INTERVIEW

Brad S Kahl, MD

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Tracks 1-21

Select Excerpts from the Interview

Track 5

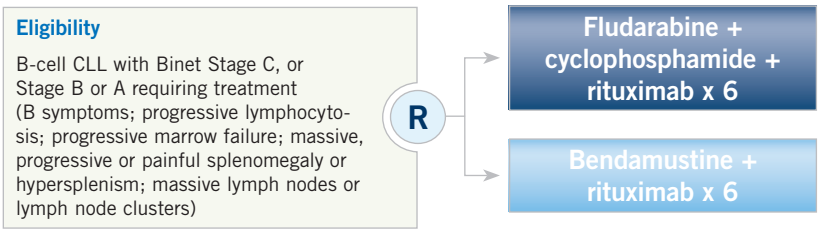
DR LOVE: What is your approach to first-line therapy for an older patient with chronic lymphocytic leukemia (CLL)?

DR KAHL: At present, I might be more inclined to start with bendamustine in combination with rituximab. Fludarabine is an active drug in CLL but has a number of potential problems — cytopenias and infectious complications — as folks get older. A presentation at ASH 2010 of a head-to-head comparison of bendamustine/rituximab (BR) to fludarabine/rituximab (FR) reported better performance with BR in patients with relapsed indolent lymphoma (Rummel 2010). If you extrapolate that to the CLL population, it may end up being a better choice for patients of all ages. An ongoing randomized trial is evaluating that question, although the comparison is BR versus fludarabine/cyclophosphamide/rituximab (FCR) (1.1).

For younger patients, the choice would be between BR and FCR. FCR is an effective therapy, but it's hard on the stem cells, bone marrow and blood counts, which sometimes makes it difficult to administer subsequent therapies. I'm eagerly awaiting the data from the randomized trial (1.1), with the expectation that BR will at least be equivalent if not superior to FCR because I believe BR will be better tolerated.

1.1 **Combined Immunochemotherapy versus Bendamustine and Rituximab as Up-Front Treatment for Chronic Lymphocytic Leukemia (CLL)**

Protocol IDs: GCLLSG-CLL10, EUDRACT-2007-007587-21, EU-20883
Target Accrual: 550



www.clinicaltrials.gov. Identifier NCT00769522.

Track 12

DR LOVE: Would you discuss the PRIMA study, which evaluated two years of rituximab maintenance for patients with follicular lymphoma (FL) responding to immunochemotherapy?

DR KAHL: The PRIMA study evaluated approximately 1,000 patients with FL. The immunochemotherapy regimen was the center's choice between R-CHOP, R-CVP and a third fludarabine-based arm, which few centers chose.

Patients who did not experience progression were then randomly assigned to observation or maintenance rituximab. A profound progression-free survival benefit was reported with maintenance rituximab (Salles 2011; [1.2]). At three years, approximately 60 percent of the patients not receiving maintenance are still in remission, but that number is closer to 80 percent for those who did receive maintenance. That's quite a striking absolute difference. No overall survival difference was observed between the two groups.

From a toxicity standpoint, immunoglobulin levels did not drop in the patients receiving maintenance rituximab. The infection rates were slightly higher, but the infections were generally not serious.

1.2

Rituximab (R) Maintenance for Patients with Follicular Lymphoma Responding to Immunochemotherapy: Survival and Adverse Events (AEs) in the PRIMA Study at 36 Months Median Follow-Up

	R maintenance (n = 501)	Observation (n = 508)	Hazard ratio (HR) or risk ratio (RR)	*p*-value
Three-year PFS	74.9%	57.6%	0.55 (HR)	<0.0001
Grade 3 or 4 AEs	24%	17%	1.46 (RR)	0.0026
Grade 2 to 4 infections	39%	24%	1.62 (RR)	<0.0001
Treatment discontinued due to AE	4%	2%	2.41 (RR)	0.029

PFS = progression-free survival

Salles G et al. *Lancet* 2011;377(9759):42-51.

Track 13

DR LOVE: Would you update us on the ECOG RESORT trial of which you are the principal investigator, which is evaluating long-term rituximab maintenance?

DR KAHL: The RESORT trial is evaluating long-term rituximab dosing strategies. Patients with previously untreated low tumor burden indolent lymphoma receive four weekly doses of single-agent rituximab. The first group of responding patients receives rituximab re-treatment on an as-needed basis upon disease recurrence. As long as disease remissions are lasting at least six months, patients continue to be re-treated at each progression until they stop responding to rituximab.

The other group of patients receives a single dose of rituximab every three months as maintenance. As long as they remain in remission, they continue to

receive the agent indefinitely. Our primary endpoint is time to rituximab resistance. We're trying to determine if one strategy is better for controlling disease. We are hoping to report our first data soon, maybe at this year's ASH meeting.

Track 15

DR LOVE: What are your thoughts on the Intergroup study of rituximab versus watch and wait in advanced-stage, nonbulky FL?

DR KAHL: This was a large trial conducted in the United Kingdom, evaluating the same patient population that we have in the RESORT trial — patients with low tumor burden, indolent lymphoma — but their question is different than ours. This study evaluated rituximab versus a watch-and-wait strategy. The presumption is that when patients with indolent lymphoma move on to chemotherapy, they experience a detriment in quality of life. If you could apply a nontoxic strategy that could delay the time it takes for patients to get to chemotherapy, that should translate into a quality-of-life benefit.

The results were presented at ASH 2010, and the authors reported that the time it takes to move to chemotherapy is substantially longer for the patients who started out receiving rituximab treatment compared to the watch-and-wait group (Ardeshna 2010). No overall survival difference was reported.

Many physicians are struggling with how to apply this information to their practice. We don't know if quality of life is being affected in a clinically meaningful manner. We have to appreciate that every patient is different and a one-size-fits-all approach is not appropriate. Some patients derive great psychological comfort from knowing their disease is in remission, whereas others are comfortable living with their disease and not receiving therapy.

This study hasn't yet changed my practice. For several years I have been having long discussions with my patients who have low tumor burdens. I tell them my recommendation is to watch and wait, but for patients who are uncomfortable with that approach we focus on rituximab monotherapy or rituximab with chemotherapy and try to make a decision together.

Tracks 17-19

DR LOVE: Would you comment on what's going on right now in mantle-cell lymphoma (MCL) research and practice?

DR KAHL: A number of active questions are being pursued for younger patients with MCL. For example, if stem cell transplant is part of your initial treatment strategy, how important is choice of induction therapy? In other words, does the induction therapy matter?

A large European trial in which patients were randomly assigned to either R-CHOP or R-CHOP with alternating R-DHAP was presented at ASH 2010. The authors reported a significant advantage in terms of progression-free survival for the patients who received high-dose cytarabine (Hermine 2010).

I believe some merit exists for trying to build that into your induction strategy, whether it be R-CHOP alternating with R-DHAP or whether it be hyper-CVAD, which has high-dose cytarabine. That's a reasonable course. Once a younger patient is in remission, it's a reasonable approach to then consolidate that remission with stem cell transplant.

Options for older patients are tougher. They can't tolerate these intensive strategies, so treatment options are more limited. We're hopeful that BR will prove to be an effective induction strategy for older patients with MCL.

A planned US cooperative group trial with a target accrual of approximately 300 patients with MCL will evaluate induction BR with or without bortezomib followed by rituximab with or without lenalidomide as maintenance therapy.

A large European trial for older patients with MCL recently reported a major benefit with rituximab maintenance after initial therapy. The Data Safety Monitoring Board closed this trial early because the rituximab maintenance group was performing substantially better (Kluin-Nelemans 2011; [1.3]). So for the first time, good evidence supports the use of rituximab maintenance in older patients with MCL. ■

1.3

Rituximab (R) Maintenance After Induction Therapy with R-CHOP or R-FC for Elderly Patients with Mantle-Cell Lymphoma: First Results from the European MCL Network Study

Response	R maintenance	IFN maintenance	Hazard ratio	*p*-value
Median remission duration	51 months	24 months	0.56	0.0117
Three-year overall survival with R-CHOP induction	85%	70%	—	0.0375

Kluin-Nelemans H et al. *Proc EHA* 2011;**Abstract 0504**.

SELECT PUBLICATIONS

Ardeshna KM et al. **An Intergroup randomised trial of rituximab versus a watch and wait strategy in patients with Stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (Grades 1, 2 and 3a). A preliminary analysis.** *Proc ASH* 2010;**Abstract 6**.

Hermine O et al. **Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net).** *Proc ASH* 2010;**Abstract 110**.

Kluin-Nelemans HC, Doordujin JK. **Treatment of elderly patients with mantle cell lymphoma.** *Semin Hematol* 2011;48(3):208-13.

Rummel MJ et al. **Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas — Final results of the randomized Phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2010;**Abstract 856**.

Salles G et al. **Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial.** *Lancet* 2011;377(9759):42-51.