5 Minute JournalClub

Key ASH Presentations
Issue 9, 2012

Lenalidomide/Rituximab in CLL

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- 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.

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Last review date: April 2012
Expiration date: April 2013

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Key ASH Presentations
Issue 9, 2012

To go directly to slides and commentary for this issue, **click here**.

For this concluding post-ASH summary we focus on a smattering of data sets that shed additional light on a number of relevant clinical questions and therapeutic strategies in the management of indolent NHL, including follicular lymphoma (FL) and CLL:

1. Rituximab (R)/lenalidomide (len) in CLL

Previous preclinical work suggested that the effect of len on natural killer cell expansion enhanced the cytotoxic impact of R, and on that basis several trials evaluating the "R squared" combination were launched, including 3 studies reported at ASH. The first was a Phase II effort evaluating R/len in 59 patients with relapsed/refractory CLL, and the combination produced an impressive overall response rate of 66% with a median time to treatment failure of 24 months. A second Phase II study attempted to assess the combination in patients with previously untreated disease, and more than 75% of patients responded. Finally, an encouraging Phase I-II study evaluating fludarabine/R and escalating doses of len as induction therapy followed by R/len maintenance in 45 previously untreated patients resulted in a 49% CR rate, but dose-limiting toxicity (mainly dermatologic) was observed in more than a third of participants. Len is currently only used by most investigators in very advanced refractory CLL.

2. Alemtuzumab/fludarabine/cyclophosphamide (AFC) in patients with high-risk CLL requiring treatment

At ASH, our understanding of how to integrate alemtuzumab into the treatment algorithm for CLL once again hit a bump in the road with the report from a Phase III trial evaluating low-dose subcutaneous A in combination with FC versus FC alone. Although the addition of the anti-CD52 antibody resulted in slightly better cancer outcomes, substantial toxicity was observed, including flulike symptoms and infection related to immune suppression, and as such this approach remains investigational.

3. Obinutuzumab (GA101)

ASH provided a vivid reminder of the impressive activity of anti-CD20 antibody treatment in B-cell lymphomas with the first results of the landmark ECOG RESORT trial commented on earlier in this series, in which the control arm of 4 weekly doses of R resulted in a 70% response rate, and without further treatment, 86% of patients who responded were progression free at 3 years.

The activity of this bellwether biologic agent is the reason there was great interest in 3 ASH data sets evaluating obinutuzumab (O) — a novel glycoengineered type 2 anti-CD20 MAB with a different functional profile than rituximab (more direct cytotoxicity and cell death but slightly less complement-dependent cytotoxicity). The first, a Phase I-II trial, reported objective responses in patients considered resistant to R, while the second, a randomized Phase II study with 175 patients comparing O to R as single agents in the relapsed setting, showed response rates modestly favoring O. Finally, a Phase I study looked at the agent in combination with CHOP or FC and provided confidence that a large Phase III trial comparing R-CHOP to O-CHOP is feasible.

4. Two data sets on up-front radioimmunotherapy (RIT) in FL

A much anticipated and somewhat disappointing SWOG trial of R-CHOP versus CHOP followed by ^{131}I-tositumomab consolidation demonstrated similar efficacy and tolerability with a few more cases of AML/MDS in the RIT arm (7 versus 3). The study raises natural questions about a more comprehensive strategy of R/chemo followed by RIT consolidation and R maintenance, which is the approach used in a subsequent Phase II SWOG study that has completed accrual but has not yet reported. Another ASH Phase II report focused on RIT alone up front — this time with 2 fractions of ^{90}Y ibritumomab. Thirteen of 76 patients received pretreatment with R in an attempt to clear bone marrow involvement greater than 20%, and 11 of the 13 were able to receive RIT. A median PFS of 36 months was observed, with manageable hematologic toxicity. However, RIT monotherapy up front is rarely utilized in clinical practice pending more definitive trial data.

5. [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scans in FL

At ASH we saw the results of a study of interim and end-of-treatment FDG-PET scans in 121 patients with FL receiving R-CHOP. Approximately one quarter had positive end-of-treatment scans, and not surprisingly 2-year PFS and OS were worse in this group. (About half of all patients with positive scans at the end of treatment had disease progression at 2 years.) The challenge of managing these patients remains unanswered and, hopefully, more guidance will come from future clinical research.

6. Bortezomib in FL

A prior report from the 676-patient randomized Phase III LYM3001 study of R alone or with bortezomib in relapsed/refractory disease demonstrated a modest advantage to the combination, and at ASH an impressive translational data set was presented looking at prespecified sera and tissue endpoints that identified a subset of approximately a third of patients in the trial who achieved a greater benefit with the addition of bortezomib. These markers are not "ready for prime time" but are sure to be looked at in studies like ECOG-E2408, evaluating bendamustine/rituximab (BR) followed by R versus bortezomib/BR followed by R versus BR followed by R/len in high-risk FL.

Next we return to our recent breast cancer Patterns of Care survey, this time focusing on management of HER2-positive tumors in the early and advanced disease setting.

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Lenalidomide/Rituximab in CLL

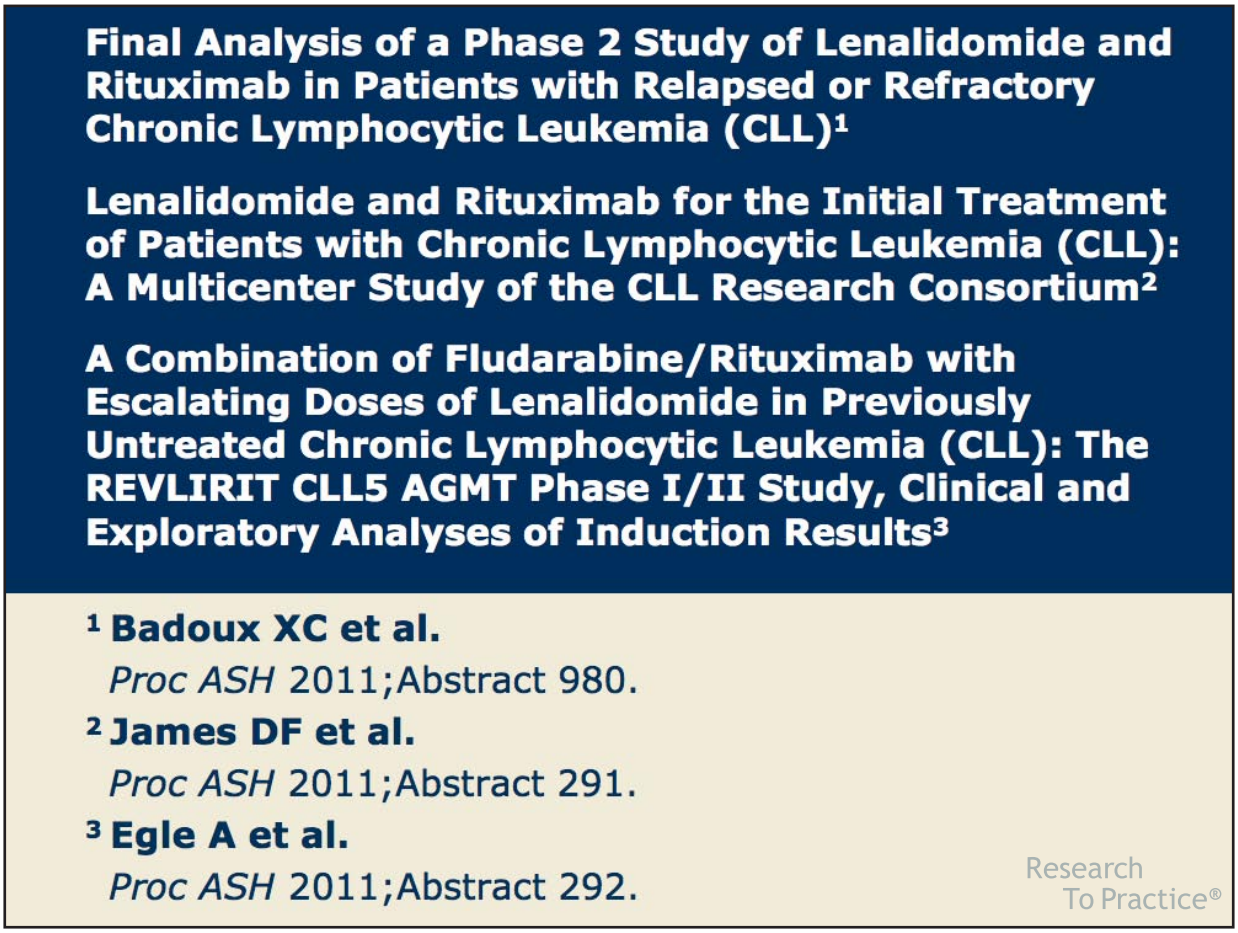
Presentations discussed in this issue

Badoux XC et al. **Final analysis of a Phase 2 study of lenalidomide and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL).** *Proc ASH* 2011;**Abstract 980**.

James DF et al. **Lenalidomide and rituximab for the initial treatment of patients with chronic lymphocytic leukemia (CLL): A multicenter study of the CLL research consortium.** *Proc ASH* 2011;**Abstract 291**.

Egle A et al. **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.** *Proc ASH* 2011;**Abstract 292**.

Slides from presentations at ASH 2011 and transcribed comments from recent interviews with John P Leonard, MD (4/6/12) and Brad S Kahl, MD (1/26/12)



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.

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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 ≤2 mg/dL
Bilirubin ≤2 mg/dL

→

L + R (n = 59)

L 10 mg/d PO*, d9-28 x 12 cycles

R 375 mg/m^2 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 ≥3 hematologic toxicity

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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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

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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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

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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Select Adverse Events (AEs) (Abstract)

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

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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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.

Badoux XC et al. *Proc ASH* 2011;Abstract 980.

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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.

James DF et al. *Proc ASH* 2011;Abstract 291.

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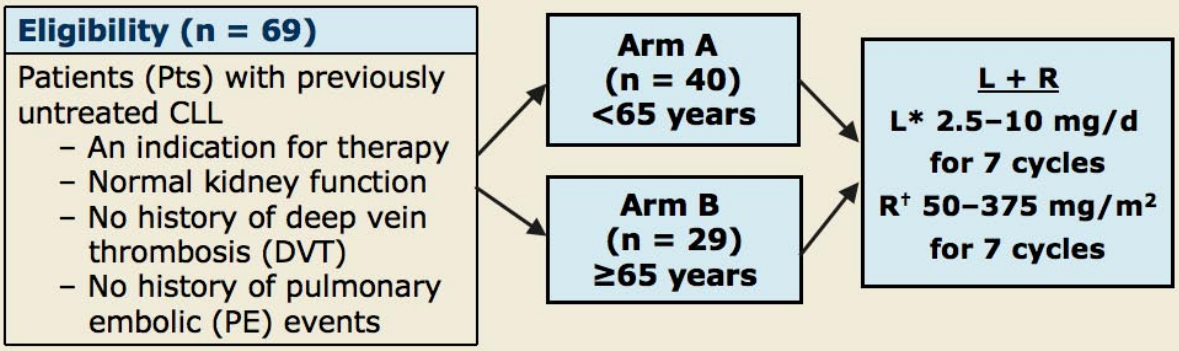
Study Design



* 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/m² (d29), 325 mg/m² (d31), 375 mg/m² (d33) then 375 mg/m² 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).

James DF et al. *Proc ASH* 2011;Abstract 291.

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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

James DF et al. *Proc ASH* 2011;Abstract 291.

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Progression-Free Survival (Abstract)

	Arm A (n = 35)	Arm B (n = 22)
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

James DF et al. *Proc ASH* 2011;Abstract 291.

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Select Adverse Events (Abstract)

Event (n)	Arm A		Arm B	
Grade	**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

James DF et al. *Proc ASH* 2011;Abstract 291.

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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 (≥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.

James DF et al. *Proc ASH* 2011;Abstract 291.

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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.

Egle A et al. *Proc ASH* 2011;Abstract 292.

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REVLIRIT CLL5 AGMT Trial Design

Eligibility (n = 45)

Previously untreated CLL

Induction therapy

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

F 40 mg/m^2 PO, d1-3
q4wk x 6 cycles

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

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

Maintenance therapy†

R + L

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.

Egle A et al. *Proc ASH* 2011;Abstract 292.

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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 ≥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%

Egle A et al. *Proc ASH* 2011;Abstract 292.

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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.

Egle A et al. *Proc ASH* 2011;Abstract 292.

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Adverse Events (Abstract)

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

Egle A et al. *Proc ASH* 2011;Abstract 292.

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.

Egle A et al. *Proc ASH* 2011;Abstract 292.

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