5 Minute JournalClub

Key ASH Presentations
Issue 2, 2011

Lenalidomide in the Management of Chronic Lymphocytic Leukemia (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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVES

- Recall the activity and safety of lenalidomide combined with rituximab in the treatment of relapsed or refractory CLL.
- Describe the impact of lenalidomide consolidation on quality of CLL response following induction chemoimmunotherapy.

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

It's no secret that the anti-CD20 antibody rituximab has profoundly affected clinical research and management approaches in B-cell neoplasms, and in 2010 we heard about two more landmark trials that help to expand our knowledge of this very interesting agent. First, at ASCO the PRIMA study demonstrated that two years of R maintenance after prior induction with R/chemo delayed disease progression, and the ASH update of this historic study further solidified these outcomes with more follow-up. The second recent important data set came from an **Intergroup trial** that was just presented at ASH. The study randomly assigned patients with asymptomatic nonbulky advanced FL to either rituximab — for what turned out to be two years — or watch and wait (or as our prostate cancer colleagues call it, watch and worry). The trial showed that R led to a substantial delay in progression and in the need for further treatment (usually chemo).

Both of these data sets have sparked considerable debate, and as promised, last Friday in our Miami recording studio I asked the eight distinguished faculty members who participated in our clinical investigator Think Tank the bottom line on these and other seminal ASH data sets:

1. PRIMA: R maintenance after R/chemo
All of the investigators except the always free-thinking Dr Cheson offer but do not insist that patients receive two years of R maintenance.

2. Intergroup study: R versus watch and wait
None of the faculty believe that using R earlier substantially changes the natural history of the disease or overall survival, although it is important to note that there were only 21 total deaths reported in the Intergroup study and less than three years of follow-up. The Think Tank group did acknowledge that many patients find a delay in disease progression appealing in return for the modest and unchemo-like risks of this treatment.

For all the good that R has done, FL and CLL are still not curable and a litany of approaches are being evaluated in these diseases to offer patients even more. At ASH many presentations focused on other promising agents, and at our Think Tank I asked the faculty which ones they found most exciting. Here are some of their thoughts and key related data sets.

Lenalidomide
At ASH **Alessandra Ferrajoli** presented some interesting data on lenalidomide in combination with rituximab for patients with relapsed and refractory CLL. The study demonstrated a 64 percent overall response rate, and the Think Tank faculty showed considerable interest in new trials evaluating this combination up front as a means to potentially avoid the **increased incidence of therapy-related myeloid neoplasia** associated with FC and particularly FCR reported at ASH.

Bortezomib
A much-awaited ASH presentation by **Bertrand Coiffier** reported better PFS, response rate and time to next lymphoma treatment when bortezomib was added to rituximab in FL, but this study did not meet the primary endpoint of a 33 percent improvement in PFS. Ongoing cooperative trials are looking at the agent in the up-front setting, and there was uncertainty among the faculty as to whether these studies will demonstrate an acceptable benefit-risk ratio.

Small molecules
At the Think Tank Brad Kahl presented a patient responding to a new agent, CAL 101, and perhaps not surprisingly there were encouraging data **(click here to view abstract)** at ASH on this oral, relatively nontoxic PI3 kinase inhibitor and several other small molecules targeting the CD20 pathway.

Next up on this series, ASH data sets on a new generation of BCR-ABL TKIs in CML.

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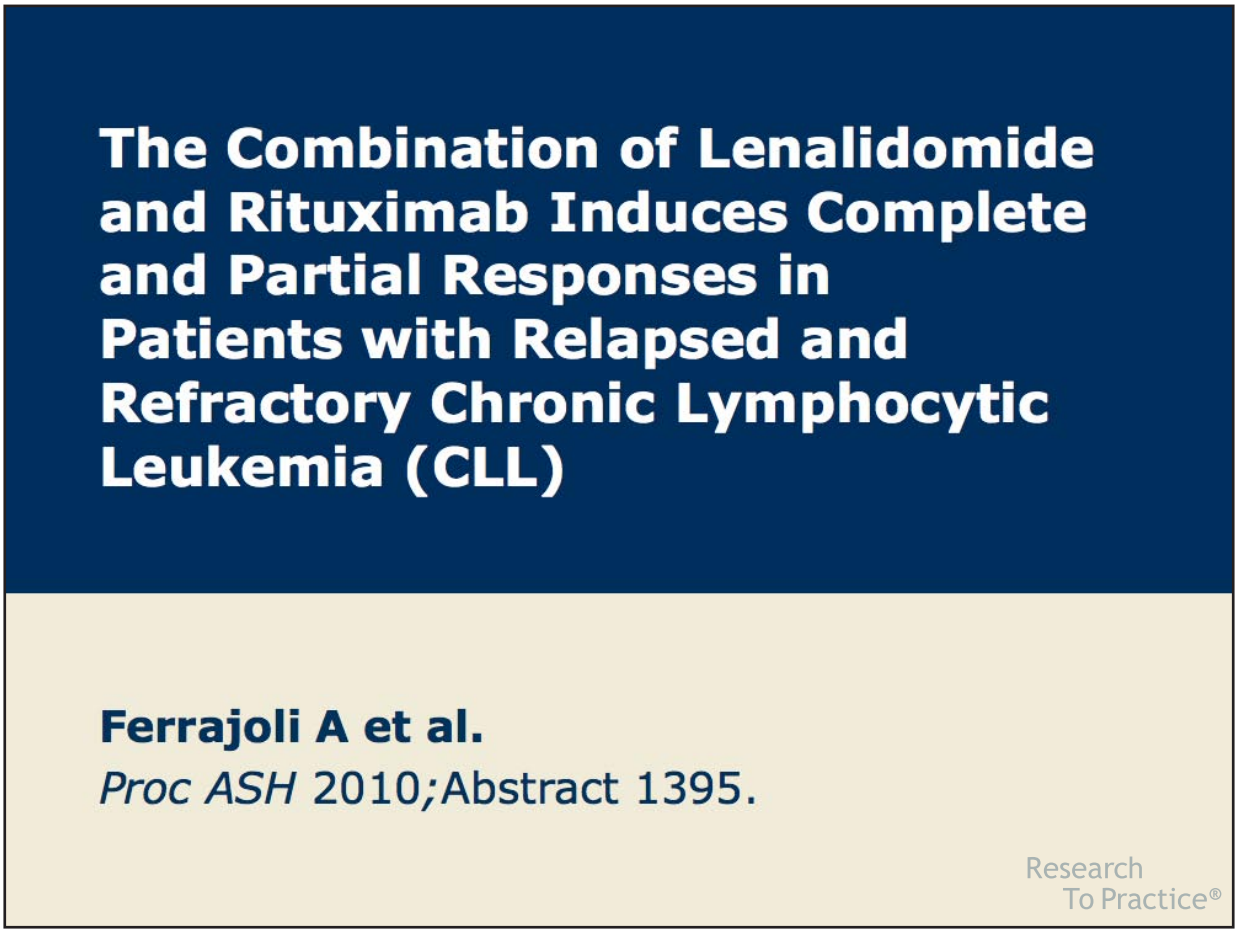
Lenalidomide in the Management of Chronic Lymphocytic Leukemia (CLL)

Presentations discussed in this issue

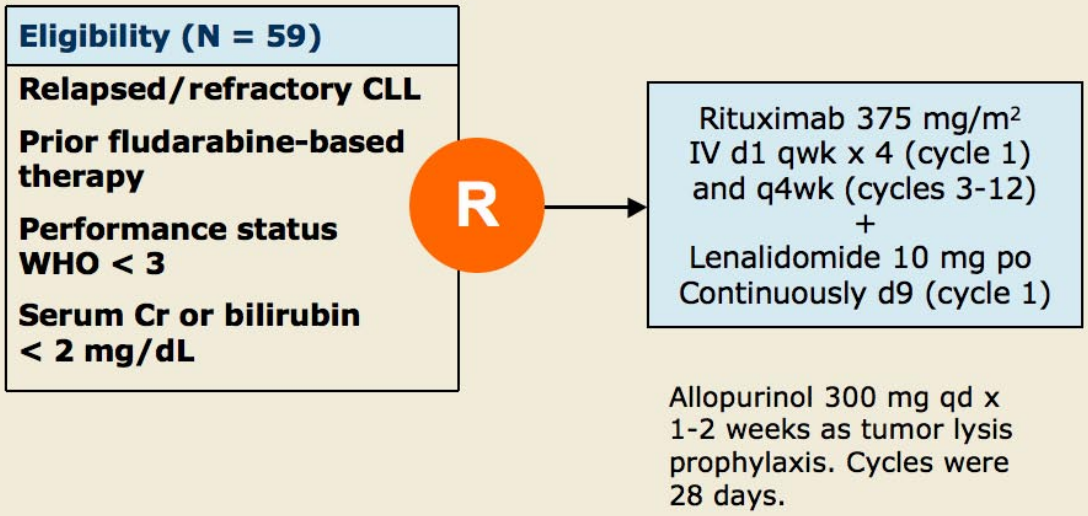
Ferrajoli A et al. **The combination of lenalidomide and rituximab induces complete and partial responses in patients with relapsed and refractory chronic lymphocytic leukemia.** *Proc ASH* 2010;**Abstract 1395**.

Shanafelt T et al. **Lenalidomide consolidation after first-line chemoimmunotherapy for patients with previously untreated CLL.** *Proc ASH* 2010;**Abstract 1379**.

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Bruce D Cheson, MD (12/23/10)



Phase II Study Schema



Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

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Efficacy and Adverse Events

All patients are evaluable for response and clinical outcome (N = 59)

Overall Response Rate (ORR)	Complete Response (CR)	CR with Incomplete Hematological Recovery (CRi)	Nodular Partial Remission (nPR)	Partial Response (PR)
64%	8%	5%	12%	39%

Neutropenia	Thrombocytopenia	Anemia	Infections
68%	22%	10%	31%

Grade 3 Tumor Lysis Syndrome	1.7%
Grade 1-2 Tumor Flare Reactions	37.3%

Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

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Conclusions

- Lenalidomide/rituximab in relapsed or refractory CLL has promising response rates and appears to be better than single-agent lenalidomide (*Blood* 2008;111(11):5291; *J Clin Oncol* 2006;23(34):5343).
- The combination of lenalidomide and rituximab in relapsed-refractory CLL is well tolerated, with the most common toxicity being myelosuppression.

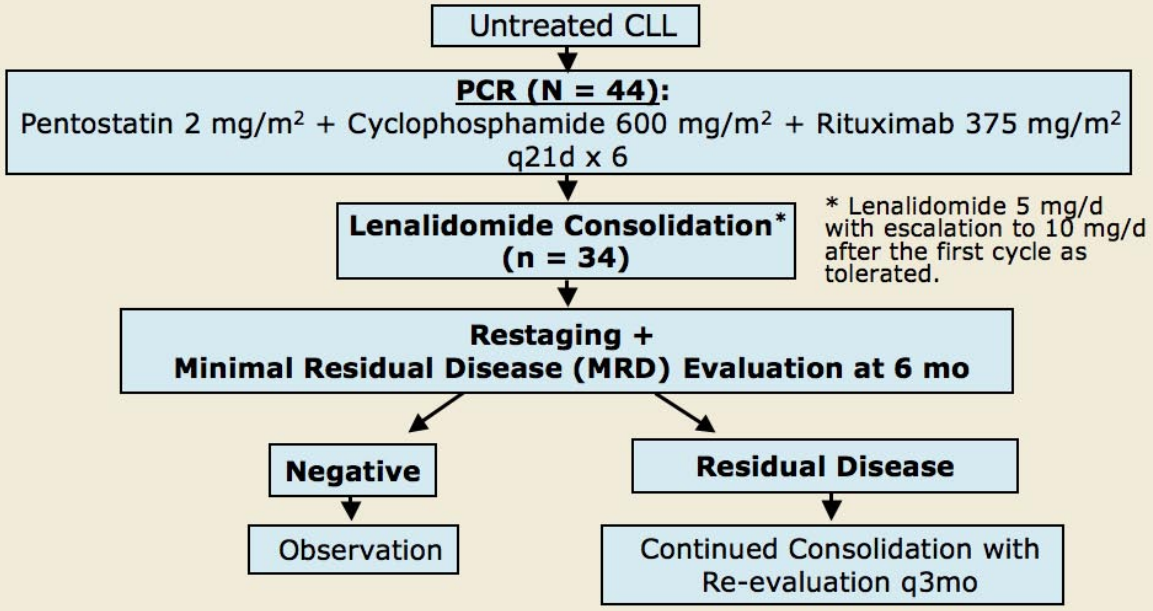
Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

Lenalidomide Consolidation After First-Line Chemoimmunotherapy for Patients with Previously Untreated CLL

Shanafelt T et al.

Proc ASH 2010;Abstract 1379.

Study Schema



Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

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Efficacy Results

PCR Induction (N = 44)

Overall Response Rate	95%
CR/CRi/CCR	38%
PR/nPR	57%

12 patients with CR/CRi underwent evaluation for MRD assessment after PCR induction

MRD-Negative, n (%)	7 (58%)

Lenalidomide Consolidation (n = 34)

Improvement in Quality of Response	21%
MRD+ to MRD-, n (%)	3 (8.8%)

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

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Select Adverse Events with Lenalidomide Consolidation

Safety Evaluable (n = 34)

Adverse Event	Grade 3	Grade 4
Neutropenia	41%	21%
Thrombocytopenia	9%	0%
Rash	6%	0%

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

Conclusions

- Lenalidomide consolidation improves the quality of response in patients with CLL receiving first-line induction.
- Lenalidomide consolidation appears to be feasible with an acceptable adverse event profile.
- Longer follow-up is necessary in order to determine the clinical benefit with this strategy.

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

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Investigator Commentary: Evaluation of Lenalidomide in CLL

Lenalidomide is active in relapsed and refractory CLL, with response rates ranging from 30 to 45 percent. Some of the complications associated with lenalidomide in this context are unique, including tumor lysis syndrome and tumor flare response. Rituximab alone has modest activity in the relapsed setting. Nevertheless, it seems to make other drugs work better. So Ferrajoli and the MD Anderson group combined lenalidomide and rituximab in patients with relapsed and refractory CLL and demonstrated an overall response rate of 64 percent, including eight percent complete responses, which is better than might be expected from either drug alone. However, this should not be considered a standard regimen and further evaluation is warranted in both the relapsed and up-front settings.

Another way to consider using lenalidomide is as consolidation after chemoimmunotherapy in patients with previously untreated CLL. In the study by Shanafelt et al, patients received a pentostatin-based regimen (PCR) followed by lenalidomide consolidation. Only 7/34 patients experienced improvement in the quality of response, and a significant proportion of patients experienced at least Grade 3 hematologic toxicity.

Interview with Bruce D Cheson, MD, December 23, 2010