5 Minute JournalClub

Key ASH Presentations
Issue 1, 2012

Phase II Study of R-FND Followed by Radioimmunotherapy and R Maintenance for High-Risk 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

- Evaluate the efficacy and toxicity outcomes of maintenance rituximab versus rituximab re-treatment upon disease progression, and incorporate this information into your personal treatment algorithm for patients with low tumor burden follicular lymphoma.
- Assess the efficacy of maintenance rituximab in disease settings in non-Hodgkin lymphoma for which standard treatment is not well established, including for elderly patients with advanced follicular lymphoma.

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

Last month's annual American Society of Hematology (ASH) meeting seems like a blur, particularly because it partially overlapped the San Antonio Breast Cancer Symposium. So in addition to poring over hundreds of abstracts I recently turned to a couple of my favorite hem-onc investigators to help piece together what happened in San Diego, beginning with the always colorful Brooklyn-born Yankees and Jets fan, Memorial's Dr Craig Moskowitz.

The first topic we dove into was perhaps the most anticipated lymphoma paper of the meeting, Dr Brad Kahl's presentation of the results of ECOG's Phase III RESORT trial evaluating indefinite rituximab (R) maintenance versus short-term R induction with R re-treatment on progression in patients with low tumor burden follicular lymphoma (FL). For years listeners to our audio programs have heard Dr Kahl describe the rationale for and early safety data from this historic study, but the mood in the huge convention hall was downright somber when the disappointing and overlapping curves for time to treatment failure popped up, although at 3 years fewer patients required chemo on the indefinite R arm (5% versus 14%). Always a creative thinker, Dr Moskowitz had another take on the findings.

"Patients in the RESORT control arm got just 4 weeks of rituximab — that's a month of treatment — and their median time to progression was almost 4 years. I'm thinking that's not terrible." Like many lymphoma investigators, Dr Moskowitz has in the past been very pro "watch and wait" in indolent lymphoma, and I was curious about his current perspective. "Already since ASH, based on RESORT I've given a patient rituximab who could have been monitored. People are taking a negative view of RESORT because of the maintenance issue, but I think of it another way. Here's my 76-year-old guy who may never need chemotherapy. That could be pretty cool for him. My sense is that it's not a totally negative study." Craig further explained that his R monotherapy strategy is based on the **SAKK regimen** of a total of 8 R courses over 9 months.

I also turned to another trusted and candid investigator, Rush University lymphoma scholar Dr Stephanie Gregory, for her perspectives, and she too had a lot to say about RESORT, quickly pointing out that in spite of the data we still have not defined the optimal duration of R maintenance, including after R/chemo up front. She also referred to a number of trials evaluating this crucial question, including a German study of 2 versus 4 years of R maintenance.

Click here for the RESORT slides and **here** for another, smaller study of R maintenance in FL, and see below for other related ASH lymphoma data sets.

R maintenance in mantle-cell lymphoma (MCL)

This was an update of a practice-changing European study that was first reported last year at EHA in London. The favorable outcome with R maintenance has now led most investigators, including Dr Gregory, to routinely use R maintenance after R/chemo induction in patients with MCL who are not candidates for transplant. A major ECOG trial is evaluating R maintenance alone or with lenalidomide in this cohort.

R maintenance in chronic lymphocytic leukemia (CLL)

The results from this Phase II Spanish study have not changed Dr Gregory's approach to R maintenance in CLL (she doesn't use it), and she noted that R is believed to have less antitumor effect in CLL than, for example, in FL. She voiced more optimism about an experimental strategy we have heard a lot about in multiple myeloma, namely lenalidomide maintenance.

R/chemo followed by radioimmunotherapy (RIT) followed by R maintenance in untreated FL

Although the results of this MD Anderson report were considered promising, there were 3 cases of MDS out of 47 total patients. Dr Gregory thinks the choice of chemo preceding RIT (R-FND and specifically the fludarabine) was problematic and notes that Dr Mark Kaminski's classic up-front FL study of 76 patients treated with RIT alone reported only 1 case of MDS (in a patient who had received chemo after relapse).

Next we proceed to a prominent part of the Moskowitz ASH lymphoma highlight reel, the continued fascinating story of the antibody-drug conjugate brentuximab vedotin.

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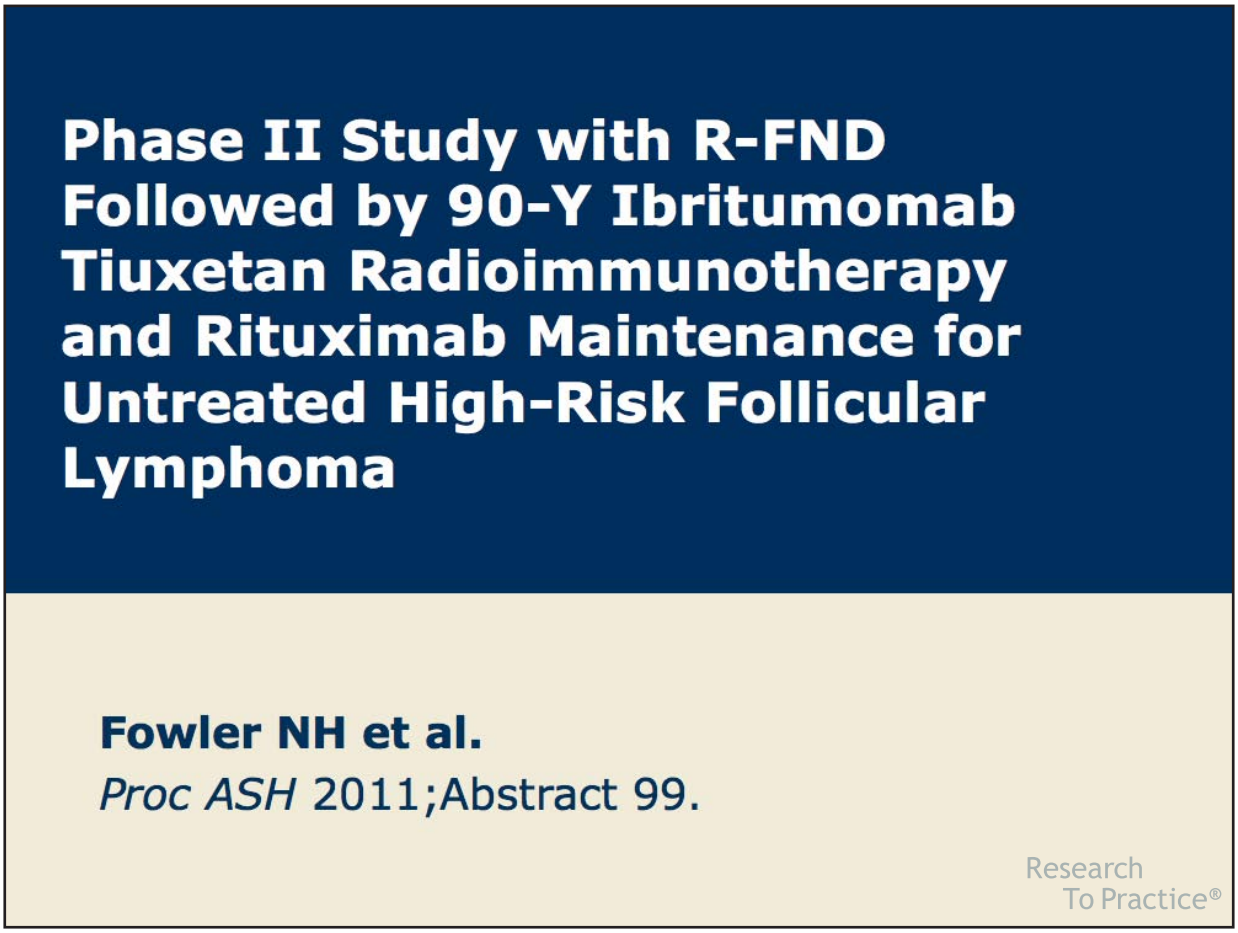
Phase II Study of R-FND Followed by Radioimmunotherapy and R Maintenance for High-Risk FL

Presentation discussed in this issue

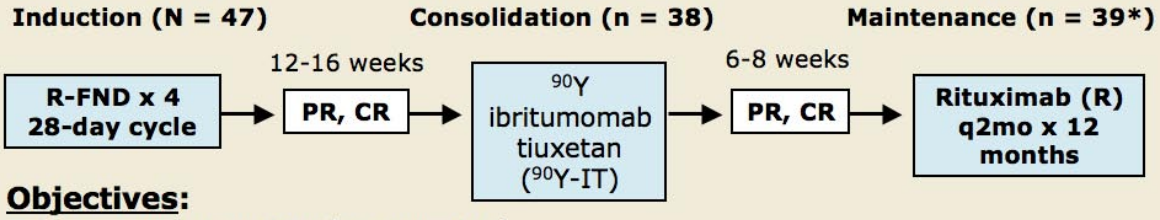
Fowler NH et al. **Phase II study with R-FND followed by 90-Y ibritumomab tiuxetan radioimmunotherapy and rituximab maintenance for untreated high-risk follicular lymphoma.** *Proc ASH* 2011;**Abstract 99**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Stephanie A Gregory, MD (1/11/12)



Study Schema

Eligibility
Untreated Stage III-IV FL, Grades 1-3
High-risk FLIPI score (≥3)
Performance score ≤2
Adequate renal, hepatic, hematologic function
No evidence of active infection



Objectives:
Primary: Progression-free survival
Secondary: Overall survival, response, safety, molecular response

* Two patients did not receive ^{90}Y-IT but received R maintenance.

Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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Response Following Treatment (Intent-to-Treat Analysis N = 47)

Response	R-FND induction	^{90}Y-IT consolidation	R maintenance
Treated N (%)	47 (100)	38 (81)	39 (83)*
ORR	46 (98)	45 (95)	41 (87)
PD	0	1 (2)	5 (11)†
Not evaluable	1 (death)	1	1

- 3 out of 6 patients converted from PR to CR following ^{90}Y-IT consolidation.
- Complete response rate in patients receiving ^{90}Y-IT consolidation: 95%

* Two patients did not receive ^{90}Y-IT but received R maintenance.
† One patient with PD refused R maintenance.

Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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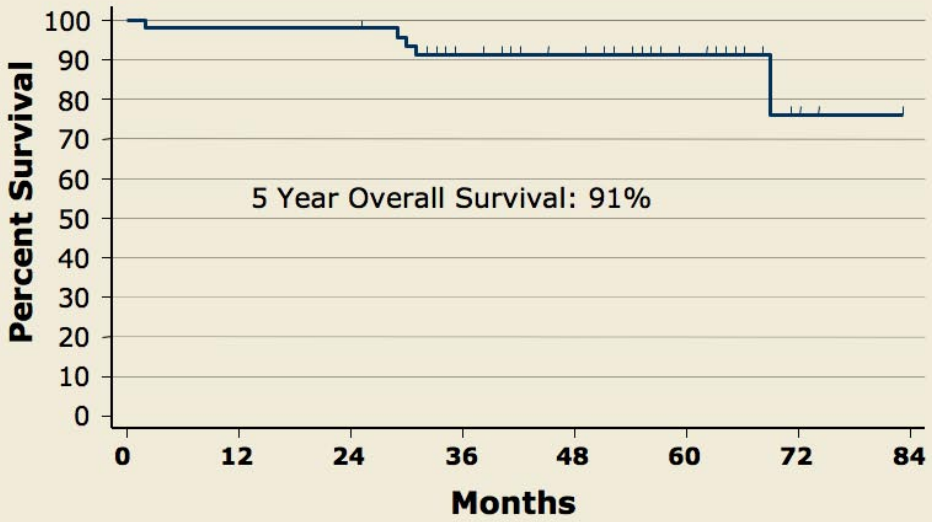
Overall Survival



With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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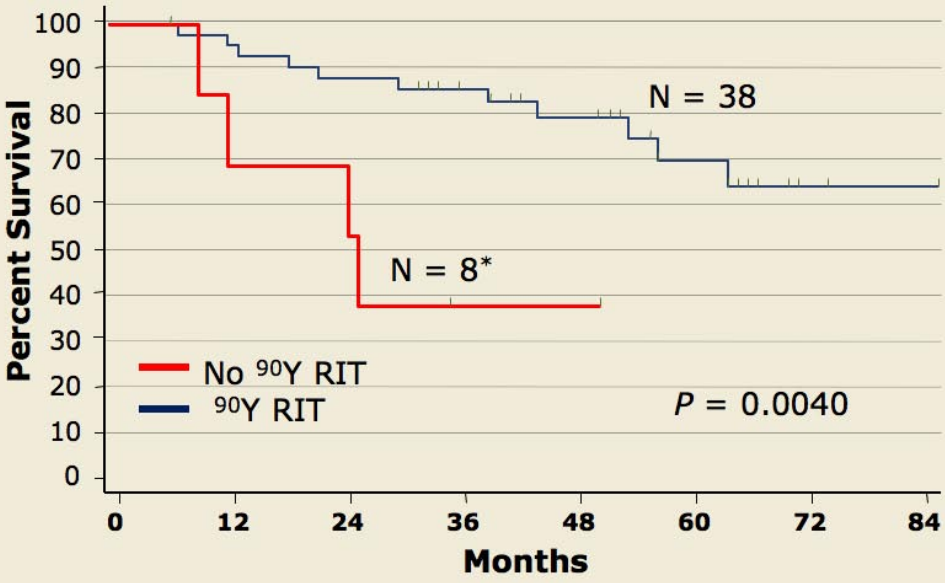
Failure-Free Survival (FFS) with Radioimmunotherapy



* One patient excluded due to unrelated death during cycle 1

With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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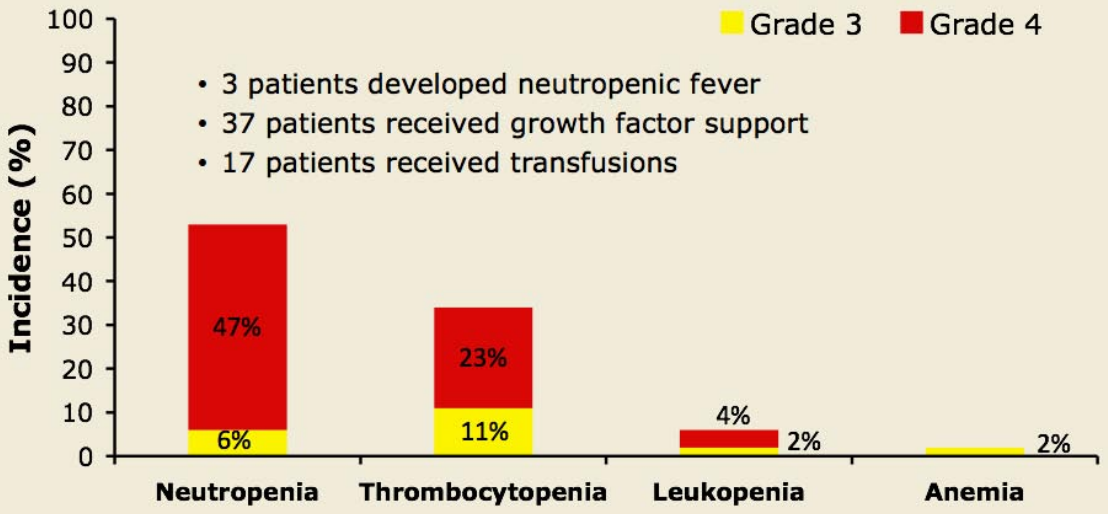
Grade 3 or 4 Hematologic Toxicity and Secondary Malignancies



Secondary malignancies: MDS (3, 1 case in patient who did not receive 90Y-RIT), breast (1), DCIS (1), papillary thyroid (1)

With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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Author Conclusions

- R-FND followed by ^{90}Y ibritumomab tiuxetan and rituximab maintenance results in high OS and FFS in high-risk FLIPI patients.
- High levels of molecular response were observed with the combination (data not shown).
- Although there are notable toxicities (eg, MDS), the benefits of this combination are substantial in this high-risk subset of patients.

Fowler NH et al. *Proc ASH* 2011;Abstract 99.

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Investigator Commentary: R-FND Followed by Radioimmunotherapy and R Maintenance

This is one of the first studies that evaluated rituximab/chemotherapy followed by radioimmunotherapy (RIT) and rituximab maintenance. We need larger studies to evaluate rituximab/chemotherapy followed by RIT consolidation and rituximab maintenance, or a trial of rituximab/chemotherapy randomly assigning patients to either RIT or rituximab maintenance.

The high incidence of MDS was surprising. Another group at ASH showed that RIT increases the risk of transformation to a more aggressive lymphoma in patients with follicular lymphoma treated with a fludarabine regimen. I conducted a small Phase II trial of 20 patients who received R-FND, then RIT consolidation and R maintenance and have 3 cases of MDS. We have to be careful about fludarabine and RIT. There is a worry, but it's not significant enough to stop one from administering RIT. I like to point out Mark Kaminski's data with front-line treatment with RIT in 76 patients with follicular lymphoma. He has had 1 case of MDS, and the study is now in its eighth year of follow-up.

Interview with Stephanie A Gregory, MD, January 11, 2012