



*Hematologic Oncology*  
Issue 4, 2013

**CALGB-50803 and RELEVANCE  
Trials of Lenalidomide and  
Rituximab in Previously Untreated  
Follicular Lymphoma**

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## CME INFORMATION

### OVERVIEW OF ACTIVITY

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

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

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on treatment approaches and novel agents in non-Hodgkin lymphoma (NHL) from the latest ASCO, EHA and ICML meetings, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

### LEARNING OBJECTIVES

- Appraise recent clinical research findings on the efficacy and safety of radioimmunotherapy with <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.

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Hardware/Software Requirements:

A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later  
Adobe Flash Player 10.2 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

Last review date: November 2013

Expiration date: November 2014

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

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

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

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

### **1. R squared (again)**

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

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

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

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

## **3. Bendamustine + R (BR) in indolent lymphoma**

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

## **4. Len in MCL**

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

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

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

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

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

### **Aren't all anti-CD20 MoAbs the same?**

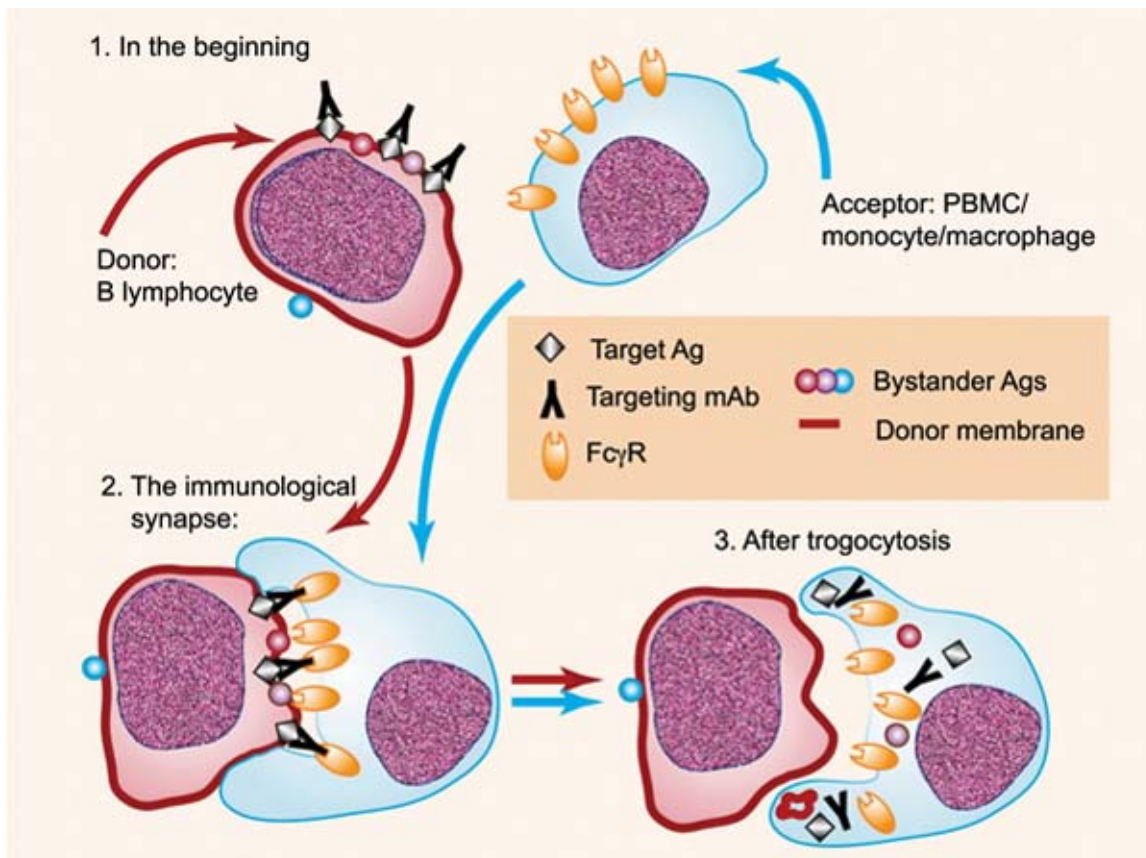
Until maybe yesterday most lymphoma investigators have been generally unexcited about the possibility that a whole lot more could be squeezed out of new anti-CD20 agents compared to R in B-cell neoplasia, but the new O data are likely to result in a lot more interest in exactly how MoAbs improve cancer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

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

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

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

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



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

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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

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

# **CALGB-50803 and RELEVANCE Trials of Lenalidomide and Rituximab in Previously Untreated Follicular Lymphoma**

## **Presentations discussed in this issue**

Martin P et al. **CALGB 50803 (ALLIANCE): A Phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Proc ICML 2013*; **Abstract 063.**

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

**Slides from presentations at ICML 2013 and transcribed comments from a recent interview with Jonathan W Friedberg, MD, MMSc (7/19/13)**

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

**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<sup>2</sup>**

**<sup>1</sup>Martin P et al.**

*Proc ICML 2013*; Abstract 063.

**<sup>2</sup>Morschhauser F et al.**

*Proc ICML 2013*; Abstract 136.

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# 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.*

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## 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<sup>2</sup>) 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.*

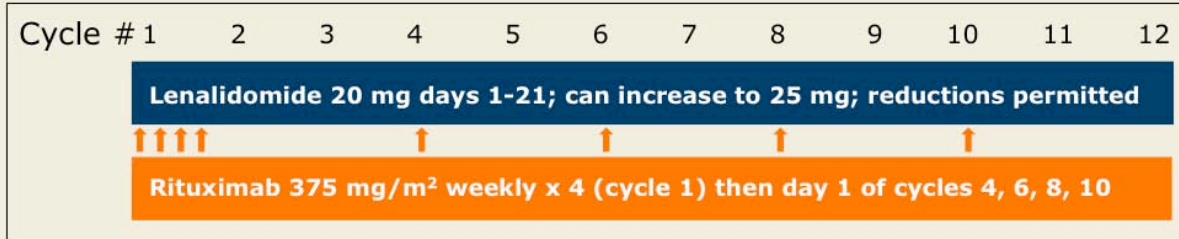
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# Phase II CALGB-50803 Trial Design

## 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.

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## 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%

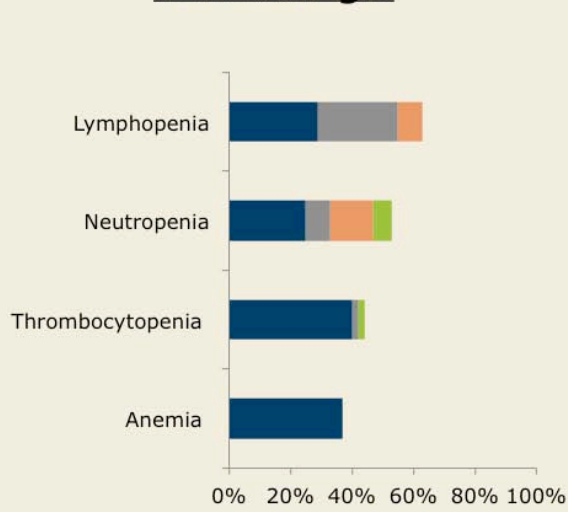
- 4 additional patients in PET CR but not confirmed by bone marrow biopsy
- No significant association was found between CR rate and FLIPI score, presence of bulky disease or grade.
- Median time to first response: 10 weeks
- Progressive disease: 7/57 (12%)

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

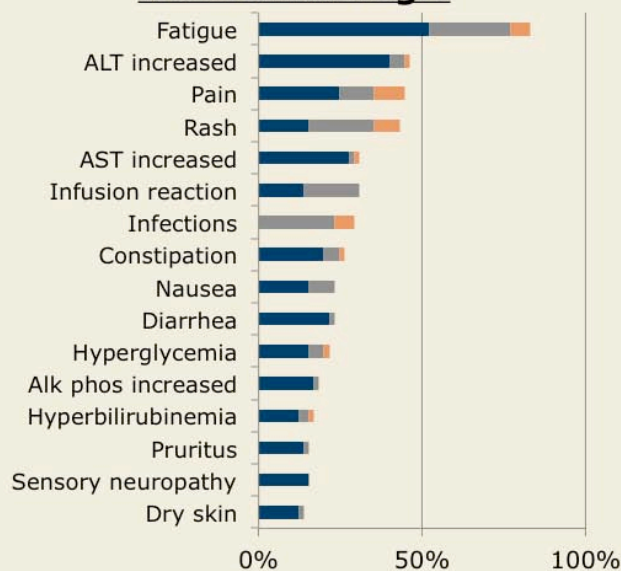
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## Adverse Events

### Hematologic



### Nonhematologic



■ Grade 1   ■ Grade 2   ■ Grade 3   ■ Grade 4

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## Comparison to Other Phase II CALGB Trials of Rituximab

Characteristic	50803 (n = 65)	50701* (n = 59)	50402† (n = 61)
Regimen	R <sup>2</sup>	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)	72%	42%	48%
FLIPI 0-1/2	77%/70%	31%/44%	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.

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## 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.

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### **Investigator Commentary: CALGB-50803 Phase II Trial of Lenalidomide/Rituximab (R<sup>2</sup>) in Previously Untreated FL**

This CALGB single-arm Phase II study of R<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> is better than lenalidomide alone, and this CALGB study demonstrated that.

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

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## **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.

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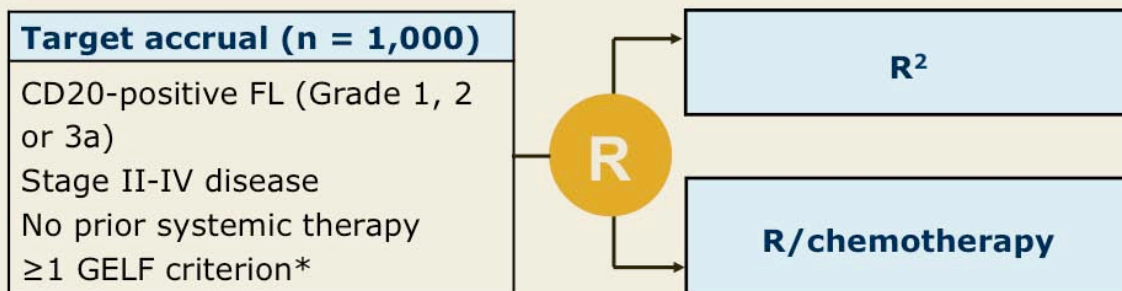
# Background

- 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<sup>2</sup>) 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<sup>2</sup> to R/chemotherapy for patients with previously untreated FL.

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

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## 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](http://www.clinicaltrials.gov), November 2013.

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## 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> of rituximab every 8 weeks for 12 cycles.

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

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## 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<sup>2</sup> of rituximab every 8 weeks for 12 cycles.

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

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## 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)

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## 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)

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## **Investigator Commentary: Ongoing Phase III RELEVANCE Trial of R<sup>2</sup> 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<sup>2</sup> for untreated FL. The trial will randomly assign patients to the R<sup>2</sup> 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<sup>2</sup> regimen.

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

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