INTERVIEW

Peter Martin, MD

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Tracks 1-14

Select Excerpts from the Interview

Track 4

DR LOVE: Would you discuss the Phase II study presented by your group at ASH 2014 evaluating the R^2 regimen of lenalidomide and rituximab for patients with untreated mantle-cell lymphoma (MCL) (Ruan 2014; [4.1])?

DR MARTIN: We've known for a long time that lenalidomide has significant activity in MCL. So we wanted to determine if a subset of patients with MCL could benefit from less aggressive therapy with R^2.

In this study patients with newly diagnosed MCL received R^2 as induction for 1 year, followed by R^2 maintenance until disease progression. Overall the regimen was reason-

ably well tolerated. Many patients required a dose reduction of lenalidomide. In some cases, we stopped the rituximab alone if patients developed infections.

To our surprise, the regimen was also remarkably effective. At 2 years, the PFS rate was about 85%. This is significant considering that the average PFS with R-CHOP is in the range of 18 months to 2 years (Ruan 2014; [4.1]).

One could argue that that the R^2 regimen is continuous therapy, as opposed to R-CHOP, which is intermittent over 18 weeks. Nonetheless, I believe that for patients with MCL who require treatment and have higher MIPI scores, these results are promising. In the future, I believe we'll see more trials that use continuous therapies with creative regimens in the up-front setting.

4.1

Phase II Trial of Lenalidomide with Rituximab (R^2) as Initial Treatment for Mantle-Cell Lymphoma

Efficacy	(n = 38)
ORR	84.2%
CR	52.6%
Median PFS	Not reached
2-year PFS	83.9%
Select adverse events	**Grade 3 or 4** (n = 38)
Neutropenia	47%
Thrombocytopenia	13%
Anemia	8%
Rash	26%
Tumor flare	11%

ORR = overall response rate; CR = complete response; PFS = progression-free survival

Ruan J et al. *Proc ASH* 2014;**Abstract 625**.

Tracks 5-6

DR LOVE: How do you approach the issue of maintenance rituximab for patients with MCL?

DR MARTIN: Our preference is to enroll patients with MCL who require treatment in the ECOG-E1411 trial. This is a US intergroup study in which patients with untreated MCL receive induction with BR with or without bortezomib. In the maintenance phase patients receive rituximab with or without lenalidomide for 2 years (NCT01415752).

Off study, we generally administer BR, but occasionally, for young patients with aggressive disease, we recommend a cytarabine-containing induction regimen followed by autologous stem cell transplant (ASCT). We do not routinely administer rituximab maintenance in the post-stem cell transplant setting.

Many oncologists do not consider rituximab maintenance after chemotherapy induction to be standard. We know that it's beneficial after R-CHOP. The European Mantle Cell Lymphoma Network study in older patients with MCL showed compelling data

with an OS benefit in patients who received ongoing rituximab maintenance after that regimen (Kluin-Nelemans 2012). We don't have data on the efficacy of rituximab maintenance after BR, but we prefer to give patients the benefit of the doubt and often offer them rituximab maintenance.

DR LOVE: Can you talk about the results of the Phase III LYMA study evaluating the efficacy of rituximab maintenance in young patients with previously untreated MCL after R-DHAP followed by ASCT?

DR MARTIN: In the LYMA trial, young patients with newly diagnosed MCL received 4 cycles of R-DHAP induction therapy followed by ASCT and then were randomly assigned to rituximab maintenance versus watch and wait for 3 years. If patients did not achieve at least a partial response after R-DHAP, they could receive R-CHOP. However, most patients fared well with R-DHAP.

A clear benefit in PFS was observed, but no OS benefit has been achieved so far (Le Gouill 2014; [4.2]). The lack of evidence of an OS benefit is the main reason that I do not recommend rituximab maintenance after ASCT. I would like to see the data published and evaluated in a peer review setting. The other reason I don't offer it is that we don't do ASCT for many patients at our center.

4.2

First Interim Analysis of the Phase III LYMA Trial of Rituximab Maintenance versus Watch and Wait After R-DHAP and Autologous Stem Cell Transplant in Young Patients with Untreated Mantle-Cell Lymphoma

Efficacy	Rituximab (n = 119)	Watch and wait (n = 119)	*p*-value
Two-year EFS	93.2%	81.5%	0.015*
Two-year OS	93.4%	93.9%	NS

EFS = event-free survival; OS = overall survival; NS = not significant

* Hazard ratio = 2.1

Progression-free survival was statistically significant between the study arms ($p = 0.015$).

Le Gouill S et al. *Proc ASH* 2014;**Abstract 146**.

Tracks 12-14

DR LOVE: Would you discuss the study that led to the approval of idelalisib for follicular lymphoma (FL) and how that agent fits into your practice?

DR MARTIN: Idelalisib was approved by the FDA based on a Phase II trial in which patients with FL that was refractory to both rituximab and an alkylating agent received single-agent idelalisib. In this treatment-resistant group of patients, the median PFS was 11 months and the response rate was 57% (Gopal 2014). So patients without other good options responded well to idelalisib.

Interestingly, that study included a variety of histologies, but the FDA approved idelalisib only for patients with FL who had received at least 2 prior therapies. We generally recommend idelalisib for patients with disease that is refractory to rituximab and an alkylating agent. When patients do not have a lot of other treatment options, idelalisib is an attractive agent.

It is also a good option for older patients and those who have to travel long distances and prefer to have an oral agent. At our academic center at Cornell, we have multiple clinical trials open for these patients. We offer single-agent idelalisib for patients who don't want to participate in these studies.

DR LOVE: What do you recommend for patients with FL who experience relapse after up-front BR?

DR MARTIN: Most patients with FL in the United States receive BR as front-line therapy, although some patients still undergo treatment with R-CHOP. We have good data for bendamustine-based therapies in the second-line setting as well. We don't have data on the efficacy of R-CHOP for patients whose disease progresses on bendamustine-based therapy.

FL is a heterogeneous disease. Some patients experience progression quickly and are likely to have chemotherapy-resistant disease. These patients are at high risk and require immediate treatment. One approach is to administer more intensive chemotherapy. If they've received an anthracycline, ICE and DHAP would be options. Otherwise, R-CHOP followed by ASCT for patients who are eligible for transplant would be reasonable. Another alternative would be to try an approach without chemotherapy. Idelalisib would be a good option, particularly for older patients who are not candidates for an anthracycline-based regimen or ASCT.

Patients who experience disease progression late after BR or R-CHOP may not need treatment for a long period of time. My preference is to observe these patients. I believe it's important to remember that we're not treating FL to cure it but rather to improve longevity and, most importantly, improve quality of life. If patients do need treatment, the same options as in the front-line setting can be considered, namely, single-agent rituximab, immunochemotherapy, idelalisib, lenalidomide or a clinical trial.

DR LOVE: What is your view on the efficacy of the R^2 regimen for newly diagnosed FL?

DR MARTIN: R^2 is clearly active in FL. CALGB-50401 was a Phase II clinical trial in which patients with recurrent FL were randomly assigned to the R^2 regimen or lenalidomide alone. The R^2 arm was superior to lenalidomide (Leonard 2015). The CALGB-50803 study by our group also showed that this regimen was active as up-front therapy for patients with FL (Martin 2014).

I believe that based on the synergy between lenalidomide and rituximab they should be used in combination. However, lenalidomide is not yet approved by the FDA for the treatment of FL, and that has an effect on insurance coverage. ■

SELECT PUBLICATIONS

Gopal AK et al. **PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma.** *N Engl J Med* 2014;370(11):1008-18.

Kluin-Nelemans HC et al. **Treatment of older patients with mantle-cell lymphoma.** *N Engl J Med* 2012;367(6):520-31.

Leonard JP et al. **Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance).** *J Clin Oncol* 2015;133(31):3635-40.

Martin P et al. **CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Proc ASCO* 2014;**Abstract 8521**.

Ruan J et al. **Sustained remission with the combination biologic doublet of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma: A multi-center phase II study report.** *Proc ASH* 2014;**Abstract 625**.