



POST-ASH Issue 3, 2014

**Results of the Phase III
SAKK 35/03 Trial of Rituximab
Maintenance for a Maximum of
5 Years in Follicular Lymphoma**

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on therapeutic options in the management of non-Hodgkin lymphomas from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Compare the efficacy of consolidation therapy with a single dose of ⁹⁰Y-ibritumomab tiuxetan to that of rituximab maintenance for patients with newly diagnosed follicular lymphoma (FL).
- Examine the utility of early disease progression within 2 years of R-CHOP therapy as a way to identify a subset of patients with FL who are at high risk of death.
- Assess the efficacy and safety of short-term versus long-term rituximab maintenance in FL.
- Evaluate the benefits and risks of brentuximab vedotin for newly diagnosed cutaneous T-cell lymphoma or relapsed or refractory B-cell lymphomas and the effect of CD30 expression on response to this agent.
- Appraise recent clinical findings on the use of front-line lenalidomide with rituximab in mantle-cell lymphoma and of single-agent crizotinib in advanced, chemoresistant ALK-positive non-Hodgkin lymphoma.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee and Contracted Research: Celgene Corporation, Millennium: The Takeda Oncology Company, Seattle Genetics.

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This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech

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Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari

3.0 or later

Adobe Flash Player 10.2 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

Last review date: February 2014

Expiration date: February 2015

To go directly to slides and commentary for this issue, [click here](#).

The rapid integration of novel systemic agents into the management of B- and T-cell lymphomas has the rapt attention of all medical oncologists who see these patients in their practices every day. In the *next* issue of this series we focus on chronic lymphocytic leukemia (CLL), as Dr Brad Kahl reviews the newly approved type II anti-CD20 monoclonal antibody obinutuzumab and 3 new and exciting small molecules, the Bruton tyrosine kinase inhibitor ibrutinib (now FDA endorsed for mantle-cell lymphoma [MCL] and CLL), the PI3 kinase delta inhibitor idelalisib and ABT-199, an anti-BCL2 pro-apoptotic agent.



Andrew M Evens, DO, MSc

Similarly, a future edition of the series will delve into ASH papers on Hodgkin lymphoma, where brentuximab vedotin (BV) continues to shake up traditional paradigms. But for this program we turned our full attention to non-Hodgkin lymphoma (NHL) and asked Dr Andrew Evens, principal investigator of one of the few ongoing major randomized US Cooperative Group NHL trials — [ECOG-E2408](#), a 3-arm Phase II study evaluating bendamustine and rituximab (R) with or without bortezomib followed by R with or without lenalidomide — to provide his perspectives on a number of ASH data sets and what these mean to current practice and future research.

R² (rituximab/lenalidomide) up front in MCL

As has been observed in follicular lymphoma (FL), useful objective responses to this well-tolerated nonchemotherapy regimen are common, and perhaps not surprisingly, in [this Phase II study](#) 87% of patients with treatment-naïve MCL derived benefit from therapy. A major Phase III trial ([RELEVANCE](#)) compares R² to R-chemotherapy followed by R in previously untreated FL, and a number of studies, including Dr Evens', are evaluating the equally interesting concept of R² maintenance. However, the sudden and very welcome appearance of ibrutinib in MCL and the obvious logic of evaluating it up front has complicated current discussions regarding new trial designs. While R² involves 2 approved agents and is tempting to consider for older patients and those for whom chemotherapy may be problematic, most investigators, including Dr Evens, are currently conservative about attempting to use the regimen up front in patients with lymphoma, although it is a consideration with refractory disease.

Crizotinib in ALK-positive lymphomas, mainly anaplastic large cell lymphoma (ALCL)

ALK expression is present in more than 50% of patients with ALCL, and an intriguing 2011 *New England Journal* report revealed the impressive short-term therapeutic activity of crizotinib in 2 individuals with ALK-positive lymphoma. At ASH 2013 we saw **a small but stunning new series** in which all 9 patients with ALK-positive, refractory ALCL experienced complete responses (CRs) on crizotinib. In addition, 1 partial response was observed among 2 patients with ALK-positive diffuse large B-cell lymphoma (DLBCL) treated with the drug. This important development has Dr Evens and others scratching their heads about how to integrate crizotinib into current lymphoma practice and where it will fit in with the other fairly new kid on the block, BV, as part of new research initiatives.

Maintenance treatment for FL

A fascinating report from the Swiss group comparing R monotherapy followed by short-course (4 doses) or extended (5 years) R maintenance revealed that although the primary endpoint of event-free survival was not statistically different, an impressive prolongation of progression-free survival (PFS) was observed with longer treatment (3.5 years for patients on short maintenance versus 7.4 years with the long-term approach). These intriguing findings seem out of place given that the previously reported results of the ECOG RESORT trial were somewhat unimpressive, and because of this Dr Evens' personal standard for low-risk disease remains watchful waiting or at most 4 weeks of R with no maintenance. At ASH we also saw more follow-up from the classic **PRIMA trial** evaluating 2 years of R maintenance after R-chemotherapy in indolent lymphoma, and the 73-month follow-up continues to demonstrate a significant delay in disease progression.

A somewhat surprising Phase II report compared radioimmunotherapy (RIT) consolidation with ⁹⁰Y-ibritumomab tiuxetan to 2 years of R maintenance in patients with newly diagnosed FL responding to R-CHOP. At 3 years, a clear PFS advantage (77% versus 63%; $p = 0.044$) in favor of R maintenance was observed. Based in part on these data, Dr Evens believes that 2 years of R maintenance remains the standard, but he will still consider RIT consolidation in highly select situations in which a patient's life plans don't meld well with regular infusions.

Finally, **another report** from the now well-publicized National LymphoCare Study in FL provides some solid evidence to back up the collective impression that the approximately 20% of patients who experience relapse in the first 2 years after R-chemotherapy have a poor prognosis. In this analysis of 122 such patients who received R-CHOP up front with a median follow-up of 7 years, the 5-year overall survival rate was approximately 50%. When this is compared to the almost 100%

survival rate for those who did not relapse within 2 years, it seems clear that these individuals should be considered for clinical trials designed to find ways to reverse the rapid downhill trajectory in this situation.

BV in cutaneous lymphomas and NHL

Two fascinating papers at ASH reported on Phase II studies evaluating this always-exciting antibody-drug conjugate in several unique lymphoma subsets. **In cutaneous disease** (primarily mycosis fungoides) 34 of 48 patients obtained objective responses (71%), of which half (35%) were CRs, and in **the NHL study** 21 of 50 patients with DLBCL (42%) responded, including 16% CRs. What was intriguing and a bit confusing was that activity was observed across a broad range of CD30 expression, including in patients with low or undetectable CD30 expression by standard immunohistochemical staining. Dr Evens believes that while it is possible that BV has off-target antitumor effects, the more likely explanation is that current assays for CD30 are not detecting lower but clinically significant levels of antigen. While this is sorted out, oncologists in practice must consider that useful clinical responses have been seen with BV in patients with a variety of heavily pretreated lymphomas and that perhaps referral for trial participation should be explored for interested individuals regardless of CD30 positivity.

As stated previously, next we check in with Dr Brad Kahl about perhaps the most exciting area of new drug development in oncology — chronic lymphocytic leukemia.

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Results of the Phase III SAKK 35/03 Trial of Rituximab Maintenance for a Maximum of 5 Years in Follicular Lymphoma

Presentation discussed in this issue

Taverna CJ et al. **Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: Results of the randomized Phase III trial SAKK 35/03.** *Proc ASH 2013*; **Abstract 508.**

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Andrew M Evens, DO, MSc (2/12/14)

Rituximab Maintenance Treatment for a Maximum of 5 Years in Follicular Lymphoma: Results of the Randomized Phase III Trial SAKK 35/03

Taverna C et al.

Proc ASH 2013; Abstract 508.

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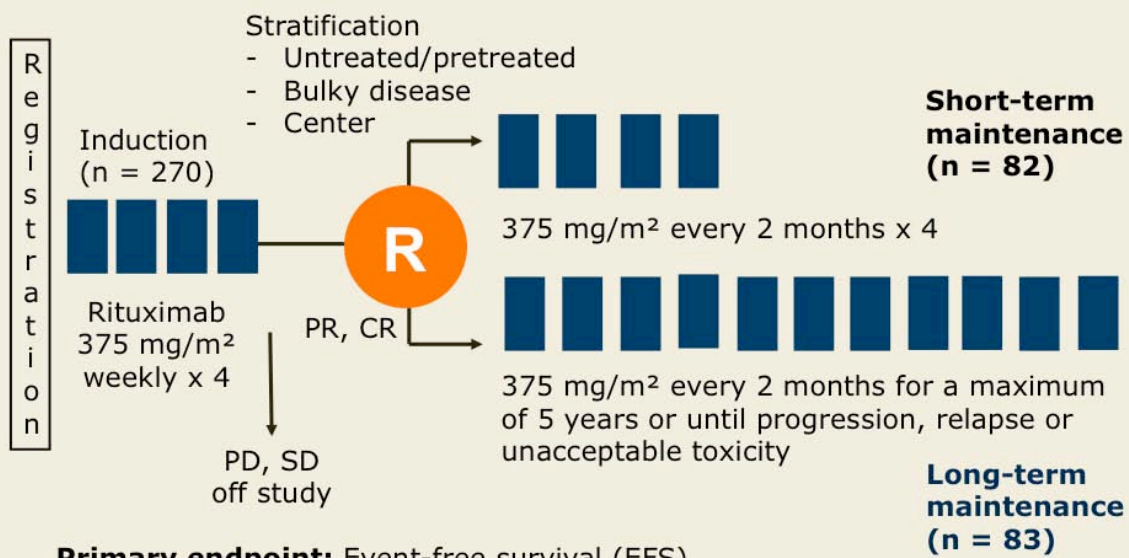
Background

- Observation continues to be adequate for patients with asymptomatic follicular lymphoma (FL) (ie, low-bulk disease and no cytopenias) (*Am J Hematol* 2012;87(10):988).
 - Most patients requiring therapy receive chemotherapy and rituximab.
- Rituximab maintenance has been shown to be an effective therapy for patients with newly diagnosed and relapsed/refractory FL (*Lancet* 2011;377(9759):42; *J Clin Oncol* 2010; 28(17):2853).
- The optimal duration of maintenance therapy remains unknown.
- **Study objective:** To investigate whether rituximab maintenance every 2 months for 5 years or until relapse/progression, unacceptable toxicity or death is superior to rituximab maintenance every 2 months x 4 for patients with FL.

Taverna C et al. *Proc ASH* 2013;Abstract 508.

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SAKK 35/03: Phase III Trial Design



Primary endpoint: Event-free survival (EFS)

Secondary endpoints: Progression-free survival (PFS), overall survival, objective response, adverse events during and after maintenance

Taverna C et al. *Proc ASH* 2013;Abstract 508.

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Response at Restaging

	(n = 261)
Overall response rate	62.8%
Complete response (CR)	13.4%
CR unconfirmed	3.4%
Partial response	46.0%
Stable disease	29.9%
Progressive disease	7.3%

Taverna C et al. *Proc ASH* 2013;Abstract 508.

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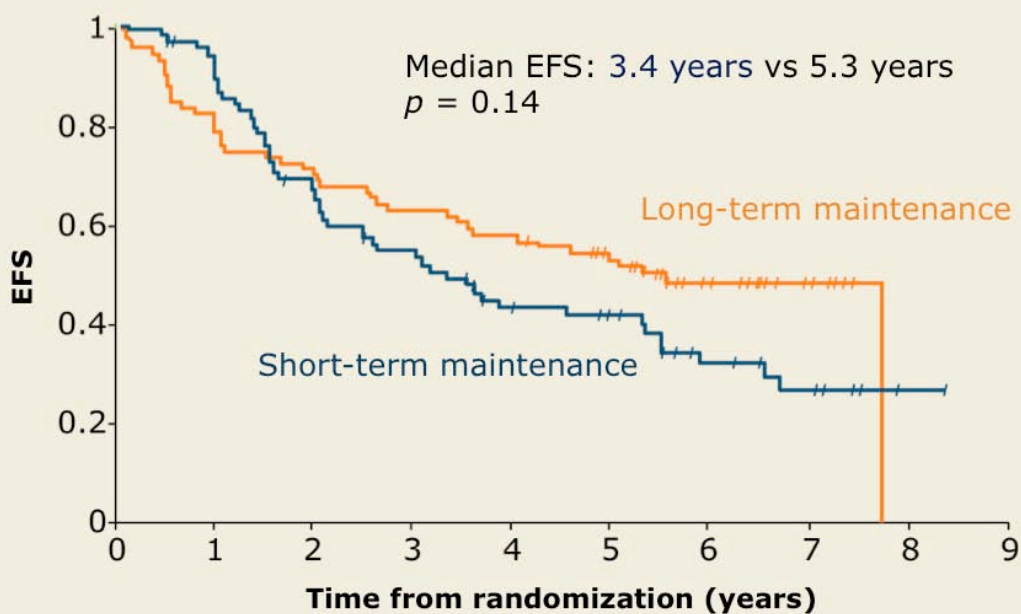
Patient Characteristics

	Short-term maintenance (n = 82)	Long-term maintenance (n = 83)
Sex		
Female	55%	69%
Male	45%	31%
Median age (range)	55 (34-81)	57 (25-81)
Disease status		
Untreated	67%	70%
Relapsed/progressed	33%	29%
Stable	0%	1%
Previous chemotherapy	24%	25%
Previous anti-CD20 therapy	11%	8%
Previous radiotherapy	9%	6%

Taverna C et al. *Proc ASH* 2013;Abstract 508.

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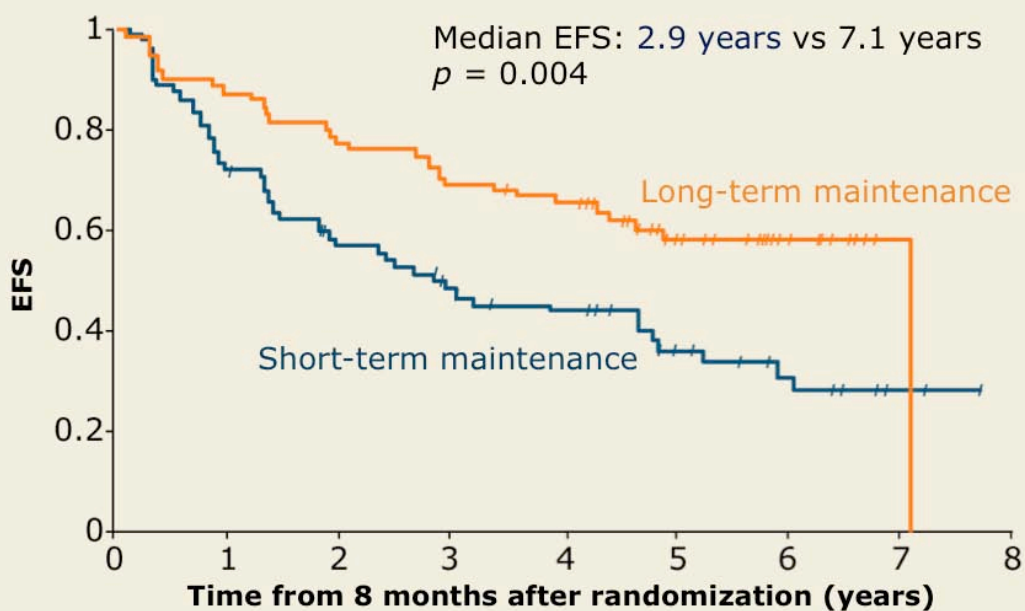
EFS



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EFS* (Retrospectively Defined Analysis)

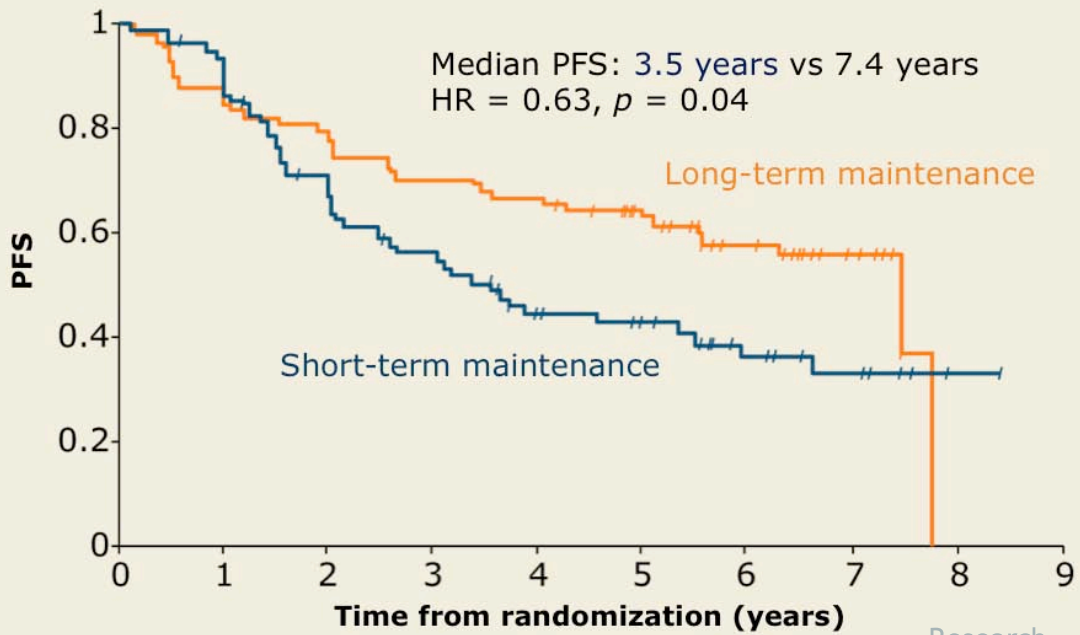


* Only patients at risk 8 months after randomization

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PFS



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Adverse Events

	Short-term maintenance (n = 82)	Long-term maintenance (n = 83)
At least 1 adverse event	50%	76%
Highest grade		
Grade 1	30%	22%
Grade 2	18%	37%
Grade 3	1%	14%
Grade 4	0%	2%
Grade ≥3 infection	1%	6%
Secondary malignancy	7%	10%

Taverna C et al. *Proc ASH 2013*;Abstract 508.

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Author Conclusions

- The primary endpoint of the Phase III SAKK 35/03 trial was not met (median EFS: 3.4 y vs 5.3 y; $p = 0.14$) due mainly to the early separation of the curves favoring short-term maintenance at a time when the treatment in both arms was the same.
- A retrospectively defined analysis considering only EFS events from the time when treatment was different in the 2 arms shows a statistically significant increase in EFS with long-term maintenance (median EFS: 2.9 y vs 7.1 y; $p = 0.004$).
- Long-term rituximab maintenance doubles the median PFS without leading to increased undue toxicity.

Taverna C et al. *Proc ASH* 2013;Abstract 508.

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Investigator Commentary: Results of SAKK 35/03 — A Phase III Trial of Rituximab (R) Maintenance Treatment for a Maximum of 5 Years in FL

These data are interesting, but they conflict with the RESORT data (*Proc ASH* 2011;Abstract LBA-6) to a certain extent. The endpoint of the RESORT study wasn't exactly the same, and among patients with at least low-risk FL no difference in the primary endpoint, time to treatment failure, was evident between R maintenance and R re-treatment at disease progression. The SAKK 35/03 study administered R maintenance for up to 5 years, and based on the curves presented at ASH, results for the primary endpoint of EFS were not significant. Results for the secondary endpoint of PFS were significant, as was an unplanned retrospective analysis of EFS. I am a bit of a statistical purist and find those types of analyses to contain biases. Obviously we'll have to wait for the formal publication.

I would say the bottom line is that the standard for patients with high-risk FL remains R/chemotherapy followed by 2 years of R maintenance. But in the low-risk setting, including patients on the RESORT study — in other words, for disease you don't have a reason to treat — my personal standard is still watchful waiting. At most I would administer 4 weeks of R and then wait with no maintenance therapy.

Interview with Andrew M Evens, DO, MSc, February 12, 2014