INTERVIEW

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Tracks 1-19

Track 1 ECOG-E4402: RESORT trial comparing rituximab maintenance to rituximab re-treatment upon disease progression for low tumor burden indolent non-Hodgkin lymphoma

Track 2 Activity and current indications for ofatumumab in relapsed or refractory chronic lymphocytic leukemia (CLL)

Track 3 Efficacy of lenalidomide alone and in combination with rituximab in indolent and aggressive lymphomas

Track 4 Novel agents under investigation in B-cell lymphomas: the PI3 kinase inhibitor GS-1101 (CAL-101) and the Bruton tyrosine kinase inhibitor (TKI) ibrutinib (PCI-32765)

Track 5 Use of radioimmunotherapy (RIT) as up-front and consolidation therapy in follicular lymphoma (FL)

Track 6 Approved and investigational treatment options for patients with CLL

Track 7 Challenges associated with the use of FCR; activity and tolerability of bendamustine/rituximab (BR) in CLL

Track 8 Diffuse large B-cell lymphoma (DLBCL): Overview of distinct subtypes and differential outcomes

Track 9 Role of interim and post-treatment PET scanning for patients receiving treatment for DLBCL

Track 10 Indications for central nervous system prophylaxis and treatment for patients with DLBCL and cardiac dysfunction or HIV infection

Track 11 **Case discussion:** A 76-year-old man with elevated white blood cell count and splenomegaly without significant lymphadenopathy is initially diagnosed with CLL but flow cytometry confirms indolent mantle-cell lymphoma (MCL) with 11;14 translocation

Track 12 Perspective on the "watch-and-wait" strategy for patients with indolent MCL

Track 13 Intergroup study of BR versus BR with bortezomib with or without lenalidomide maintenance therapy for older patients (≥60 years) with newly diagnosed MCL

Track 14 Intergroup study of R-hyper-CVAD versus BR followed by autologous stem cell transplant (ASCT) for younger patients (≤65 years) with newly diagnosed MCL

Track 15 Current indications and potential roles for bortezomib in MCL

Track 16 Survival benefit with rituximab versus interferon as maintenance therapy after R-CHOP in elderly patients with MCL

Track 17 Front-line treatment approach for younger patients with MCL

Track 18 Induction therapy options for nontransplant-eligible patients with MCL and the role of maintenance rituximab therapy

Track 19 **Case discussion:** A 55-year-old woman with nonblastoid Stage IVB MCL who experiences disease relapse 18 months after treatment with R-hyper-CVAD and ASCT attains a complete remission with ibrutinib on a clinical trial

Select Excerpts from the Interview

Track 1

DR LOVE: Would you provide an update of recent clinical trial results in indolent and follicular lymphoma?

DR WILLIAMS: The most important developments relate to the studies in low tumor burden follicular lymphoma (FL). This was the focus of the RESORT trial, which evaluated patients who could traditionally be offered "watch and wait" and deferred therapy. Four doses of rituximab were administered, and those patients who responded — with either partial or complete remission — were randomly assigned to indefinite maintenance every 3 months until disease progression or re-treatment with rituximab upon progression.

We found no benefit with maintenance compared to re-treating as necessary (Kahl 2011) and confirmed what other studies suggested — that patients may go 3 years or beyond with only 4 doses of rituximab and not experience recurrence. For patients with higher tumor burden FL who are symptomatic and need therapy, the PRIMA study indicated a benefit with rituximab maintenance after rituximab/chemotherapy (Salles 2011). These 2 are the highest-impact data sets that have emerged in this tumor type.

DR LOVE: Many investigators have told me that the findings of the control arm of the RESORT trial with 4 doses of rituximab were so impressive that they are now less likely to use watch and wait for patients with low tumor burden FL. Any thoughts?

DR WILLIAMS: I expect over time we will see that trend. In my practice, for asymptomatic patients with low tumor burden FL I typically discuss watch and wait and try to determine the pace of the disease. If patients are comfortable with that and prefer to be followed without treatment, that's fine. If they are more secure in proceeding with treatment, however, 4 doses of rituximab without maintenance is justified by the Phase III data, and the hope is that, particularly for older patients, chemotherapy may be delayed or not needed.

DR LOVE: What about the clinical practice issue of maintenance rituximab for patients with high tumor burden who receive rituximab/chemotherapy up front?

DR WILLIAMS: This approach has been widely adopted, and I believe maintenance for 2 years after induction is reasonable and an important option for discussion.

Track 5

DR LOVE: Continuing on in terms of indolent lymphoma — anything new regarding radioimmunotherapy (RIT)?

DR WILLIAMS: Yttrium-90 ibritumomab tiuxetan and ^{131}I-tositumomab are the 2 most active single treatments in relapsed FL. We use them in older patients, and you can complete treatment in 1 week. Response rates are high, and some patients experience durable responses. RIT has also been used as consolidation. Mitchell Smith recently published the results of an ECOG trial in mantle-cell lymphoma (MCL) with 4 doses of R-CHOP followed by RIT (Smith 2012), and it's safe and effective. How it compares to other approaches, such as rituximab maintenance, is unknown.

Based on the data from the FIT trial, it is also useful as consolidation for patients with FL who have achieved either a complete or a partial remission (Hagenbeek 2010). It's also being tested as whole body radiation therapy by using high doses of RIT for patients who are heading to autologous stem cell transplant (ASCT) (NCT00110071).

The Phase III SWOG-S0016 study evaluating R-CHOP versus CHOP followed by ^{131}I-tositumomab reported similar outcomes between the 2 arms (Press 2011), but

perhaps with additional maintenance one can build on the response and provide patients with better durability of remission.

Tracks 12-14

DR LOVE: Let's talk about MCL, beginning with your thoughts on the small proportion of patients who can be observed off treatment initially. What is your clinical experience?

DR WILLIAMS: A lot of patients come in having read about and having been told that they must proceed to therapy — that MCL is a bad disease. So it takes education to talk them down, and I see a considerable amount of second opinions and consults.

One man had received 3 opinions before he saw me. One physician had recommended R-CHOP, and 2 had recommended transplant — one immediate transplant after induction and the other planning transplant but potentially deferring it. However, the disease was clearly indolent. He'd been aware of some nodes that hadn't changed much for more than 2 years, had a low Ki-67 score and was asymptomatic. He was in his late sixties, healthy and active, so I recommended observation. After 2 years he developed disease progression and recently completed 1 course of bendamustine/rituximab (BR). He's in complete remission now, 4 years since we met.

DR LOVE: What are some of the key ongoing clinical trials in MCL?

DR WILLIAMS: We don't have a standard therapy for MCL, but we have a variety of active approaches. Some controversy surrounds how best to induce patients and how to sequence therapies, so clinical trials are a high priority.

Two trials in the United States are important now (1.1). One is the ECOG-E1411 study, predominantly for older patients and those who are not transplant candidates, and what we're testing in this group is a BR backbone. The patients receive either BR or bendamustine/bortezomib/rituximab induction therapy, and then they are randomly assigned to 1 of 2 different maintenance options, either rituximab alone or the R-squared regimen — lenalidomide and rituximab (1.1). For transplant-eligible patients, the SWOG-S1106 trial will compare BR to R-hyper-CVAD with methotrexate and cytarabine (Ara-C). Patients with responses will then undergo ASCT.

1.1

Phase II Intergroup Studies for Patients with Previously Untreated Mantle-Cell Lymphoma

Trial identifier	N	Age of patients	Treatment arms
SWOG-S1106 NCT01412879	180	≤65 years	• R-hyper-CVAD/MTX/Ara-C → ASCT • BR → ASCT
ECOG-E1411 NCT01415752	332	≥60 years	• BR → R • BVR → R • BR → LR • BVR → LR

MTX = methotrexate; ASCT = autologous stem cell transplant; B = bendamustine; R = rituximab; V = bortezomib; L = lenalidomide

www.clinicaltrials.gov. Accessed November 15, 2012.

Track 16

DR LOVE: What do we know about rituximab maintenance in MCL, and how do you approach this issue in practice?

DR WILLIAMS: The European Mantle-Cell Network has been extremely effective in conducting Phase III trials. The nontransplant study in older patients was recently reported in *The New England Journal of Medicine* by Dr Kluin-Nelemans (1.2).

They evaluated R-CHOP versus rituximab/fludarabine/cyclophosphamide (R-FC) induction followed by either interferon or rituximab maintenance and found that R-FC was more toxic and less efficacious than R-CHOP. For patients receiving R-CHOP, the benefit was clear in terms of duration of response and survival with rituximab maintenance versus interferon until progression.

With that we've adapted rituximab maintenance after induction therapy in our nontransplant patients. I'm using it both for patients who receive R-CHOP and for patients who've received BR induction. ■

1.2 **Rituximab Maintenance versus Interferon Alpha for Elderly Patients with Mantle-Cell Lymphoma: Efficacy and Toxicity Among Patients Responding to R-CHOP Induction**

Response	Rituximab	Interferon	*p*-value
Median remission duration	Not reached	23 mo	<0.001
Four-year overall survival rate	87%	63%	0.005
Select Grade 3 and 4 toxicities			
Leukocytopenia	4%	18%	—
Lymphocytopenia	27%	46%	—

Kluin-Nelemans HC et al. *N Engl J Med* 2012;367(6):520-31.

SELECT PUBLICATIONS

Hagenbeek A et al. **90Y-ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, Phase III First-Line Indolent Trial (FIT) in 414 patients.** *Proc ASH* 2010;**Abstract 594**.

Kahl BS et al. **Results of Eastern Cooperative Oncology Group protocol E4402 (RESORT): A randomized Phase III study comparing two different rituximab dosing strategies for low tumor burden follicular lymphoma.** *Proc ASH* 2011;**Abstract LBA-6**.

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

Press O et al. **A Phase III randomized Intergroup trial (SWOG S0016) of CHOP chemotherapy plus rituximab vs CHOP chemotherapy plus iodine-131-tositumomab for the treatment of newly diagnosed follicular non-Hodgkin's lymphoma.** *Proc ASH* 2011;**Abstract 98**.

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.

Smith MR et al. **Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by yttrium-90-ibritumomab tiuxetan in untreated mantle-cell lymphoma: Eastern Cooperative Oncology Group study E1499.** *J Clin Oncol* 2012;30(25):3119-26.