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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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OVERVIEW OF ACTIVITY

The treatment of hematologic cancers remains a challenge for many healthcare professionals despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given individual requires careful consideration of patient-specific characteristics, physician experience and available health system resources. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments and expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of evidence-based and current therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Customize the selection of systemic therapy for patients with newly diagnosed and progressive mantle-cell lymphoma, recognizing the addition of recently FDA-endorsed options for these patients.
- Develop a rational plan to incorporate B-cell receptor signaling inhibitors and novel CD20 monoclonal antibodies into the treatment of chronic lymphocytic leukemia and other B-cell neoplasms.
- Incorporate newly approved treatments, and consider the potential role of promising investigational agents in the management of relapsed or refractory multiple myeloma.
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients.
- Reevaluate your current treatment approach for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data.
- Recognize the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment.

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INTERVIEW

Christopher Flowers, MD, MS

Dr Flowers is Associate Professor of Hematology and Medical Oncology at the Emory School of Medicine Winship Cancer Institute in Atlanta, Georgia.

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Select Excerpts from the Interview

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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.

INTERVIEW

Keith Stewart, MB, ChB

Dr Stewart is Carlson and Nelson Endowed Director of the Center for Individualized Medicine and Vasek and Anna Maria Polak Professor of Cancer Research at the Mayo Clinic in Minnesota, Arizona and Florida.

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on the use of elotuzumab in the treatment of multiple myeloma (MM)?

DR STEWART: Elotuzumab is not that active as a single agent, but when used in combination with lenalidomide it has dramatically better results. ELOQUENT-2 was a study that compared the combination of elotuzumab with lenalidomide/dexamethasone to lenalidomide/dexamethasone in patients with MM who had received 1 to 3 prior therapies. The results showed an improvement in PFS of approximately 5 months on the elotuzumab arm (Lonial 2015a; [2.1]).

These results should lead to the approval of elotuzumab in combination with lenalidomide in the relapsed setting. A trial in patients with newly diagnosed disease and data in combination with bortezomib are expected soon. Once these data become available, one would expect to see elotuzumab used more broadly and in an earlier setting.

2.1

ELOQUENT-2: Results of a Phase III Study of Lenalidomide/ Dexamethasone (Len/Dex) with or without Elotuzumab (Elo) for Patients with Relapsed or Refractory Multiple Myeloma

Efficacy	Elo + len/dex (n = 321)	Len/dex (n = 325)	Hazard ratio	*p*-value
Median PFS	19.4 months	14.9 months	0.7	<0.001
ORR	79%	66%	NR	<0.001
	Elo + len/dex (n = 318)		Len/dex (n = 317)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Lymphocytopenia	99%	77%	98%	49%
Neutropenia	82%	34%	89%	44%
Fatigue	47%	8%	39%	8%
Infections	81%	28%	74%	24%

PFS = progression-free survival; ORR = overall response rate; NR = not reported

Lonial S et al. *N Engl J Med* 2015a;373(7):621-31; Lonial S et al. *Proc ASCO* 2015;**Abstract 8508**.

DR LOVE: What is known about the anti-CD38 monoclonal antibody daratumumab?

DR STEWART: The Phase II SIRIUS trial of daratumumab monotherapy in patients with refractory MM that was presented at ASCO 2015 reported that it had single-agent activity in approximately 30% of patients (Lonial 2015b; [2.2]). In combination with other agents, it's likely to be at least additive, if not synergistic. The results reported at ASCO will hopefully lead to approval of this agent in refractory MM. This drug is also being investigated in the Phase III setting, both in relapsed and newly diagnosed disease.

2.2

SIRIUS: Results of a Phase II Study of Daratumumab Monotherapy for Patients with 3 or More Lines of Prior Therapy or Double-Refractory Multiple Myeloma

Efficacy	Daratumumab (n = 106)	
Overall response rate	29%	
Median progression-free survival	3.7 months	
Select adverse events	**All grades**	**Grade 3 or 4**
Fatigue	40%	3%
Anemia	33%	24%
Thrombocytopenia	26%	25%
Neutropenia	23%	14%

Lonial S et al. *Proc ASCO* 2015b;**Abstract LBA8512**.

Tracks 3-8

DR LOVE: Would you discuss the results of the Phase III ASPIRE and ENDEAVOR trials evaluating carfilzomib in relapsed MM?

DR STEWART: ASPIRE was a large Phase III trial that evaluated the addition of carfilzomib to lenalidomide/dexamethasone (CRd). The PFS was 26.3 months on the carfilzomib arm — the best PFS that's been reported in this patient population — versus 17.6 months with lenalidomide/dexamethasone alone, which was impressive. The complete response rate was 3 times as high with the addition of carfilzomib (Stewart 2015; [2.3]). The overall survival trended in favor of the 3-drug regimen. But most astonishing to me was that the global quality of life was improved with the 3-drug regimen. It speaks to the power of deep responses and the well-being of knowing that the disease is well controlled.

The Phase III ENDEAVOR trial evaluated carfilzomib versus bortezomib in combination with dexamethasone in patients with relapsed MM. This was a real-life trial with most patients having received prior bortezomib therapy. The dose of carfilzomib was 56 mg/m^2, which is double the FDA-approved dose. It was surprising how positive the data were in favor of the carfilzomib arm in terms of response rate, depth of response and particularly the improvement in PFS (Dimopoulos 2015; [2.4]).

Patients have to come in 6 days a month when receiving carfilzomib. We also see a tradeoff in terms of toxicity. With carfilzomib less neuropathy occurs compared to with bortezomib, but more adverse effects in the cardiovascular and renal systems occur with carfilzomib.

Both of these studies cement the role of carfilzomib at first or second relapse and should result in more widespread approval of carfilzomib. These trials should also encourage the use of carfilzomib in an earlier setting and suggest that treatment should continue for an extended period of time. In my practice, I usually combine carfilzomib with cyclophosphamide or pomalidomide in the relapsed setting.

DR LOVE: Do you believe there is cardiac toxicity associated with carfilzomib?

DR STEWART: A small percent of patients receiving carfilzomib may experience a syndrome that resembles heart failure with fluid retention, shortness of breath and edema.

2.3

ASPIRE: Interim Results of a Phase III Trial of Carfilzomib/Lenalidomide/Dexamethasone (CRd) versus Rd in Relapsed Multiple Myeloma

Efficacy	CRd (n = 396)	Rd (n = 396)	Hazard ratio	*p*-value
Median PFS	26.3 mo	17.6 mo	0.69	0.0001
ORR	87.1%	66.7%	—	<0.001
CR or better	31.8%	9.3%	—	<0.001
VGPR or better	69.9%	40.4%	—	<0.001
	CRd (n = 392)		Rd (n = 389)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Dyspnea	19.4%	2.8%	14.9%	1.8%
Hypertension	14.3%	4.3%	6.9%	1.8%
Acute renal failure	8.4%	3.3%	7.2%	3.1%
Cardiac failure	6.4%	3.8%	4.1%	1.8%

PFS = progression-free survival; ORR = overall response rate; CR = complete response; VGPR = very good partial response

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

2.4

ENDEAVOR: Results of a Phase III Study Evaluating Carfilzomib/Dexamethasone (Cd) versus Bortezomib/Dexamethasone (Vd) in Relapsed Multiple Myeloma

Efficacy	Cd (n = 464)	Vd (n = 465)	Hazard ratio	*p*-value
Median PFS	18.7 mo	9.4 mo	0.53	<0.0001
ORR	77%	63%	—	<0.0001
CR or better	13%	6%	—	<0.0001
VGPR or better	54%	29%	—	<0.0001
	Cd (n = 463)		Vd (n = 456)	
Select adverse events	All grades	Grade ≥3	All grades	Grade ≥3
Dyspnea	29%	5%	13%	2.2%
Hypertension	25%	9%	9%	3%
Peripheral neuropathy	9%	1.3%	27%	5%
Acute renal failure	8%	4%	5%	3%
Cardiac failure	8%	5%	6%	1.8%

PFS = progression-free survival; ORR = overall response rate; CR = complete response; VGPR = very good partial response

Dimopoulos MA et al. *Proc ASCO* 2015;**Abstract 8509**.

In the ASPIRE trial, in which the approved dose of carfilzomib was used, the toxicity profile was favorable with the 3-drug combination. The ENDEAVOR trial demonstrated a small increase in cardiac and renal events. But in both of the Phase III trials, no effect on death or discontinuation of drug was evident.

The treating physician must be aware of the potential for hypertension and dyspnea, especially in the first couple weeks of treatment. It can be managed with dose reductions, regulating fluid administration and diuretics. Carfilzomib should preferably be avoided in patients with a history of heart failure or renal failure.

DR LOVE: What is known about carfilzomib in the front-line setting?

DR STEWART: A trial investigating the 4-drug combination of carfilzomib, cyclophosphamide, thalidomide and dexamethasone in patients with newly diagnosed MM demonstrated good efficacy. At ASCO 2015, an update was presented on the use of CRd in patients with newly diagnosed MM, and the results were impressive. The response rate was 100% if patients remained on the combination. When CRd is combined with transplant, complete response rates are in the 60% to 80% range, which is remarkable (Zimmerman 2015). Because CRd is well tolerated, patients can be kept on therapy for a longer time, resulting in deep responses and longer survival.

Tracks 9, 11

DR LOVE: Would you discuss the potential future role of the oral proteasome inhibitors ixazomib and oprozomib in MM?

DR STEWART: Ixazomib is in Phase III testing in combination with lenalidomide/dexamethasone for patients with newly diagnosed and relapsed MM and in the maintenance setting. Recent data with ixazomib have demonstrated high response rates with about 20% complete remissions. Ixazomib is well tolerated overall. Side effects include

rash, neuropathy, thrombocytopenia and gastrointestinal (GI) toxicity, but they are manageable. Carfilzomib and bortezomib delivered systemically are slightly more potent in the short term. But ixazomib may catch up with time because it can be conveniently administered for longer periods.

Oprozomib is also an active agent and is being investigated in Phase II studies. It is associated with upper GI toxicity that can be difficult to tolerate, particularly long term. The new formulation and routine administration of antiemetics have helped. Oprozomib may find its place, but I believe it won't have the impact that ixazomib will.

Track 12

DR LOVE: What are your thoughts on panobinostat, which was recently approved for MM?

DR STEWART: The Phase III PANORAMA 1 trial comparing panobinostat with bortezomib/dexamethasone to bortezomib/dexamethasone in patients with relapsed or refractory MM showed a significantly improved PFS from 8 months to 12 months. Panobinostat was ultimately approved in combination with bortezomib and dexamethasone for patients with MM who have received prior bortezomib and an immunomodulatory agent (San-Miguel 2014).

The concern has been the high frequency of adverse events, which include thrombocytopenia, fatigue and diarrhea that can sometimes be severe. At ASCO 2015, a study showed panobinostat in combination with carfilzomib was much better tolerated than the bortezomib combination previously reported (Berdeja 2015). In my practice I would reserve panobinostat for younger patients with relapsed MM who are at high risk.

Track 13

DR LOVE: Pomalidomide has been approved for more than 2 years now. How do you integrate it into your practice?

DR STEWART: Pomalidomide is a potent drug that can be combined with almost any other agent. Neutropenia is a bit more common than it is with the other 2 agents in this class. One still has to be concerned about deep venous thrombosis as well.

Many oncologists tend to use pomalidomide as an agent of last resort, but it should be considered as an option earlier in the treatment algorithm. My own bias is to use it either alone or in combination with carfilzomib early on in the treatment course, even at first relapse or for patients who cannot tolerate lenalidomide. It's well tolerated in the majority of patients. ■

SELECT PUBLICATIONS

Berdeja J et al. **A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM).** *Proc ASCO* 2015;**Abstract 8513**.

San-Miguel JF et al. **Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial.** *Lancet Oncol* 2014;15(11):1195-206.

Zimmerman TM et al. **Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM).** *Proc ASCO* 2015;**Abstract 8510**.

INTERVIEW

Jorge E Cortes, MD

Dr Cortes is DB Lane Cancer Research Distinguished Professor for Leukemia Research and Deputy Chairman and Section Chief of AML and CML in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-14

Track 1 SAL-SORAML: A Phase II study of sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia (AML)

Track 2 Incidence of hand-foot syndrome and other common side effects with sorafenib in AML

Track 3 Interim report of a Phase I/II trial of quizartinib with azacitidine or low-dose cytarabine in patients with FLT3-ITD-mutated myeloid leukemias

Track 4 Role of ruxolitinib in patients with myeloproliferative neoplasms

Track 5 Monitoring for splenomegaly and symptom resolution in patients with myelofibrosis (MF) receiving ruxolitinib

Track 6 PERSIST-1: A Phase III study of the novel JAK2 inhibitor pacritinib versus best available therapy in primary MF, postpolycythemia vera MF or postessential thrombocythemia MF

Track 7 Use of ruxolitinib in patients with symptomatic, earlier-stage MF

Track 8 Clinical experience with ruxolitinib in polycythemia vera

Track 9 Arsenic trioxide and ATRA in the treatment of acute promyelocytic leukemia (APL)

Track 10 Management of high-risk APL

Track 11 Choice of first-line tyrosine kinase inhibitor (TKI) therapy in chronic myeloid leukemia (CML)

Track 12 Indications to change TKI therapy in patients with CML

Track 13 Perspective on discontinuation of TKI therapy for patients with CML and prolonged major molecular responses

Track 14 Efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase CML

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the results of the Phase II SORAML study of sorafenib or placebo in combination with standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)?

DR CORTES: In this study, regardless of whether the patient's disease harbored FLT3-ITD mutations or not, they were randomly assigned to receive chemotherapy alone or with sorafenib. Sorafenib was administered during induction, consolidation and in the maintenance phase.

For the overall population, a benefit was noted in event-free survival in favor of sorafenib (Rollig 2014). This is interesting because, as far as we know, sorafenib doesn't have much of a role, certainly not as a single agent, in patients without FLT3-ITD

mutations. So this result is puzzling and cannot be explained by the benefit that was seen in the subset of patients with FLT3-ITD mutations because it's a relatively small percent of patients. More research is required to understand how sorafenib helps patients without the mutation.

DR LOVE: Would you also comment on the results of the Phase I/II trial of quizartinib and azacitidine or low-dose cytarabine for patients with FLT3-ITD mutation-positive myeloid leukemias?

DR CORTES: That is an interesting study because it is evaluating whether quizartinib can be beneficial, particularly in the older patient population. The response rate was high at about 70% (Borthakur 2014). Perhaps more impressive were event-free survival and the duration of response. Responses to FLT3-ITD inhibitors as single agents tend to be transient, but when you combine quizartinib with either one of these two agents, you see durable responses. Also, the addition of quizartinib produced little toxicity, with the main toxicity being QTc prolongation. Because the study used low-dose/low-intensity chemotherapy, the regimens ended up being well tolerated.

Tracks 4-6

DR LOVE: What is your perspective on the role of ruxolitinib in patients with myeloproliferative neoplasms outside of a trial setting?

DR CORTES: When ruxolitinib was initially approved, we had a fixed dose to use. Further studies have evaluated different doses, and we've learned that perhaps doses as low as 10 mg can be appropriate, especially when factors such as lower platelet counts come into play. So I believe this demonstrates that ruxolitinib is valuable. It can help many patients, including patients who do not meet the criteria for a clinical trial. As with all the drugs, one needs to monitor the patient.

DR LOVE: For a typical symptomatic patient with myelofibrosis (MF) and splenomegaly, what are your expectations if ruxolitinib is administered?

DR CORTES: Ruxolitinib typically improves symptoms, including splenomegaly, rapidly. Usually, within the first few weeks, you will see significant improvement. I don't discontinue treatment if I've seen no improvements within a month, as some patients have a more subtle and delayed response.

We tend to ask patients if they feel better now than before ruxolitinib therapy was initiated. We must keep improvements in context in terms of how the drug is working for that patient. If the patient feels better, eats better and can walk more, that patient is benefiting and ruxolitinib is continued indefinitely. If we see no improvement, we discontinue therapy.

DR LOVE: What is known about the efficacy and safety of pacritinib in the management of myeloproliferative neoplasms?

DR CORTES: Pacritinib is a novel and selective inhibitor of JAK2 and FLT3. Compared to other JAK2 inhibitors, it may be associated with less myelosuppression. In terms of efficacy, we know that pacritinib works and yields improvements in spleen size and symptoms. In the results of the randomized Phase III PERSIST-1 trial of pacritinib versus best available therapy for patients with primary MF, postpolycythemia vera MF or postessential thrombocythemia MF, one of the key investigations was its efficacy among patients with low platelet counts (Mesa 2015; [3.1]).

PERSIST-1 demonstrated that pacritinib was significantly better than best available therapy. Pacritinib causes more GI toxicities than ruxolitinib. Although one should not compare across trials, it appears that pacritinib does not yield as great a benefit when compared to best available therapy as ruxolitinib does. ■

3.1

PERSIST-1: A Phase III Trial of Pacritinib (Pac) versus Best Available Therapy (BAT) in Primary Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	ITT population			Evaluable patients*		
	Pac (n = 220)	**BAT** (n = 107)	*p*-value	**Pac** (n = 168)	**BAT** (n = 85)	*p*-value
SVR ≥35%†	19.1%	4.7%	0.0003	25.0%	5.9%	0.0001
	n = 220	n = 107	*p*-value	n = 132	n = 71	*p*-value
TSS ≥50%†	24.5%	6.5%	<0.0001	40.9%	9.9%	<0.0001
Correlation of SVR with OS†	**Pac** (n = 220)			**BAT** (n = 106)		
SVR	Hazard ratio		*p*-value	Hazard ratio		*p*-value
≥10% and <20%	0.15		0.071	2.31		0.287
≥20%	0.26		0.014	NA		NA
Select AEs	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Diarrhea	53.2%	5.0%	0%	12.3%	0%	0%
Nausea	26.8%	0.9%	0%	6.6%	0%	0%
Anemia	22.3%	14.5%	2.3%	19.8%	12.3%	2.8%
Thrombocytopenia	16.8%	5.5%	6.4%	13.2%	6.6%	2.8%
Vomiting	15.9%	0.9%	0%	5.7%	0%	0%
Neutropenia	3.6%	0.5%	1.8%	1.9%	0.9%	0.9%

* Patients with both baseline and week 24 spleen assessment by MRI or CT

† At week 24

ITT = intent to treat; SVR = spleen volume reduction; TSS = total symptom score; OS = overall survival; NA = not applicable; AEs = adverse events

- SVR ≥35% in patients with baseline thrombocytopenia (ITT):
  - <50,000/uL: 22.9% (pac) versus 0% (BAT), $p = 0.0451$
  - <100,000/uL: 16.7% (pac) versus 0% (BAT), $p = 0.0086$
- Patients achieving transfusion independence: 25.7% (pac) versus 0% (BAT)

Mesa RA et al. *Proc ASCO* 2015;**Abstract LBA7006**.

SELECT PUBLICATIONS

Borthakur G et al. **The combination of quizartinib with azacitidine or low dose cytarabine is highly active in patients (pts) with FLT3-ITD mutated myeloid leukemias: Interim report of a Phase I/II trial.** *Proc ASH* 2014;**Abstract 388**.

Mesa RA et al. **Results of the PERSIST-1 phase III study of pacritinib (PAC) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2015;**Abstract LBA7006**.

Rollig C et al. **Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: Results from 267 patients treated in the randomized placebo-controlled SAL-Soraml trial.** *Proc ASH* 2014;**Abstract 6**.

Vannucchi A et al. **Ruxolitinib versus standard therapy for the treatment of polycythemia vera.** *N Engl J Med* 2015;372(5):426-35.

INTERVIEW

Gilles A Salles, MD, PhD

Dr Salles is Professor of Medicine at Université Claude Bernard and Head of the Hematology Department at the Hospices Civils in Lyon, France.

Tracks 1-17

Track 1 Results of the Phase III GADOLIN study of bendamustine with or without obinutuzumab in rituximab-refractory indolent NHL

Track 2 Effectiveness and tolerability of obinutuzumab compared to rituximab

Track 3 Efficacy and management of gastrointestinal toxicities in patients with FL receiving idelalisib

Track 4 Approach to first-line and maintenance therapy in FL

Track 5 Efficacy of the R^2 regimen (lenalidomide and rituximab) for newly diagnosed FL

Track 6 Second-line therapy options for patients with FL

Track 7 Incorporation of idelalisib into the treatment algorithm for FL

Track 8 Effectiveness of ibrutinib in FL

Track 9 Activity of venetoclax in FL and chronic lymphocytic leukemia (CLL)

Track 10 Efficacy of venetoclax and ibrutinib in patients with CLL and adverse cytogenetics

Track 11 Use of ibrutinib alone or in combination with rituximab or obinutuzumab as front-line therapy for CLL

Track 12 Management of atrial fibrillation in patients receiving ibrutinib

Track 13 Use of anticoagulants or antiplatelets in patients with CLL or indolent NHL receiving idelalisib

Track 14 First interim analysis of the Phase III LyMa trial: Rituximab maintenance versus watch and wait after 4 courses of R-DHAP → ASCT in younger patients with previously untreated MCL

Track 15 Use of bendamustine and ibrutinib for RR MCL

Track 16 Perspective on the Phase III LYM-3002 trial results: Bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) versus R-CHOP for newly diagnosed, transplant-ineligible MCL

Track 17 Approach to CD30 testing in T-cell and diffuse large B-cell lymphomas and the use of brentuximab vedotin

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the Phase III GADOLIN trial evaluating the combination of bendamustine and the type 2 anti-CD20 monoclonal antibody obinutuzumab for patients with rituximab-refractory indolent non-Hodgkin lymphoma (NHL)?

DR SALLES: This trial randomly assigned 413 patients with rituximab-refractory disease to single-agent bendamustine or bendamustine with obinutuzumab followed by obinutuzumab maintenance for 2 years. The median PFS on the bendamustine arm was approximately 15 months and was not reached on the bendamustine/obinutuzumab arm. These results are striking, with a hazard ratio of 0.55 (Sehn 2015; [4.1]). This

4.1

GADOLIN: Results of a Phase III Study of Bendamustine (B) with or without Obinutuzumab (O) in Rituximab-Refractory Indolent Non-Hodgkin Lymphoma

Efficacy	B + O	B	HR, *p*-value
Overall response rate (n = 188, 189) Complete response Partial response	69.2% 11.2% 58%	63% 12.2% 50.8%	NR
Median PFS (n = 194, 202)	Not reached	14.9 mo	0.55, 0.0001

Select Grade 3 or 4 adverse events	B + O (n = 194)	B (n = 198)
Infusion-related reactions	10.8%	5.6%
Neutropenia	33%	26.3%
Thrombocytopenia	10.8%	16.2%
Anemia	7.7%	10.1%

HR = hazard ratio; NR = not reported; PFS = progression-free survival

Sehn LH et al. *Proc ASCO* 2015;**Abstract LBA8502**.

suggests that the addition of obinutuzumab to bendamustine in patients with rituximab-refractory disease is beneficial. I believe that these results will be practice changing.

Infusion-related reactions were the only side effect in the GADOLIN trial that were significantly more common on the combination arm. Hematological toxicities were comparable. Infusion-related reactions in older patients can be a problem. They can be managed with steroids and antihistamines.

DR LOVE: Do you believe that obinutuzumab has greater efficacy than rituximab in FL?

DR SALLES: The question regarding which agent is more effective cannot be answered from the GADOLIN study. A head-to-head comparison of obinutuzumab versus rituximab as single agents in indolent NHL demonstrated some benefit in response rates with obinutuzumab but no benefit in PFS (Sehn 2011). Ongoing Phase III trials that are currently underway comparing obinutuzumab to rituximab will provide a more definitive answer to this question (NCT01332968; NCT01287741).

Tracks 5, 7-9

DR LOVE: In what situations, if any, do you use rituximab alone or in combination with lenalidomide as up-front therapy for patients with FL?

DR SALLES: I use single-agent rituximab treatment for some patients with low tumor burden but who still have minor symptoms and are not comfortable with the watch-and-wait approach.

The R^2 regimen (lenalidomide/rituximab) was evaluated in patients with untreated indolent NHL by Nathan Fowler and colleagues. Those results were recently published in *The Lancet Oncology* and showed a high response rate. The regimen is associated with some toxicity. Approximately 30% to 40% of patients experienced Grade 3 or 4 neutropenia. Side effects such as fatigue, muscle pains and thrombosis were also reported (Fowler 2014; [4.2]). I would not use R^2 in the first-line setting until longer follow-up data are presented. The Phase III RELEVANCE trial comparing R^2 to rituximab with chemotherapy in untreated FL has completed accrual (NCT01476787).

4.2

Phase II Trial: Activity and Safety of Lenalidomide/ Rituximab for Untreated Indolent Lymphomas

	All patients		By lymphoma type		
Efficacy	ITT (n = 110)	Eval (n = 103)	FL (n = 46)	MZL (n = 27)	SLL (n = 30)
ORR	85%	90%	98%	89%	80%

Select Grade 3 and 4 adverse events included neutropenia (35%), rash (7%), fatigue (5%) and thrombocytopenia (4%).

ITT = intent-to-treat population; eval = evaluable patients; FL = follicular lymphoma; MZL = marginal-zone lymphoma; SLL = small lymphocytic lymphoma; ORR = overall response rate

Fowler NH et al. *Lancet Oncol* 2014;15(12):1311-8.

DR LOVE: What is your view on the role of idelalisib in the treatment algorithm for FL?

DR SALLES: Currently idelalisib is indicated for patients with relapsed FL who have received at least 2 prior systemic therapies. We presented the results of a Phase II study at ASCO 2015 on the efficacy and safety of idelalisib in patients with relapsed/refractory FL. The data demonstrated that the patients who experience response, especially those who achieve complete response, have a long duration of response (Salles 2015).

DR LOVE: What are your thoughts on the efficacy of ibrutinib in FL?

DR SALLES: At ASH 2014, preliminary results from a Phase II study of single-agent ibrutinib in patients with relapsed/refractory FL were presented. The response rate with ibrutinib was 30%, which is less than that with idelalisib in the same setting. The PFS is less than a year, which is not that different from what is observed with idelalisib (Bartlett 2014). So I believe this drug is not as effective in this setting but may be useful for select patients.

DR LOVE: What is known about the activity of venetoclax in FL?

DR SALLES: Venetoclax is an inhibitor of Bcl-2, a protein that is overexpressed in FL, so we do have a rationale to investigate this agent. However, we currently have limited data regarding the efficacy of venetoclax in FL. The response rates that have been reported are in the range of 30% to 40%. Clinical trials are underway evaluating venetoclax in combination with rituximab, BR or R-CHOP. We need to see more definitive data with longer follow-up before we can establish if venetoclax will be useful for patients with FL. ■

SELECT PUBLICATIONS

Bartlett NL et al. **Ibrutinib monotherapy in relapsed/refractory follicular lymphoma (FL): Preliminary results of a Phase 2 consortium (P2C) trial.** *Proc ASH* 2014;**Abstract 800**.

Fowler NH et al. **Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: An open-label, phase 2 trial.** *Lancet Oncol* 2014;15(12):1311-8.

Salles GA et al. **Idelalisib efficacy and safety in follicular lymphoma patients from a phase 2 study.** *Proc ASCO* 2015;**Abstract 8529**.

Sehn LH et al. **Randomized Phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non Hodgkin lymphoma: Preliminary analysis of the GAUSS study.** *Proc ASH* 2011;**Abstract 269**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III LYM-3002 study, which evaluated R-CHOP versus VR-CAP for newly diagnosed, transplant-ineligible MCL, demonstrated a significant improvement in median PFS with the VR-CAP regimen.**
   a. True
   b. False

2. **In the Phase III AETHERA trial evaluating brentuximab vedotin versus placebo after ASCT among patients with HL, the rate of 2-year PFS with brentuximab vedotin was approximately _____.**
   a. 40%
   b. 60%
   c. 80%

3. **Which of the following anti-PD-1 antibodies has demonstrated antitumor activity in patients with HL?**
   a. Pembrolizumab
   b. Nivolumab
   c. Both a and b
   d. Neither a nor b

4. **The Phase III ENDEAVOR trial evaluating carfilzomib versus bortezomib in combination with dexamethasone in patients with relapsed MM demonstrated a statistically significant improvement in _____ on the carfilzomib arm.**
   a. Median PFS
   b. Overall response rate
   c. Both a and b
   d. Neither a nor b

5. **Panobinostat was recently approved by the FDA for use in combination with bortezomib/dexamethasone for patients with MM _____.**
   a. Who have received 1 prior treatment with bortezomib
   b. Who have received 1 prior treatment with an IMiD
   c. Who have received at least 2 prior regimens, including bortezomib and an IMiD
   d. All of the above

6. **The Phase III ELOQUENT-2 study demonstrated that treatment with elotuzumab _____ resulted in a significant improvement in PFS for patients with relapsed/refractory MM.**
   a. As a single agent
   b. In combination with pomalidomide
   c. In combination with lenalidomide/dexamethasone

7. **The results of the Phase III PERSIST-1 trial of pacritinib versus best available therapy for patients with primary MF, postpolycythemia vera MF or postessential thrombocythemia MF demonstrated a statistically significant improvement in _____ with pacritinib in the overall patient population.**
   a. Spleen volume reduction of 35% or more
   b. Total symptom score of 50% or more
   c. Both a and b

8. **A Phase I/II trial evaluating the addition of quizartinib to azacitidine or low-dose cytarabine for patients with FLT3-ITD-mutated AML demonstrated that quizartinib was not active.**
   a. True
   b. False

9. **The Phase III GADOLIN trial of bendamustine with or without obinutuzumab in rituximab-refractory indolent NHL demonstrated a statistically significant improvement in progression-free survival on the obinutuzumab arm.**
   a. True
   b. False

10. **Common side effects with the lenalidomide/rituximab regimen when used in patients with indolent NHL include _____.**
    a. Neutropenia
    b. Thrombosis
    c. Muscle pains
    d. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2015

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
ELOQUENT-2: Results of a Phase III trial of lenalidomide/dexamethasone with or without elotuzumab for relapsed/refractory MM	4 3 2 1	4 3 2 1
Bortezomib as front-line therapy for patients with MCL	4 3 2 1	4 3 2 1
Phase III trial results with carfilzomib/dexamethasone versus bortezomib/dexamethasone (ENDEAVOR) and with the addition of carfilzomib to lenalidomide/dexamethasone (ASPIRE) for relapsed MM	4 3 2 1	4 3 2 1
Importance of hydration in the management of venetoclax-associated tumor lysis syndrome	4 3 2 1	4 3 2 1
Results of the Phase III GADOLIN study of bendamustine with or without obinutuzumab in rituximab-refractory indolent NHL	4 3 2 1	4 3 2 1
Monitoring splenomegaly in patients with MF initiating ruxolitinib	4 3 2 1	4 3 2 1

Practice Setting:

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice

☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Customize the selection of systemic therapy for patients with newly diagnosed and progressive mantle-cell lymphoma, recognizing the addition of recently FDA-endorsed options for these patients. . . . . 4 3 2 1 N/M N/A
- Develop a rational plan to incorporate B-cell receptor signaling inhibitors and novel CD20 monoclonal antibodies into the treatment of chronic lymphocytic leukemia and other B-cell neoplasms.. . . . . 4 3 2 1 N/M N/A
- Incorporate newly approved treatments, and consider the potential role of promising investigational agents in the management of relapsed or refractory multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients. . . . . 4 3 2 1 N/M N/A
- Reevaluate your current treatment approach for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data. . . . . 4 3 2 1 N/M N/A
- Recognize the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment. . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain: .....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.
☐ No, I am not willing to participate in a follow-up survey.

PART 2 — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Christopher Flowers, MD, MS	4 3 2 1	4 3 2 1
Keith Stewart, MB, ChB	4 3 2 1	4 3 2 1
Jorge E Cortes, MD	4 3 2 1	4 3 2 1
Gilles A Salles, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

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