



**POST-ASH** Issue 3, 2015

## **Efficacy of Maintenance Therapy with Rituximab or Ofatumumab in CLL**

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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 Hematology (ASH) annual meeting, 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're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider 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 the management of chronic lymphocytic leukemia (CLL) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

### LEARNING OBJECTIVES

- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including next-generation anti-CD20 antibodies and PI3 kinase, BTK and Bcl-2 inhibitors — under evaluation for previously untreated and relapsed/refractory CLL and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appreciate the recent FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed/refractory CLL, and discern how these treatments can be appropriately integrated into clinical practice.
- Compare and contrast the benefits and risks of chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab versus bendamustine/rituximab as first-line therapy for fit patients with CLL.
- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the care of patients with previously untreated CLL.
- Recall the activity of salvage therapy with obinutuzumab and chlorambucil after treatment failure of chlorambucil alone in patients with CLL and comorbidities.

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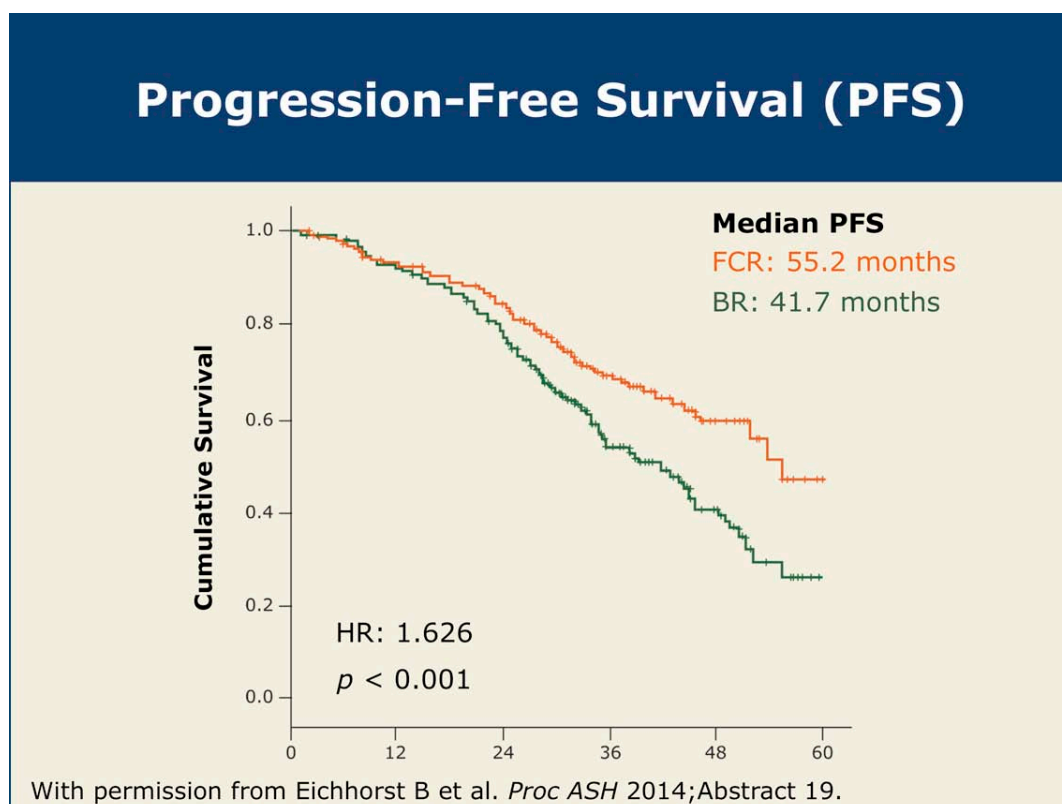
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Last review date: April 2015  
Expiration date: April 2016

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

When the German CLL Study Group — one of the most prolific clinical trial organizations in the world — launched the landmark Phase III CLL10 trial in 2008, few, if any, expected that the central question the study sought to answer would in essence be outdated by the time the results became available. CLL10 focused on a classic oncology research issue — the comparative clinical benefits of 2 chemobiologic regimens (fludarabine/cyclophosphamide/rituximab [FCR] and bendamustine/rituximab [BR]), and although the results as summarized below have important practical clinical implications today, it is increasingly evident that the overall treatment strategy in this disease is undergoing a massive reconfiguration. For that reason, this issue of *5-Minute Journal Club* evaluates not only the seminal CLL10 trial findings but also a sample of 2014 ASH data sets on several new agents, regimens and strategies that have burst onto the scene in the past couple of years and have many investigators thinking that chronic lymphocytic leukemia (CLL) may soon fall into the basic clinical paradigm of chronic myelogenous leukemia (CML) — namely a chronic disease requiring long-term outpatient management that may be associated with prolonged survival.

Here's a summary of what happened in San Francisco related to CLL.



## **CLL10: FCR versus BR (patients without del[17p])**

**The updated data from CLL10** continue to support what clinical experience had already strongly suggested, namely that FCR yields clear-cut improvements in disease-related outcomes, including a statistically and clinically significant increase in median progression-free survival (PFS) (55.2 versus 41.7 months) and rates of bone marrow minimal residual disease (MRD) negativity at final restaging (26.6% versus 11.1%). However, with less than 3 years of follow-up, no overall survival benefit has been seen. Just as predictably, the data reveal that FCR produced considerably more toxicity, particularly in older individuals (>65 years) in whom the rate of infection was 47.7% compared to 20.6% with BR. The bottom line is that most investigators believe that both regimens have a role and the risk for toxicity must be carefully considered during patient selection.

### **Impact of MRD status**

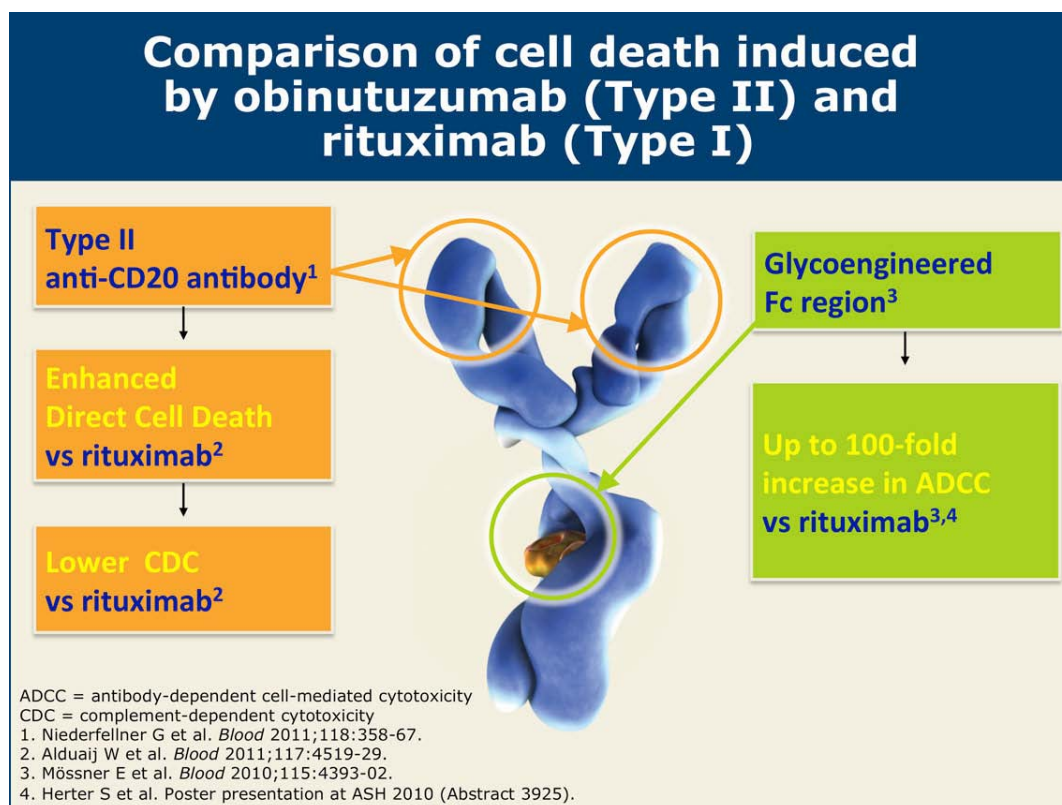
The intriguing concept of defining undetectable levels of disease after treatment to better understand potential prognosis has been explored in various forms across many hematologic cancers. In this regard, at ASH we saw a **report from the German group** evaluating pooled data from the CLL8 (FC versus FCR) and CLL10 trials examining the value of peripheral blood MRD-negative status at response evaluation. What was seen was a strong correlation between MRD status and outcome that seemed at least as predictive of PFS as clinical response, and of particular interest, patients considered to have a partial response clinically had a much better prognosis if their bone marrow was MRD-negative (61.7 versus 28.1 months). Discussions are now ongoing about how to integrate MRD status into prospective trial design and potentially clinical decision-making.

### **Obinutuzumab (Ob)**

Since the FDA approval of Ob in combination with chlorambucil — a drug that many had not been regularly using for CLL — there has been constant questioning about whether this novel Type II anti-CD20 antibody could be employed with other chemotherapeutic regimens. Not surprisingly, a number of studies are ongoing that examine this issue, including the Phase III GREEN trial, which is targeting 800 patients with both previously treated and untreated CLL and evaluates Ob alone or with one of several types of chemotherapy. This effort is also interesting in that it examines a modified dosing scheme of 25 mg on day 1 and 975 mg on day 2 in an attempt to address the high rates of infusion-related reactions that have previously been reported with Ob. At ASH we saw **early safety data** from the previously untreated cohort in the study, which showed a 13.3% rate of Grade 3 or higher infusion-related reactions with 2.5% of patients discontinuing treatment due to this side effect. As greater experience is gained with this interesting agent, it has become clear that these infusion reactions occur mainly during the first cycle and may be related to cell death and/or cytokine release. Efficacy findings from this study are not yet available, and until then, clinicians will need to consider whether they want to dust off chlorambucil and give it a go with Ob. Interestingly, during a recent interview for our audio series with investigator Dr Jeffrey

Sharman, I was surprised to learn that he avoids this issue altogether and unabashedly uses Ob alone as up-front therapy in select patients.

Clearly, the German CLL group was busy at ASH as they also treated us to **more from the pivotal CLL11 trial**, which was first presented at ASCO 2013 and paved the way for the approval of Ob. From that and related presentations, we learned, among other things, that Ob/chlorambucil is superior to rituximab/chlorambucil in a number of ways, including rates of MRD negativity in blood (38% versus 3%). Additional data unveiled at ASH evaluated patients in the trial who were initially randomly assigned to chlorambucil alone but upon relapse (generally due to lack of response to chlorambucil) were crossed over to Ob/chlorambucil. Of great interest, 26 of 30 patients (87%) experienced objective responses, further suggesting that Ob itself might have significant and perhaps underappreciated intrinsic anti-CLL activity that is greater than that previously observed with rituximab monotherapy, an important and useful therapeutic tool in follicular lymphoma.



## Anti-CD20 maintenance in CLL

Although maintenance rituximab has been commonly used in many patients receiving R-chemotherapy for follicular and mantle-cell lymphoma, our survey and polling data have clearly illustrated that hematologic investigators do not endorse this approach in CLL. However, provocative results from **2 interesting trials** unveiled at ASH have some beginning to reevaluate this stance.

First, the AGMT-CLL8/a trial randomly assigned 263 patients who completed first- or second-line chemotherapy/rituximab to 24 months of rituximab maintenance or observation and demonstrated an approximately 50% reduction in the rate of disease



progression with maintenance. No survival benefit was seen, although crossover in the control group was allowed. The other related and cleverly named Phase III effort (the PROLONG trial) evaluated ofatumumab maintenance after second- or third-line treatment with chemotherapy/anti-CD20, and again there was an approximate 50% reduction in risk of disease progression. Although more data on this important question would be ideal, some investigators feel that these results are enough to compel clinicians to discuss and/or recommend this approach in select patients, at least until the many new options and treatments are sorted out.

### **Ibrutinib**

You can't attend a conference these days without witnessing a new and relevant data set with this blockbuster Bruton tyrosine kinase inhibitor, and ASH was no exception, as we saw results from the Phase II RESONATE™-17 trial focused on 144 patients with del(17p) CLL who experienced disease progression while receiving between 1 and 4 prior lines of therapy. Perhaps not surprisingly, as few of these studies fail to disappoint, most patients had objective responses, and about 80% were progression free at 1 year. These relevant findings are central to the current first-line approval of the drug in this situation. However, it is important to note that although ibrutinib results in similar response rates in this population, these patients have shorter PFS and overall survival.

Interestingly, there is a belief that del(17p) may only be part of the story, and for that reason investigators at MD Anderson evaluated CKT (complex metaphase karyotype by whole genome sequencing defined as 3 or more distinct chromosomal abnormalities) in 100 consecutive cases of CLL treated with ibrutinib. What they found is that CKT is a better predictor of benefit from ibrutinib than del(17p). However, this clearly needs additional confirmation before whole genome sequencing makes its way into trials or clinical practice.

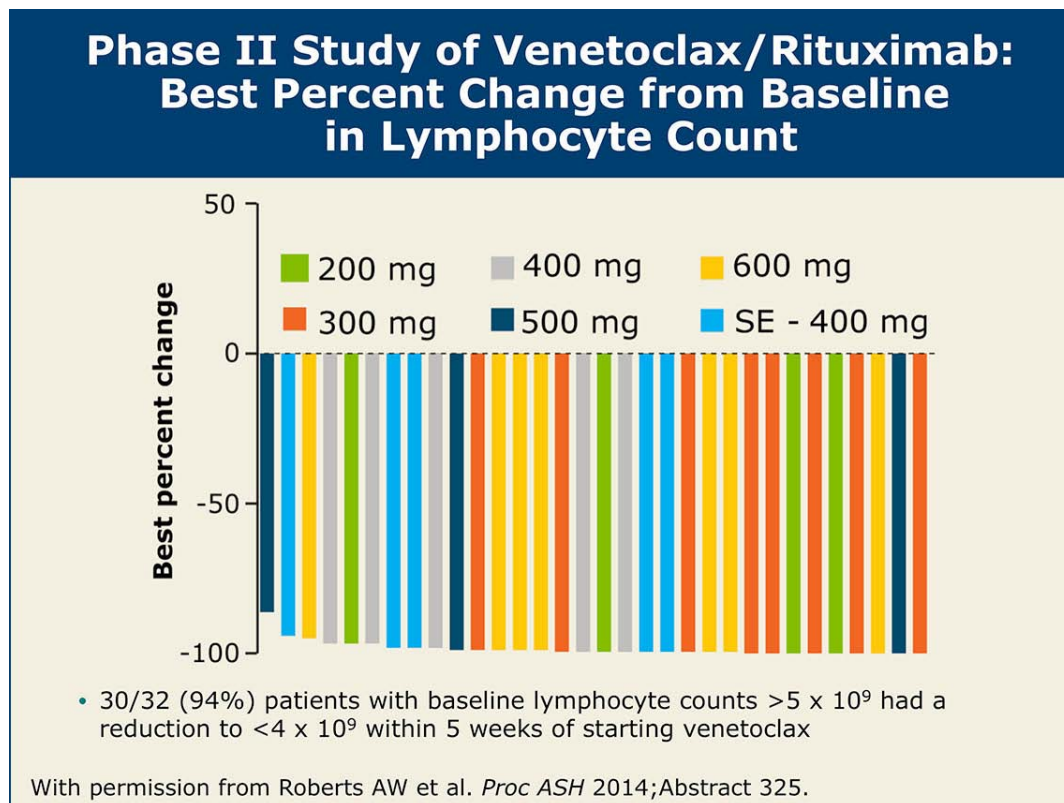
### **Idelalisib**

One of the important features of ibrutinib in CLL is the consistency of response in patients with adverse prognostic factors like 17p deletion, but the drug is not alone in this regard. At ASH we saw a **subset analysis** from the major Phase III trial reported in the *New England Journal* demonstrating that idelalisib/rituximab is a highly effective regimen, including in patients with del(17p), del(11q) and unmutated IGHV. These findings suggest that this regimen may have an important early role in patients with these genetic abnormalities who have previously received or are not candidates for ibrutinib.

### **Venetoclax (formerly ABT-199)**

Despite the new moniker, more data presented at ASH reveal that things remain entirely the same and that this novel Bcl-2 inhibitor/antiapoptotic agent is a very active drug. Most notably, in a **Phase II trial** of 49 patients with relapsed or refractory CLL/small lymphocytic lymphoma, the combination of venetoclax with rituximab demonstrated an impressive 88% objective response rate with 31% complete response (CR) or CR with incomplete blood count recovery, including in 7 of 9 patients with

del(17p). MRD negativity in the bone marrow was recorded in 17 patients. Significantly, 5 dose cohorts were studied, and it appears that a schedule was uncovered that seems to avoid tumor lysis syndrome — a complication reported previously with this agent.



Although it remains to be seen how these novel and encouraging therapies will be optimally mixed, matched and sequenced in CLL, it seems highly likely that the survival of patients will continue to be extended and perhaps soon mirror the normal life expectancies of patients under active treatment for CML. ASH 2014 will be remembered as another important step forward in this rewarding march toward a new standard.

Next on this series, we provide an ASH update on myeloproliferative neoplasms, including more data on the most recently approved treatment in these diseases, the use of ruxolitinib in polycythemia vera.

Neil Love, MD

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Miami, Florida

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# **Efficacy of Maintenance Therapy with Rituximab or Ofatumumab in CLL**

## **Presentations discussed in this issue**

Greil R et al. **Rituximab maintenance after chemoimmunotherapy induction in 1<sup>st</sup> and 2<sup>nd</sup> line improves progression free survival: Planned interim analysis of the international randomized AGMT-CLL8/a Mabtenance trial.** *Proc ASH* 2014;**Abstract 20**.

van Oers MHJ et al. **Ofatumumab (OFA) maintenance prolongs PFS in relapsed CLL: Prolong study interim analysis results.** *Proc ASH* 2014;**Abstract 21**.

**Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Stephen M Ansell, MD, PhD (1/20/15)**

**Rituximab Maintenance After  
Chemoimmunotherapy Induction in 1<sup>st</sup>  
and 2<sup>nd</sup> Line Improves Progression Free  
Survival: Planned Interim Analysis of  
the International Randomized AGMT-  
CLL8/a Mabtenance Trial<sup>1</sup>**

**Ofatumumab (OFA) Maintenance  
Prolongs PFS in Relapsed CLL: Prolong  
Study Interim Analysis Results<sup>2</sup>**

**<sup>1</sup> Greil R et al.**

*Proc ASH* 2014;Abstract 20.

**<sup>2</sup> van Oers MHJ et al.**

*Proc ASH* 2014;Abstract 21.

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# Rituximab Maintenance After Chemoimmunotherapy Induction in 1<sup>st</sup> and 2<sup>nd</sup> Line Improves Progression Free Survival: Planned Interim Analysis of the International Randomized AGMT-CLL8/a Maintenance Trial

**Greil R et al.**

*Proc ASH 2014;Abstract 20.*

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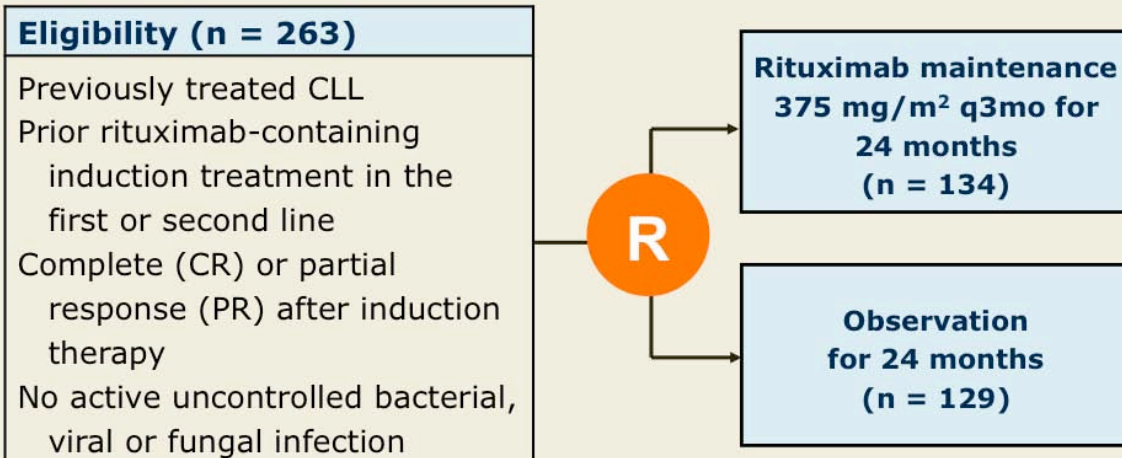
## Background

- Chemoimmunotherapy has become a standard approach in previously untreated and pretreated chronic lymphocytic leukemia (CLL).
- The addition of rituximab to fludarabine/cyclophosphamide (FC) for fit patients has proven superior to chemotherapy alone, and more recently an anti-CD20 agent was shown to improve outcomes in patients who received chlorambucil (*Proc ASH 2014;Abstract 3327*).
  - These results suggest that immunotherapy may be of benefit independent of the chosen chemotherapy backbone.
- In follicular and mantle-cell lymphoma, rituximab maintenance treatment has become a clinical standard.
- **Study objective:** To determine the preliminary efficacy and safety results of rituximab maintenance after induction therapy with a rituximab-containing chemoimmunotherapy regimen.

Greil R et al. *Proc ASH 2014;Abstract 20.*

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# Phase III AGMT-CLL8/a Maintenance Trial Design (NCT01118234)



- Randomization was stratified by country, line of therapy, induction response and type of induction regimen
- **Primary endpoint:** Progression-free survival (PFS)
- A planned sample size of 256 patients was calculated

Greil R et al. *Proc ASH* 2014;Abstract 20.

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## Patient Characteristics at Interim Analysis

All patients	n = 263
Median age	63 years
Female	28.9%
Patients enrolled at 1 <sup>st</sup> induction therapy	80.6%
Available FISH cytogenetic risk results	221 (84%)
Del(17p)	3.1%
Del(11q)	27.6%
Trisomy 12	10.8%
Del(13q)	36.2%
Normal FISH karyotype	21.2%
Patients with known IgVH status	161 (61%)
Patients with unmutated IgVH	67%

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).



## Treatment Outcomes

Outcome	Rituximab (n = 134)	Observation (n = 129)
17.3-month PFS	85.1%	75.5%
p-value	0.007	
Disease progression	14.9%	27.9%
Deaths	7 (5.2%)	10 (7.8%)

- Median observation time: 17.3 months

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

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## Induction Regimens and Response to Induction Therapy

Induction regimen	n = 263
FCR	73.5%
BR	20.2%
Response to induction treatment	
CR/CRi	58%
PR	41.8%
MRD negativity*	57%

\* By an 8-color MRD flow cytometric analysis after induction

- FCR = fludarabine/cyclophosphamide/rituximab; BR = bendamustine/rituximab; CRi = incomplete CR; MRD = minimal residual disease

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

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## Benefit from Treatment

- To account for toxicities and secondary neoplasms, event-free survival was calculated counting as events secondary cancer, termination of treatment due to toxicities, disease progression or death.
- In this analysis the benefit was preserved, albeit with a lower  $p$ -value of 0.03.
- The observed benefit seemed independent of response after induction (CR versus PR).
- However, the observed benefit was associated with a positive MRD state after induction.
- Further factors that influenced benefit from treatment in exploratory analyses of patient subgroups were sex, cytogenetics, IgVH and B symptoms at diagnosis.

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

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## Adverse Events (AEs)

- Current toxicity monitoring allows an analysis on the level of serious AEs (SAEs) only.
- The causes of SAEs were well balanced between arms, with the exception of infectious SAEs:
  - Rituximab arm ( $n = 32$ ) versus observation arm ( $n = 22$ )
- Treatment-related deaths ( $n = 3$ ) were attributed to infections:
  - Rituximab arm ( $n = 1$ ) versus observation arm ( $n = 2$ )
- Secondary cancer:
  - Rituximab arm ( $n = 8$ ) versus observation arm ( $n = 1$ )
- Four of the neoplasms in the rituximab arm were localized nonmelanoma skin cancers
  - 2 deaths from malignomas occurred: 1 in each arm

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

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## Author Conclusions

- Rituximab maintenance after chemoimmunotherapy induction in CLL seems feasible:
  - It shows signs of efficacy.
  - However, it is associated with an increase in infectious complications.
- This interim analysis refutes the alternative hypothesis and allows the trial to continue.
- Exploratory analyses suggest that with longer follow-up it may be possible to define subpopulations with larger benefit from extended immunotherapy.

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

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### **Investigator Commentary: Maintenance — Interim Analysis of Efficacy and Safety of Rituximab Maintenance in CLL**

This study specifically investigated the use of rituximab maintenance versus observation for patients with CLL who had received either FCR, the standard approach, or BR. About three quarters of the patients received FCR induction.

There are few data from randomized studies on rituximab maintenance in this setting. Hence, this study is important, especially because the whole concept of prolonged therapy is at the forefront of many people's minds. Clearly, if you treat rather than observe, you are likely to get a PFS benefit. The biggest question is, does it make a significant difference overall to how long patients live? That is uncertain, and this study demonstrated no overall survival benefit. It is not clear whether it's necessary to treat on a prolonged basis or whether one can treat and then allow a treatment break and thereafter reinstitute therapy. This is still an open debate.

***Interview with Stephen M Ansell, MD, PhD, January 20, 2015***

continued



### **Investigator Commentary: Maintenance — Interim Analysis of Efficacy and Safety of Rituximab Maintenance in CLL (continued)**

Overall the treatment was well tolerated. The PFS at 17.3 months favored rituximab maintenance, with 85.1% of the patients progression free versus 75.5% on the observation arm. This suggests that rituximab maintenance may prolong benefit from initial therapy.

In conclusion, the rituximab maintenance approach was feasible. Although some treatment-related infections were observed, the regimen was efficacious and merits further evaluation. In general practice this maintenance approach is not completely standard, but I believe it is certainly going to be evaluated in the future.

***Interview with Stephen M Ansell, MD, PhD, January 20, 2015***

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## **Ofatumumab (OFA) Maintenance Prolongs PFS in Relapsed CLL: Prolong Study Interim Analysis Results**

**van Oers MHJ et al.**

*Proc ASH 2014;Abstract 21.*

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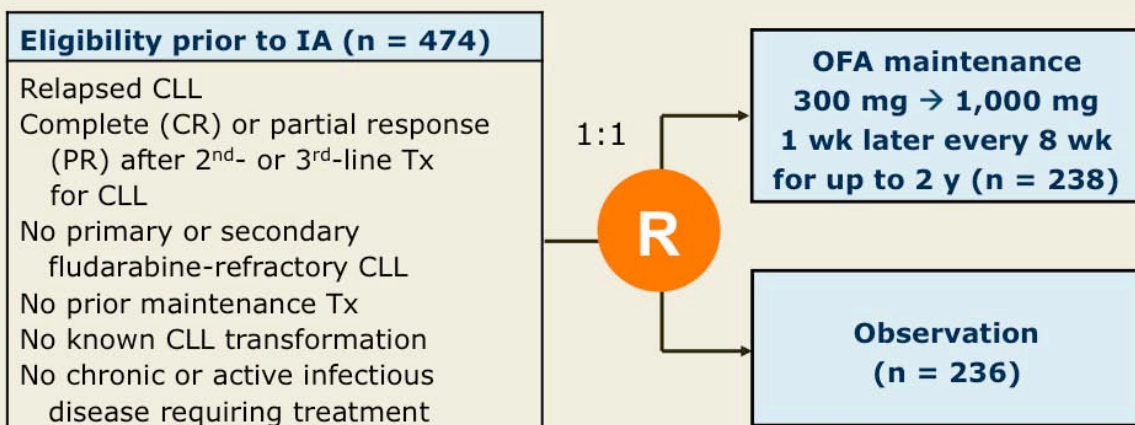
# Background

- Despite encouraging progress in treatment results, CLL remains incurable and patients eventually experience disease relapse.
- Currently, the effects of maintenance therapy are unknown for CLL.
- Ofatumumab (OFA), a human anti-CD20 monoclonal antibody, has proven efficacy as monotherapy in refractory CLL.
- **Study objective:** To report the interim analysis of efficacy and safety of OFA maintenance for patients in remission after induction therapy for relapsed CLL.

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21.

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## Phase III PROLONG Trial Design (NCT01039376)



IA = interim analysis

- Premedication for patients receiving OFA included acetaminophen, antihistamines and glucocorticoids
- Stratification was by number and type of prior treatments and by CR or PR after induction
- **Primary endpoint:** Progression-free survival (PFS)

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21.

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## Patient Characteristics

Characteristic	OFA (n = 238)	Observation (n = 236)
Mean age	63.8 years	64.2 years
Male	68%	67%
Median time since diagnosis	5.24 years	4.59 years
Response to last CLL Tx		
CR	17%	18%
Incomplete CR	2%	2%
PR	81%	80%
Missing	0%	0.4%

- Types of prior therapies:
  - Alkylator only: OFA (3%) versus observation (2%)
  - Chemoimmunotherapy: OFA (84%) versus observation (84%)
  - Other: OFA (13%) versus Observation (14%)

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

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## Efficacy Results

Outcome	OFA (n = 238)	Observation (n = 236)
Median PFS	28.6 mo	15.2 mo
Hazard ratio ( <i>p</i> -value)	0.48 (<0.0001)	
Median time to start of next Tx	38.0 mo	27.4 mo
Hazard ratio ( <i>p</i> -value)	0.63 (0.0076)	

- Median duration of OFA treatment: 12.5 mo
- Median follow-up: 26.1 mo (OFA) versus 24.0 mo (observation)
- At the time of interim analysis there was no difference in overall survival
  - Hazard ratio = 0.92; *p* = 0.74

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

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## Adverse Events (AEs)

Event	OFA	Observation
All grades	87%	75%
All Grade 3 or 4 AEs	25%	17%
Grade 3 or 4 infections	18%	13%
Most common (>5%) Grade 3 or 4 AEs		
Neutropenia	22%	9%
Pneumonia	7%	4%
Death rate	14%	14%
AEs leading to permanent discontinuation	8%	N/A

NA = not applicable

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

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## Author Conclusions

- Ofatumumab maintenance therapy provided significant clinical benefit for patients with relapsed CLL.
- Ofatumumab was well tolerated with no unexpected toxicities.
- Additional data analyses are ongoing for efficacy outcomes according to patient subgroups.

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

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### **Investigator Commentary: Interim Analysis of the Phase III PROLONG Trial of Ofatumumab Maintenance in Relapsed CLL**

In this study patients who achieved CR or PR after second- or third-line therapy for CLL were randomly assigned to receive ofatumumab maintenance or no further therapy. Patients might have received a variety of other regimens ahead of time. A highly significant benefit was recorded for patients who received ofatumumab in comparison to observation. The median PFS for the ofatumumab arm was 28.6 months versus 15.2 months for the observation arm. However, no difference in overall survival was evident between the 2 arms.

Even though one must be a little cautious comparing directly between trials, the overall outcomes of this trial seem similar to those of the Mabtenance trial. So one could probably lump the Mabtenance and the PROLONG trials into a group to state that for CD20-directed therapy, there appears to be a PFS benefit for patients who receive the antibody. I believe that if you take CLL as a part of the spectrum of indolent lymphomas, including low-grade and incurable forms of these diseases, as far as we know at this point there is certainly a trend and a theme for the maintenance strategy, and this may well be the reasonable approach to take.

***Interview with Stephen M Ansell, MD, PhD, January 20, 2015***