INTERVIEW

Christopher Flowers, MD, MS

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Tracks 1-17

Select Excerpts from the Interview

Tracks 14-15

DR LOVE: What are your thoughts on the AETHERA trial in Hodgkin lymphoma (HL) and brentuximab vedotin consolidation therapy after autologous transplant?

DR FLOWERS: The data are provocative (Moskowitz 2015; [1.1]). The AETHERA trial demonstrated a benefit in PFS for patients who went on to post-transplant consolidation therapy after autologous peripheral blood stem cell transplant. It is not something that we've applied regularly to our patients with HL who experience relapse after initial therapy, but I believe it merits careful consideration, and we're contemplating applying it in our practice as a whole.

DR LOVE: Would you discuss the available data with anti-PD-1 antibodies in HL?

1.1

AETHERA: Results of a Phase III Trial of Brentuximab Vedotin (BV) as Consolidation Therapy After Autologous Stem Cell Transplant in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

	Per independent review		Per investigator	
Progression-free survival (PFS)	BV (n = 165)	Placebo (n = 164)	BV (n = 165)	Placebo (n = 164)
Median PFS	42.9 mo	24.1 mo	—	16.0 mo
Two-year PFS rate	63%	51%	65%	45%
Hazard ratio (*p*-value)	0.57 (0.0013)		0.50 (Not reported)	
	BV (n = 167)		**Placebo (n = 160)**	
Select adverse events	Any grade	Grade ≥3	Any grade	Grade ≥3
Peripheral sensory neuropathy	56%	10%	16%	1%
Neutropenia	35%	29%	12%	10%
Fatigue	24%	2%	18%	3%
Nausea	22%	3%	8%	0%
Diarrhea	20%	2%	10%	1%
Pyrexia	19%	2%	16%	0%
Vomiting	16%	2%	7%	0%

Moskowitz CH et al; AETHERA Study Group. *Lancet* 2015;385(9980):1853-62.

DR FLOWERS: The data are exciting. Two back-to-back presentations at ASH evaluated pembrolizumab and nivolumab respectively (Moskowitz 2014; Ansell 2015). We've also been involved in one of the follow-up nivolumab trials, and PD-1 inhibition for patients with relapsed HL appears to be an active approach. On the basis of those findings some patients with relapsed disease have been able to receive nivolumab outside of a clinical trial.

Of the patients we enrolled on the Phase II clinical trial of nivolumab, the majority have experienced response. The challenging question for that agent is, how long do we continue it? The way the trials are designed is that patients continue on therapy as long as they are experiencing response. Nivolumab appears to be an active agent with a high overall response rate. We have not observed any complete responses yet.

Tracks 2, 6

DR LOVE: Bortezomib was recently approved as up-front therapy for mantle-cell lymphoma (MCL). Would you discuss the data behind that approval and your take on it as well as other treatment options in this setting?

DR FLOWERS: Up-front treatment for MCL is more confusing than ever. R-CHOP is probably the one regimen that would be less likely to be used in the modern era. We now have data from a trial comparing R-CHOP to VR-CAP, in which bortezomib replaces vincristine from the traditional R-CHOP regimen. The results demonstrated benefits in terms of both response rate and progression-free survival (PFS) with VR-CAP compared to R-CHOP (Robak 2015; [1.2]).

1.2

LYM-3002: Results of a Phase III Trial of Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (VR-CAP) versus R-CHOP for Newly Diagnosed, Transplant-Ineligible Mantle-Cell Lymphoma

Efficacy	VR-CAP	R-CHOP	Hazard or risk ratio	*p*-value
Median progression-free survival (n = 243, 244)	24.7 mo	14.4 mo	0.63	<0.001
Median overall survival* (n = 243, 244)	NR	56.3 mo	0.80	0.173
Overall response rate (n = 229, 228)	92%	89%	1.03	—
Complete response	53%	42%	1.29	—
Median duration of response (n = 211, 204)	36.5 mo	15.1 mo	—	—

Select adverse events (Grade ≥3)	VR-CAP (n = 240)	R-CHOP (n = 242)
Neutropenia	85%	67%
Thrombocytopenia	57%	6%
Febrile neutropenia	15%	14%
Peripheral neuropathy	8%	4%

Median follow-up: 40 months; * Data not mature; NR = not reached

Robak T et al; LYM-3002 Investigators. *N Engl J Med* 2015;372(10):944-53.

We also have data from the Rummel trial comparing bendamustine and rituximab (BR) to R-CHOP, which reported improved PFS with BR in the subset of patients with MCL (Rummel 2013). In addition, data from Europe investigating R-CHOP followed by rituximab maintenance demonstrate benefit with that regimen compared to R-CHOP alone for those patients for whom autologous stem cell transplant (ASCT) or more aggressive therapies would not be considered (Kluin-Nelemans 2012).

So at this time administering R-CHOP alone as an up-front regimen is not a viable option. I believe that for patients for whom you're not considering ASCT, other options are now available.

DR LOVE: How are you currently sequencing bortezomib, lenalidomide and ibrutinib for patients who experience relapse after up-front therapy?

DR FLOWERS: That's a complicated discussion to have with patients. I tend to administer the most effective and most active agent first, which is ibrutinib. It has the highest complete response rate and overall response rate and produces a prolonged PFS. We have substantial data to suggest a role for lenalidomide among patients who have experienced relapse after bortezomib, based on the EMERGE trial that led to the approval of that agent in MCL (Goy 2015). We don't know how well lenalidomide works after ibrutinib or how bortezomib works after ibrutinib. Sequencing in that way can be more challenging.

Tracks 7-8

DR LOVE: Would you discuss the efficacy of ABT-199, now known as venetoclax, in MCL and other B-cell lymphomas? What is the rationale behind combining it with ibrutinib?

DR FLOWERS: Venetoclax is an inhibitor of Bcl-2. Bcl-2 is a protein commonly overexpressed in lymphoid cancers that inhibits apoptosis. Venetoclax helps chemotherapy push cells through that process.

Phase I data on the combination of BR and venetoclax show impressive response rates and tolerability for patients in a number of lymphoma subsets (de Vos 2014). In particular, it is quite active in follicular lymphoma (FL).

Preclinical data also suggest that the B-cell receptor inhibitor ibrutinib and venetoclax interact to help promote apoptosis, so that is compelling, and we hope to continue testing in a clinical trial (Cervantes-Gomez 2015). In MCL venetoclax appears to have meaningful single-agent activity.

DR LOVE: What is your take on the tumor lysis syndrome that occurs with venetoclax therapy?

DR FLOWERS: It is a serious issue. The management strategy for patients with low-grade lymphomas on the clinical trial with BR and for single-agent venetoclax in chronic lymphocytic leukemia is to admit all patients to the hospital for cycle 1, administer aggressive hydration and follow them closely for signs of tumor lysis syndrome.

For patients who experience tumor lysis syndrome with cycle 1, we continue to admit them for the subsequent therapy cycles as it continues to occur. The patients with lymphoma whom we admit for cycle 1 do not experience tumor lysis syndrome with aggressive hydration. And for subsequent cycles, they are able to tolerate the regimen as outpatients.

My hope is that eventually we'll be able to define better risk strata. Some patients will still be at high risk for tumor lysis syndrome and will need this process of admission, but I hope that we will be able to define many more patients who are at lower risk and administer all of their care in the outpatient setting. ■

SELECT PUBLICATIONS

Ansell SM et al. **PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.** *N Engl J Med* 2015;372(4):311-9.

Cervantes-Gomez F et al. **Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with ibrutinib in chronic lymphocytic leukemia.** *Clin Cancer Res* 2015;21(16):3705-15.

Davids MS, Letai A. **ABT-199: A new hope for selective BCL-2 inhibition.** *Cancer Cell* 2013;23(2):139-41.

de Vos S et al. **The BCL-2 inhibitor ABT-199 (GDC-0199) in combination with bendamustine and rituximab in patients with relapsed or refractory non-Hodgkin's lymphoma.** *Proc ASH* 2014;**Abstract 1722**.

Goy A et al. **Longer-term follow-up and outcome by tumour cell proliferation rate (Ki-67) in patients with relapsed/refractory mantle cell lymphoma treated with lenalidomide on MCL-001 (EMERGE) pivotal trial.** *Br J Haematol* 2015;170(4):496-503.

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

Moskowitz CH et al. **PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a Phase 1b study (KEYNOTE-013).** *Proc ASH* 2014;**Abstract 290**.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial.** *Lancet* 2013;381(9873):1203-10.