeks, PFS
- **Secondary endpoints include:** Event-free survival, time to next lymphoma treatment, overall survival, minimal residual disease using PCR and health-related quality of life

Morschhauser F et al. *Proc ICML* 2013;Abstract 136; www.clinicaltrials.gov, November 2013.

# Study Methods

- Patients will be stratified prior to randomization by:
  - FLIPI score (0-1 vs 2 vs 3-5)
  - Longest diameter of the largest node (>6 vs ≤6 cm)
  - Age (≤60 vs >60 years)
- Patients randomly assigned to the $R^2$ arm will receive:
  - Lenalidomide dose: 20 mg on d2-22 every 28 d x 6 cycles
    - If CR achieved, then 10 mg on d2-22 for 12 cycles
    - If PR, continue with 20 mg for 3-6 cycles and then 10 mg on d2-22 every 28 d for ≤18 cycles
  - Rituximab dose: 375 mg/m$^2$ on d1,8,15,22 of cycle 1; d1 of cycles 2-6
    - After 8 weeks, patients with responsive disease will continue with 375 mg/m$^2$ of rituximab every 8 weeks for 12 cycles.

Morschhauser F et al. *Proc ICML* 2013;Abstract 136. (Abstract only)

# Study Methods (Continued)

- Patients randomly assigned to the control arm of the trial will receive the investigator's choice of 6-8 cycles of one of the following:
  - R-CHOP
  - R-CVP
  - R-bendamustine
- After 7 or 8 weeks, patients with responsive disease will continue to receive 375 mg/m$^2$ of rituximab every 8 weeks for 12 cycles.

Morschhauser F et al. *Proc ICML* 2013;Abstract 136. (Abstract only)

# Determination of Efficacy

- Efficacy determination will be based on the coprimary endpoints of complete response rate at 120 weeks and PFS using the International Working Group's response criteria (Cheson 1999).
- The current study design hypothesizes a superiority of the experimental arm.
- The secondary objectives are to compare event-free survival, time to next lymphoma treatment, overall survival, minimal residual disease using PCR and health-related quality of life.

Morschhauser F et al. *Proc ICML* 2013;Abstract 136. (Abstract only)

# Study Progress

- So far, 213 patients have been enrolled in 50 centers in the United States, France and Belgium.
- Additional centers from Australia (ALLG), Canada (NCCI-CTG), Germany (GLSG), Portugal, Spain (GELTAMO) and Italy will join the study in the second quarter of 2013.

Morschhauser F et al. *Proc ICML* 2013;Abstract 136. (Abstract only)

## Investigator Commentary: Ongoing Phase III RELEVANCE Trial of $R^2$ for Patients with Previously Untreated FL

The ongoing Phase III RELEVANCE trial is based on the extremely promising results obtained in Phase II trials of $R^2$ for untreated FL. The trial will randomly assign patients to the $R^2$ regimen or to physician's choice of R-CHOP, R-CVP or R-bendamustine. The target accrual of the RELEVANCE trial is 1,000 patients, with coprimary endpoints of CR/CRu and PFS.

Patients on both treatment arms will receive a component of rituximab maintenance therapy. The trial is designed to determine whether large groups of patients may be able to avoid chemotherapy and still have the same excellent outcomes. I've heard anecdotally from investigators participating in this trial that, surprisingly, even patients with bulky disease and those who seem ill and appear to need chemotherapy are responding well to the $R^2$ regimen.

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

# Disease Characteristics, Patterns of Care, and Outcomes of Follicular Lymphoma (FL) in the Oldest Old: Report from the US National Lymphocare Study (NLCS)

**Nabhan C et al.**

*Proc ICML* 2013;Abstract 102.

# Background

- Data on disease characteristics, treatment patterns and outcomes of patients older than age 80 are rarely reported.
- The US National Lymphocare Study (NLCS) is a prospective multicenter registry of patients with follicular lymphoma (FL) without study-specific treatment.
- **Study objective:** To analyze the disease characteristics, patterns of care and treatment outcomes for patients with FL who are older than age 80 using the NLCS database.

Nabhan C et al. *Proc ICML* 2013;Abstract 102.

# Study Methods

- All evaluable patients with newly diagnosed FL in the NLCS database were included (n = 2,649).
- Associations of age groups with disease characteristics and response rate (RR) were examined using the Pearson's Chi-squared test.
- The median progression-free survival (PFS) and overall survival (OS) by treatment regimen were estimated for each age group.
- Cox regression adjusted for baseline disease factors and use of maintenance rituximab (MR) were used:
  - To assess treatment differences in PFS and OS.
  - To determine the significance of age by treatment interactions.

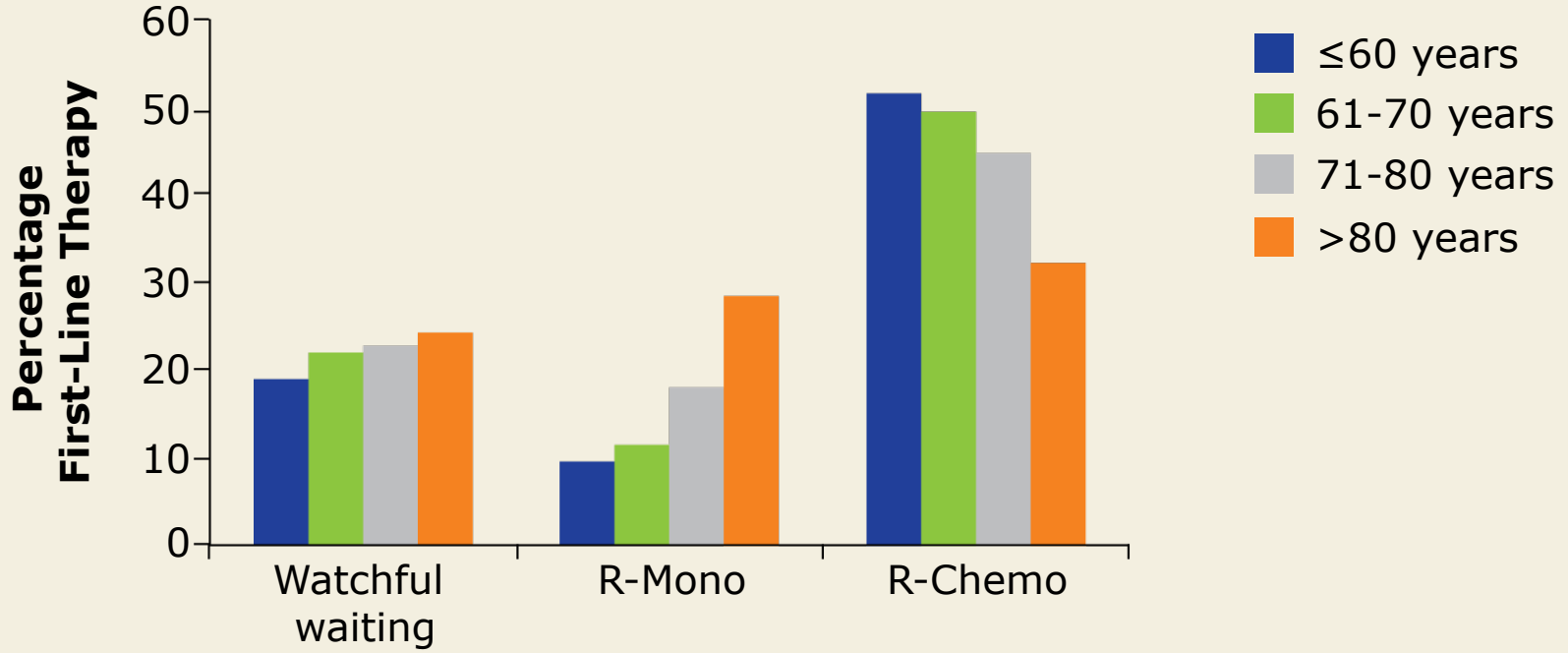
Nabhan C et al. *Proc ICML* 2013;Abstract 102.

# Baseline Characteristics

| Characteristic | ≤60 years (n = 1,255) | 61-70 years (n = 666) | 71-80 years (n = 519) | >80 years (n = 209) |
|---|---|---|---|---|
| White race | 88% | 92% | 92% | 94% |
| Stage III or IV disease | 71% | 64% | 63% | 63% |
| Grade 3 histology | 18% | 22% | 22% | 27% |
| ≥5 nodal sites | 39% | 32% | 31% | 18% |
| Hemoglobin <12 g/dL | 16% | 22% | 26% | 38% |
| ECOG PS 0 | 76% | 65% | 60% | 45% |
| Bone marrow involvement | 41% | 33% | 37% | 33% |

Nabhan C et al. *Proc ICML* 2013;Abstract 102.

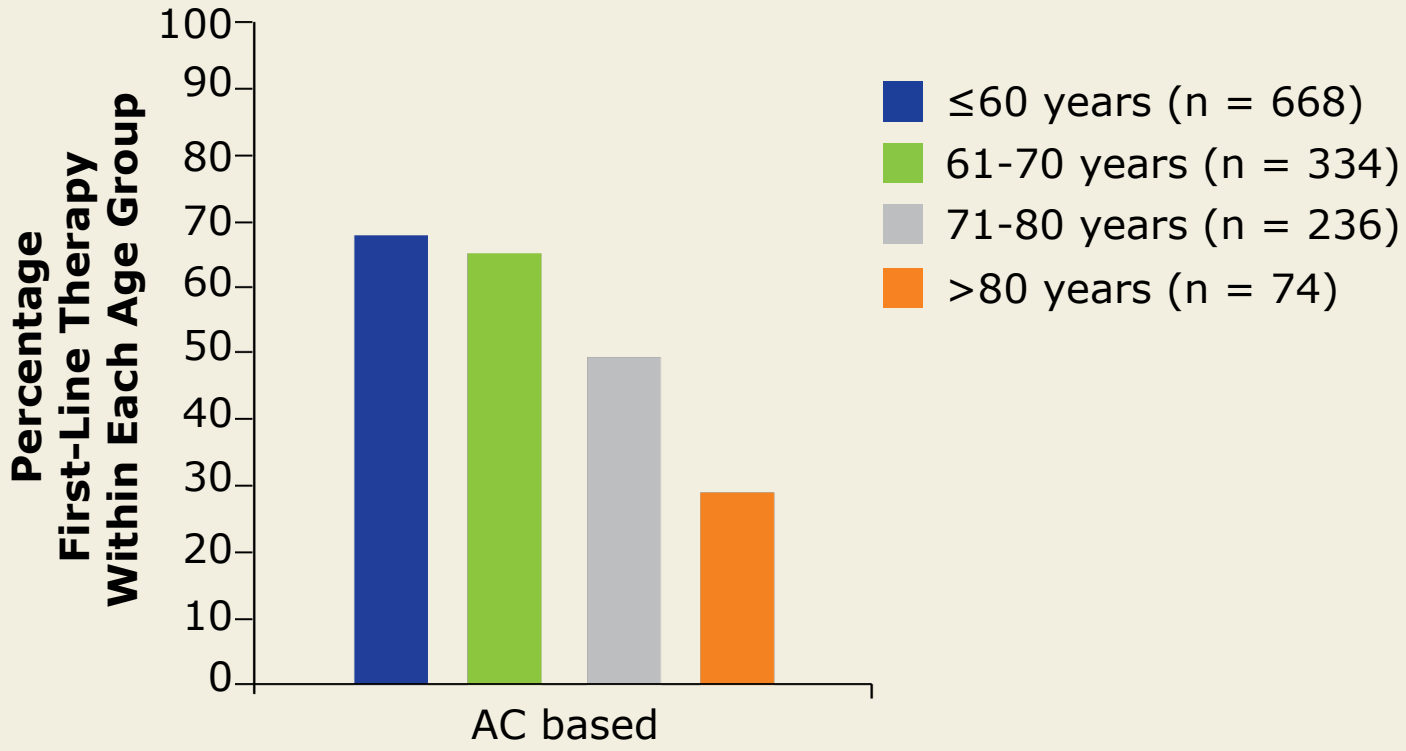
# Initial Treatment Regimen by Age




- Patients aged >80 years (treatment patterns significantly different than for patients aged ≤60; $p < 0.0001$):
  - Underwent watchful waiting more often (24% vs 19%)
  - Received rituximab monotherapy more often (29% vs 10%)
  - Received R-Chemo as initial strategy less often (32% vs 52%)

With permission from Nabhan C et al. *Proc ICML* 2013;Abstract 102.

# Anthracycline (Ac) Use by Age




- Patients aged >80 who received chemotherapy alone or in combination with rituximab were less likely to receive Ac than were patients aged ≤60 (28% vs 68%, $p < 0.0001$).
- Only Grade 3 histology significantly predicted Ac use for all age groups.

With permission from Nabhan C et al. *Proc ICML* 2013;Abstract 102.

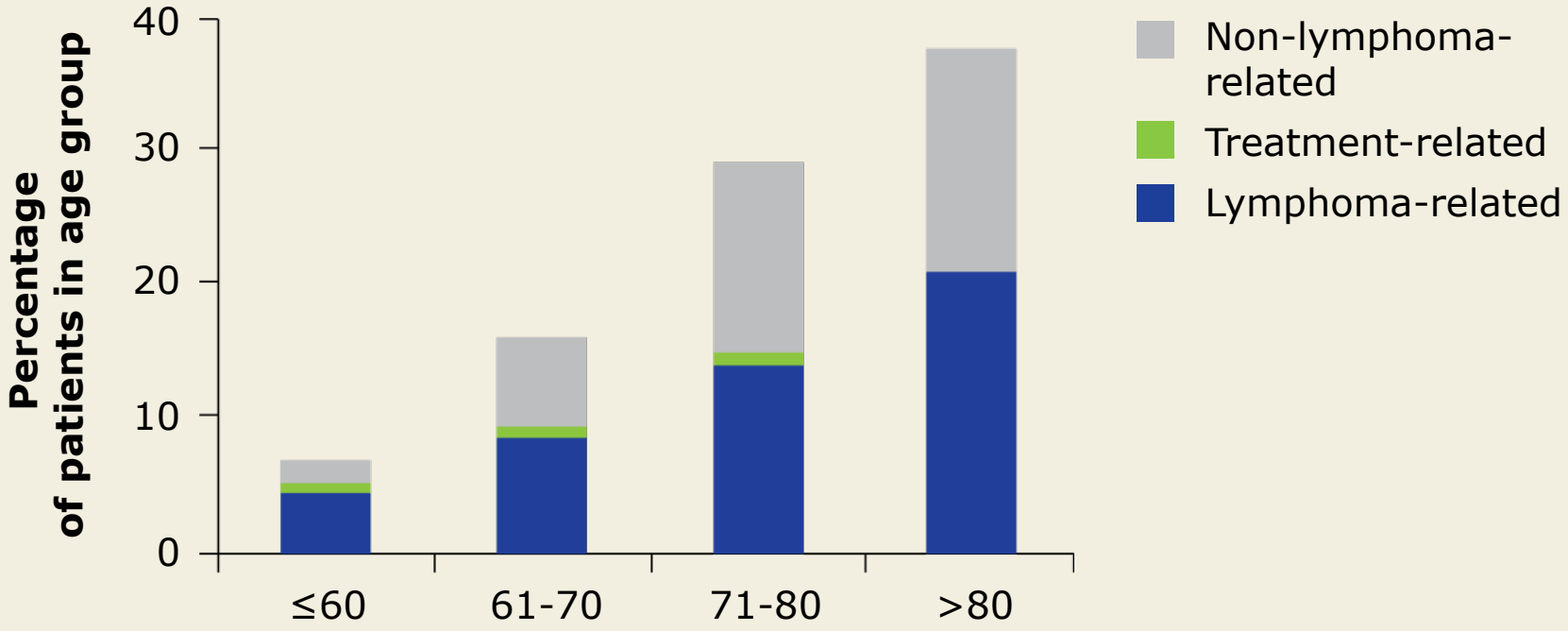
# Response Rates by Treatment and Age Groups

| % CR or PR | ≤60 | 61-70 | 71-80 | >80 | *p*-value |
|---|---|---|---|---|---|
| **All patients** | **75.7** | **73.6** | **71.0** | **66.0** | **0.020** |
| Watchful waiting | 14.1 | 22.0 | 21.1 | 14.6 | 0.225 |
| R monotherapy | 80.4 | 80.3 | 77.3 | 80.4 | 0.946 |
| R/chemotherapy | 92.1 | 92.6 | 88.5 | 83.9 | 0.056 |
| **AC-based** | **93.3** | **95.2** | **90.8** | **77.8** | **0.031** |
| Non-AC-based | 86.2 | 83.0 | 84.3 | 77.6 | 0.504 |

Note: Bold and orange font indicates significant ($p < 0.05$) differences by age group.

Nabhan C et al. *Proc ICML* 2013;Abstract 102.

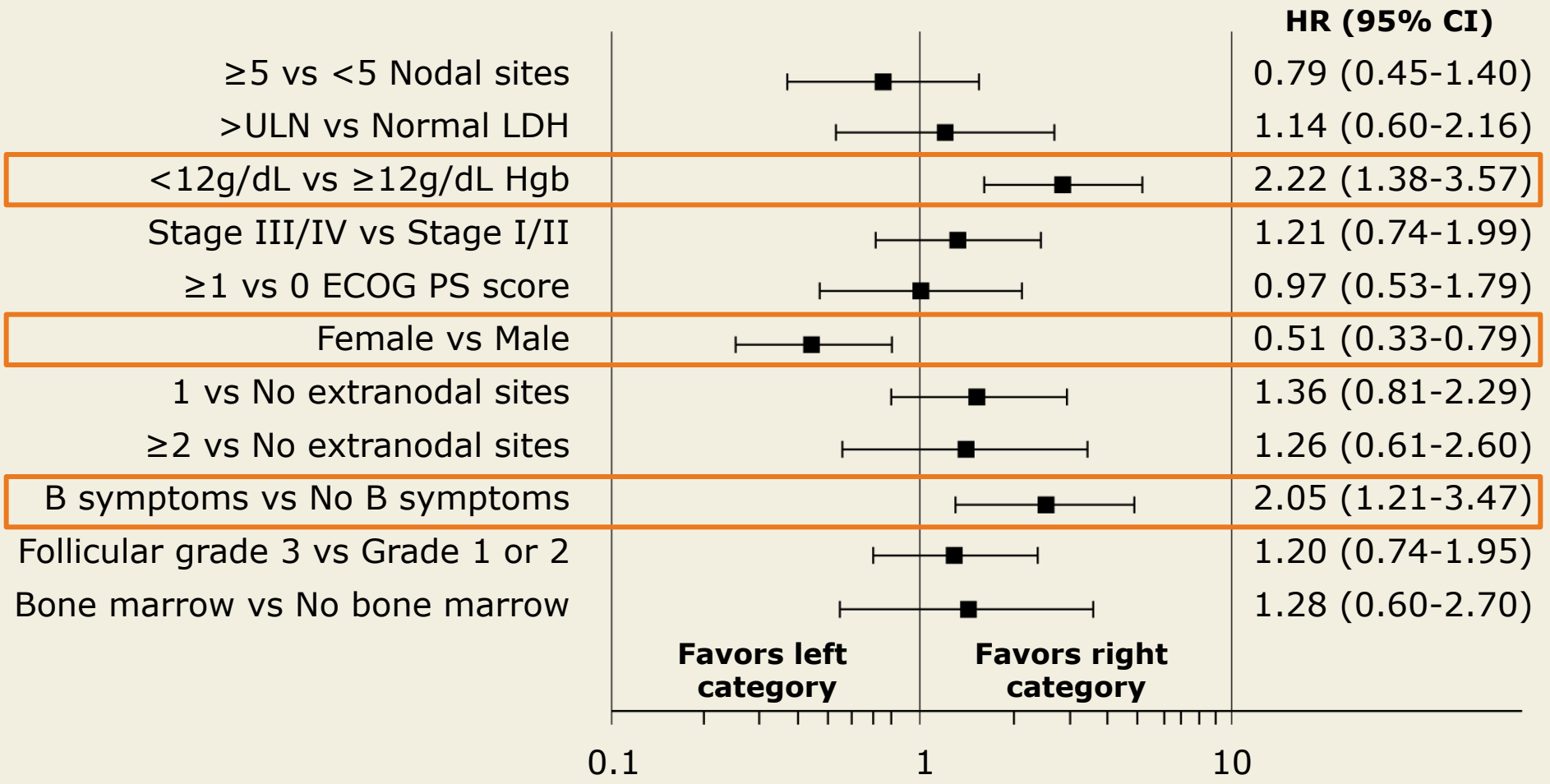
# Cause of Death by Age




| | ≤60 | 61-70 | 71-80 | >80 |
|---|---|---|---|---|
| Number of deaths | 110 | 130 | 199 | 107 |
| Proportion lymphoma-related | 48% | 42% | 36% | 40% |

With permission from Nabhan C et al. *Proc ICML* 2013;Abstract 102.

# Variables Affecting Overall Survival in Patients >80 Years: Male Sex, Lower Hemoglobin and B Symptoms




Model adjusted for first-line treatment and maintenance rituximab

With permission from Nabhan C et al. *Proc ICML* 2013;Abstract 102.

# Author Conclusions

- PFS was influenced less by choice of therapy for patients older than age 80 with FL than for younger patients.
- Patients older than age 80 are more likely to receive rituximab monotherapy or to be observed.
- B symptoms, male sex and Hgb <12 g/dL predict inferior OS in patients with FL who are older than age 80.
- In patients with FL who are older than age 80, 40% of deaths were attributed to lymphoma, which did not differ considerably from patients younger than age 60.
- Prospective trials designed specifically for this patient population are needed.

Nabhan C et al. *Proc ICML* 2013;Abstract 102.

## Investigator Commentary: Report from the US NLCS in Patients Older Than Age 80 with FL

This was an interesting study to characterize US patterns of care for patients older than age 80 in the NLCS. Although this was a prospective observational study, it represents the largest population of oldest "old" patients ever observed in terms of the kinds of therapies administered. It showed that this patient group was less likely to receive R/chemotherapy. Importantly, these patients were diagnosed with FL in the era when R was gaining in use in FL after its approval but was not necessarily routinely used up front for all patients. As such, these older patients received up-front R/chemotherapy less commonly. Twenty-eight percent of patients older than age 80 received an anthracycline as part of up-front therapy compared to 68% in the group of patients aged 60 or younger, and that was markedly different. It's clear that some of our prejudgments about the kinds of therapies administered to older patients might affect quality of care and survival.

***Interview with Christopher Flowers, MD, MS, July 19, 2013***

We all approach a patient with FL at age 80 differently than we would a 30-year-old. We are planning to determine whether these patients die of FL. If we demonstrate that most of the deaths in this group are from other comorbid problems, then the conservative approach taken by many practitioners is the right one. However, if it is shown that FL is the key problem, doctors need to do a better job of controlling the disease.

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

# Radioimmunotherapy as Consolidation in MCL (Mantle Cell Lymphoma) — 8 Years Follow-Up of a Prospective Phase 2 Polish Lymphoma Research Group Study

**Jurczak W et al.**

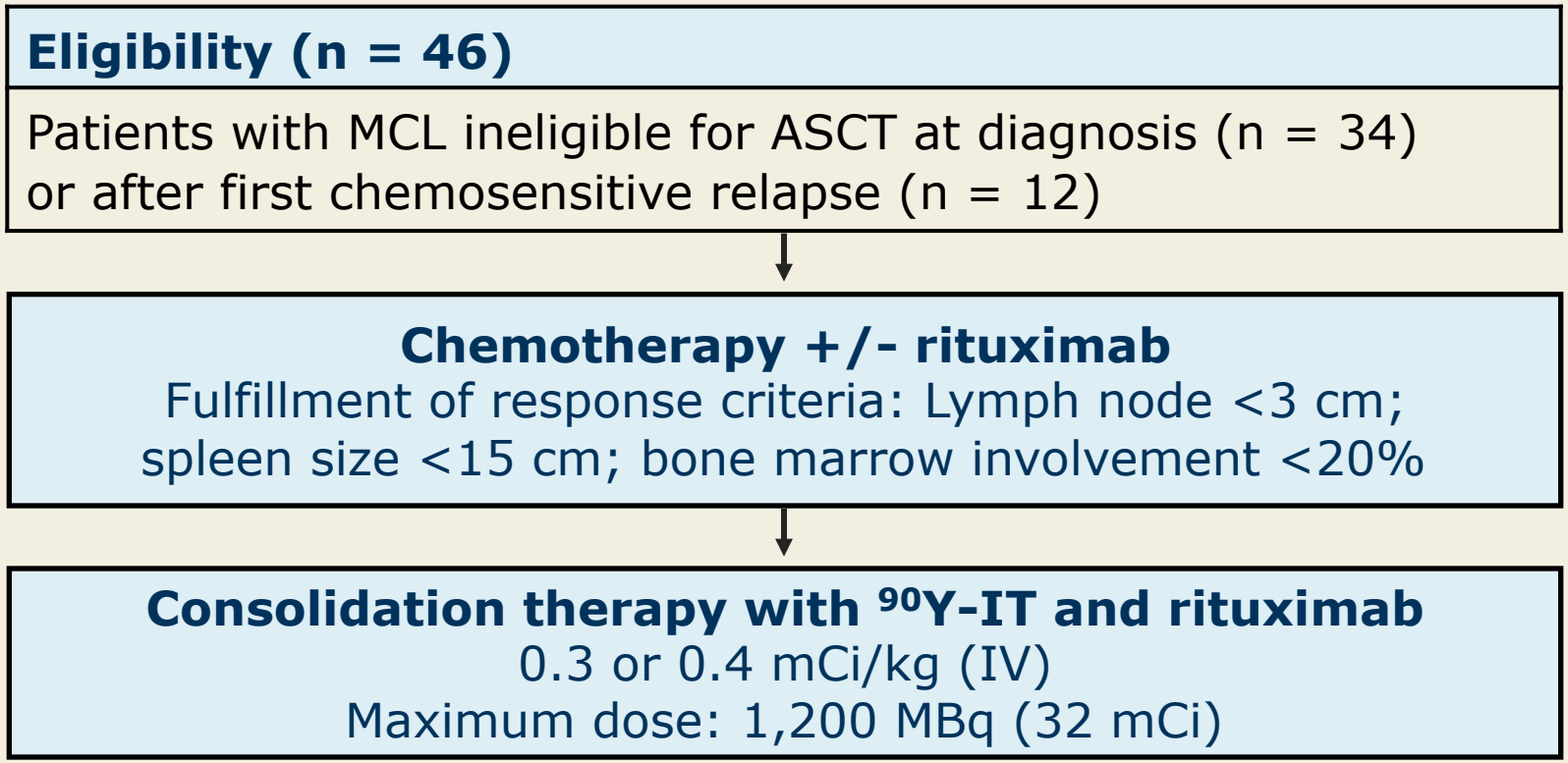
*Proc ICML* 2013;Abstract 111.

# Background

- Fewer than 20% of patients with MCL are candidates for high-dose chemotherapy with autologous stem cell transplant (ASCT) because of elderly age and comorbidities.
- Ibritumomab tiuxetan is an immunoconjugate of the monoclonal antibody ibritumomab, which, when linked to the radioisotope yttrium-90 ($^{90}$Y), targets the CD20 antigen on B-cell surfaces.
- Radioimmunotherapy (RIT) with $^{90}$Y-ibritumomab tiuxetan ($^{90}$Y-IT) may be an alternative consolidation therapy approach for elderly, frail patients.
- **Study objective:** To determine the feasibility of $^{90}$Y-IT as an alternative consolidation method in a prospective study for elderly patients with MCL.

Jurczak W et al. *Proc ICML* 2013;Abstract 111.

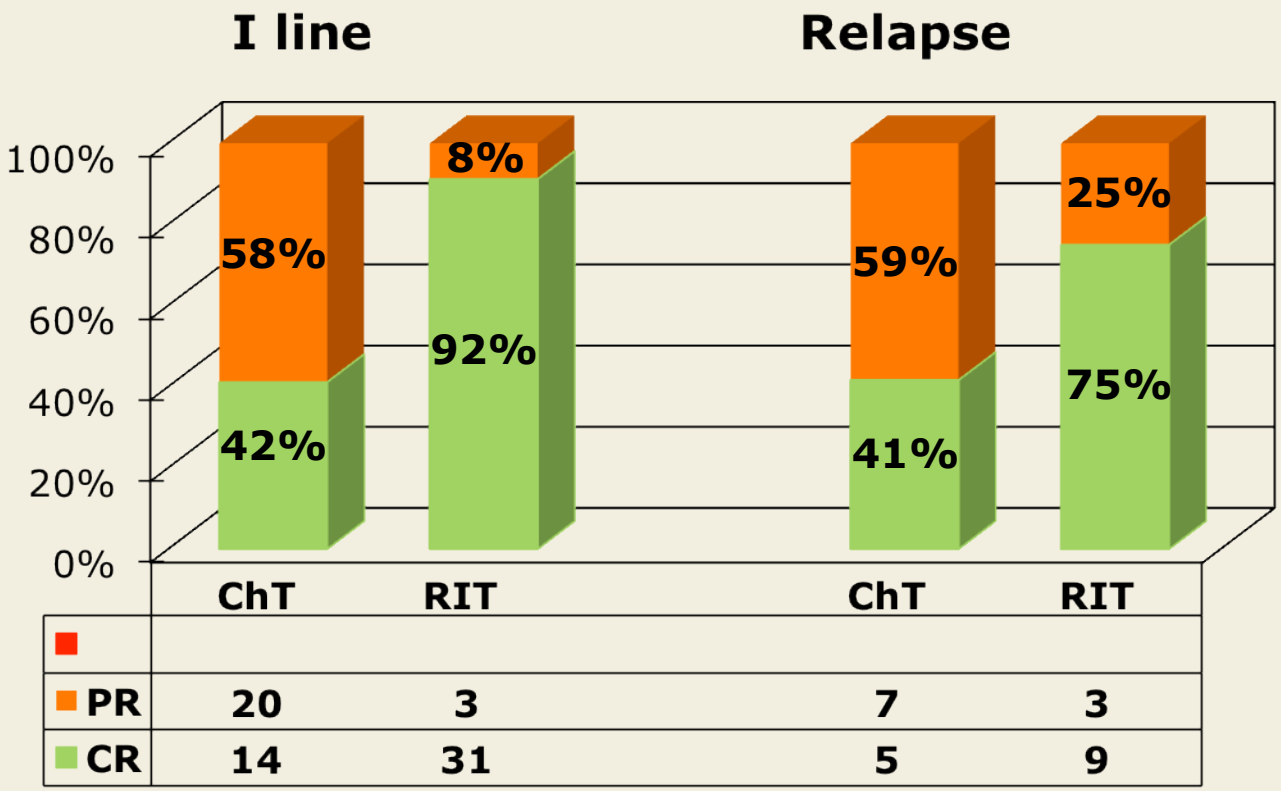
# Prospective Phase II Trial Design




- Chemotherapy regimens used before RIT consolidation: FC/FCM, CVP/CHOP

Jurczak W et al. *Proc ICML* 2013;Abstract 111.

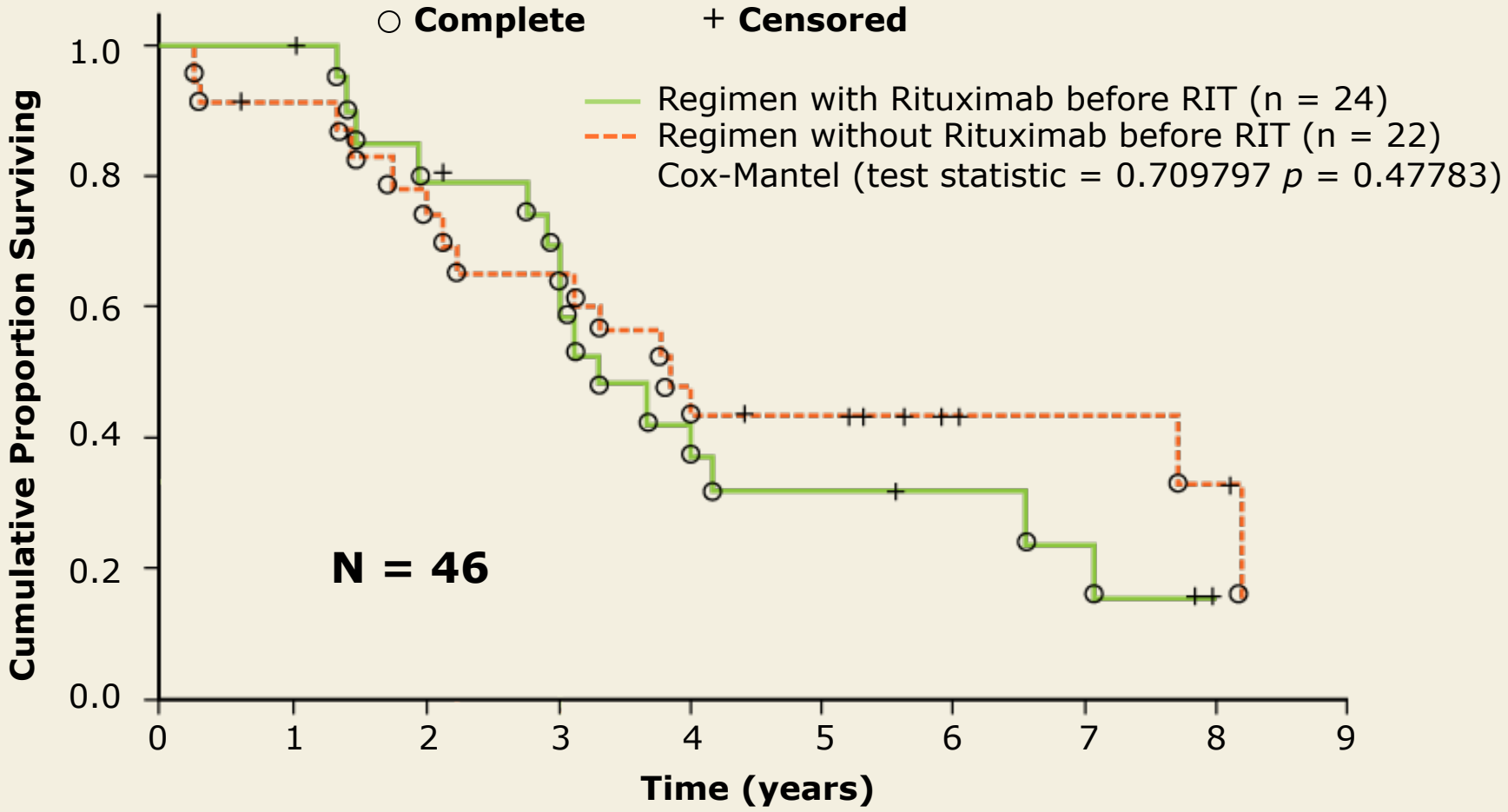
# Response to Chemotherapy and Consolidation RIT




N = 46

With permission from Jurczak W et al. *Proc ICML* 2013;Abstract 111.

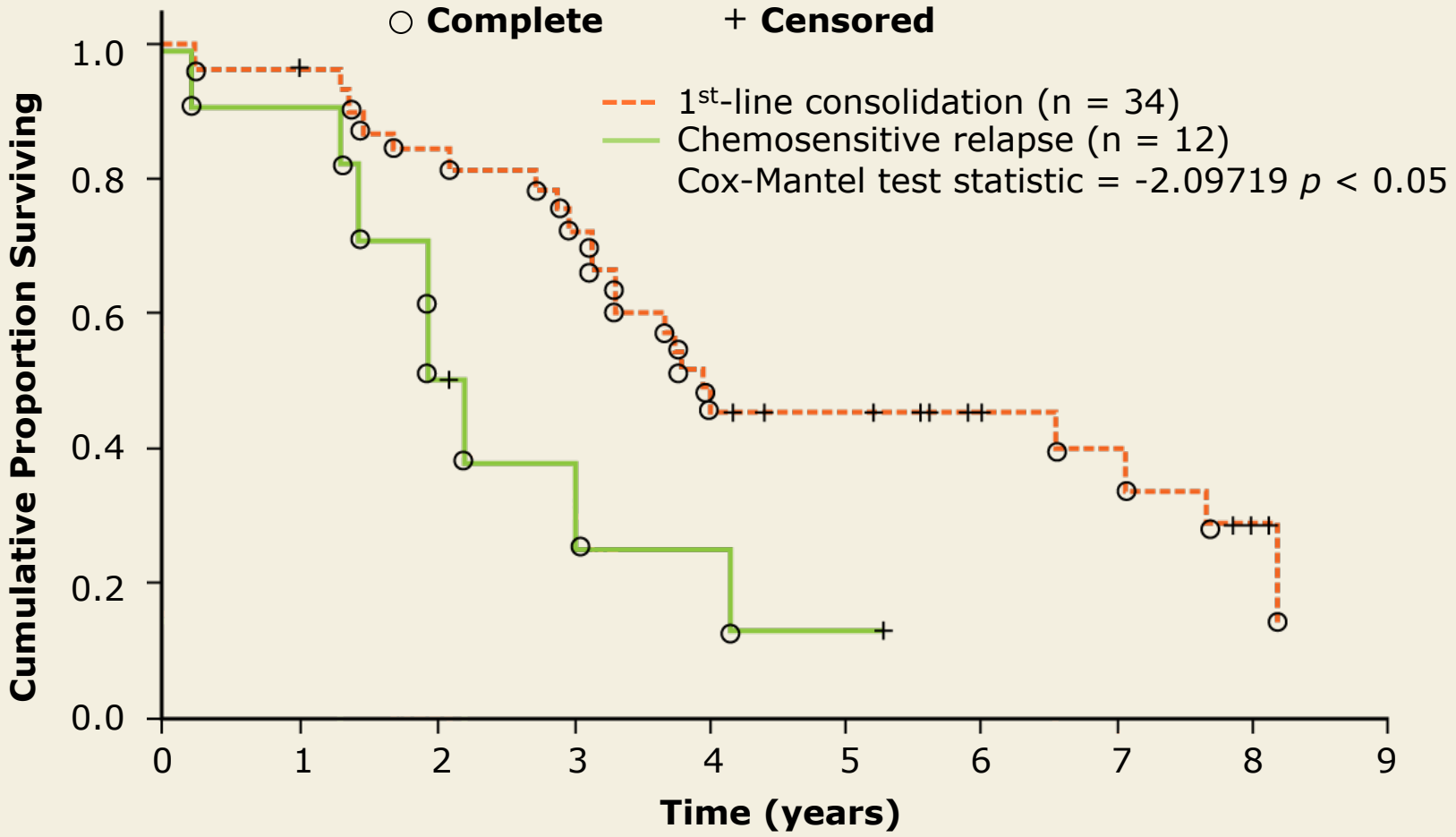
# Progression-Free Survival (PFS) with or without Rituximab Before RIT with $^{90}$Y-IT




- Median PFS (n = 46): 42 months

With permission from Jurczak W et al. *Proc ICML* 2013;Abstract 111.

# PFS with $^{90}$Y-IT Consolidation After First-Line versus Relapse




With permission from Jurczak W et al. *Proc ICML* 2013;Abstract 111.

# Hematologic Adverse Events After Consolidation by Preconsolidation Therapy Received

| Adverse event | FCM (n = 9) | FC (n = 12) | CHOP/CVP (n = 25) |
|---|---|---|---|
| WBC <2,000/uL | 8.5 weeks | 4.7 weeks | 2.0 weeks |
| Platelets <50,000/uL | 10.1 weeks | 3.0 weeks | 1.0 week |
| Infections | 43% | 10% | 20% |
| Required G-CSF | 23% | 10% | 0% |
| PLT transfusions | 60% | 30% | 0% |
| RBC transfusions | 50% | 20% | 20% |

WBC = white blood cell; G-CSF = granulocyte colony stimulating factor; PLT = platelet; RBC = red blood cell

- None of the patients experienced infection-related mortality
- Procedure-related mortality: FCM (3.3%); FC (0%); CHOP/CVP (0%)

Jurczak W et al. *Proc ICML* 2013;Abstract 111.

# Author Conclusions

- $^{90}$Y-IT consolidation for patients with MCL after induction chemoimmunotherapy appears to result in an excellent PFS.
  - Median PFS: 3.5 years
- The PFS was longest for patients with MCL who received consolidation therapy after first-line therapy.
  - At 7 years 40% remained in continuous CR.
- $^{90}$Y-IT consolidation is feasible for elderly patients with comorbidities who are not eligible for high-dose chemotherapy.
- Toxicity associated with $^{90}$Y-IT consolidation is considerable but manageable and appears to be more pronounced after fludarabine-based induction regimens.

Jurczak W et al. *Proc ICML* 2013;Abstract 111.

## Investigator Commentary: Radioimmunotherapy as Consolidation for MCL

Without intensive up-front therapy, such as hyper-CVAD, relapse occurs in approximately half of patients with MCL within 18 months, despite a high response rate. This has led administration of consolidation therapy, the most efficacious of which is ASCT, to become the standard. However, because those regimens are usually intolerable for older patients, an acceptable option that provides an overall survival advantage for these patients is the administration of rituximab for 2 years.

The data from this Phase II study demonstrated that one dose of $^{90}$Y-IT was highly active, with the CR rate doubling from 41% after induction to 87% after $^{90}$Y-IT. It is critical to follow up on the number of patients who remain in remission, but the data are encouraging of the idea that $^{90}$Y-IT could be an alternative consolidation treatment for patients who cannot tolerate transplant or do not want to receive 2 years of rituximab. The ECOG-1499 study of R-CHOP followed by $^{90}$Y-IT reported similar results, which is reassuring.

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

# Efficacy and Safety of Therapy with 90Y Ibritumomab Tiuxetan, in B Cell NHL Patients over 65 Years Old

**Campos M et al.**

*Proc EHA* 2013;Abstract B2009.

# 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.

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

# Trial Design

**Eligibility (n = 39)**

CD20-positive, B-cell NHL

Age >65 years

Neutrophils: ≥1.5 x $10^9$/L; platelets: ≥100 x $10^9$/L

Bone marrow lymphocytes CD20-positive: ≤25%

↓

**$^{90}$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

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

# Patient Demographics

| Characteristic | Patients (n = 39) |
|---|---|
| Mean age (range) | 72.8 years (65-87) |
| Male | 46% |
| ECOG PS 0-1 | 92.3% |
| NHL-follicular | 69.2% |
| Mantle-cell lymphoma | 17.9% |
| Diffuse large B-cell lymphoma | 10.3% |
| Mucosa-associated lymphoid tissue lymphoma | 2.6% |

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

# Response Rates

| Response | Patients (n = 39) |
|---|---|
| ORR | 84.6% |
| Complete response | 74.3% |
| Partial response | 10.2% |
| Progressive disease | 15.4%* |

* 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

| **All patients** | **n = 39** |
|---|---|
| Mean PFS | 39.5 months |
| Median PFS | Not reached |
| Estimated mean OS since $^{90}$Y-IT | 63.1 months |
| Estimated mean OS since diagnosis | 158 months |
| **Patients who received $^{90}$Y-IT as consolidation of first-line therapy*** | **n = 13** |
| Mean PFS | 52.1 months |

* 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

| Adverse event (AE) | n = 39 |
|---|---|
| Neutropenia* (Grade 3/4) | 41.0% |
| Thrombocytopenia† (Grade 3/4) | 35.9% |
| Severe mucositis | 2.6% |
| Concomitant associated tumors (breast, colon, lung, prostate) | 10.3% |
| Rectal carcinoma after 18 months of Tx (age >77 y) | 5.1% |

* 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

- $^{90}$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 $^{90}$Y-IT for Elderly Patients with B-Cell NHL

These data show that $^{90}$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 $^{90}$Y-IT or other radioimmunoconjugates better, including studies combining them with other agents.

It is important to be cautious about the use of $^{90}$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 $^{90}$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***

**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)[1]**

**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)[2]**


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

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

# 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.**

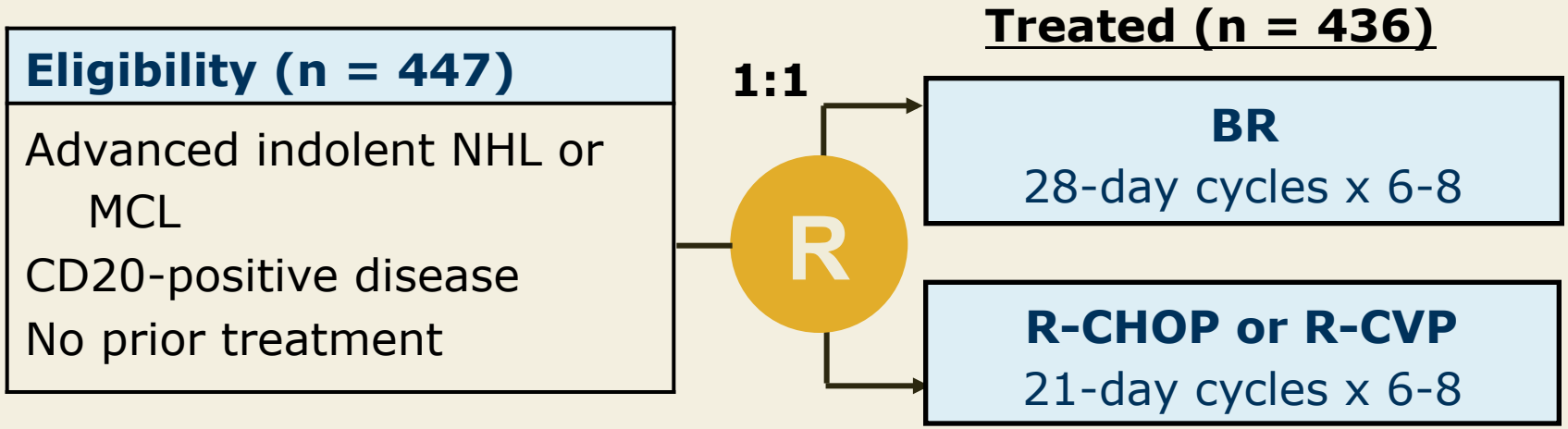
*Proc ICML* 2013;Abstract 084.

# 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.

# 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.

# 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)

# 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)

# 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)

# 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)

## 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***

# 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.

# 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.

# 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.

# 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.

## 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***

**Single-Agent Lenalidomide in Patients with Relapsed/Refractory Mantle Cell Lymphoma Following Bortezomib: Efficacy, Safety and Pharmacokinetics from the Multicenter Phase II MCL-001 "EMERGE" Trial[1]**

**Single-Agent Lenalidomide in Patients with Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study[2]**

**Goy A et al.**

[1] *Proc EHA* 2013;Abstract S1156.

[2] *J Clin Oncol* 2013;31(29):3688-95.

# Background

- Relapsed/refractory mantle-cell lymphoma (MCL) is characterized by frequent chemoresistance, and no standard therapy is available for patients for whom bortezomib (BTZ) has failed.
- Lenalidomide is an immunomodulatory agent with established tumoricidal and antiproliferative effects in MCL.
- Two Phase II studies (NHL-002 and NHL-003) showed activity and tolerability with single-agent lenalidomide in relapsed/refractory aggressive NHL, including MCL (*Ann Oncol* 2011;22:1622-7; *Br J Haematol* 2009;145:344-9).
- **Study objective:** To evaluate the efficacy and safety of lenalidomide in patients with MCL who experienced relapse or had disease that was refractory to BTZ.

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# MCL-001 (EMERGE) Phase II Study Design

**Eligibility (n = 134)**

- Relapsed, refractory or progressive MCL after treatment with BTZ*
- Prior anthracycline or mitoxantrone, cyclophosphamide, rituximab and BTZ

→ **Lenalidomide**
25 mg PO d1-21, q28d

- **Primary endpoints:** Overall response rate (ORR), duration of response (DOR)
- **Secondary endpoints** included complete response (CR) rate, progression-free survival, overall survival and safety

* Relapsed/progressed ≤12 mo from last dose of BTZ after CR or partial response (PR) or refractory with <PR after ≥2 cycles of BTZ

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Prior Treatment History at Baseline

| Characteristic | n = 134 |
|---|---|
| Median no. of prior regimens (range) | 4 (2-10) |
| No of prior systemic antilymphoma therapies | |
| 2 | 22% |
| 3 | 25% |
| ≥4 | 53% |
| Refractory to prior BTZ | 60% |
| Received prior high-dose or dose-intensive therapy | 33% |
| Refractory to last therapy | 55% |

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Response to Lenalidomide

| Response | Central review (n = 134) | Investigator review (n = 134) |
|---|---|---|
| ORR | 28% | 32% |
| CR/CRu | 7.5% | 16% |
| PR | 20% | 16% |
| SD | 29% | 27% |
| PD | 26% | 32% |
| Median DOR | 16.6 mo | 18.5 mo |
| Median DOR for CR/CRu | 16.6 mo | 26.7 mo |

CRu = unconfirmed CR; SD = stable disease; PD = progressive disease

- No response assessments available for 23 patients (central review) and 12 patients (investigator review)

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Subgroup Analysis of ORR and DOR by Central Review

| Characteristic | N | ORR | Median DOR |
|---|---|---|---|
| Median age, years | | | |
| <65 | 49 | 31% | 20.5 mo |
| ≥65 | 85 | 26% | 9.2 mo |
| MIPI score at enrollment | | | |
| Low | 39 | 36% | 20.5 mo |
| Intermediate | 51 | 23% | 16.7 mo |
| High | 39 | 26% | 7.7 mo |
| Relapsed/refractory to prior bortezomib | | | |
| Refractory | 81 | 27% | 20.5 mo |
| Relapsed/progressed | 51 | 29% | 16.6 mo |

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Survival Outcomes

| Outcome | Central review (n = 134) | Investigator review (n = 134) |
|---|---|---|
| Median PFS | 4.0 mo | 3.8 mo |
| Median OS* | 19.0 mo | |
| Median time to progression | 5.4 mo | 4.0 mo |
| Median time to treatment failure | 3.8 mo | |

* Median follow-up 9.9 mo

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Select Adverse Events (AEs)

| AE* (n = 134) | Any grade | Grade 3/4 |
|---|---|---|
| Neutropenia | 49% | 43% |
| Thrombocytopenia | 36% | 27% |
| Anemia | 31% | 11% |
| Leukopenia | 15% | 6% |
| Fatigue | 34% | 7% |
| Dyspnea† | 18% | <6% |
| Pneumonia‡ | 14% | 8% |

* AEs in ≥10% of patients; † 1 Grade 5 event per AE; ‡ 2 Grade 5 events

The most common Grade 3/4 adverse event (≥5% of patients) was myelosuppression.

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

# Author Conclusions

- The MCL-001 study demonstrated rapid and durable efficacy of lenalidomide in patients with heavily pretreated MCL who had experienced relapse or progression while receiving BTZ or whose disease was refractory to BTZ.
- The safety profile was manageable and consistent with other studies of lenalidomide in NHL.
- These findings support the clinical benefit of oral lenalidomide in patients with heavily pretreated MCL, including those with advanced-stage disease.

Goy A et al. *J Clin Oncol* 2013;31(29):3688-95.

## Investigator Commentary: MCL-001 "EMERGE": Efficacy and Safety of Lenalidomide in Relapsed/Refractory/Progressive MCL

The caveat to the EMERGE trial design was that it evaluated lenalidomide for patients whose MCL had relapsed or progressed after 1 year or less of bortezomib or was refractory to bortezomib after 2 or more cycles. The median number of prior regimens was 4 — the study population was heavily pretreated. In this population, lenalidomide is active: The ORR was 28%, with a CR rate of 7.5%, which is modest but comparable to ibrutinib, the "new kid on the block." Based on this study, lenalidomide recently received FDA approval for patients with MCL whose disease has relapsed or progressed after 2 prior therapies, 1 of which included bortezomib. In essence, this was the pivotal study.

The next question is, where does lenalidomide fit in? Clearly it fits in this population with bortezomib-refractory MCL, but other data suggest that its activity may be better in less heavily pretreated MCL. Some clinicians may not be convinced to use it with these modest response rates and survival benefits. It will be good to know if lenalidomide achieves response rates of >50% in a specific subgroup of patients. I am hopeful that the 28% response rate in this population can be improved on with other biologic correlates.

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

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

**Thompson C et al.**

*Proc ASCO* 2013;Abstract 8504.

# 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.

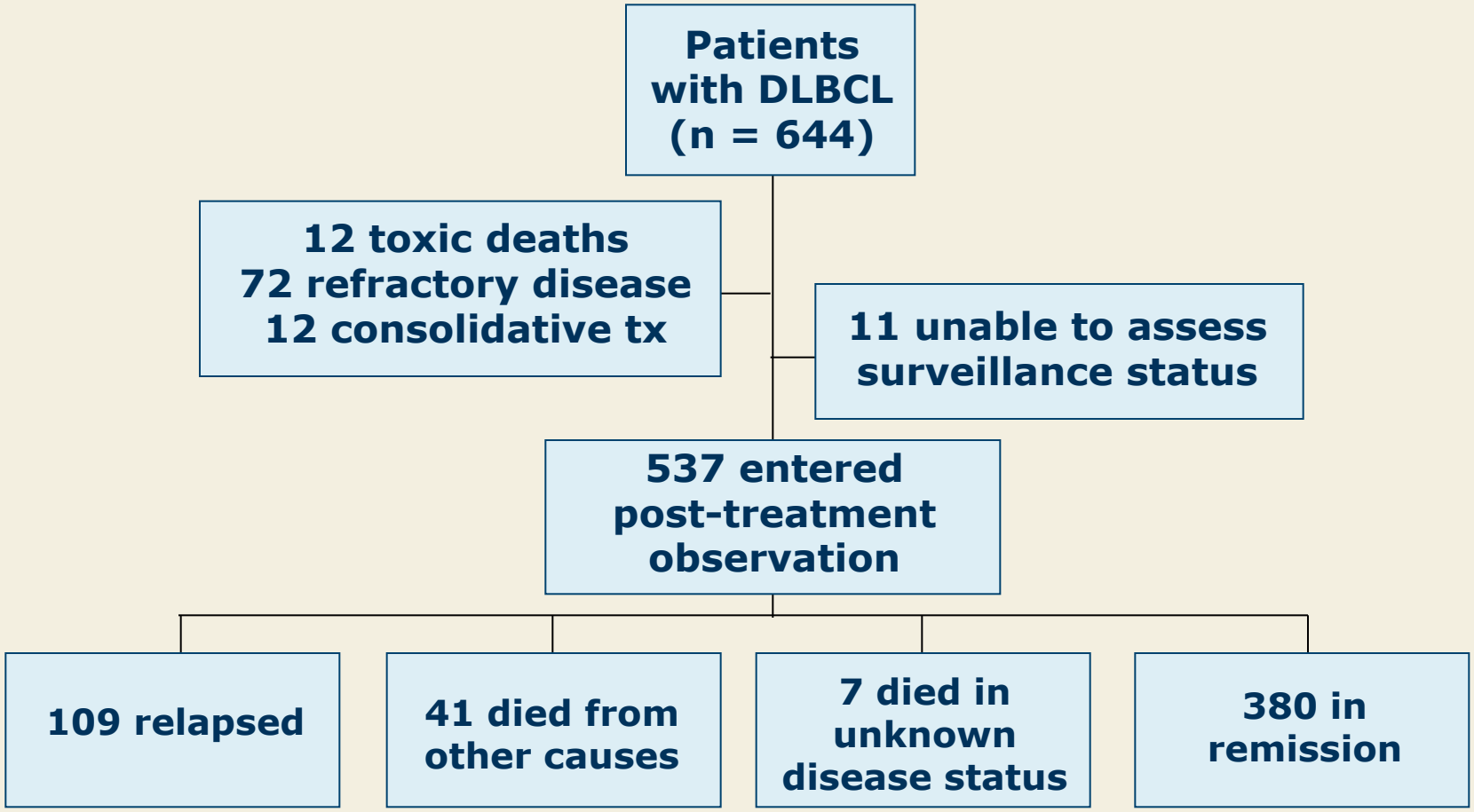
Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

# 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

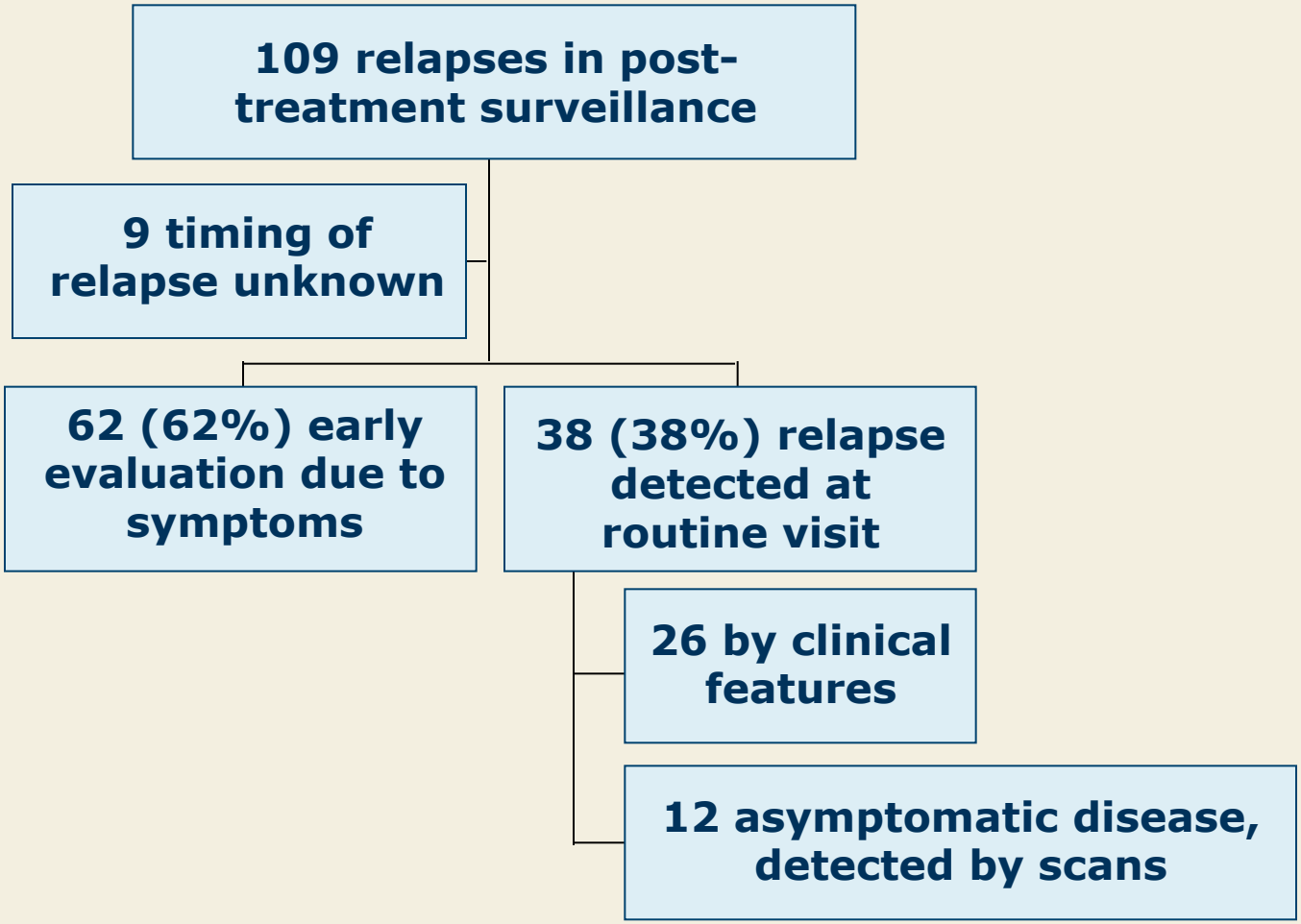
Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

# Enrollment and Outcomes



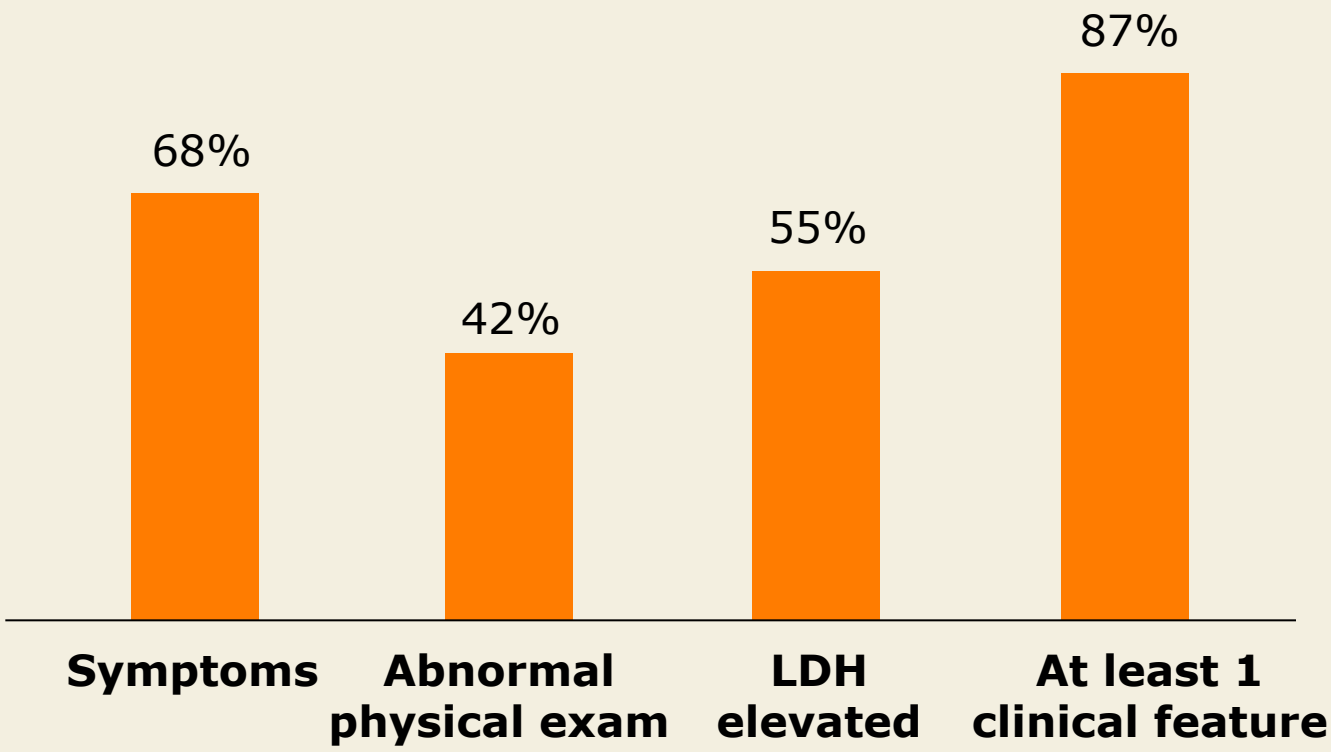

With permission from Thompson C et al. *Proc ASCO* 2013;Abstract 8504.

# Detection of Relapses




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

# Clinical Features of Relapse in 109 Patients




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

# 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.

# 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.

# 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.

## 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***

**NHL13: A Multicenter, Randomized Phase III Study of Rituximab as Maintenance Treatment versus Observation Alone in Patients with Aggressive B-Cell Lymphoma (DLBCL & FL G3)[1]**

**Rituximab Maintenance Treatment versus Observation in Patients with Aggressive B-Cell Lymphoma: Results of the AGMT NHL13 Trial[2]**

**Jaeger U et al.**

[1] *Proc EHA* 2013;Abstract P309.

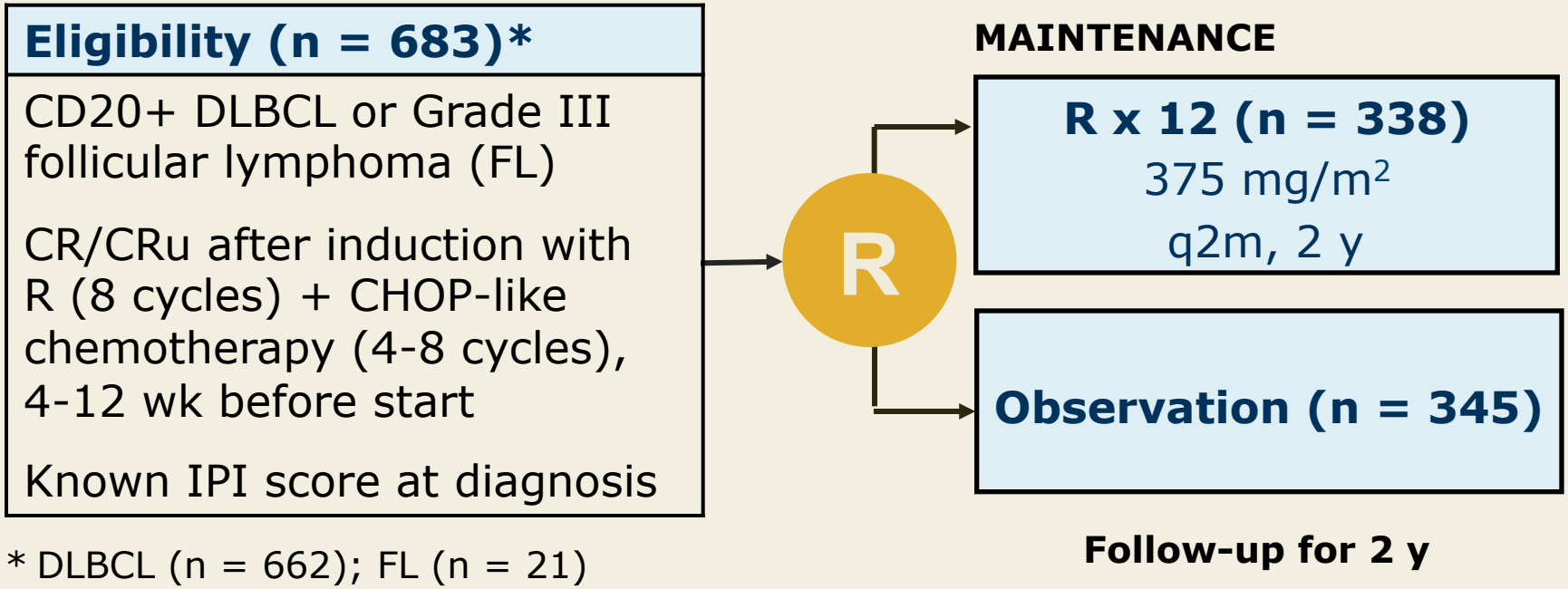
[2] *Proc ICML* 2013;Abstract 119.

# Background

- The impact of rituximab (R) maintenance treatment after intensive induction immunochemotherapy in diffuse large B-cell lymphoma (DLBCL) is unclear.
- The large, randomized ECOG-4494 trial showed no benefit with R maintenance in older patients with DLBCL after R-CHOP induction (*J Clin Oncol* 2006;24:3121).
- A potential benefit for R maintenance in DLBCL was recently reported in a nonrandomized, retrospective study (*J Cancer Res Clin Oncol* 2012;138:125).
- **Study objective:** To evaluate the efficacy and safety of R maintenance versus observation in patients with aggressive B-cell lymphoma after induction therapy with R-CHOP-like chemotherapy.

Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Phase III NHL-13 Study Design



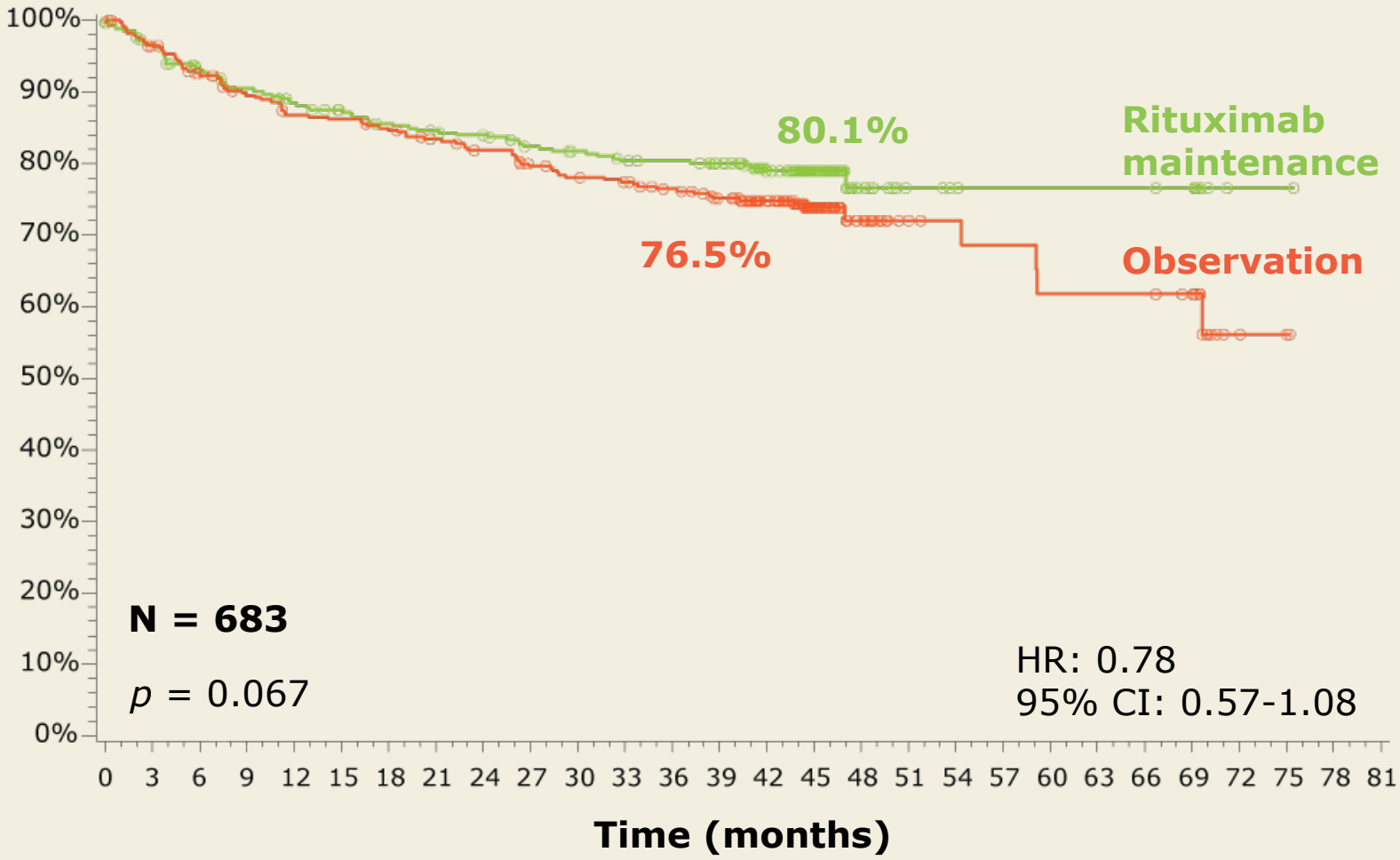

* DLBCL (n = 662); FL (n = 21)

**Primary endpoint:** Event-free survival (EFS)
**Secondary endpoints** included progression-free survival, overall survival and safety

Stratification prior to randomization by:
- Type of CHOP-like induction therapy (eg, R-CHOP-14, 21; R-CHOEP)
- Number of chemotherapy cycles during induction (≤6 vs >6)
- Geographical region

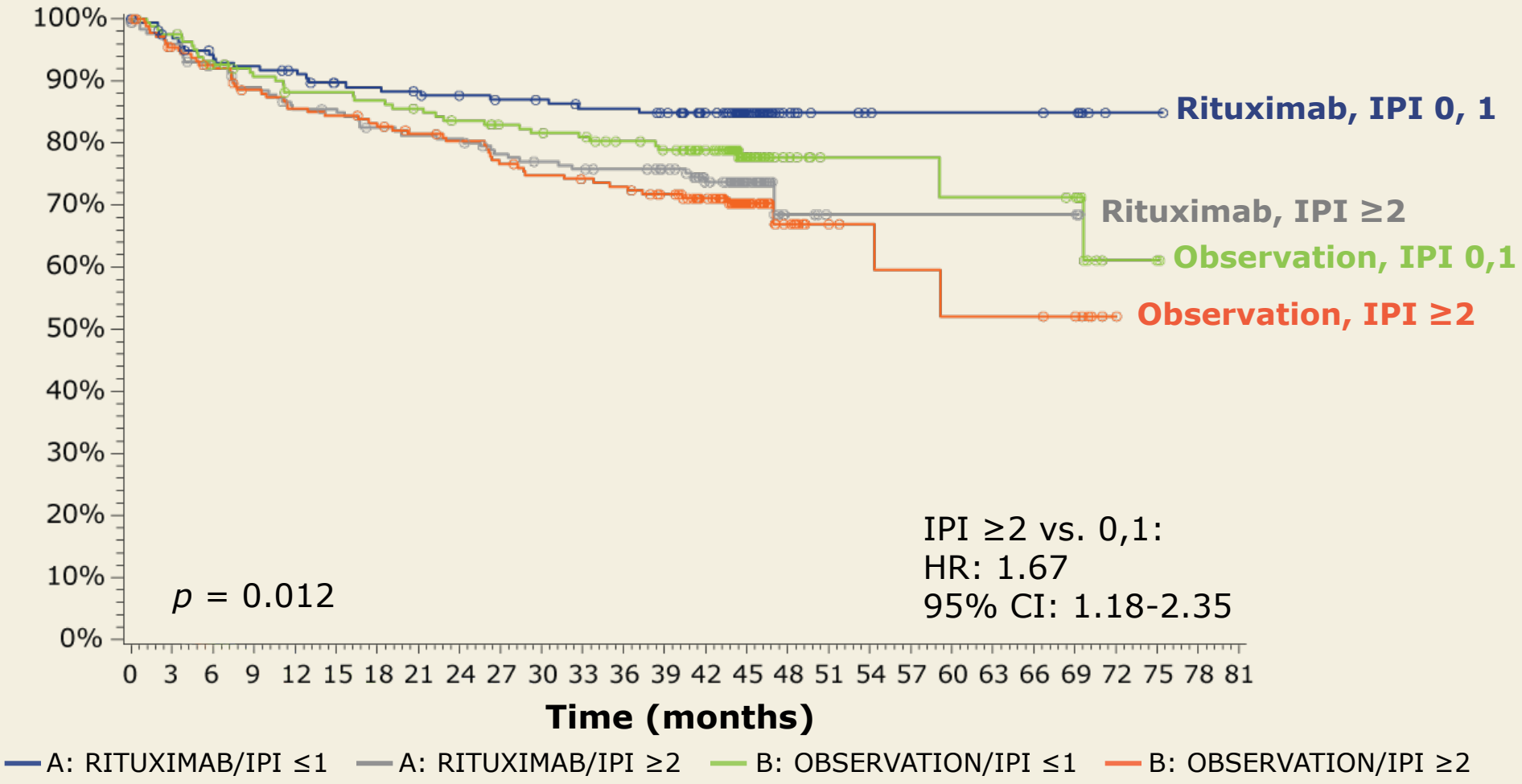
Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Event-Free Survival (ITT Population)



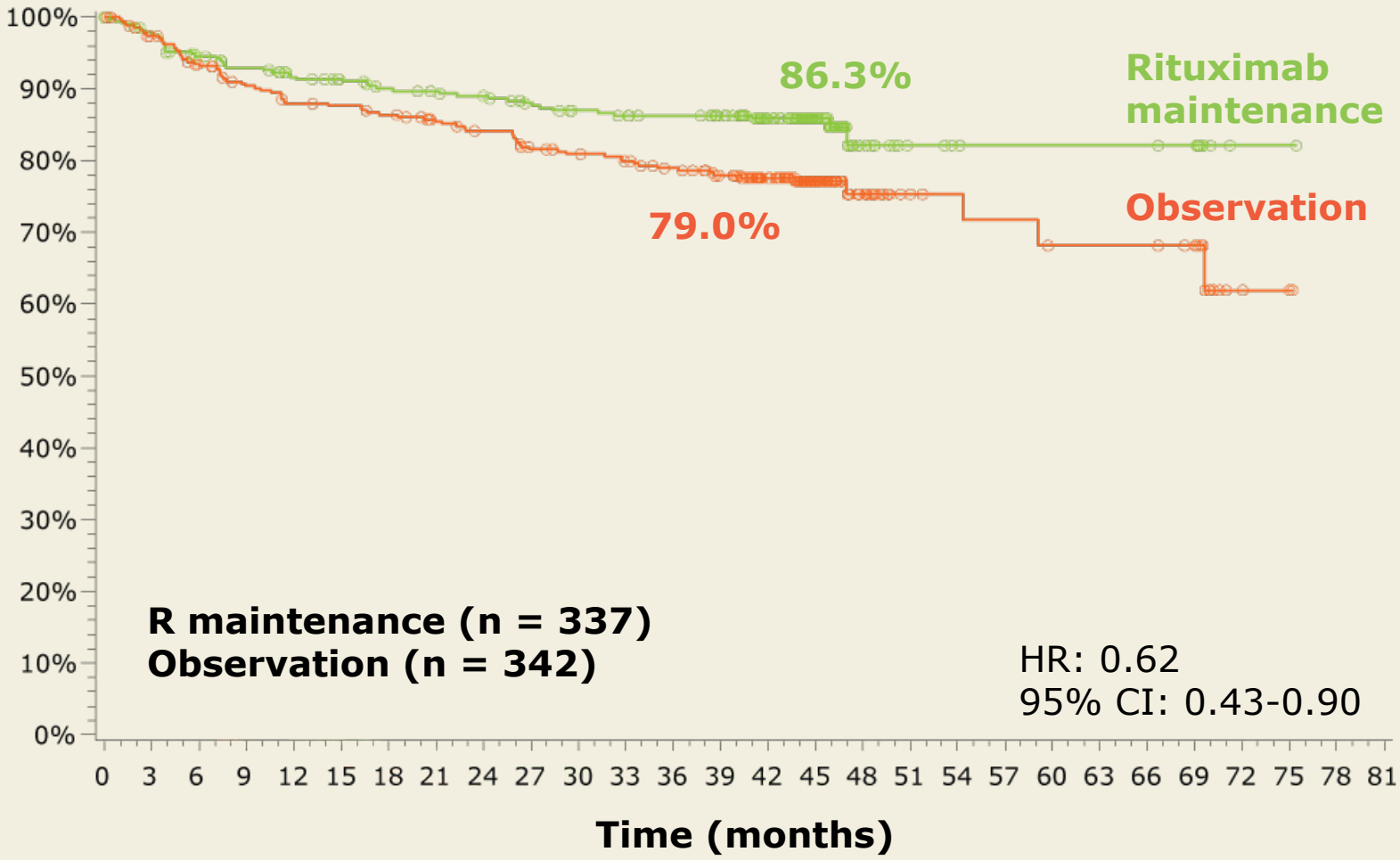

With permission from Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Event-Free Survival by Treatment Arm and IPI Score




With permission from Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Progression-Free Survival (ITT Population)




With permission from Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Progression-Free Survival Multivariate Analysis

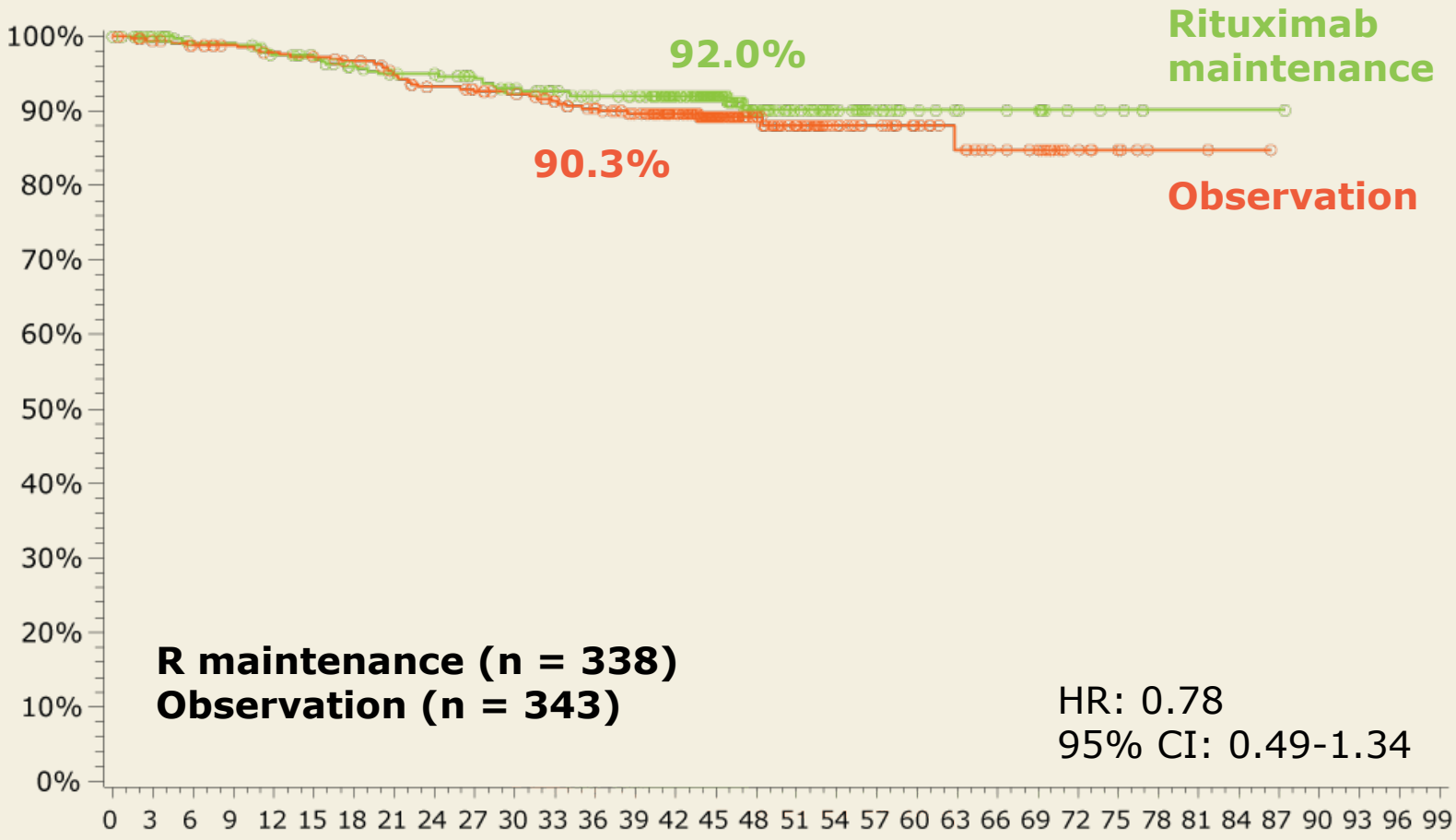
| Parameter | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Treatment (R vs observation) | 0.64 | 0.44-0.93 | 0.0200 |
| Age class (>60 vs ≤60) | 1.37 | 0.96-1.96 | 0.0797 |
| Grade III FL vs DLBCL | 1.94 | 0.91-4.11 | 0.0844 |
| Stage (3/4 vs 1/2) | 1.36 | 0.90-2.07 | 0.1367 |
| ENS (>1 vs ≤1) | 1.41 | 0.95-2.15 | 0.1097 |
| LDH (above upper limit vs normal) | 1.39 | 0.96-2.03 | 0.0805 |
| BM involvement (no vs yes) | 0.72 | 0.43-1.21 | 0.2228 |

ENS = extranodal spread; BM = bone marrow

For PFS the following factors had a *p*-value <0.1 in a significant model together with group: Age class, Stage, ENS, LDH, BM involvement. These factors were taken into the multivariate model.

Jaeger U et al. *Proc ICML* 2013;Abstract 119.

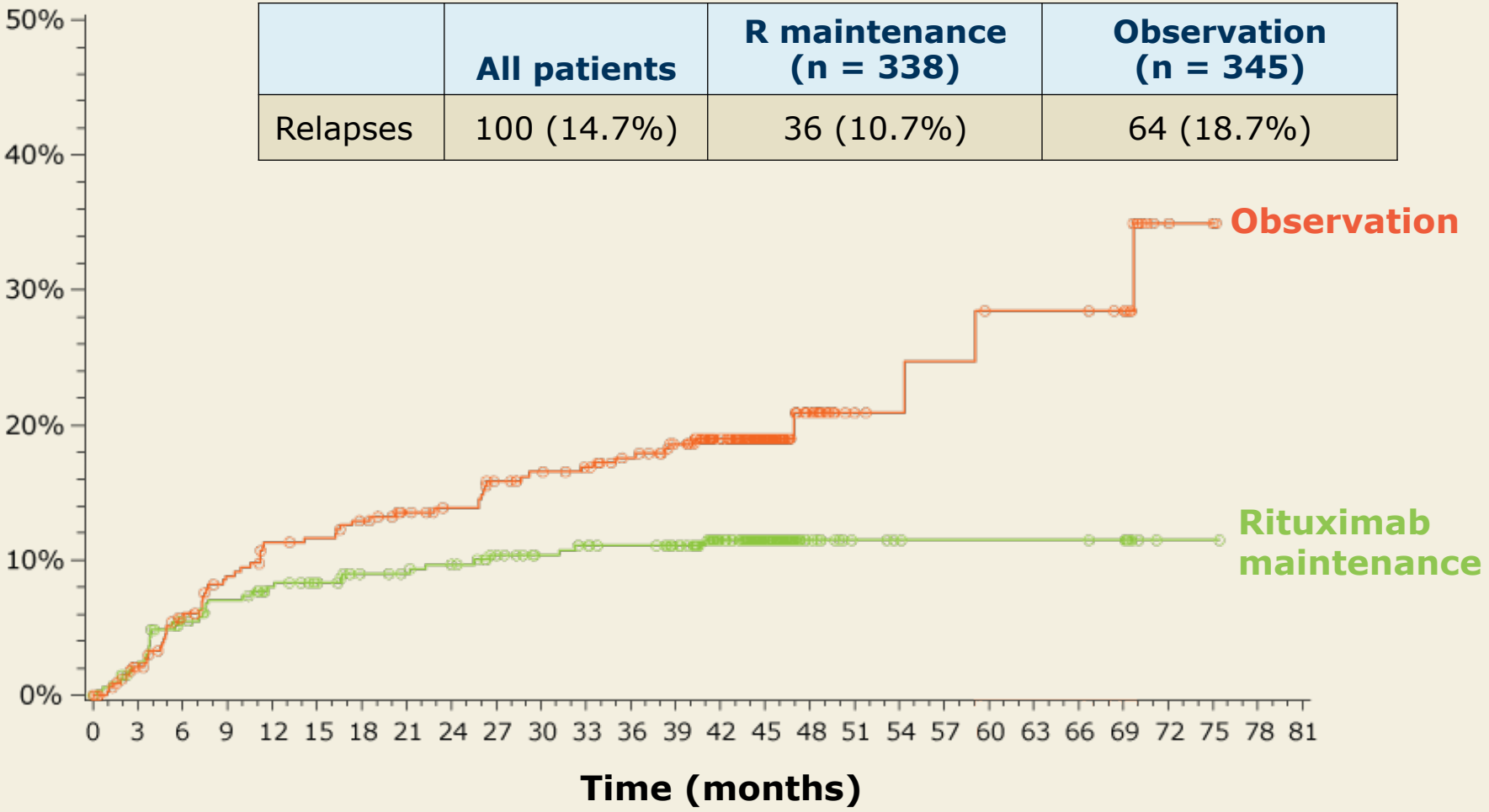
# Overall Survival (ITT Population)




With permission from Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Cumulative Relapse Rate (ITT Population)

| | All patients | R maintenance (n = 338) | Observation (n = 345) |
|---|---|---|---|
| Relapses | 100 (14.7%) | 36 (10.7%) | 64 (18.7%) |




With permission from Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Select Adverse Events (AEs)

| AE | Maintenance (n = 338) | Observation (n = 345) |
|---|---|---|
| At least 1 treatment-related AE | | |
| Any grade | 25.4% | NA |
| Grade 3/4 | 6.5% | NA |
| Infection | | |
| Any grade | 21.9% | 18.9% |
| Grade 3/4 | 3.6% | 1.2% |
| AE leading to dose adjustment/ discontinuation | 11.2% | NA |

NA = not applicable

- Median observation time: 45 mo (maintenance); 44.9 mo (observation)

Jaeger U et al. *Proc ICML* 2013;Abstract 119.

# Author Conclusions

- R maintenance treatment did not statistically significantly prolong EFS in patients with DLBCL or Grade III FL.
- However, there was a trend in favor of R maintenance in EFS ($p$ = 0.06), and lymphoma relapses were reduced by 44% (from 18.7% to 10.7%).
- These signals warrant further exploration of dosing and scheduling (including maintenance) of R in DLBCL.

Jaeger U et al. *Proc ICML* 2013;Abstract 119.

## Investigator Commentary: Phase III Study of R Maintenance Therapy versus Observation in Aggressive B-Cell Lymphoma

Patients who achieved CR/CRu after induction therapy with 8 cycles of R and 4 to 8 cycles of CHOP-like chemotherapy were randomly assigned to R maintenance therapy or observation for 2 years. No statistically significant difference was observed in EFS or overall survival (OS). In the ITT population a hazard ratio of 0.62 was recorded. So the reduction in risk with R maintenance, in terms of PFS, was 38%.

In the multivariate analysis PFS was significantly prolonged with R maintenance. Subanalyses of PFS did not demonstrate a statistically significant difference between treatments in the subgroups. No subgroup analysis of OS was performed. We need to obtain significant OS results for this study to be a game changer. If a huge PFS difference were to emerge, that might also be a game changer, but based on these data, the standard treatment will not change. I don't believe the book is yet quite closed on this topic, however, and we should await the final analysis data. I am also interested in seeing data on maintenance dosing and determining whether any subgroups of patients with DLBCL, such as elderly males, require more rituximab.

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