

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

# 5 Minute Journal Club

***Key ASH Presentations***

Issue 9, 2012

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# CME Information

## LEARNING OBJECTIVES

- Develop evidence-based treatment algorithms for patients presenting with high tumor mass follicular lymphoma (FL).
- Optimize outcomes for patients with relapsed or refractory FL through the application of emerging clinical research data.
- Evaluate the benefits and risks of therapy with different monoclonal antibodies as mono- or combination therapy in the treatment of relapsed or refractory FL or other indolent non-Hodgkin lymphomas or previously untreated chronic lymphocytic leukemia.
- Compare and contrast the benefits and risks of radioimmunotherapy and standard immunochemotherapy in the management of newly diagnosed FL.

## CREDIT DESIGNATION STATEMENT

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# CME Information (Continued)

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## **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:

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Advisory Committee: Cephalon Inc, Genentech BioOncology; Consulting Agreement: Mundipharma International Limited; Data and Safety Monitoring Board: Lilly USA LLC; Paid Research: Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

# CME Information (Continued)

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Corporation, Cephalon Inc, Genentech  
BioOncology, GlaxoSmithKline,  
Millennium: The Takeda Oncology  
Company.

# Final Analysis of a Phase 2 Study of Lenalidomide and Rituximab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)<sup>1</sup>

## Lenalidomide and Rituximab for the Initial Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): A Multicenter Study of the CLL Research Consortium<sup>2</sup>

## A Combination of Fludarabine/Rituximab with Escalating Doses of Lenalidomide in Previously Untreated Chronic Lymphocytic Leukemia (CLL): The REVLIRIT CLL5 AGMT Phase I/II Study, Clinical and Exploratory Analyses of Induction Results<sup>3</sup>

**<sup>1</sup> Badoux XC et al.**

*Proc ASH 2011; Abstract 980.*

**<sup>2</sup> James DF et al.**

*Proc ASH 2011; Abstract 291.*

**<sup>3</sup> Egle A et al.**

*Proc ASH 2011; Abstract 292.*

# Final Analysis of a Phase 2 Study of Lenalidomide and Rituximab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

**Badoux XC et al.**

*Proc ASH 2011; Abstract 980.*

# Background

- Lenalidomide has therapeutic activity as a single agent in untreated and relapsed or refractory CLL.
- In vitro studies have demonstrated that lenalidomide enhances natural killer (NK)-cell mediated antibody-dependent cytotoxicity of rituximab against CLL cells (*Clin Cancer Res* 2008; 14: 4650).
- There are no overlapping toxicities between lenalidomide and rituximab and there is the potential for synergistic activity between these two agents.
- **Objective:**
  - Determine the efficacy and safety of lenalidomide (L) in combination with rituximab (R) as salvage therapy for patients with CLL.

# Phase II Study Design

## Eligibility (n = 59)

Relapsed or refractory CLL  
Prior purine analogue-containing therapy  
Indications for therapy per NCI-WG criteria  
Adequate organ function  
    Serum creatinine  $\leq 2$  mg/dL  
    Bilirubin  $\leq 2$  mg/dL

## L + R (n = 59)

L 10 mg/d PO\*, d9-28 x 12 cycles  
R 375 mg/m<sup>2</sup> IV, q1wk x 4  
    Cycle 1: d1  
    Cycles 3-12: d1

Allopurinol was administered from days 1-14 of cycle 1.

\* Lenalidomide dose reduced for Grade  $\geq 3$  hematologic toxicity



# Response Rates (Abstract)

Response	No. of patients
All patients (n = 59)	
ORR	66%
Complete response	10%
Nodular partial response	17%
Partial response	39%
17p deletion (n = 15)	
ORR	53%
Complete response	13%
Nodular partial response	13%
Partial response	27%

ORR assessed after cycles 3 and 6, then after every 6 cycles

# Clinical Outcomes (Abstract)

Outcome	Patients (n = 59)
2-year overall survival (%)	83%
Deaths during treatment (n)	3
Stroke	1
Infectious exacerbation of chronic obstructive pulmonary disease	1
Treatment-unrelated cardiac arrhythmia	1
Deaths on subsequent therapy (n)	
Progressive disease	1
Richter's transformation	1
Diagnosis of secondary malignancy during treatment (n)	
Colon cancer after 10 months	1
Myelodysplastic syndrome after 6 months	1

Median follow-up: 25 months; patients remaining on therapy: 25%;  
estimated median time to treatment failure: 24 months

# Select Adverse Events (AEs) (Abstract)

AEs	n = 59
Hematologic AEs (Grade $\geq 3$ ) Neutropenia Thrombocytopenia Anemia	 47% 22% 10%
Infections (Grade $\geq 3$ )	31%
Tumor lysis (Grade 3)	2%
Tumor flare (Grades $\leq 2$ )	27%
Nonhematologic AEs (Grades $\leq 2$ ) Fatigue Diarrhea Rash Sensory peripheral neuropathy Constipation	 71% 39% 27% 25% 22%

# Author Conclusions

- The combination of lenalidomide with rituximab leads to durable responses in patients with relapsed or refractory CLL.
- Lenalidomide/rituximab combination therapy demonstrated activity in patients with relapsed or refractory CLL with deletion of chromosome 17p.
- Overall, this combination is feasible and safe and requires further investigation in patients with relapsed or refractory CLL, as these patients have limited therapeutic options.

## **Investigator Commentary: Final Analysis of a Phase II Study of Lenalidomide and Rituximab in Patients with Relapsed or Refractory CLL**

A good rationale exists for lenalidomide/rituximab combination therapy because the 2 agents appear to act synergistically. Preclinical data show that lenalidomide increases NK cell numbers and enhances NK cell-mediated killing by rituximab. In this study, the combination of lenalidomide with rituximab produced an outstanding ORR of 66% and a median time to treatment failure of 24 months in patients with relapsed or refractory CLL. The results were much better than one would have expected with either of the agents alone, where the response rate and duration tend to be about half of what was observed in this study. This is good evidence demonstrating that the lenalidomide/rituximab combination is potent and has synergistic effects.

*Interview with Brad S Kahl, MD, January 26, 2012*

# Lenalidomide and Rituximab for the Initial Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): A Multicenter Study of the CLL Research Consortium

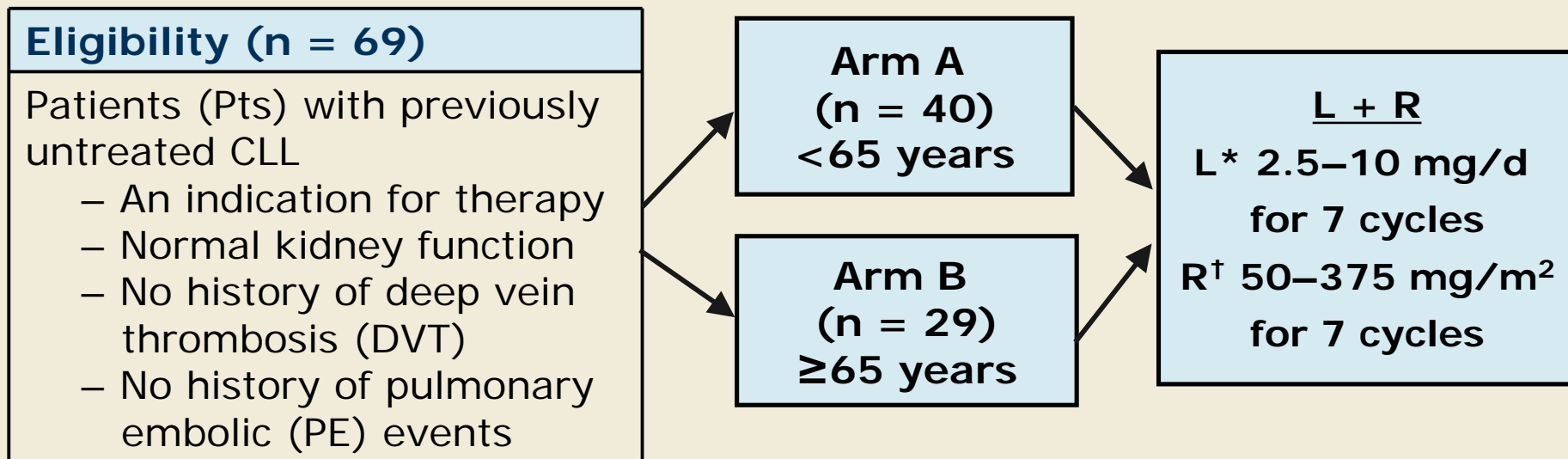
**James DF et al.**

*Proc ASH 2011; Abstract 291.*

# Background

- Whereas lenalidomide has therapeutic activity in chronic lymphocytic leukemia (CLL), rituximab as monotherapy has limited activity (*Blood* 2008;111:5291).
- In preclinical studies, lenalidomide treatment led to natural killer (NK) cell expansion and was shown to enhance the cytotoxic effects of rituximab (*Clin Cancer Res* 2008;14:4650).
- **Objective:**
  - Evaluate the safety and efficacy of combination therapy with lenalidomide (L) and rituximab (R) in patients with previously untreated CLL in a dual-stage Phase II trial.

# Study Design



\* L was started at 2.5 mg/d and could escalate to 5 mg/d on d8 of cycle 1 and then to a maximum of 10 mg/d on d1 of cycle 3, if tolerated. L was administered for 21/35 d (cycle 1) and then for 21/28 d (cycles 2-7).

† R was started at the end of cycle 1 at 50 mg/m<sup>2</sup> (d29), 325 mg/m<sup>2</sup> (d31), 375 mg/m<sup>2</sup> (d33) then 375 mg/m<sup>2</sup> weekly x 4 for cycle 2 and d1 for cycles 3-7.

Pts received allopurinol (300 mg/d) and, after protocol amendments, aspirin (81 mg/d).



# Response Rates (Abstract)

Patient population	Arm A			Arm B		
	CR	PR	ORR*	CR	PR	ORR*
All patients (n = 35, 22)	20%	57%	94%	9%	68%	77%
Unmutated IgVH (n = 22, 13)	18%	68%	96%	8%	77%	85%
Mutated IgVH (n = 13, 9)	23%	38%	92%	11%	56%	67%
Median L dose 10 mg (n = 24, 8)	29%	50%	100%	25%	63%	88%
Rai stage III/IV (n = 9, 11)	22%	56%	89%	9%	55%	64%
17p deletion (n = 3, 1)	0%	67%	67%	0%	0%	0%
11q deletion (n = 3, 4)	33%	67%	100%	0%	75%	75%
TFR present (n = 28, 14)	18%	57%	93%	0%	79%	79%

\* ORR included the rates of CR, PR and nodular PR

CR = complete response; PR = partial response; ORR = overall response rate;

TFR = tumor flare reactions

# Progression-Free Survival (Abstract)

	<b>Arm A (n = 35)</b>	<b>Arm B (n = 22)</b>
Estimated median PFS	19 months*	7 months†

PFS = progression-free survival

\* Median follow-up of 17 months

† Median follow-up of 7 months with an estimated 85% of patients remaining progression free

# Select Adverse Events (Abstract)

Event (n)	Arm A		Arm B	
	I/II	III/IV	I/II	III/IV
Tumor flare reaction	32	—	16	1
Neutropenia, neutropenic fever	11, —	19, 2	1, —	15, 2
Anemia	15	3	14	1
Thrombocytopenia	21	1	13	1
Fatigue	25	—	14	2
AST/ALT elevation	18	3	11	3
Hypophosphatemia	19	2	7	1
Respiratory infection, pneumonia	17, —	—, 1	5, 2	—, 3
Rash	14	2	12	1
PE/DVT	—	—	—	2

# Author Conclusions

- A defined course of 7 cycles of lenalidomide and rituximab administered as initial therapy for CLL was associated with a high response rate.
- Older patients ( $\geq 65$  years) in Arm B demonstrated lower response rates (CR and ORR) probably because:
  - They were more likely to have advanced Rai stage disease at baseline.
  - They were less likely to escalate to or maintain the maximal lenalidomide dose.
  - They were less likely to complete 7 cycles of combined lenalidomide/rituximab therapy.

## **Investigator Commentary: A Multicenter Study of Lenalidomide and Rituximab for Initial Treatment of CLL**

Both lenalidomide and rituximab are known to have activity in relapsed CLL. This prospective study evaluated the combination of lenalidomide and rituximab in untreated CLL in 2 cohorts of patients based on age.

The results showed high response rates, and the regimen was reasonably well tolerated. More than 90% of patients in the younger group and about 75% of patients in the older group responded. The older patients did not fare as well because of the quality of their disease and the tolerability of treatment. The estimated progression-free survival data were limited by the short follow-up. Adverse events were as expected, the most significant one being neutropenia.

The question that arises is, how does the lenalidomide/rituximab combination compare to standard treatments such as fludarabine-based regimens in younger patients and novel approaches such as kinase inhibitors in older patients. This combination could also be a promising approach for maintenance therapy. It would be interesting to determine whether lenalidomide either alone or in combination with rituximab would be more beneficial to patients after induction chemotherapy as compared to stand-alone treatment.

Overall, this is an interesting prospective study done in a multicenter setting, but we need longer follow-up and more studies comparing this regimen to other treatments for CLL.

***Interview with John P Leonard, MD, April 6, 2012***

# A Combination of Fludarabine/Rituximab with Escalating Doses of Lenalidomide in Previously Untreated Chronic Lymphocytic Leukemia (CLL): The REVLIRIT CLL5 AGMT Phase I/II Study, Clinical and Exploratory Analyses of Induction Results

**Egle A et al.**

*Proc ASH 2011; Abstract 292.*

# Background

- Lenalidomide monotherapy has shown remarkable clinical activity in CLL (*Blood* 2011; 118: 3489).
- However, tumor lysis and tumor flare reactions have been major obstacles in the development of lenalidomide as a drug for CLL (*J Clin Oncol* 2007; 25: 5047).
- In addition, problems of marked and unexplained differences in drug tolerance between individual patients remain unsolved (*J Clin Oncol* 2008; 26: 2519).
- Furthermore, the potential for interaction with standard therapies for CLL is unknown.
- **Objective:**
  - Determine the efficacy of combining fludarabine (F) with rituximab (R) in the early reduction of tumor load.
  - Establish a tolerable lenalidomide (L) dose in combination with the F/R duo as a backbone.

# REVLIRIT CLL5 AGMT Trial Design

## Eligibility (n = 45)

Previously untreated CLL

## Primary endpoint

- Systematic toxicity determining a maximal tolerated dose (MTD) of L

\* Toxicity permitting, L dose was escalated to 5, 10, 15, 20 and 25 mg over cycles 2 to 6.

† Data from the maintenance phase will be presented later.

## Induction therapy

F + R + L (6 cycles) (n = 45)

F 40 mg/m<sup>2</sup> PO, d1-3  
q4wk x 6 cycles

R 375 mg/m<sup>2</sup> IV, d4, cycle 1;  
500 mg/m<sup>2</sup>, d1, cycles 2-6, q28d

L\* 2.5 mg, d7-21, cycle 1;  
2.5-25 mg, d1-21, cycles 2-6

## Maintenance therapy<sup>†</sup>

R + L



# Exploratory Analyses of Induction Therapy (Abstract)

Patient population	n = 45
Systemic toxicity determining an MTD	0%
Proceeded through planned dose escalation steps to receive 25 mg of L with final F/R cycle	34%
Individual MTD $\geq$ 10 mg of L in the intent-to-treat (ITT) population	73%
Dose-limiting due to individual differences in myelotoxicity	71%
Individual MTD < 10 mg of L in the ITT population	27%

# Response Assessments (Abstract)

Response	No. of patients
Complete response (ITT) (n = 39)	49%
Partial response (ITT) (n = 39)	38%
Minimal residual disease (MRD) by flow (n = 35) MRD negativity	29%
17p deletion (n = 3) MRD-negative complete response	33%

- Response quality was not associated with risk factors, age or lenalidomide dose.
- Extensive immunophenotyping of T cells was performed. Employing a combined endpoint including nonhematologic dose-limiting events (NHDLE) or MTD <10 mg as a comparator:
  - A fraction of nonexhausted memory CD4 cells was identified as a predictor of NHDLE events ( $p < 0.005$ ).
  - The T cell fraction negative predictive value of 85% for such events could possibly allow for future identification of patients who will have difficulty with higher lenalidomide doses.

# Adverse Events (Abstract)

Event	n = 45
Neutropenia (Grade 3/4)	88%
Myelotoxicity (dose limiting)	42%
Infections (Grade 3)	11%
Skin toxicity (>Grade 2)	33%
Dose limiting	20%
Tumor lysis	0%
Flare reactions (>Grade 2)	0%

Patients (n = 5) discontinued induction therapy: rashes (n = 2); patient's choice (n = 2); early Richter's transformation (n = 1)

# Author Conclusions

- The combination of lenalidomide with F/R appears to be clinically feasible.
- The combination did not result in a clear dose-dependent limiting toxic effect.
- However, more than a third of the patients were dose limited, mainly due to nonhematologic, skin-related toxicities.
  - Novel biomarkers may aid in the identification of these patients.
- The regimen shows encouraging clinical efficacy with limited complications, particularly in patients tolerating doses >5 mg.
- Based on these results, a follow-up study with a higher starting dose of lenalidomide is planned.

## **Investigator Commentary: Combination of Fludarabine/Rituximab with Escalating Doses of Lenalidomide in Untreated CLL**

This study in patients with untreated CLL used a fludarabine/rituximab (FR) backbone with the addition of increasing doses of lenalidomide followed by maintenance rituximab and lenalidomide. Fludarabine and rituximab were used initially to debulk the patient's disease, with lenalidomide added as part of long-term maintenance therapy. The response rate was high with 85% to 90% of patients demonstrating a clinical response. A major side effect, as would be expected, was myelosuppression. In previous studies with lenalidomide in B-cell lymphomas, a significant proportion of patients developed rash. This is a side effect that has to be kept in mind when using this regimen.

It will be interesting to determine how this regimen compares to other treatments. A large ongoing randomized study is being led by the CALGB that will compare FCR (fludarabine/cyclophosphamide/rituximab) to FR with or without lenalidomide consolidation in patients with CLL. The results from this study will help to better assess the value of lenalidomide in combination with FR.

***Interview with John P Leonard, MD, April 6, 2012***

**Immunochemotherapy with Low-Dose Subcutaneous Alemtuzumab (A) plus Oral Fludarabine and Cyclophosphamide (FC) Is Safe and Induces More and Deeper Complete Remissions in Untreated Patients with High-Risk Chronic Lymphocytic Leukemia (CLL) Than Chemotherapy with FC Alone. An Early Analysis of the Randomized Phase-III HOVON68 CLL Trial**

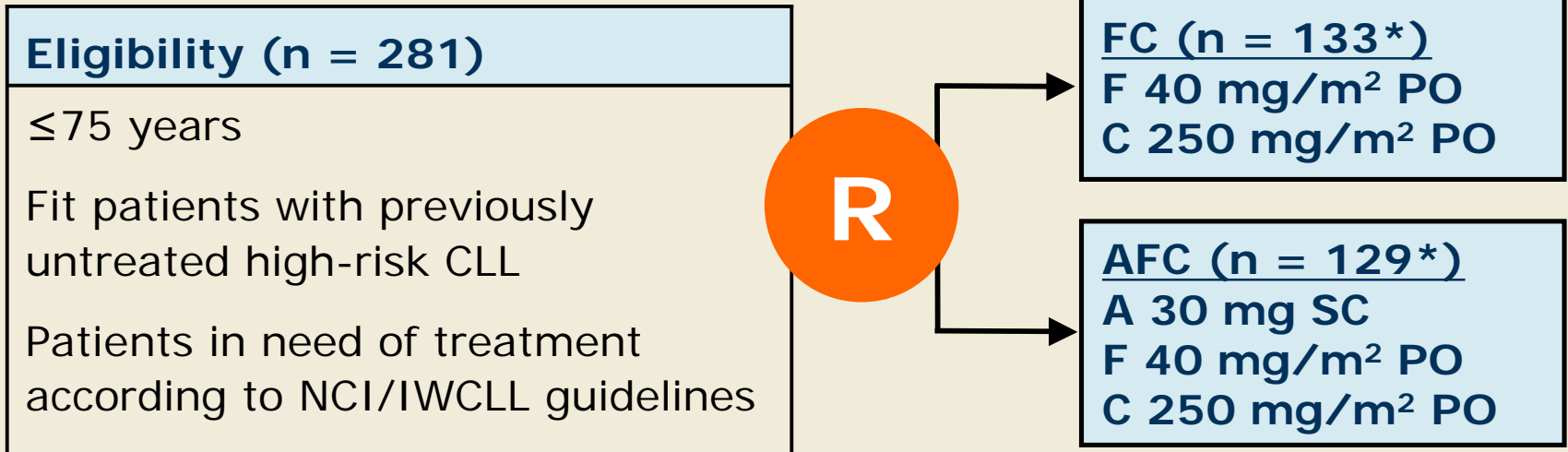
**Geisler C et al.**

*Proc ASH 2011; Abstract 290.*

# Background

- Genomic aberrations and unmutated immunoglobulin heavy chain genes are associated with an unfavorable outcome in CLL (*Leukemia* 2002;16:993).
- Although previous studies showed promising results with fludarabine and cyclophosphamide (FC) in combination with rituximab, the optimal regimen for patients with high-risk CLL is unknown (*Blood* 2008;112:975).
- Alemtuzumab (A), an anti-CD52 antibody, has shown promising results as first-line therapy for CLL and for fludarabine-refractory CLL (*J Clin Oncol* 2007;25:5616; *Blood* 2002;99:3554).
- Objective:
  - Improve the outcome of high-risk CLL by adding low-dose A to FC.

# Phase III HOVON68 Trial Design



\* The number of patients with evaluable disease at time of analysis

## **Primary endpoint:**

Progression-free survival (PFS) in the intent-to-treat population

## **Secondary endpoints:**

Rate of complete remission (CR), rate of minimal residual disease (MRD)-negative CR, overall survival (OS) and toxicity



# Response Rates (Abstract)

Rate	AFC (n = 129)	FC (n = 133)	p-value
Overall response	88%	80%	—
CR	57%	45%	0.049
MRD-negative CR	29%	17%	<0.02

Median follow-up was 30 months

There was no difference in response between treatments when patients were classified according to Binet stage or beta-2-microglobulin level.

# Survival Rates (Abstract)

Response	AFC (n = 129)	FC (n = 133)	<i>p</i> -value
Median PFS	37 months	31 months	0.08

- Though statistically insignificant, there was a trend toward improved PFS with AFC treatment in the patient subgroups with 17p deletions, 11q deletions, trisomy 12 or unmutated IGH genes.
- There was no difference in PFS between treatments when patients were classified according to Binet stage or beta-2-microglobulin level.
- The median OS has not yet been reached.

# Adverse Events (AEs) (Abstract)

Event	AFC	FC	<i>p</i> -value
Severe AEs (mostly Grade 3)	145	90	<0.0001
Flulike symptoms	27	2	—
Opportunistic infections	25	11	—
Organ toxicity	34	14	—
Treatment-related death	6	6	—

- There were no differences between treatment arms in the number of neutropenic events and the occurrence of other infections.
- Vigilance and prophylaxis against infection were maintained throughout the study.

# Author Conclusions

- The addition of low-dose alemtuzumab, administered subcutaneously, to FC induced a higher rate and quality of CR versus FC therapy alone.
- However, neither PFS nor OS results differed significantly between treatment arms in this early analysis.
- Because combination therapy with AFC is more immunosuppressive than FC only, there was a greater number of opportunistic infections with AFC.
  - With proper vigilance and prophylactic measures, these infections were manageable and did not lead to excessive mortality.

## **Investigator Commentary: Immunochemotherapy with Alemtuzumab in Combination with Fludarabine and Cyclophosphamide Is Safe and Induces More and Deeper Complete Remissions in Untreated High-Risk CLL than FC Alone**

This study is important because it was a randomized trial comparing FC to alemtuzumab and FC (AFC). The efficacy of the AFC and FC arms was comparable, with similar overall and complete remission rates. However, the complete remission rates statistically favored the AFC arm. More toxicity was seen in the AFC arm, particularly flulike symptoms and infections, which are known to occur with alemtuzumab.

The big question that arises is how a standard regimen like rituximab in combination with FC (FCR) would compare to AFC and FC with regard to efficacy and tolerability. Data from certain groups, such as the MD Anderson group, showed that when you add alemtuzumab to an FCR regimen, this 4-drug regimen results in more infectious complications.

Overall, although this is an interesting approach to treatment, I don't believe it is practice changing.

*Interview with John P Leonard, MD, April 6, 2012*

**Efficacy and Safety of Obinutuzumab (GA101) Monotherapy in Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma: Results from a Phase I/II Study (GAUGUIN, BO20999)<sup>1</sup>**

**Randomized Phase II Trial Comparing GA101 (Obinutuzumab) with Rituximab in Patients with Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Preliminary Analysis of the GAUSS Study<sup>2</sup>**

**Obinutuzumab (GA101) in Combination with FC or CHOP in Patients with Relapsed or Refractory Follicular Lymphoma: Final Results of the Phase I GAUDI Study (BO21000)<sup>3</sup>**

**<sup>1</sup> Salles GA et al.**

*Proc ASH 2011; Abstract 268.*

**<sup>2</sup> Sehn LH et al.**

*Proc ASH 2011; Abstract 269.*

**<sup>3</sup> Radford J et al.**

*Proc ASH 2011; Abstract 270.*

# **Efficacy and Safety of Obinutuzumab (GA101) Monotherapy in Relapsed/ Refractory Indolent Non- Hodgkin's Lymphoma: Results from a Phase I/II Study (GAUGUIN, BO20999)**

**Salles GA et al.**

*Proc ASH 2011; Abstract 268.*

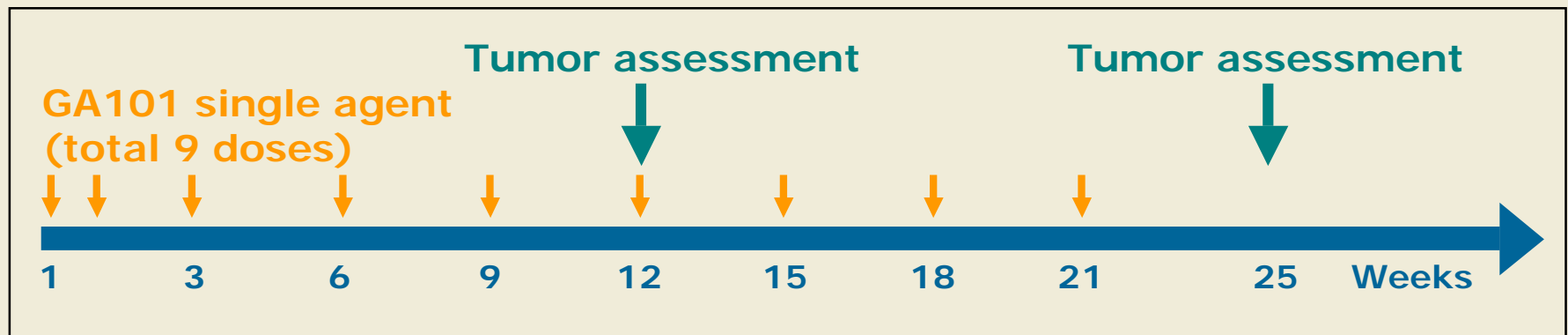
# Background

- GA101 is a Type II glycoengineered, humanized anti-CD20 monoclonal antibody with superior preclinical activity to Type I antibodies in vitro and in vivo.
- Anti-CD20 antibodies with different functional activity from rituximab may have better efficacy.
- GAUGUIN is a Phase I/II study of GA101 in patients with relapsed/refractory non-Hodgkin lymphoma (NHL).
- **Objectives:**
  - Evaluate the safety, pharmacokinetics (PK) and clinical activity of escalating doses of GA101 in a Phase I study.
  - Compare end-of-treatment response, safety, PK, best overall response and progression-free survival (PFS) of 2 dose regimens of GA101 in a Phase II study.



# GAUGUIN Phase I Study Design

- Eligibility: Patients with relapsed/refractory/indolent CD20+ NHL for whom “no treatment of higher priority was available” (FL: n = 13, small lymphocytic lymphoma: n = 1, lymphoplasmacytic lymphoma: n = 1, Waldenstrom’s lymphoma, n = 1)
- Nonrandomized, adaptive dose-escalation design



# Phase I Dose Escalation Design

Cohort (n = 3/group)	GA101 dose (mg) Dose 1/doses 2-9
1	50/100
2	100/200
3	200/400
4	400/800
5	800/1,200
6	1,200/2,000
7	1,600/1,600/800*

\* Dose 1/dose 2/dose 3-9

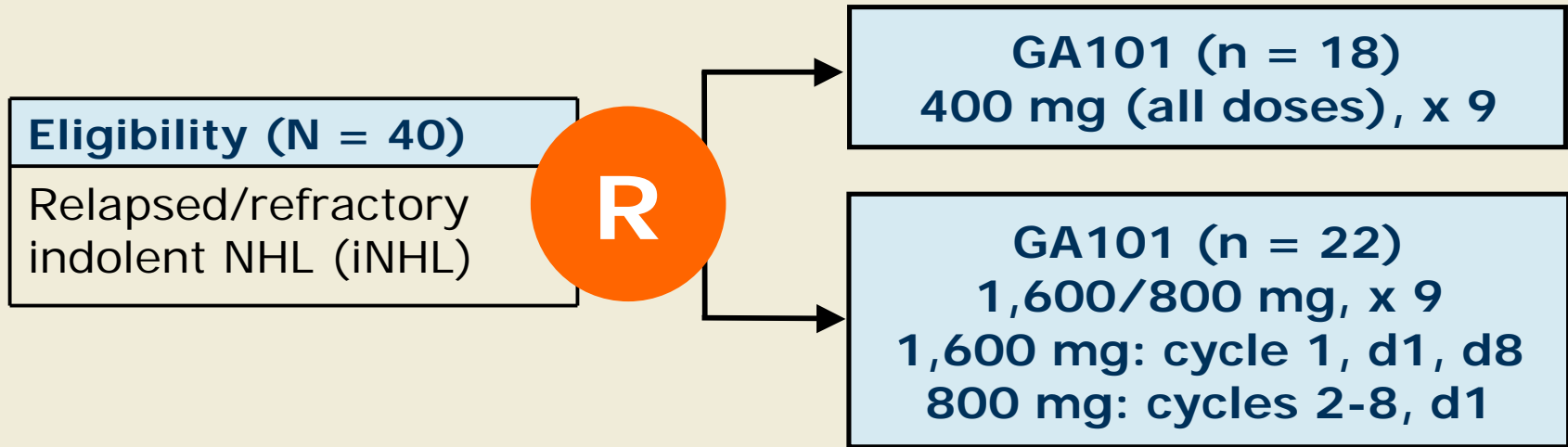
Re-treatment with GA101 on relapse was allowed.

# Responses in Phase I Study

	<b>Best overall response</b>	<b>End of treatment</b>
Overall response rate (ORR)	56%	44%
Complete response (CR)	31%	25%
Partial response (PR)	25%	19%

- Responses were observed across all dose levels
  - No clear dose-response relationship
- Median duration of response: 32 mo

# GAUGUIN Phase II Study Design



GA101 schedule: d1 and d8 cycle 1, d1 of cycles 2-8, 3 weekly cycles

**Primary endpoint:** End-of-treatment response, assessed 4 weeks after last infusion

**Secondary endpoint:** Safety, PK, best overall response, progression-free survival (PFS)

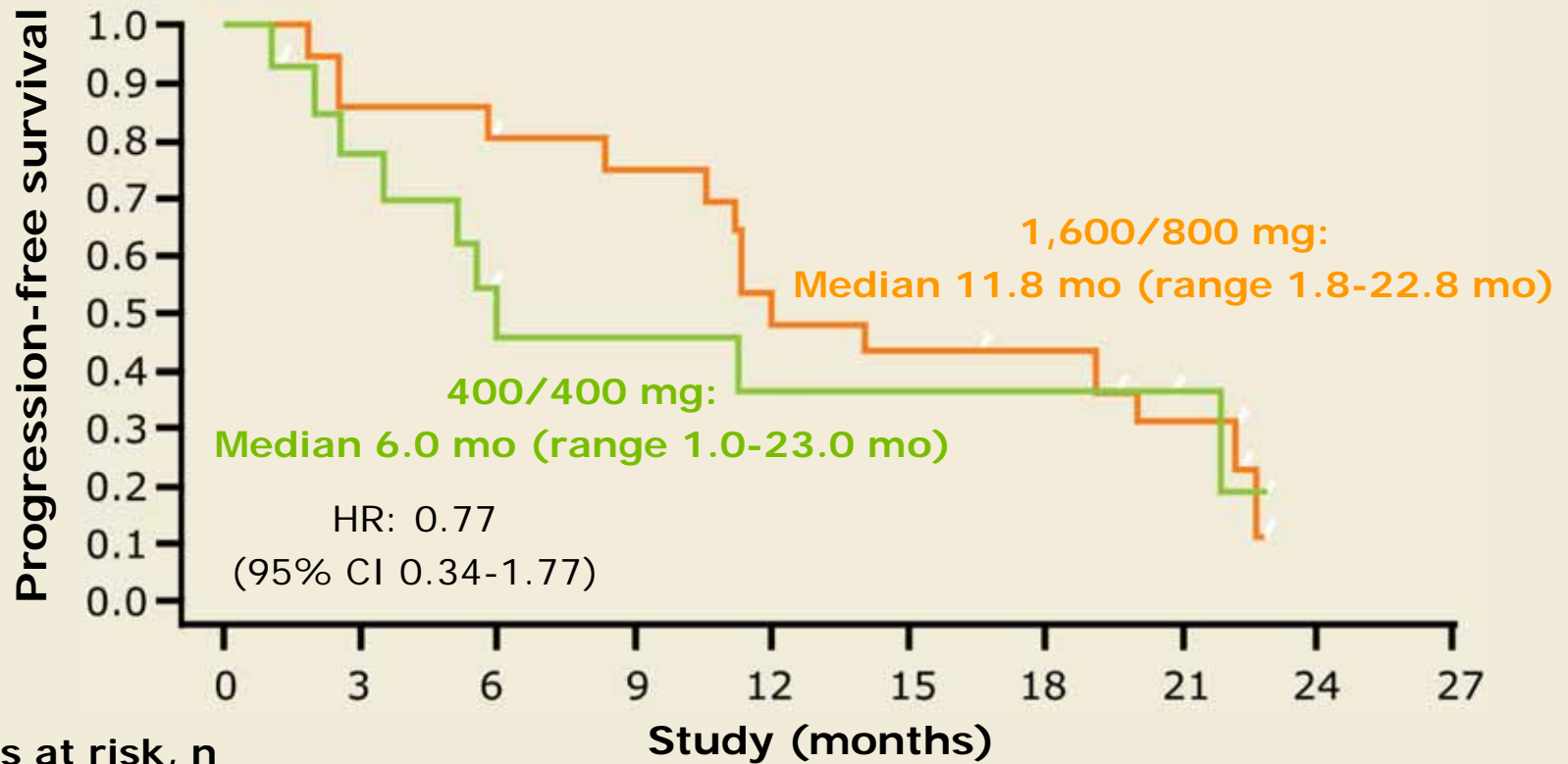
# Phase II End-of-Treatment Response

	400/400 mg (n = 18)	1,600/800 mg (n = 22)
<b>Overall population</b>		
ORR	17%	55%
CR/CRu	—	9%
PR	17%	45%
Stable disease	33%	27%
Progressive disease	50%	18%
<b>Rituximab-refractory population</b>	<b>(n = 12)</b>	<b>(n = 10)</b>
ORR	8%	50%
CR/CRu	—	10%
PR	8%	40%
Stable disease	33%	30%
Progressive disease	58%	20%

CRu = unconfirmed CR

Median duration of response: 17 mo

# PFS in Patients with FL



Patients at risk, n	0	3	6	9	12	15	18	21	24	27
400/400 mg	14	10	5	5	4	4	4	2	0	0
1,600/800 mg	20	17	15	14	9	8	7	5	0	0

Median observation time: 23.1 mo

With permission from Salles GA et al. *Proc ASH* 2011; Abstract 268.

# Phase II: Select Grade 3-4 Treatment-Related Adverse Events (AEs)

<b>AE</b>	<b>400/400 mg (n = 18)</b>	<b>1,600/800 mg (n = 22)</b>
Thrombocytopenia	0%	5%
Lymphopenia	6%	9%
Neutropenia/febrile neutropenia	0%	19%
Infections and infestations	0%	5%
Infusion-related reactions	0%	9%
Asthenia	0%	5%
Cytolytic hepatitis	0%	5%

Total AEs = 1 in 400/400-mg arm and 12 in 1,600/800-mg arm

# Author Conclusions

- GA101 as a single agent has encouraging efficacy in this group of patients with heavily pretreated relapsed/refractory iNHL.
  - A higher response was observed with the 1,600/800-mg dose of GA101 vs the 400/400-mg dose.
  - A response rate of 50% was observed in patients with rituximab-refractory disease in this cohort.
- Promising PFS and response duration for GA101 as a single agent were observed.
- GA101 demonstrated an acceptable safety profile in both dose regimens.
- Based on these data and pharmacokinetic results a 1,000-mg dose will be taken forward for future studies.



## **Investigator Commentary: GA101 Monotherapy in Relapsed or Refractory Indolent NHL**

GA101 has several features that differentiate it from rituximab. It is a Type 2 monoclonal antibody, which means that when it binds to the CD20 epitope, the intracellular cascade that occurs is different. It is believed that a Type 2 antibody may have more direct cytotoxicity and cell death and slightly less complement-dependent cytotoxicity.

The results from this study hint that GA101 might be better than rituximab. This was not a comparative study, but one can say that because responses occurred in patients with rituximab-refractory disease. However, you have to keep in mind that if you were refractory to rituximab long ago and you receive it again, there might be a response.

In terms of tolerability, despite the fact that it is a humanized antibody, studies suggest that the initial infusion-related reactions in particular are worse than those with rituximab. Many trials now include a low dose on the first day of administration. Most oncologists are comfortable managing even severe infusion reactions. Otherwise the tolerability is similar to rituximab, with not much immunosuppression or other toxicity.

***Interview with Jonathan W Friedberg, MD, MMSc, January 11, 2012***

# Randomized Phase II Trial Comparing GA101 (Obinutuzumab) with Rituximab in Patients with Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Preliminary Analysis of the GAUSS Study

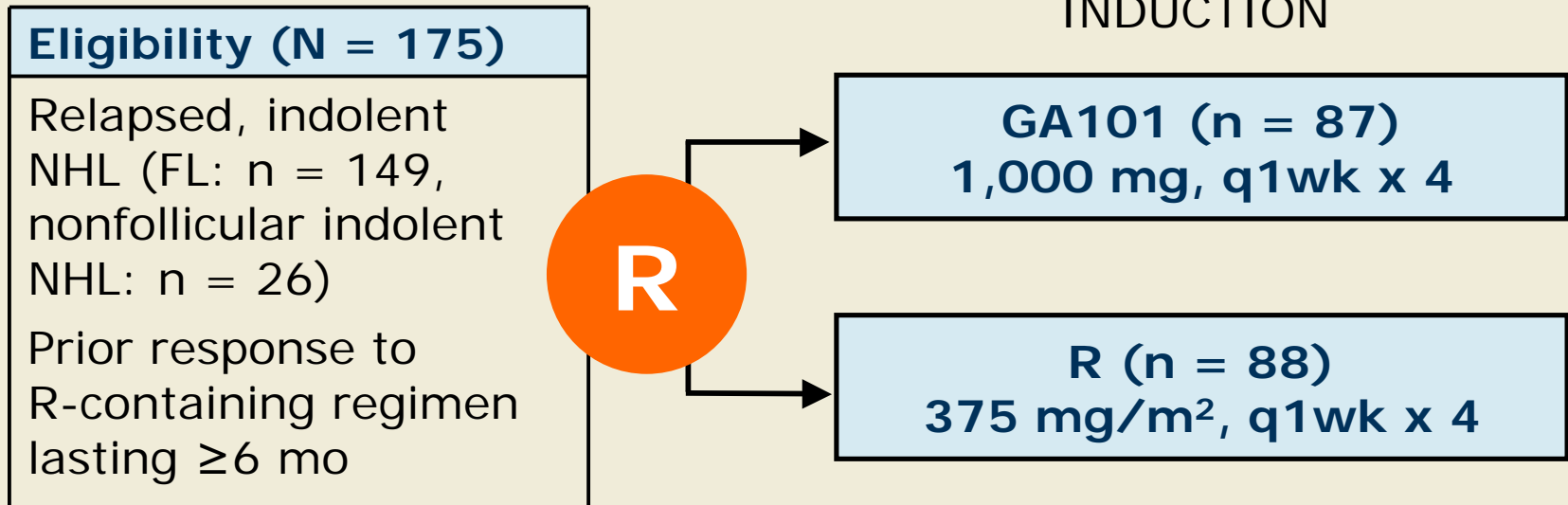
**Sehn LH et al.**

*Proc ASH 2011; Abstract 269.*

# Background

- In preclinical models GA101 has demonstrated enhanced direct cell death and increased ADCC compared to other anti-CD20 antibodies.
- GA101 single-arm clinical studies have demonstrated responses in patients with relapsed/refractory NHL and CLL.
- However, no direct comparisons to rituximab (R) have been reported to date.
- **Objective:** Compare the efficacy and safety of monotherapy with GA101 to those of R in patients with relapsed indolent NHL.

# GAUSS Study Design



Patients with no disease progression after induction received maintenance GA101 or R every 2 months for 2 years at the same dose.

**Primary endpoint:** Overall response rate (ORR) in the FL population

**Secondary endpoints:** PFS, overall survival (OS), safety

# Response to GA101 versus Rituximab (Abstract)

	FL population			
	GA101 (n = 74)		R (n = 75)	
Response	INV	IRF	INV	IRF
ORR	43.2%	43.2%	38.7%	28%
CR/CRu	10.8%	NR	6.7%	NR
Disease progression	20.3%		17.3%	
	FL+ nonfollicular indolent NHL			
	GA 101 (n = 88)		R (n = 87)	
ORR	43.2%	42.0%	35.6%	24.1%

INV = investigator assessment; IRF = independent central blinded radiology review;  
NR = not reported

End-of-treatment response assessed 28-42 d after last induction dose

# Select Adverse Events (AEs) (Abstract)

AE	GA101 (n = 88)	Rituximab (R) (n = 87)
Infusion-related reaction (IRR)		
Any grade	72%	49%
Grade 3/4	11%	5%
Fatigue (any grade, $\geq 5\%$ )	23%	17%
Back pain (any grade, $\geq 5\%$ )	7%	2%
Decreased appetite (any grade, $\geq 5\%$ )	7%	2%
Insomnia (any grade, $\geq 5\%$ )	5%	0%

- Serious AEs: GA101 arm (n = 5) due to IRR (n = 2), febrile neutropenia (n = 1), pleural effusion (n = 1), nephrolithiasis (n = 1); R arm (n = 9)
- Deaths: GA101 (n = 1) due to pulmonary aspergillosis, R (n = 1) due to cardiopulmonary arrest
- Discontinuations: GA101 (n = 4, 3 due to IRR, 1 due to orthostatic hypotension), R (n = 7)

# Author Conclusions

- Treatment with GA101 in patients with relapsed NHL resulted in higher response rates compared to R as assessed by both investigators and the IRF at an early time point.
- GA101 was well tolerated. Although a higher rate of IRRs were noted, the majority were Grade 1/2 in severity and did not result in significant differences in treatment discontinuation.
- This first head-to-head trial of GA101 against R demonstrated higher response rates without appreciable differences in safety.
- GA101 is under study in Phase III trials in combination with chemotherapy (NCT01287741, NCT01332968, NCT01059630).

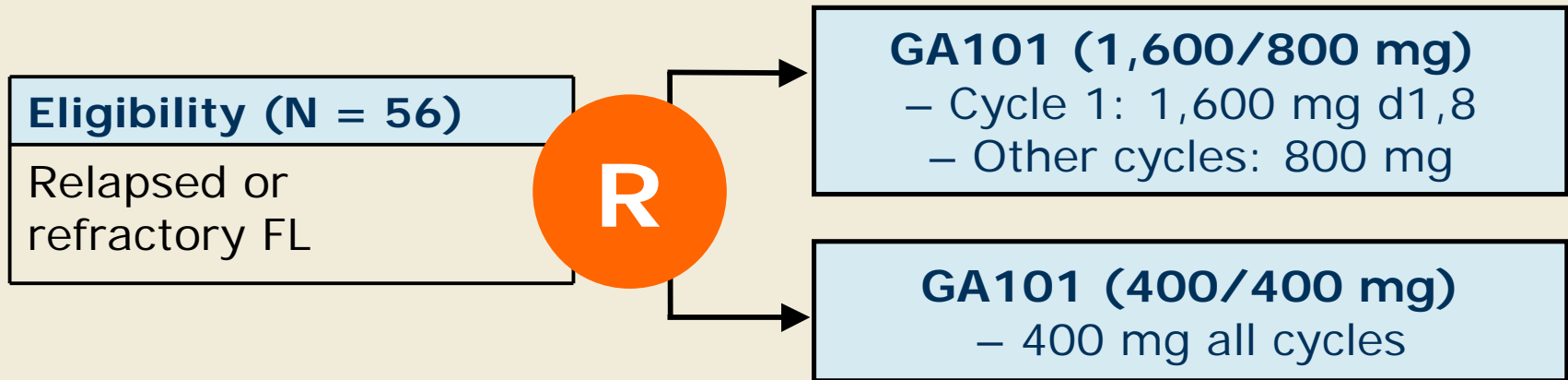
# Obinutuzumab (GA101) in Combination with FC or CHOP in Patients with Relapsed or Refractory Follicular Lymphoma: Final Results of the Phase I GAUDI Study (BO21000)

**Radford J et al.**

*Proc ASH 2011; Abstract 270.*



# GAUDI Study Design



- Patients were stratified by prior chemotherapy regimens before randomization:
  - **CHOP** (n = 28): 6-8, 21-d cycles
  - **Fludarabine/cyclophosphamide (FC)** (n = 28): 4-6, 28-d cycles
- Patients responding to GA101 were offered maintenance treatment for 2 years or until progression.

**Primary endpoint:** Safety

**Secondary endpoint:** Response rate

# Adverse Events (Abstract)

Adverse event	G-CHOP (n = 28)	G-FC (n = 28)
Infusion-related reactions (IRR)* Any grade	64%	79%
Grade 3/4	7%	7%
Neutropenia (Grade 3/4)	39%	50%
Cycles delayed due to hematologic toxicity or infections	6%	10%
Dose of chemotherapy reduced due to toxicity	29%	36%

\* IRRs were mostly during the first infusion.

G = GA101

- No evidence of increased toxicity with the 1,600/800-mg dose vs 400/400 mg
- 28/28 pts in G-CHOP, 22/28 pts in G-FC completed treatment

# Response to Therapy (Abstract)

Response*	G-CHOP (n = 28)	G-FC (n = 28)
ORR	96.4%	92.9%
CR	39.3%	50.0%
PR	57.1%	42.9%
Stable disease	3.6%	0%
Progressive disease	0%	3.6%

\* Assessed by IWG criteria modified to classify unconfirmed CR as PR

- 3.6% of patients in G-FC arm were not assessed.
- Response rates in the G-CHOP arm compared favorably to those in the rituximab in combination with CHOP cohort from the EORTC 20981 study in a matched-pair analysis.

# Author Conclusions

- GA101 can be safely combined with chemotherapy regimens used in the treatment of FL and demonstrated a high level of activity compared to historical controls.
- G-CHOP could be delivered at the protocol-specified 3-weekly interval in most patients.
- G-FC in a more heavily pretreated population showed worse tolerability than G-CHOP.
- Following these promising results, GA101 will be studied in combination with CHOP and other chemotherapies in a randomized Phase III study against the standard of care, R-CHOP (NCT01287741).

## **Investigator Commentary: Comparison of GA101 to Rituximab in Relapsed CD20+ Indolent NHL**

The GAUSS study, which I was a part of, showed 2 important results. The first is that both CR rates and overall response rates were slightly higher in the GA101 group compared to the rituximab group. However, it was disappointing that the PFS data presented at the meeting showed overlapping curves for the GA101 and rituximab groups. So the higher response rate did not translate into an improvement in PFS. This Phase II study was powered to investigate response, not to study differences in PFS. Even though these data are preliminary, they are still disappointing. Despite these results, a Phase III study to determine the durability of GA101 has been planned.

*Interview with Jonathan W Friedberg, MD, MMSc, January 11, 2012*

## **GA101 in Combination with FC or CHOP in Relapsed or Refractory FL**

The GAUDI study was a pilot study that showed that GA101 can be safely combined with CHOP chemotherapy. It gives the investigators confidence that they can go ahead with the big Phase III study comparing R-CHOP to G-CHOP (NCT01287741).

*Interview with Brad S Kahl, MD, January 26, 2012*

**A Phase III Randomized Intergroup Trial (SWOG S0016) of CHOP Chemotherapy plus Rituximab vs CHOP Chemotherapy plus Iodine-131-Tositumomab for the Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphoma<sup>1</sup>**

**Fractionated <sup>90</sup>Y Ibritumomab Tiuxetan Radioimmunotherapy as an Initial Therapy of Follicular Lymphoma — First Results from a Phase II Study in Patients Requiring Treatment According to GELF/BNLI Criteria<sup>2</sup>**

**<sup>1</sup> Press OW et al.**

*Proc ASH 2011; Abstract 98.*

**<sup>2</sup> Illidge T et al.**

*Proc ASH 2011; Abstract 102.*

**A Phase III Randomized Intergroup  
Trial (SWOG S0016) of CHOP  
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Hodgkin's Lymphoma**

**Press OW et al.**

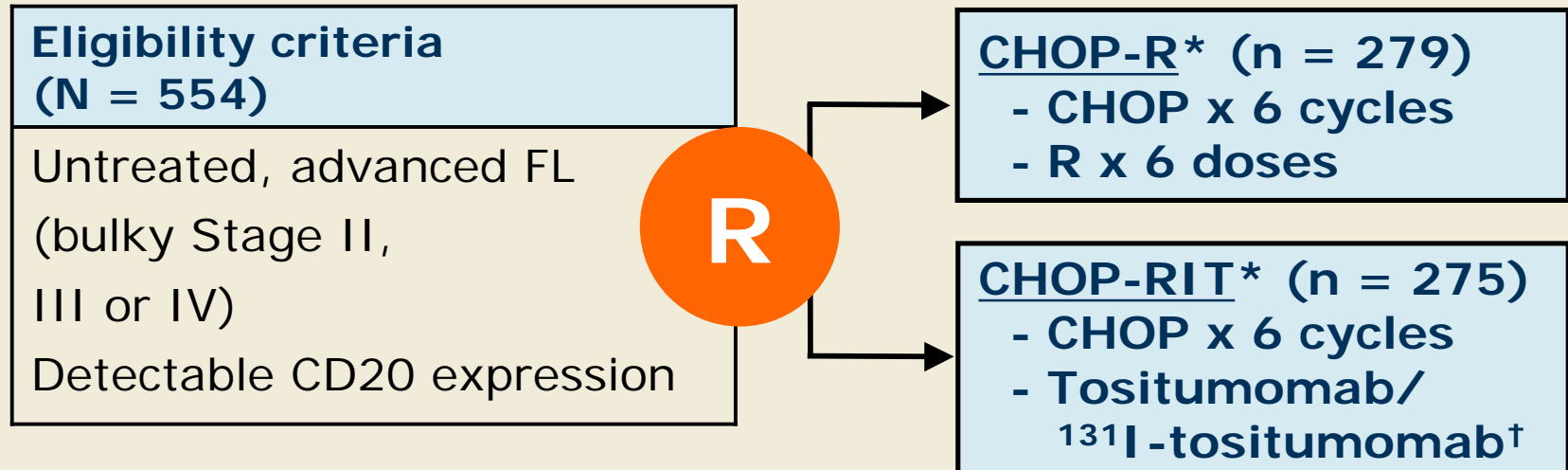
*Proc ASH 2011; Abstract 98.*

# Background

- Advanced follicular lymphoma (FL) is incurable with conventional chemotherapy and there is no consensus on the best treatment approach.
- The SWOG-9911 study with CHOP followed by  $^{131}\text{I}$ -tositumomab showed promising results with a 60% progression-free survival (PFS) and 79% overall survival (OS) after a 10-year follow-up for patients with newly diagnosed FL.
- **Objective**: Compare the safety and efficacy of CHOP-R versus CHOP-RIT for newly diagnosed FL.



# S0016 Phase III Study Design



\* Maintenance R not used on this study

<sup>†</sup> Dosimetric infusion of tositumomab/<sup>131</sup>I-tositumomab followed 1-2 weeks later by a therapeutic infusion of <sup>131</sup>I-tositumomab (total dose: 75 cGy)

# Response and Survival Analysis (Abstract)

<b>Response</b>	<b>CHOP-R (n = 263)</b>	<b>CHOP-RIT (n = 260)</b>	<b>p-value</b>
ORR	85%	86%	0.9
CR/ CRu	41%	46%	0.25
<b>Two-year survival</b>	<b>CHOP-R (n = 267)</b>	<b>CHOP-RIT (n = 265)</b>	<b>p-value</b>
PFS	76%	80%	0.11
OS	97%	93%	0.08

- Median follow-up: 4.9 years
- Hazard ratio (HR) for PFS = 0.79, HR for OS = 1.55
- Response assessment not possible: 10% CHOP-R arm, 8% CHOP-RIT arm

# Adverse Events (Abstract)

Adverse event	CHOP-R (n = 263)	CHOP-RIT (n = 263)	p-value
Hematologic toxicity (Grade 4)	36%	30%	0.19
Nonhematologic toxicity (Grade 4)	1.5%	1.9%	1.0
Treatment-related mortality	0.4%	1.5%	0.37
Second malignancies	8.7%	8.3%	1.0
AML/MDS	1.1%	2.7%	0.34

# Author Conclusions

- No statistically significant differences in PFS, OS or serious toxicities were demonstrable with either regimen administered in this trial.
- PFS and OS are outstanding with both regimens, and median time to progression has not been reached for either treatment.
- Future studies will need to assess if combining CHOP-R with RIT consolidation and maintenance rituximab will confer additive benefit.
- A follow-up trial (SWOG protocol S0801; NCT00770224) that has recently completed accrual will address this question.

## **Investigator Commentary: Phase III Randomized Trial of CHOP plus Rituximab vs CHOP plus <sup>131</sup>I-Tositumomab for Newly Diagnosed FL**

The patients in this study had both high and low tumor burden FL. This has to be kept in mind when comparing results from this study to previous studies. Comparison of R-CHOP to CHOP-RIT showed excellent results with both regimens, with a few more cases of AML/MDS in the CHOP-RIT arm. The outcome in the CHOP-RIT arm may have been better with R-CHOP induction followed by a maintenance regimen. However, this study was started 10 years ago and was designed according to what was known at the time. If they had to choose 1 of these 2 strategies, I believe most people would pick R-CHOP because they are more familiar with it and it is more convenient to administer.

***Interview with Brad S Kahl, MD, January 26, 2012***

The hope was that the RIT arm would show a much better response. I believe that the CHOP chemotherapy negated the beneficial effect of RIT. This study should have had rituximab added to chemotherapy followed by consolidation RIT followed by rituximab maintenance. The follow-up S0801 study did just that and should be interesting.

***Interview with Stephanie A Gregory, MD, January 11, 2012***

# Fractionated $^{90}\text{Y}$ Ibritumomab Tiuxetan Radioimmunotherapy as an Initial Therapy of Follicular Lymphoma — First Results from a Phase II Study in Patients Requiring Treatment According to GELF/BNLI Criteria

**Illidge T et al.**

*Proc ASH 2011; Abstract 102.*

# Background

- Radioimmunotherapy (RIT) has demonstrated high response rates and durable remission in relapsed follicular lymphoma (FL).
- There are currently few data with RIT in untreated FL.
- $^{90}\text{Y}$  ibritumomab tiuxetan used as front-line treatment for FL resulted in an ORR of 72% and a CR of 52% 1 year after therapy (*Blood* 2010; 116:Abstract 593).
- $^{131}\text{I}$  tositumomab has demonstrated an ORR of 97% and a CR rate of 72% in patients with low-risk disease (*N Engl J Med* 2005; 352:441).
- **Objective**: Evaluate the efficacy and safety of 2 fractions of  $^{90}\text{Y}$  ibritumomab tiuxetan in patients with untreated FL.

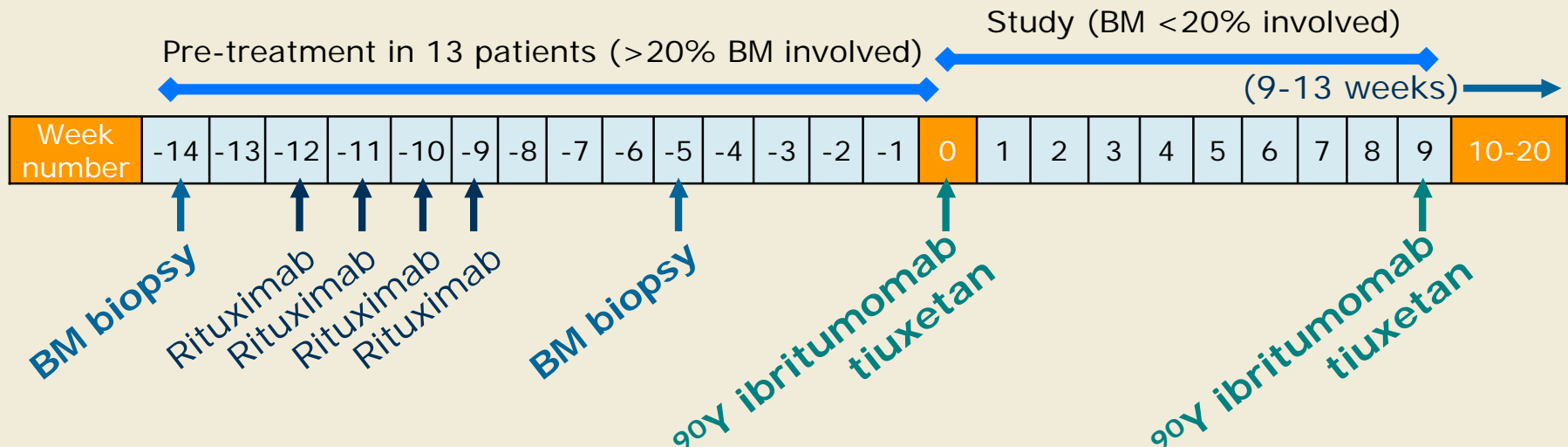
# Study Design

## Eligibility criteria (N = 76)

Untreated FL Grade I, II or IIIa

At least one symptom requiring treatment initiation:

- Nodal mass >7 cm, at least 3 nodes
- B symptoms
- Elevated serum LDH or  $\beta 2$  microglobulin
- Symptomatic splenic enlargement
- Compressive syndrome





# Response to Therapy

<b>End of treatment response* (n = 72)</b>	
ORR	95.8%
<b>Best response†</b>	
ORR CR	97.2% 65%
<b>Single <sup>90</sup>Y ibritumomab tiuxetan infusion (n = 17)</b>	
ORR	100%
CR/CRu	75%

\* Evaluated at 3 months.

† Five patients converted from PR to CR, 1 SD to PR.

# Survival

Two-year PFS	67%
Median PFS	36 months
Two-year OS	99%
Further treatment-free survival at 2 years*	74%

\* Nineteen of 28 patients whose disease progressed were re-treated.

# Adverse Events

<b>Grade 3/4 hematologic AE (n = 72)</b>	
Platelets (1 <sup>st</sup> fraction)	20.8%
Platelets (2 <sup>nd</sup> fraction)	56.4%
WBC (1 <sup>st</sup> fraction)	20.8%
WBC (2 <sup>nd</sup> fraction)	29.1%
Neutrophils (1 <sup>st</sup> fraction)	20.8%
Neutrophils (2 <sup>nd</sup> fraction)	36.4%

- Four episodes of infection, 2 hospitalizations with neutropenic sepsis
- Two cases of MDS, 1 potentially treatment related
- Two deaths: 1 due to metastatic breast cancer, 1 due to AML

# Author Conclusions

- Patients with >20% bone marrow (BM) infiltration can be treated with RIT after 4 weekly cycles of rituximab to clear the BM.
- High ORR (97.2%) and CR (65%) rates were observed in a high-risk population.
- Hematologic toxicity was manageable with very few infectious complications.
- Median PFS of 36 months is comparable with nonanthracycline-based regimens.
- This is a convenient and feasible regimen for patients with FL.

## **Investigator Commentary: Fractionated Radioimmunotherapy as an Initial Therapy of FL**

This study used 2 doses of RIT with the hope of getting a better response. But the patient gets more radiation exposure with 2 doses, and I am concerned about increasing radiation. I'm not convinced of the benefit of administering it in fractionated doses versus the standard single dose.

I believe that RIT is underutilized largely for financial reasons. In addition, it is easier to administer rituximab maintenance. Oncologists state that the reason they do not use RIT is the risk of MDS. But if you look at the studies with RIT alone, the incidence is not higher than in patients with low-grade lymphoma who have received multiple treatments. More cases of MDS seem to occur when you administer chemotherapy in addition to RIT. All chemotherapeutic regimens have alkylating agents, which result in a double hit. Two agents I'm particularly concerned about are bendamustine and fludarabine.

Some patients are fearful about radiation therapy and we need to talk to them about radiation safety. Radiolabelled  $^{90}\text{Y}$  ibritumomab tiuxetan only has a beta emitter and does not result in as much radiation exposure as tositumomab. It is easier to work with and I prefer it to tositumomab.

***Interview with Stephanie A Gregory, MD, January 11, 2012***

# Significant Prognostic Impact of [18F]Fluorodeoxyglucose-PET Scan Performed During and at the End of Treatment with R-CHOP in High-Tumor Mass Follicular Lymphoma Patients: A GELA-GOELAMS Study

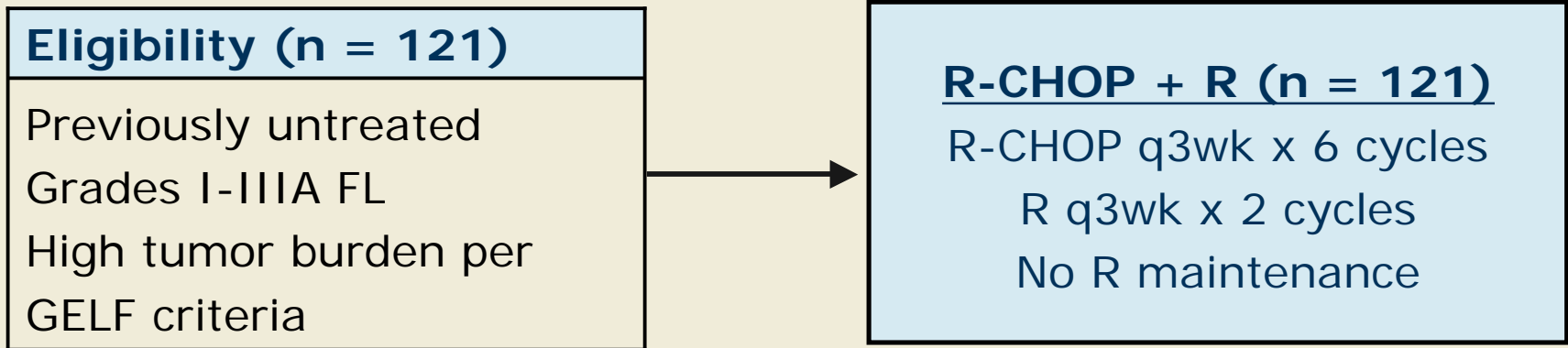
**Dupuis J et al.**

*Proc ASH 2011; Abstract 877.*

# Background

- Patients with follicular lymphoma (FL) usually respond well to initial treatment with immunochemotherapy, which also increases survival benefits.
- However, a small proportion of patients relapse or develop refractory disease.
- The identification of this subgroup of patients can lead to early therapeutic interventions, potentially leading to better prognosis.
- Little is known about the use of [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with FL, although it is widely used for the staging and restaging of aggressive lymphomas.
- **Objective:**
  - Evaluate the prognostic value of FDG-PET performed in the middle and at the end of treatment in patients with high tumor mass FL treated with first-line immunochemotherapy.

# GELA-GOELAMS Trial Design



R-CHOP = rituximab (R), cyclophosphamide, doxorubicin, vincristine, prednisone

- FDG-PET was performed
  - Before treatment (initial FDG-PET)
  - After 4 cycles of R-CHOP (interim FDG-PET)
  - At the end of treatment (final FDG-PET)
- FDG-PET scans were first interpreted in each center, then centrally reviewed by 3 investigators blinded to clinical data.
- Positivity or negativity was rated according to the Deauville visual semi-quantitative criteria.



# Centrally Reviewed\* FDG-PET Scans (Abstract)

Time of FDG-PET scan	Positive scans	Negative scans
Initial FDG-PET (n = 118)	99%	1%
Interim (I)-FDG-PET (n = 111)	24%	76%
Final (F)-FDG-PET (n = 106)	22%	78%

- \* The Kappa coefficient indicated a good degree of concordance among the 3 PET reviewers.
- Positivity was defined as fixation at level 4 (FDG uptake superior to that of the liver) or 5 (FDG uptake clearly superior to liver and/or new sites of disease).

# Survival Rates (Abstract)

Response	I-PET-negative	I-PET-positive	<i>p</i> -value
2-y PFS	86%	61%	0.0046
Response	F-PET-negative	F-PET-positive	<i>p</i> -value
2-y PFS	87%	51%	<0.0001
2-y OS	100%	88%	0.0128

PFS = progression-free survival; OS = overall survival

# Author Conclusions

- In patients receiving first-line therapy for FL, FDG-PET scans performed either after 4 cycles of R-CHOP or at the end of immunochemotherapy induction are strongly predictive of treatment outcomes.
- Therapeutic intervention based on PET results during inductive treatment should be evaluated in the future.

## **Investigator Commentary: Significant Prognostic Impact of [18F]Fluorodeoxyglucose-PET Scans — A GELA-GOELAMS Study**

The evaluation of PET scans is a recommended criterion at the end of treatment for diffuse large B-cell lymphoma. Importantly, a negative PET scan is needed for long-term survival and cure. PET scanning has never been a recommendation for low-grade lymphomas because results reveal some as positive PET scans and others as negative scans. Because FLs have a high avidity for PET scanning, they are often positive on initial evaluation. This study demonstrated that negative PET scans are significant, as a longer PFS was observed in these cases. As such, it may be helpful to perform PET scanning at the end of treatment in low-grade lymphomas, especially in patients with bulky masses.

***Interview with Stephanie A Gregory, MD, January 11, 2012***

This is an interesting study demonstrating that PET scans at the end of treatment are good predictors of treatment outcome as indicated by the 2-year PFS rates. A modest OS difference was also seen based on the final PET scans. Although this trial does not give information about what to do with the patients with F-PET-positive scans, these data indicate that about 50% of these patients will relapse and 12% will die.

***Interview with Brad S Kahl, MD, January 26, 2012***

# Identification of Patient Subgroups Demonstrating Longer Progression-Free Survival (PFS) Benefit with Bortezomib-Rituximab versus Rituximab in Patients with Relapsed or Refractory Follicular Lymphoma (FL): Biomarker Analyses of the Phase 3 LYM3001 Study

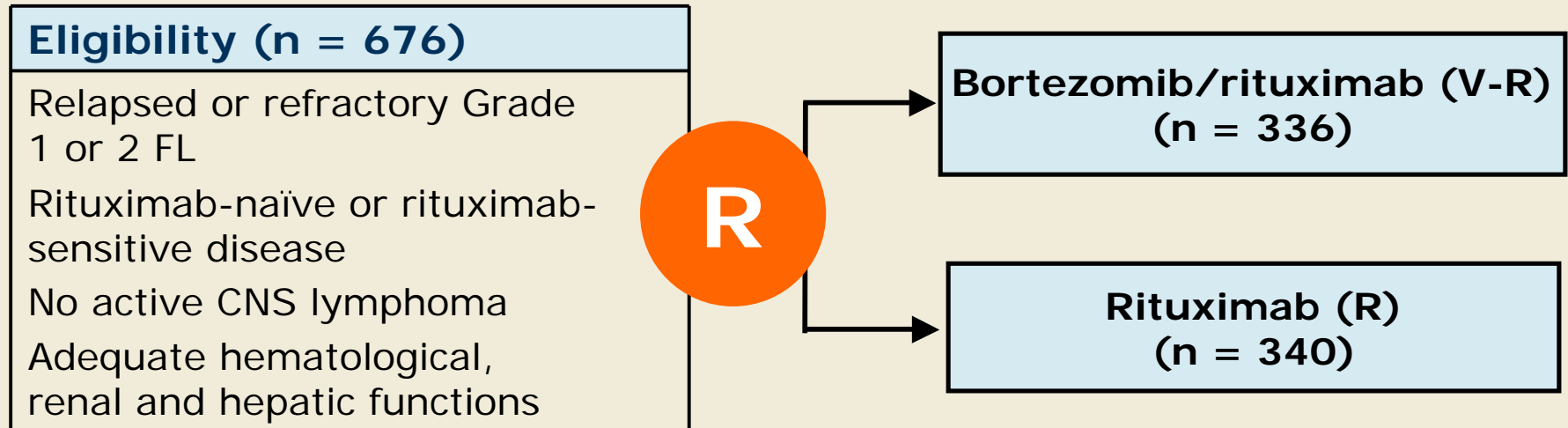
**Coiffier B et al.**

*Proc ASH 2011; Abstract 265.*

# Background

- In order to optimize treatment in individual patients, it is essential to identify the patient subgroup that is most likely to benefit from a specific therapy.
- The Phase III LYM3001 trial in patients with relapsed or refractory follicular lymphoma (FL) demonstrated significantly improved clinical outcomes with bortezomib/rituximab versus rituximab treatment alone (*Lancet Oncol* 2011;12:773).
- However, these results were reported in an unselected patient population.
- **Objective:**
  - Present exploratory biomarker analyses of LYM3001 to identify patient subgroups most likely to derive a longer PFS benefit and also showing a trend for better overall survival (OS) with bortezomib/rituximab therapy.

# Phase III LYM3001 Trial Design



- Response was assessed with modified International Working Group response criteria.
- Archived tumor tissue was collected at baseline.
- Whole blood samples for germline DNA testing were collected on d1 of treatment.

- Protocol-specified candidate biomarkers were based on associations with V (NF- $\kappa$ B, p65, PSMA5, p27, PSMB1/5/8/9) or R (CD68, FCGR2A/3A) activity.
- Further analysis included the division of all biomarker-evaluable patients into discovery and confirmation cohorts.

# Single Markers and Biomarker Pairs Indicating Subgroups with Improved Clinical Outcomes (Abstract)

Outcome with V-R over R	Markers* (n = 102)
PFS $\geq 6$ months	14 pairs
Significantly improved PFS ( $p < 0.0001$ )	1 pair <sup>†</sup>

\* Single markers and biomarker pairs highlighting patient subsets with significantly improved outcomes with V-R versus R therapy.

<sup>†</sup> Using false discovery rate (FDR) to control for multiple comparison corrections, the biomarker pair is presence of *PSMB1* P11A C/G heterozygote and low CD68 expression (0-50 CD68-positive macrophages in the follicular space).



# Efficacy Outcomes in All Patients with the Presence of *PSMB1* P11A C/G and Low CD68 (Abstract)

Outcome (n = 356)*	V-R	R	HR	p-value	FDR
Median PFS	16.6 mo	9.1 mo	0.407	<0.0001	0.051
Median OS	Not reached	Not reached	0.426	0.055	—
Overall response rate	73.7%	47.5%	—	0.0077	—
Complete response rate	33.3%	23%	—	0.3044	—
Median time to next therapy	33.1 mo	14.8 mo	—	0.0013	—

\* Biomarker evaluable patients; HR = hazard ratio; FDR = false discovery rate

- Frequency of biomarker pair in patients offering a significant PFS benefit: 33%
- Patients with high-risk features were represented in the biomarker-selected population:
  - High tumor burden: 54%; high FLIP1: 41%; >2 prior lines of therapy: 30%
- In patients lacking this biomarker pair (n = 238), there were no significant differences in efficacy outcomes

# Efficacy Results with the Presence of *PSMB1* P11A C/G and Low CD68: Cohort Classification (Abstract)

Outcome	Discovery cohort (n = 198)			
	V-R	R	HR	p-value
Median PFS	14.2 mo	8.4 mo	—	0.0003
OS	—	—	0.47	0.1291
Outcome	Confirmation cohort (n = 108)			
Median PFS	18.2 mo	9.5 mo	0.44	0.0817

# Author Conclusions

- The analyses of the Phase III LYM3001 trial identified biomarker combinations in one third of patients offering a significant PFS benefit with bortezomib/rituximab therapy versus rituximab alone.
- The use of biomarker assays in patients with relapsed or refractory FL may aid in the identification of patient subgroups deriving maximal benefits from bortezomib/rituximab therapy.

## **Investigator Commentary: Identification of Patient Subgroups Demonstrating Longer PFS Benefit with V-R versus R in Relapsed or Refractory FL — Biomarker Analysis of LYM3001**

This is a correlative study of the Phase III LYM3001 trial. Although there was a statistically significant benefit of the V-R treatment arm of the LYM3001 trial, it is not necessarily the result of a biologic or clinical difference. This is because V-R only extended PFS by a few weeks and it is well known that the addition of bortezomib to the treatment regimen increases toxicity. In addition, the LYM3001 trial did not include maintenance therapy, which may have lengthened the PFS. This study attempts to find patient groups that may particularly benefit from the addition of bortezomib. The study concludes stating that such a group, where PFS was almost doubled with V-R treatment, was identified. Although some form of statistical adjustment for corrections was used, without a validation group, this study is merely hypothesis generating. In practice, therefore, these data cannot be used to determine the choice of therapy until further research is performed in this area.

***Interview with Jonathan W Friedberg, MD, MMSc, January 11, 2012***