5 Minute JournalClub

Key ASCO Presentations

Issue 3, 2010

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CME Information

LEARNING OBJECTIVES

- Summarize the efficacy and safety of maintenance rituximab for patients with FL responding to front-line induction rituximab/chemotherapy.
- Describe the clinical impact of in vivo purging and/or maintenance rituximab in patients with relapsed FL who have experienced a response to reinduction and proceeded to transplant.
- Recall the Phase II efficacy and safety of lenalidomide/rituximab as front-line treatment of indolent lymphoma.
- Cite the most common adverse events and objective response rates with lenalidomide in the initial treatment of elderly patients with CLL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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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CME Information (Continued)

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Rituximab Maintenance for 2 Years in Patients with Untreated High Tumor Burden Follicular Lymphoma After Response to Immunochemotherapy

Salles GA et al.

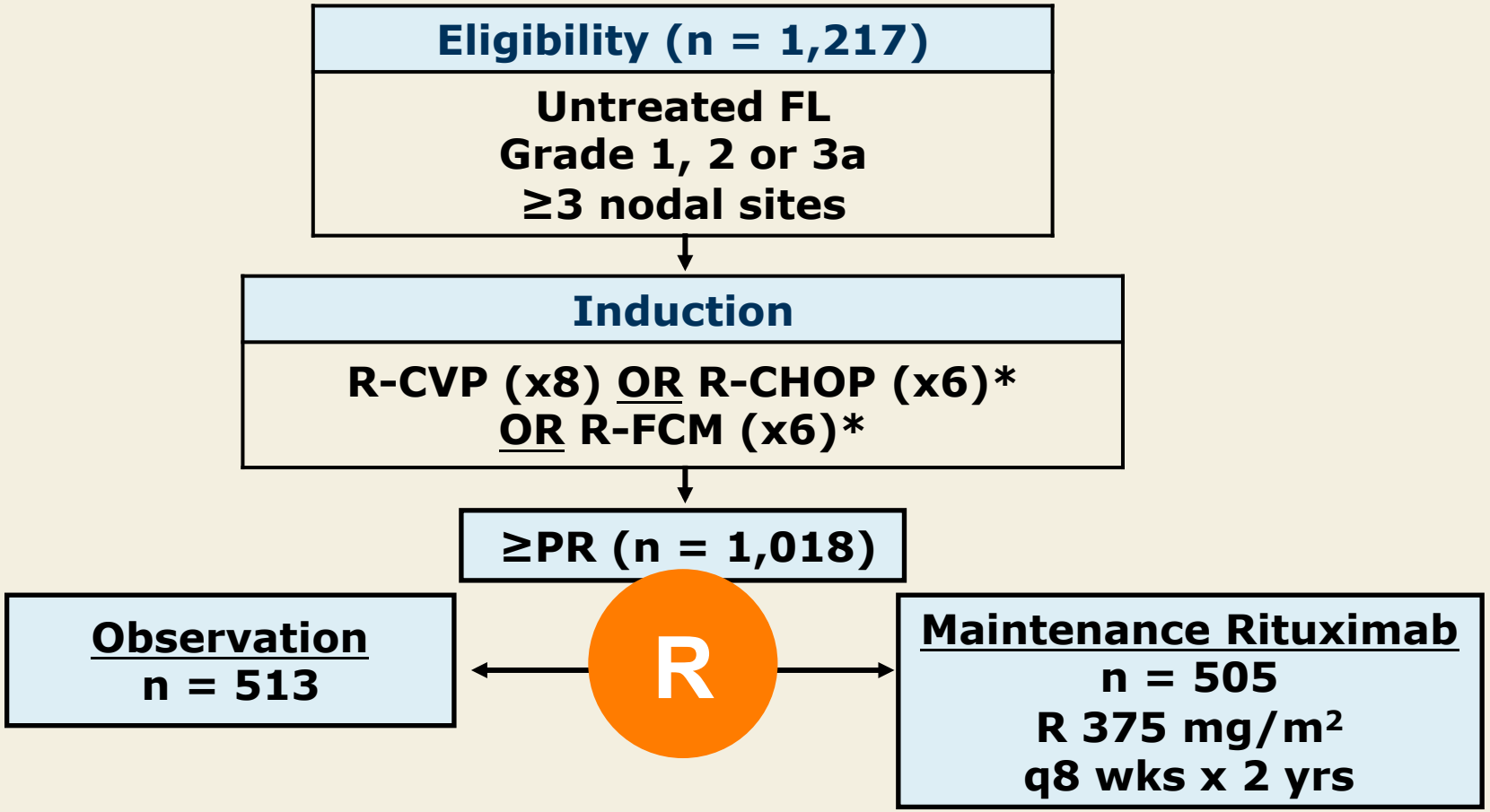
Proc ASCO 2010;Abstract 8004.

Introduction

- Rituximab (R) maintenance has shown clinical benefit for patients with follicular lymphoma (FL):
  - In the relapsed setting after induction with chemotherapy alone or chemotherapy plus R (*J Clin Oncol* 2010;28:2853).
  - In the first-line setting after induction chemotherapy alone[1] or R alone[2] ([1] *J Clin Oncol* 2009;27:1607, [2] *Blood* 2004;103:4416).
- The role of R maintenance in FL after first-line R-chemotherapy induction remains unknown.
- **Current study objective:**
  - Assess the benefit of R maintenance over the course of two years for patients with FL responding to first-line R-chemotherapy induction.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

PRIMA Study Design



* Followed by two additional R infusions (for a total of R x 8)

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Primary Endpoint: Progression-Free Survival

	Observation n = 513	R Maintenance n = 505
2-yr progression-free survival (PFS)	66%	82%
Hazard ratio (95% CI)	0.50 (0.39-64)	
p-value	<0.0001	

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Response Status at the End of Maintenance

	Observation n = 398	Rituximab (R) n = 389
Progressive Disease (PD)	162 (40.7%)	79 (20.3%)
Stable Disease (SD)	1 (0.3%)	0 (0%)
Partial Response (PR)	29 (7.3%)	28 (7.2%)
Complete Response (CR/CRu)	190 (47.7%)	260 (66.8%)
Response: End of Induction to End of Maintenance	**Observation**	**Rituximab**
Patients remaining in CR/CRu	153 (56%)	209 (75%)
Patients converting from PR/SD to CR/CRu	37 (30%)	49 (45%)

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

PFS Benefits with Rituximab Maintenance Maintained Across Major Subgroups

Category	Subgroup	N	Hazard Ratio	95% CI
All	All	1,018	0.49	0.38–0.64
Age	<60	624	0.45	0.33–0.62
	≥60	394	0.59	0.39–0.90
FLIPI index	FLIPI ≤1	216	0.38	0.19–0.77
	FLIPI = 2	370	0.39	0.25–0.61
	FLIPI ≥3	431	0.61	0.43–0.67
Induction chemotherapy	R-CHOP	768	0.43	0.31–0.59
	R-CVP	222	0.69	0.44–1.08
	R-FCM	28	0.51	0.13–2.07
Response to induction	CR/CRu	721	0.52	0.38–0.70
	PR	290	0.45	0.29–0.72

Hazard ratio <1 favors rituximab maintenance.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Safety During Rituximab Maintenance

	Observation n = 508	Rituximab n = 501
Any adverse event	35%	52%
Grade ≥2 infections	22%	37%
Grade 3/4 adverse events	16%	23%
Grade 3/4 neutropenia	<1%	4%
Grade 3/4 infections	<1%	4%

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Conclusions

- R maintenance for two years significantly improved PFS for patients with previously untreated FL who responded to induction with chemotherapy plus R.
- Benefits of R maintenance were seen in all major sub-groups.
- Consistent improvements were observed in secondary endpoints including CR, OR and time to next treatment (data not shown).
- The results of the PRIMA study provide evidence for a new standard of care for patients with FL who are in need of initial treatment.
- Data from the ongoing ECOG-E4402 (RESORT) trial will address how maintenance R compares to re-treatment with R at disease progression.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004; Fisher RI. *Proc ASCO* 2010;Discussion.

Investigator comment on the PRIMA trial findings

These patients with follicular lymphoma (FL) required treatment, so it wasn't necessarily your watch-and-wait patient. Three quarters received R-CHOP, and the majority of the others received R-CVP.

Eighty-two percent of patients who received rituximab (R) maintenance were in remission at two years versus 66 percent in the observation arm. Overall survival wasn't reported, but that is always a question in FL. The toxicity was similar in the two arms, as was the quality-of-life analysis. A minor increase in Grade I and Grade II infections occurred in the maintenance arm, but no difference was apparent in serious life-threatening infections.

I will likely use maintenance therapy more than I did in the past, but I don't believe all patients need it. Certain patients like having a break from the doctor, but many prefer the idea of the security blanket of continual treatment and monitoring that maintenance therapy offers.

In the discussion, Rich Fisher argued that maintenance rituximab therapy is currently indicated following all treatment programs for patients with rituximab-sensitive FL, and I think that's a reasonable point.

Interview with John P Leonard, MD, June 28, 2010

Investigator comment on the PRIMA trial findings

As in the Gelmini trial, which compared prolonged treatment with rituximab to no further treatment after standard rituximab therapy, in the PRIMA study, there were more complete responses at the end of R maintenance. The concepts behind immune therapy are that it takes time to kill the last tumor cell and that the drug continues to work with time. It's important to know that more responses occur as patients continue to receive treatment.

I think R maintenance in FL will be embraced by most clinicians. In Dr Richard Fisher's discussion, he was quite positive, and although we do need to wait for more follow-up to determine whether long-term complications occur, I do think R maintenance is here to stay.

It's interesting that Dr Mathias Rummel's new trial in Germany is comparing bendamustine/rituximab (BR) with either two or four years of R maintenance, so we're not going to get away from R maintenance in low-grade lymphomas.

Interview with Stephanie A Gregory, MD, June 18, 2010

Investigator comment on the PRIMA trial findings

I was surprised by the clear evidence favoring maintenance therapy, and the difference was clinically relevant and obviously highly statistically significant. It was a bit of a surprise for me that the results were so clear. The magnitude of difference was much greater than I expected.

In Germany — as in the US — private practitioners were already administering R maintenance off study in more than 50 percent of FL cases prior to the presentation of these data. The academic-based hospitals were saying, "We need more evidence." At this point, the PRIMA study appears quite convincing.

For more than a year, our StiL group in Germany has been accruing patients with FL to our current study, which uses the new BR backbone followed by two years versus four years of R maintenance. This trial concept is, of course, a challenge to execute, but the physicians asked for it and are highly interested in it. The study is accruing quickly and should recruit the last of 876 patients by the end of 2011. The Swiss study group is also evaluating long-term R, in this case until relapse.

Interview with Mathias J Rummel, MD, PhD, June 7, 2010

Randomized Study of Rituximab in Patients with Relapsed or Resistant Follicular Lymphoma Prior to High-Dose Therapy as In Vivo Purging and to Maintain Remission Following High-Dose Therapy

Pettengell R et al.

Proc ASCO 2010;Abstract 8005.

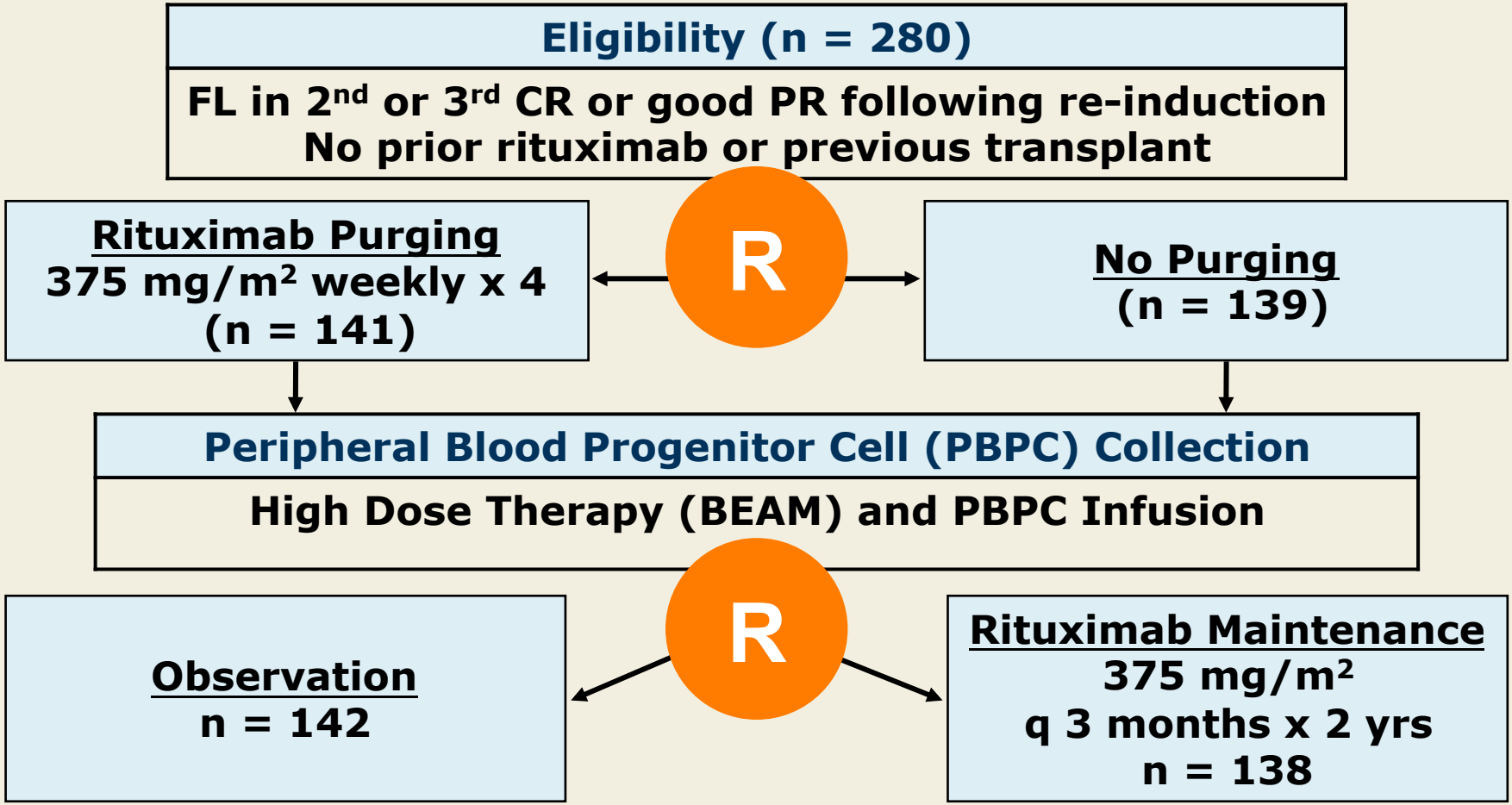
Introduction

- Retrospective series have shown improved progression-free survival (PFS) with in vivo rituximab purging with or without rituximab maintenance in patients with follicular lymphoma (FL) undergoing transplantation (*Bone Marrow Transplant* 2008;43:701, *JCO* 2008;26:3614).

- **Current study objective:**
  - To evaluate the effects of in vivo rituximab purging and maintenance rituximab on PFS in patients with relapsed FL undergoing high-dose therapy with BEAM conditioning.

Pettengell R et al. *Proc ASCO* 2010;Abstract 8005.

Study Design



Pettengell R et al. *Proc ASCO* 2010;Abstract 8005.

Survival Analysis

	5-Year PFS*	5-Year OS†
Purging and maintenance (n = 69)	62.9%	79.5%
Purging only (n = 72)	46.0%	84.8%
Maintenance only (n = 69)	56.0%	80.5%
No purging or maintenance (n = 70)	37.6%	78.4%

* *p*-value = 0.004 (trend test), hazard ratio = 0.76
† *p*-value > 0.1 (trend test); OS = overall survival

Pettengell R et al. *Proc ASCO* 2010;Abstract 8005.

Effect of Rituximab Purging and Maintenance on Survival

	Purging	No Purging
5-year PFS	54.1%	48.0%
Hazard ratio (*p*-value)	0.81 ($p>0.2$)	
	Maintenance	**No Maintenance**
5-year OS	80.0%	81.5%
Hazard ratio (*p*-value)	0.88 ($p>0.6$)	

Pettengell R et al. *Proc ASCO* 2010;Abstract 8005.

Conclusions

- Rituximab maintenance after transplant improves PFS (p = 0.01).
- A combination of in vivo purging with rituximab before stem cell collection and rituximab maintenance after transplant results in superior PFS compared to no rituximab.
- No improvement in overall survival with either in vivo rituximab purging or rituximab maintenance was seen in this patient population.

Pettengell R et al. *Proc ASCO* 2010;Abstract 8005; Fisher RI. ASCO 2010;Discussion.

Investigator comments on rituximab purging and maintenance after transplant for FL

In this study, the European Bone Marrow Transplant Group evaluated patients with relapsed follicular lymphoma who were going to go through autologous stem cell transplant. The question was, can you obtain better results if you purge prior to the transplant preparative regimen? Purging consisted of administering four weeks of rituximab prior to transplant. After transplant, a second randomization took place to maintenance rituximab or observation. Progression-free survival was much better in the group that received both purging and maintenance therapy.

Most of these patients were being transplanted after first relapse. You want to ensure that if you're going to perform a transplant, you perform it sooner rather than later — usually at first or second relapse. That's what this study demonstrated.

Neutropenia had previously been reported with rituximab after transplant, but Dr Pettengell stated that they did not observe neutropenia in their patients who received maintenance rituximab.

I think purging with rituximab and administering maintenance rituximab is probably going to be a new standard.

Interview with Stephanie A Gregory, MD, June 18, 2010

Investigator comments on rituximab purging and maintenance after transplant for FL

One of the kickers in this study is that although autologous stem cell transplant has a role in recurrent indolent lymphoma and certainly can be associated with long-term positive outcomes for some patients, it is not something that we're doing frequently lately, particularly because so many new drugs have come along. However, the use of rituximab in conjunction with autotransplant has become more common, particularly in follicular lymphoma, and this trial provides support for it.

One major caveat of this study is that it dates back. Many of these patients had not received rituximab prior to entering this protocol. So these patients had largely rituximab-naïve disease prior to receiving an autologous stem cell transplant. Obviously, someone undergoing an autologous stem cell transplant today will have received rituximab at various points in time, and it is not clear whether these data apply to patients who have received prior rituximab on multiple occasions prior to autotransplant for follicular lymphoma. This is the main criticism of these data.

Interview with John P Leonard, MD, June 28, 2010

Complete Response Rates with Lenalidomide plus Rituximab for Untreated Indolent B-Cell Non-Hodgkin's Lymphoma

Fowler NH et al.

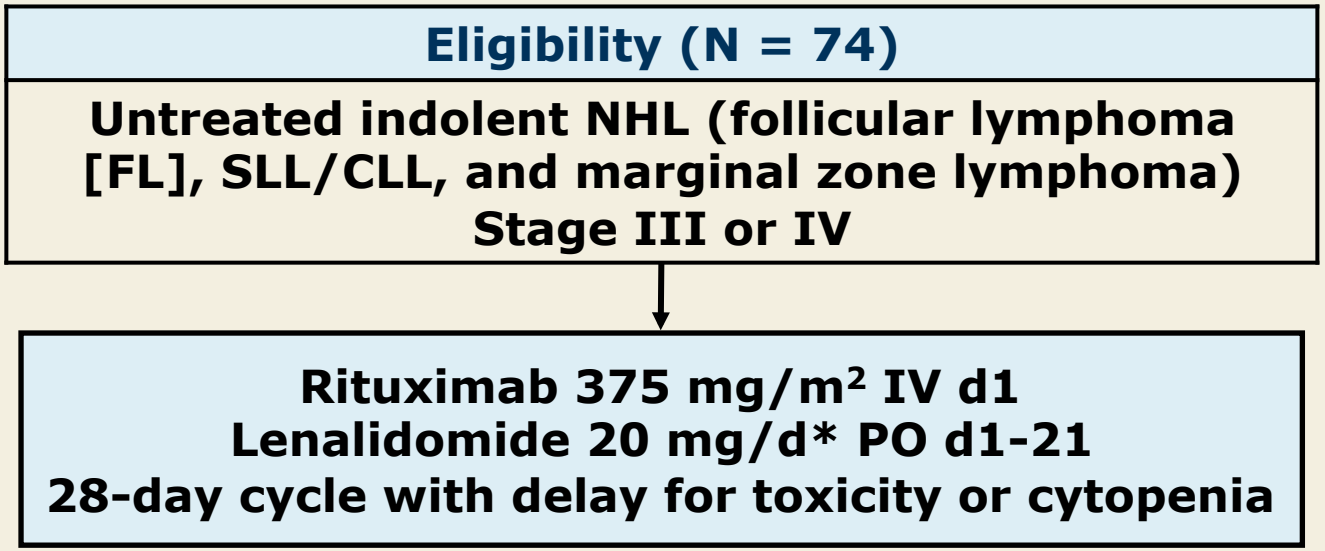
Proc ASCO 2010;Abstract 8036.

Introduction

- The optimal treatment for newly diagnosed indolent non-Hodgkin's lymphoma (NHL) has not been established.
- Several combination chemotherapy regimens have response rates approaching 90%, but toxicity is common with genotoxic agents.
- The combination of rituximab and lenalidomide has shown responses in relapsed NHL (*Proc ASH* 2009;Abstract 2719).
- In pre-clinical models, the combination of rituximab and lenalidomide showed a higher cell kill than either agent alone (*Proc ASH* 2009;Abstract 3441, *Am J Hematol* 2009;84:553).
- **Current study objective:**
  - To evaluate the efficacy and safety of lenalidomide plus rituximab in patients with previously untreated indolent lymphoma.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Phase II Study of Lenalidomide plus Rituximab Therapy for Untreated Indolent NHL



Response assessed after cycles 3 and 6

* Lenalidomide was increased to 25 mg/d after 3 cycles if stable disease. Patients with SLL/CLL received 10 mg/d cycle 1, 15 mg/d cycle 2, 20 mg/d cycle 3.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Efficacy Results (Intent-to-Treat Population)

- Of 74 patients enrolled, 48 had completed six cycles of therapy and were included in efficacy and toxicity analyses.

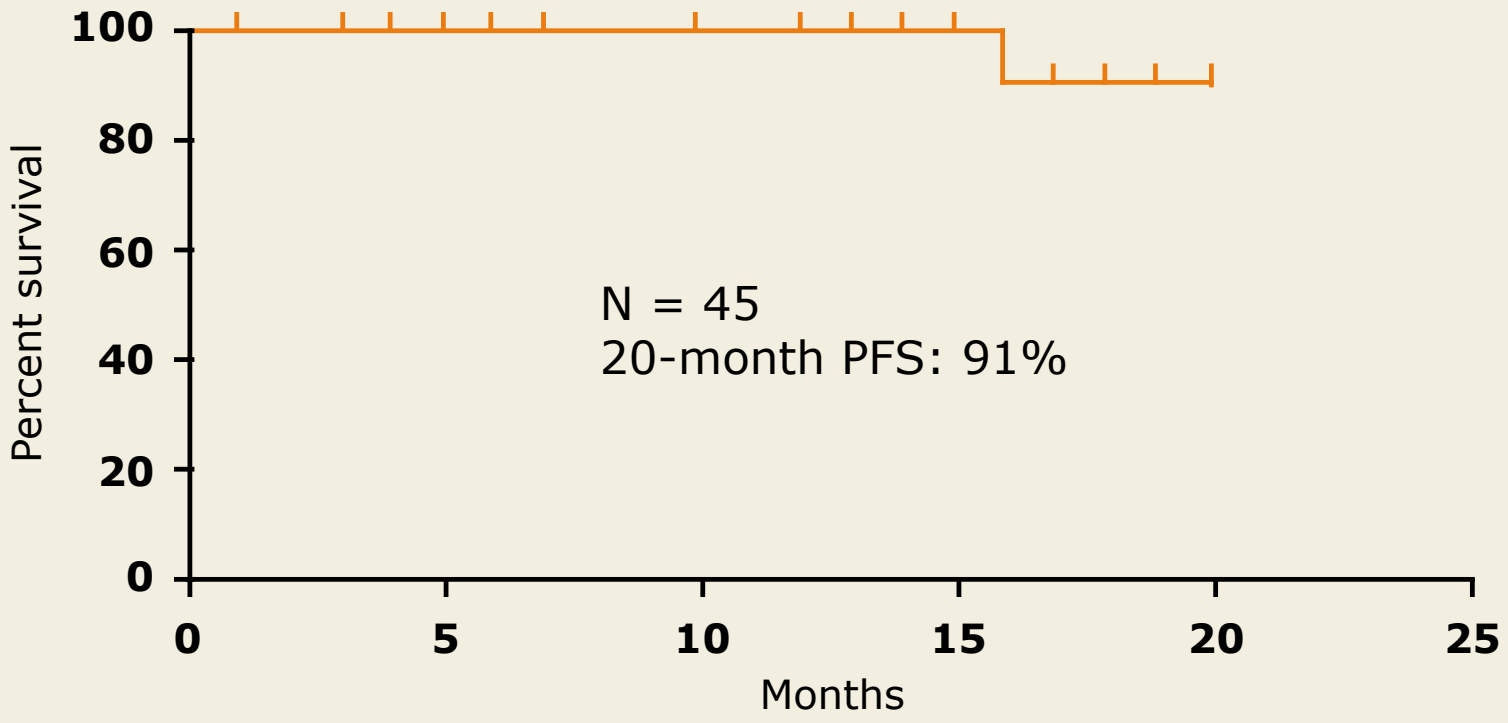
Histology	Response Rates		
	CR/CRu	PR	ORR
FL (n = 30)	83%	10%	93%
SLL/CLL (n = 5)	40%	40%	80%
Marginal zone lymphoma (n = 13)	46%	16%	62%
Total (n = 48)	69%	14%	83%

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

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Progression-Free Survival (Median Follow-Up 12 Months)

- Progression-free survival (PFS): at a median of 12 months (range, 3-20) 1 patient (FL) has progressed



With permission from Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Molecular Response

- Bone marrow and peripheral blood were analyzed in 29 patients by PCR at baseline and after cycles 3 and 6.
- Nearly all patients were PCR negative by cycle 6.

PCR Result	Baseline n	Post-Cycle 3 n (%)	Post-Cycle 6 n (%)
BCL-2 positive	11	3	1
BCL-2 negative	18	26	28
Total % conversion	—	8/11 (73%)	10/11 (91%)

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Adverse Events

Adverse Event*	Grade 3/4 (n = 48)
Neutropenia	21%
Thrombocytopenia	13%
Rash	13%
Thrombosis	4%
Fatigue	2%
Infection	2%
Neuropathy	2%

* Rash (all grades) was seen in 22 (46%) patients. The most common Grade 1/2 events were fatigue and myalgia. No patient developed tumor lysis syndrome.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Conclusions

- The combination of rituximab and lenalidomide produces excellent overall and complete response rates in patients with untreated indolent NHL.
- Toxicity profile of rituximab-lenalidomide combination is mild with manageable hematologic side effects.
- Future randomized trials are planned.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

Investigator comments on a Phase II study of lenalidomide and rituximab for untreated indolent NHL

We've observed activity with lenalidomide in recurrent lymphomas of all types, and now we're starting to see combinations with rituximab.

In fact, we have a Phase II CALGB study going on right now in recurrent indolent lymphoma, in which patients are randomly assigned to lenalidomide alone or lenalidomide with rituximab, to determine what rituximab adds to lenalidomide. It makes sense to start evaluating this agent in combination with rituximab and other agents, and as we move away from the relapse setting, it makes sense to evaluate it in the up-front setting as well.

The findings from this study suggest that this combination might be a building block for other nonchemotherapy-containing regimens, which would be a nice alternative to chemotherapy for many patients. In the CALGB, we've been developing this sort of concept for a while with biologic doublets, and we're getting ready to open a trial of lenalidomide with rituximab as initial therapy for follicular lymphoma, which is similar to this MD Anderson study.

Interview with John P Leonard, MD, June 28, 2010

Investigator comments on a Phase II study of lenalidomide and rituximab for untreated indolent NHL

This was an impressive paper. Laboratory data suggest synergy with the combination of lenalidomide and rituximab, and here they resulted in an overall response rate of 93 percent and a complete response rate of 83 percent. This is interesting and it looks as if the combination might be best used in patients with indolent lymphoma and low tumor burdens for whom many doctors are using rituximab alone.

Interview with Stephanie A Gregory, MD, June 18, 2010

A Phase II Study of Lenalidomide as Initial Treatment of Elderly Patients with Chronic Lymphocytic Leukemia

Badoux X et al.

Proc ASCO 2010;Abstract 6508.

Introduction

- Median age of diagnosis of patients with chronic lymphocytic leukemia (CLL) is 72 years.
- Elderly patients with CLL are under-represented in clinical trials and have increased toxicity with immunochemotherapy.
- Lenalidomide is an oral immunomodulatory drug that has activity in relapsed CLL (*J Clin Oncol* 2006;24:5343, *Blood* 2008;111:5291).
- **Current study objective:**
  - To evaluate the activity of lenalidomide as initial treatment in elderly patients with CLL.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Phase II Study of Lenalidomide in Elderly Patients with CLL

Eligibility (N = 60)

Untreated and symptomatic CLL
Age ≥ 65 years
PS 0-2

↓

Lenalidomide 5 mg/day x 2 cycles (56 days)
Increase by 5 mg/cycle (28 days) to maximum 25 mg/day
Treatment continued until progression

Allopurinol 300 mg PO QD days 1-14 cycle 1

No mandated antibiotic, antiviral, DVT or tumor flare prophylaxis

Response assessed at the end of cycle 3 and then every 6 cycles

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Efficacy Results

Clinical Parameter	NCI Response* (N = 60)	
	Patients, n	%
Complete response (CR)	6	10
CRi	3	5
Nodular partial response	3	5
Partial response	25	42
Overall response rate (ORR)	**37**	**62**

Clinical Parameter	Response at Assessment Times			
	3 cycles	9 cycles	15 cycles	21 cycles
ORR, n (%)	24 (40)	34 (57)	36 (61)	30 (57)

* 2008 NCI-WG criteria used; CRi = CR with incomplete blood count recovery.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Efficacy by Patient Pre-Treatment Characteristics

Patient Characteristic		n	ORR
Age, years	65-74	43	72%
	≥75	**17**	**35%***
IGHV genes	mutated	22	50%
	unmutated	33	73%
FISH hierarchy	del13q	15	73%
	negative	12	50%
	trisomy 12	13	92%
	del 11q	14	57%
	del 17p	**6**	**0%***

* $p < 0.05$

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Adverse Events (N = 60)

Adverse Event	Grade ≥3
Neutropenia	38%
Thrombocytopenia	<14%
Neutropenic fever	5%
Pneumonia/bronchitis	3%
Fatigue	3%
Sepsis	2%
Tumor flare*	0%

* 50% of patients had Grade 1/2 tumor flare.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Conclusions

- Lenalidomide as a single agent induces clinical responses in the front-line treatment of elderly patients with CLL.
  - ORR: 62%
  - 2-year overall survival: 90% (data not shown)
  - 2-year progression-free survival: 60% (data not shown)
- Quality of responses improve over time.
- Myelosuppression is the most common toxicity.
- No severe tumor flare or tumor lysis syndrome was observed.
- A Phase II trial of lenalidomide in combination with rituximab as up-front treatment in CLL is ongoing.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508; Rai K. ASCO 2010;Discussion.

Investigator comment on lenalidomide as initial treatment for CLL in the elderly

With lenalidomide in CLL, we don't use the doses used in myeloma or MDS because patients with CLL get tumor lysis syndrome and tumor flare, in which the lymph nodes become large, swollen, red and painful.

In this MD Anderson study of patients with CLL over 65 and requiring treatment, investigators started gingerly with a 5-mg daily dose of lenalidomide for two 28-day cycles, and then if patients tolerated that, they escalated by another five mg every cycle, up to a 25-mg dose.

There was a 62 percent response rate and it was relatively nontoxic. There was no Grade III or IV tumor lysis or tumor flare. The presenter also noted that the drug continues to work over time, so you can't be impatient and stop after the first couple of cycles because best response occurred after nine cycles.

A new trial concept in CLL is maintenance lenalidomide — after patients have had a response from FCR, for example. A few years ago we investigated alemtuzumab maintenance but there was too much toxicity from immunosuppression. We need something in CLL for maintenance, similar to the rituximab maintenance in the low-grade lymphomas.

Interview with Stephanie A Gregory, MD, June 18, 2010