5 Minute JournalClub

Key ASH Presentations
Issue 2, 2011

Bortezomib/Rituximab Combination in the Management of Relapsed Follicular Lymphoma

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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

- Describe the emerging body of evidence with the combination of bortezomib and rituximab in follicular lymphoma.
- Compare and contrast the incremental benefit of bortezomib when added to rituximab for patients with relapsed follicular lymphoma who have high- versus low-risk disease.

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Advisory Committee: Allos Therapeutics, Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium Pharmaceuticals Inc; Consulting Agreement: Millennium Pharmaceuticals Inc.

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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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Bortezomib/Rituximab Combination in the Management of Relapsed Follicular Lymphoma

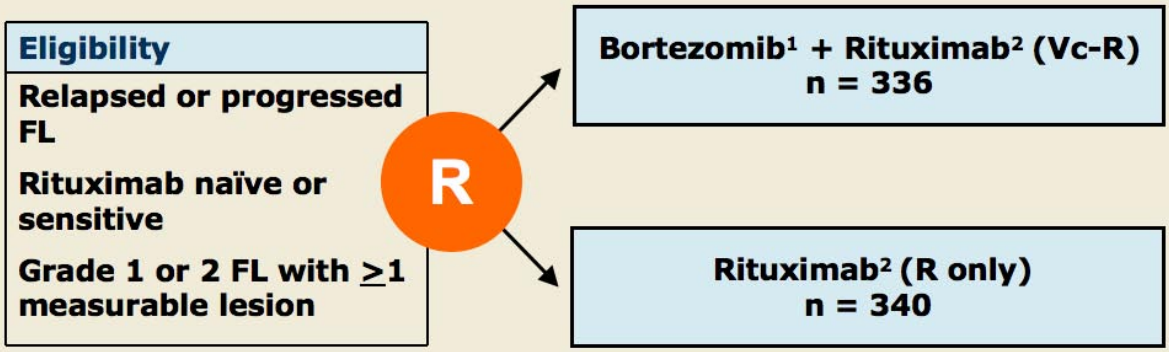
Presentations discussed in this issue

Coiffier B et al. **A Phase 3 trial comparing bortezomib plus rituximab with rituximab alone in patients with relapsed, rituximab-naïve or -sensitive, follicular lymphoma.** *Proc ASH* 2010;**Abstract 857**.

Sacchi S et al. **Phase II study of Velcade® plus Mabthera® in relapsed follicular lymphomas.** *Proc ASH* 2010;**Abstract 1801**.

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

Study Schema



[1] Bortezomib 1.6 mg/m^2 d1, 8, 15, 22 q5wk x 5 cycles

[2] Rituximab 375 mg/m^2 d1, 8, 15, 22 in cycle 1 and d1 only in cycles 2-5

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

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Efficacy Endpoints

	Vc-R (n = 315)	R Only (n = 324)	Odds Ratio	*p*-value
Overall Response	63%	49%	0.569	<0.001
Durable Response (>6 months)	50%	38%	0.608	0.002
Complete Response	25%	18%	0.665	0.035
	Vc-R (n = 336)	**R Only (n = 340)**	**Hazard Ratio**	***p*-value**
Progression-Free Survival (PFS)	12.8 mo	11.0 mo	0.822	0.039
Time to next treatment	23.0 mo	17.7 mo	0.802	0.027

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

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Progression-Free Survival in High-Risk Follicular Lymphoma

	Vc-R	R Only	Hazard Ratio	*p*-value
Median PFS (FLIPI ≥ 3) (n = 139; 140)	11.4 months	7.9 months	0.707	0.0133
Median PFS (High Tumor Burden by GELF) (n = 185; 179)	11.3 months	8.4 months	0.751	0.0186

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Select Adverse Events

	Vc-R (n = 334)	R Only (n = 339)
Diarrhea		
All Grades	52%	8%
Grade ≥3	7%	0%
Neutropenia		
All Grades	17%	7%
Grade ≥3	11%	4%
Peripheral Sensory Neuropathy		
All Grades	16%	1%
Grade ≥3	3%	0%
Febrile Neutropenia (Grade ≥3)	1%	1%

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Conclusions

- Addition of weekly bortezomib to rituximab therapy in patients with relapsed FL is associated with statistically significant improvements in:
  - PFS (primary endpoint)
  - Response rate
  - Time to next antilymphoma treatment
- Patients at high risk in the bortezomib–rituximab arm had significantly longer PFS than patients treated with rituximab alone.
- Increase in side effects did not affect feasibility of treatment or quality of life (data not shown).

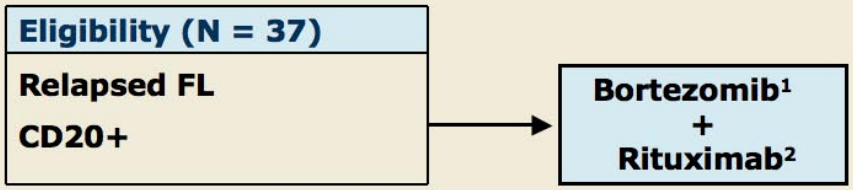
Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Phase II Study of Bortezomib plus Rituximab in Relapsed Follicular Lymphomas

Sacchi S et al.

Proc ASH 2010;Abstract 1801.

Study Schema



[1] Bortezomib 1.3 mg/m^2 d1, 4, 8, 11 q21d x 6 cycles
[2] Rituximab 375 mg/m^2 d1 in cycles 3-6, and q21d x 2 additional doses

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

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Efficacy and Safety Results

Response Evaluable (n = 33)

Overall Response	Complete Response	Partial Response
58%	49%	9%

Safety Evaluable (n = 33)

Neuropathy		Neutropenia		Infections	
Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
30%	15%	6%	3%	15%	3%

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

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Conclusions

- Bortezomib and rituximab combination in relapsed follicular lymphoma has a promising percentage of responses.
- Longer follow-up is needed to evaluate response duration and survival.
- Toxicity with the combination of bortezomib and rituximab in relapsed FL is acceptable.

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

Investigator Commentary: Bortezomib with Rituximab for Relapsed FL

Coiffier and colleagues demonstrated a higher overall response rate, complete response rate and time to disease progression with the combination arm in a large number of patients. Unfortunately, it was a negative study, because they did not meet their goal of a 33 percent improvement in progression-free survival. It remains to be seen whether this regimen will be adopted by practicing clinicians, because it is associated with considerably more toxicity, particularly peripheral neuropathy.

The study reported by Sacchi evaluated the same regimen of bortezomib/rituximab, but it was not a randomized trial and it included a smaller number of patients. Approximately 50 percent of the patients achieved a complete response, with an overall response rate of 58 percent. Other regimens, such as bendamustine/rituximab, for this patient population are associated with a considerably higher response rate and might be considered a preferable therapy.

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