5 Minute JournalClub

Key ASH Presentations
Issue 9, 2012

Bortezomib/Rituximab versus Rituximab for Relapsed/ Refractory FL

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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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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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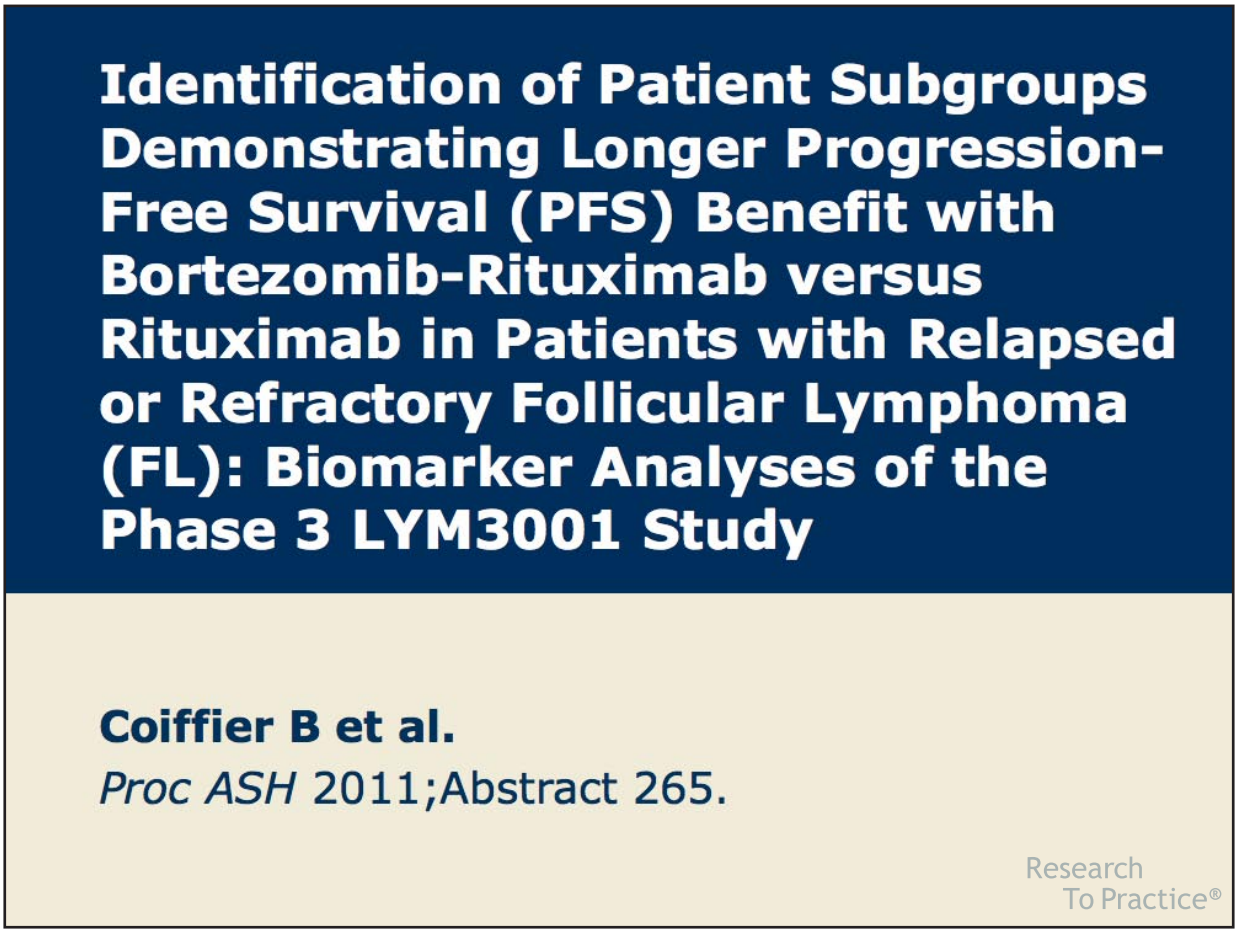
Bortezomib/Rituximab versus Rituximab for Relapsed/ Refractory FL

Presentation discussed in this issue

Coiffier B et al. **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.** *Proc ASH* 2011;**Abstract 265**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Jonathan W Friedberg, MD, MMSc (1/11/12)



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.

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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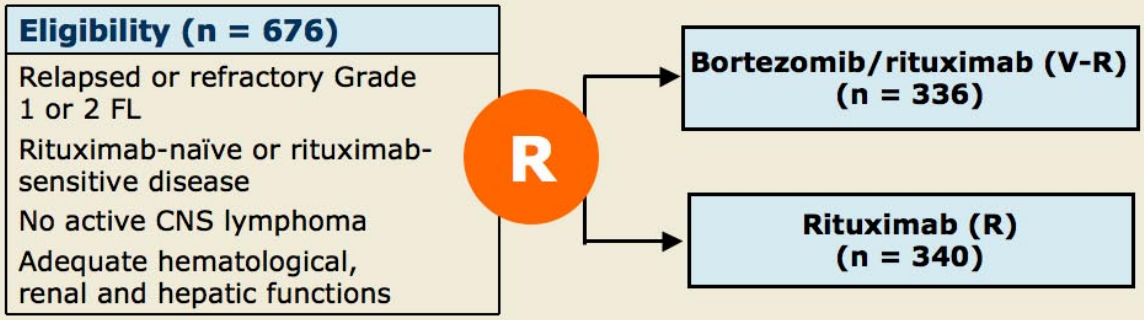
Phase III LYM3001 Trial Design



- 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-kB, 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.

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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

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

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

† 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).

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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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

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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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

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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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.

Coiffier B et al. *Proc ASH* 2011;Abstract 265.

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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