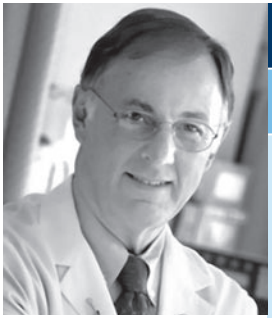


INTERVIEW

Richard I Fisher, MD

Dr Fisher is Samuel E Durand Professor of Medicine, Director of the James P Wilmot Cancer Center, Director of the University of Rochester Medical Faculty Group, Senior Associate Dean for Clinical Affairs and Vice President of the University of Rochester Medical Center in Rochester, New York.

Tracks 1-19

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the data from the PRIMA trial evaluating rituximab maintenance after initial rituximab/chemotherapy induction in follicular lymphoma (FL)?

DR FISHER: A number of studies suggested the value of maintenance rituximab in relapsed FL. However, the question remains whether maintenance

rituximab after initial rituximab/chemotherapy induction in FL provides a real benefit versus waiting and then re-treating later. In the PRIMA study, patients with FL received up-front rituximab/chemotherapy and were then randomly assigned to maintenance rituximab versus observation. The results show an absolute benefit of 16 percent in two-year progression-free survival in favor of the maintenance arm (Salles 2010; [3.1]).

Rituximab was administered every two months for two years, and clearly it delays recurrence. Although no survival benefit has been observed yet, that may come with longer follow-up. We need to put the PRIMA data in the context of all available data for maintenance rituximab. In the relapsed setting, some of the data sets have shown a survival advantage with longer follow-up. It's clear to me that maintenance rituximab should be considered as up-front therapy for FL.

The side effects of two years of maintenance rituximab were minimal, with no catastophic infections, but I believe that outside of a clinical protocol we should not go beyond two years at this time. I believe prolonged immunosuppression and the absence of B cells will ultimately deplete new antigen reactivity and might have adverse consequences. Ongoing trials examining longer rituximab maintenance, such as four or five years, will eventually indicate whether longer maintenance might be of further benefit.

We are starting to observe some immunodeficiency in terms of lower immunoglobulin levels in patients who have undergone extensive treatment with rituximab, and some of these patients are developing signs of pulmonary infections. My guess is that there is an inflection point and a tipping point, such that an optimal duration of maintenance exists beyond which toxicity will overcome the benefits. Currently, we don't know that tipping point.

With the overwhelming weight of evidence from the PRIMA study, I am comfortable now with two years of maintenance in the up-front setting.

3.1

Phase III PRIMA Study: Efficacy Results with Maintenance Rituximab for Previously Untreated Follicular Lymphoma

	Observation (n = 513)	Maintenance rituximab (n = 505)	Hazard ratio	*p*-value
Two-year PFS	66%	82%	0.50	<0.0001

PFS = progression-free survival

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

Tracks 3, 5

DR LOVE: Does a role exist for radioimmunotherapy (RIT) consolidation as part of initial therapy for patients with FL?

DR FISHER: Next year we might have an answer on the role of RIT as part of initial therapy. An Intergroup trial, S0016, comparing R-CHOP to CHOP followed by tositumomab for the initial treatment of FL, is ongoing (3.2). This is a large trial that is maturing, and hopefully we will have an abstract at ASCO 2011.

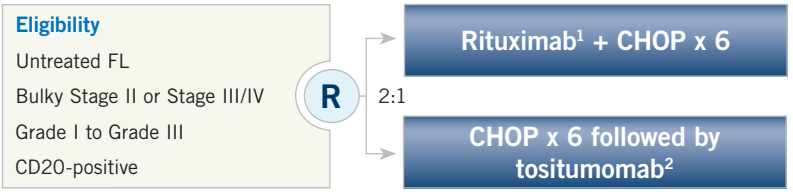
The results are currently blinded by the Data and Safety Monitoring Board. However, the study is pivotal in the sense that it may "make or break" RIT as an option as consolidation for up-front FL. RIT has been slow to take off in popularity for a number of reasons, and we look forward to the results of S0016. Then we will have to decide where to go from there.

I believe RIT is in danger of disappearing soon if these studies are not positive, although RIT is active and physicians who have used it know that it is active. We would like to see it used, and hopefully within a year we will know the answer to that.

3.2

Randomized Phase III Trial Comparing R-CHOP to CHOP Followed by Tositumomab for the Initial Treatment of Follicular Lymphoma

Protocol ID: SWOG-S0016 **Target Accrual:** 500



[1] A total of six doses of rituximab are administered. Two doses are administered before CHOP cycle 1, a third and a fourth dose of rituximab are administered with CHOP cycle 3 and cycle 5, respectively, and the last two rituximab doses are administered after CHOP cycle 6.
[2] Two doses of tositumomab are administered after CHOP cycle 6.

www.clinicaltrials.gov. Identifier NCT00006721.

Tracks 7-8

DR LOVE: Would you discuss bendamustine/rituximab in the treatment of FL?

DR FISHER: Bendamustine is an extremely active agent. I don't believe anyone in the United States predicted that this drug would have this kind of activity. It has properties of both an alkylating agent and a purine analog.

The study comparing R-CHOP to BR presented at ASH 2009 looks good, and we use BR extensively (Rummel 2009; [3.3]). The data are not published in a peer-reviewed journal yet, so we don't have a lot of knowledge of how the statistics were obtained and how the follow-ups were performed.

Overall, I believe it is interesting and worthy of consideration, particularly when contraindications to anthracycline-based chemotherapy are present. Even for patients without contraindications, such as a healthy 60-year-old, I believe it is a reasonable option and would be appropriate for use. In our center we still use R-CHOP as the standard, but we also use BR a great deal.

The toxicity profile is different, and not much hair loss occurs. Some marrow toxicity is still present along with significant fatigue. The Rummel data suggest that BR is significantly less toxic than R-CHOP (Rummel 2009; [3.4]). We have not administered BR to enough patients with good performance status or to those in great health to know how it compares. We are using it for a preselected population that, by definition, is less healthy, and that makes it difficult for me to make the comparison — my database is skewed against BR because I am using it for the less healthy people. ■

3.3

Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in Front-Line Indolent Lymphomas

	Overall response	Complete response	Progression-free survival	Median time to next treatment
BR (n = 260)	92.7%	39.6%	54.9 months	Not reached
R-CHOP (n = 253)	91.3%	30.0%	34.8 months	46.7 months
p-value	—	0.0262	0.00012	0.0281

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

3.4

Safety Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in Front-Line Indolent Lymphomas

	Grade 3 or 4 neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Drug-related rash	Alopecia
BR	10.7%	36.5%	6.9%	6.2%	16.2%	15%
R-CHOP	46.5%	47.8%	28.8%	18.6%	9.1%	62%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	—

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

SELECT PUBLICATIONS

Morschhauser F et al. **Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.** *J Clin Oncol* 2008;26(32):5156-64.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.