INTERVIEW

Michael E Williams, MD, ScM

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Tracks 1-16

Select Excerpts from the Interview

Tracks 1-3, 7

DR LOVE: Would you discuss the use of ibrutinib for patients with relapsed chronic lymphocytic leukemia (CLL)?

DR WILLIAMS: Ibrutinib inhibits the Bruton tyrosine kinase (BTK) and has a direct antitumor effect. It also has effects on the tumor microenvironment. With treatment lymphocytes from the spleen, lymph nodes and bone marrow rapidly mobilize into the peripheral blood, resulting in lymphocytosis that is temporary.

The overall response rate to ibrutinib is quite high. However, complete responses are usually observed in a small proportion of patients. A subgroup of patients who develop persistent lymphocytosis have a similar progression-free survival to that of those who experience traditional responses (Woyach 2014a). Patients with prolonged lymphocytosis do not have resistance mutations. Those who experience relapse on ibrutinib, however, have mutations in the BTK binding site or in a downstream molecular target of BTK that mediates true ibrutinib resistance (Woyach 2014b).

DR LOVE: How would you care for patients with CLL progressing on ibrutinib?

DR WILLIAMS: That question is currently being investigated. I have not had any patients develop disease progression while receiving ibrutinib, but I would consider another B-cell receptor inhibitor, such as idelalisib, or obinutuzumab with or without chlorambucil or the lenalidomide/rituximab combination. A clinical trial of an agent like ABT-199 is another option.

DR LOVE: In what situations, if any, would you consider ibrutinib in the front-line setting for patients with CLL?

DR WILLIAMS: We have not yet used ibrutinib in the front-line setting except for patients who have deletion 17p. Ongoing trials are investigating ibrutinib alone or in combination with immunotherapy or chemoimmunotherapy for patients with previously untreated CLL.

Tracks 5, 13

DR LOVE: What is known about the recently approved agent idelalisib for relapsed CLL?

DR WILLIAMS: Idelalisib is a PI3Kδ inhibitor that is active in relapsed CLL. A recent study demonstrated that for patients with heavily pretreated disease the combination of idelalisib and rituximab elicited an overall response rate of 81% versus 13% with rituximab alone. Patients who received the combination had an overall survival advantage compared to those on the rituximab arm (Furman 2014; [1.1]).

The combination of an anti-CD20 antibody with idelalisib or ibrutinib might yield faster and deeper responses. We and others are investigating combinations of B-cell receptor inhibitors to enable a shorter course of therapy and deep responses.

DR LOVE: The FDA also granted accelerated approval for single-agent idelalisib for the treatment of relapsed follicular lymphoma (FL) or relapsed small lymphocytic leukemia in patients who had received at least 2 prior systemic therapies. What are your thoughts on using the agent in these settings?

DR WILLIAMS: Idelalisib has demonstrated single-agent activity in indolent non-Hodgkin lymphoma (NHL). The study that led to its FDA approval was a single-arm study that enrolled patients with heavily pretreated, relapsed indolent NHL. Patients had received a median of 4 prior therapies and their disease was refractory to both rituximab and an alkylating agent. The complete response rate was only 6%, but approximately half the patients achieved a partial response. Patients who responded to the drug responded quickly, by 1 to 2 months (Gopal 2014).

A higher incidence of diarrhea has been noted with idelalisib compared to ibrutinib. Some cases of pneumonia, liver enzyme elevations and late-onset colitis have been

observed. It may be that immunomodulatory effects lead to pneumonitis or colitis in some patients, and this is important to watch for.

1.1

Phase III Study Comparing Idelalisib and Rituximab to Rituximab Alone for Relapsed Chronic Lymphocytic Leukemia

Efficacy	Idelalisib + rituximab (n = 110)	Rituximab (n = 110)	HR	*p*-value
Overall response rate	81%	13%	NR*	<0.001
Median progression-free survival	Not reached	5.5 mo	0.15	<0.001
Overall survival rate at 12 months	92%	80%	0.28	0.02

Select adverse events (any grade)	Idelalisib + rituximab (n = 110)	Rituximab (n = 107)
Pyrexia	29%	16%
Fatigue	24%	27%
Diarrhea	19%	14%
Pneumonia	6%	8%
Febrile neutropenia	5%	6%
ALT or AST elevation	35%	19%

* Odds ratio = 29.92; HR = hazard ratio; NR = not reported

Furman R et al. *N Engl J Med* 2014;370(11):997-1007.

Track 6

DR LOVE: Would you discuss the recently approved anti-CD20 antibody obinutuzumab for previously untreated CLL?

DR WILLIAMS: A recent study comparing the Type II antibody obinutuzumab and chlorambucil to rituximab and chlorambucil for elderly patients with coexisting morbidities demonstrated a benefit with the obinutuzumab combination for previously untreated CLL. The obinutuzumab arm had higher response rates and prolonged progression-free survival compared to the rituximab arm (Goede 2014).

A couple of reasons may explain why obinutuzumab demonstrated such an impressive benefit. One is that it induces direct cell death. It also exhibits enhanced antibody-dependent cellular cytotoxicity, which may be important because of the relatively low density of CD20 in CLL compared to other B-cell cancers.

In our practice we use obinutuzumab and chlorambucil as front-line therapy for older patients who are not candidates for bendamustine with rituximab (BR). I believe that a rationale is building for making obinutuzumab the preferred antibody for CLL. Ongoing studies are investigating obinutuzumab in combination with other agents.

Tracks 10-12

DR LOVE: Let's talk about mantle-cell lymphoma (MCL). How do you approach initial therapy for elderly patients?

DR WILLIAMS: I would consider BR followed by rituximab maintenance. We don't have data with maintenance specifically after BR, but with such data pending I would use rituximab for 2 years based on findings with other regimens. In terms of new approaches, preliminary data from a study investigating lenalidomide and rituximab for mostly older patients with newly diagnosed MCL demonstrated a nearly 90% response rate and a high rate of complete remissions. The regimen was also well tolerated. This is an exciting approach, and if the data hold up we may be moving toward less toxic regimens that yield deep, durable responses (Ruan 2013).

DR LOVE: Would you discuss the recent ASCO presentation comparing R-CHOP to bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) for transplant-ineligible patients with newly diagnosed MCL?

DR WILLIAMS: This was a Phase III study with approximately 500 patients with MCL. It compared standard R-CHOP to VR-CAP, which is R-CHOP in which the vincristine is substituted with bortezomib. The bortezomib was administered intravenously because that's the way it was used when the study was designed. The results demonstrated a significant increase in complete response rates and improvement in the duration of response with VR-CAP (Cavalli 2014; [1.2]).

A higher rate of thrombocytopenia was observed in the VR-CAP arm, including Grade 3 and 4 thrombocytopenia, some of which required platelet transfusions. Whether that can be reduced by subcutaneous administration or a different schedule of bortezomib must be investigated. But the results make an argument for using bortezomib in the front-line treatment of MCL.

Editor's note: Subsequent to this interview, on October 10, 2014 the FDA approved VR-CAP for patients with previously untreated MCL.

DR LOVE: Would you also comment on the recently approved agents ibrutinib and lenalidomide for relapsed MCL?

1.2

Results of a Phase III Trial of R-CHOP versus Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (VR-CAP) for Newly Diagnosed, Transplant-Ineligible Mantle-Cell Lymphoma

Efficacy	R-CHOP	VR-CAP	HR	*p*-value
Overall response rate (n = 228, 229) CR + CRu	90% 42%	92% 53%	NR NR	0.275 0.007
Median duration of response (n = 228, 229)	15.1 mo	36.5 mo	—	—
Median progression-free survival (n = 244, 243)	14.4 mo	24.7 mo	0.63	<0.001
Median overall survival* (n = 244, 243)	56.3 mo	Not reached	0.8	0.173
Select adverse events (Grade ≥3)	**R-CHOP** (n = 242)		**VR-CAP** (n = 240)	
Neutropenia	67%		85%	
Thrombocytopenia	6%		57%	
Febrile neutropenia	14%		15%	
Peripheral neuropathy	4.1%		7.5%	

Median follow-up: 40 mo; * Data not mature
HR = hazard ratio; NR = not reported; CR = complete response; CRu = unconfirmed CR

Cavalli F et al. *Proc ASCO* 2014;**Abstract 8500**.

DR WILLIAMS: We generally recommend ibrutinib as next-line therapy for patients with MCL who have experienced relapse or whose disease is refractory to chemoimmunotherapy. Because of the convenience of administration and the side-effect profile of ibrutinib, we prefer it in the relapsed setting.

I have observed deep and durable responses with lenalidomide. That agent was approved by the FDA for patients with relapsed MCL on the basis of a study led by Dr Andre Goy in which I participated. The overall response rate in that heavily pretreated population was only approximately 30%, but the responses are durable (Goy 2013).

Track 14

DR LOVE: What are your thoughts on the results of the ECOG-E4402 RESORT trial evaluating maintenance therapy with rituximab versus re-treatment at disease progression for low tumor burden FL?

DR WILLIAMS: I co-chaired the RESORT trial with Brad Kahl, who led the study. Patients with asymptomatic, low tumor burden FL were enrolled. They received 4 doses of rituximab, and those who responded were assigned to either maintenance rituximab or re-treatment at disease progression. The re-treatment approach was as effective as maintenance rituximab and involved much less therapy. No difference was observed in quality of life between the 2 arms (Kahl 2014). Approximately one third of the patients are still in remission at 5 years, so responses are durable.

A recent study by Ardeshna and colleagues compared "watch and wait" to rituximab monotherapy and suggested that rituximab monotherapy should be considered a standard approach for patients with low tumor burden FL (Ardeshna 2014). I tell such patients that although a watch-and-wait approach is reasonable, treatment with 4 doses of rituximab should be a consideration. If they are in the majority who achieve a good response, I monitor them without maintenance and then if they experience disease progression I recommend 4 more doses of rituximab. ■

SELECT PUBLICATIONS

Ardeshna K et al. **Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: An open-label randomised phase 3 trial.** *Lancet Oncol* 2014;15(4):424-35.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.

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

Goy A et al. **Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study.** *J Clin Oncol* 2013;31(29):3688-95.

Kahl BS. **Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: Eastern Cooperative Oncology Group protocol e4402.** *J Clin Oncol* 2014;32(28):3096-102.

Ruan J et al. **Combination biologic therapy without chemotherapy as initial treatment for mantle cell lymphoma: Multi-center Phase II study of lenalidomide plus rituximab.** *Proc ASH* 2013;**Abstract 247**.

Woyach JA et al. **Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy.** *Blood* 2014a;123(12):1810-7.

Woyach JA et al. **Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib.** *N Engl J Med* 2014b;370(24):2286-94.