

Hematologic Oncology™

U P D A T E

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

FACULTY INTERVIEWS

Jeff Sharman, MD
Jonathan L Kaufman, MD
Elias Jabbour, MD
Bruce D Cheson, MD

EDITOR

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2 Audio CDs
Monograph



Hematologic Oncology Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise 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 in the context of 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

- 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.
- 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.
- 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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FACULTY INTERVIEWS



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EDITOR



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INTERVIEW

Jeff Sharman, MD

Dr Sharman is Director of Research at the Willamette Valley Cancer Institute and Medical Director of Hematology Research for The US Oncology Network in Eugene, Oregon.

Tracks 1-11

- Track 1** **Case discussion:** A 57-year-old woman who presented in 2011 with Stage IIIA follicular lymphoma (FL) with high tumor burden, refused chemoimmunotherapy, received lenalidomide/rituximab (R²) and remains in complete remission (CR) after 4 years
- Track 2** Synergy of the R² regimen
- Track 3** Efficacy and side-effect profile of idelalisib for relapsed FL or chronic lymphocytic leukemia (CLL)
- Track 4** **Case discussion:** A 55-year-old man with previously treated CLL with 17p deletion receives idelalisib/ofatumumab on a clinical trial
- Track 5** Integrating the B-cell receptor signaling inhibitors idelalisib and ibrutinib into the treatment algorithm for CLL with and without adverse cytogenetics
- Track 6** **Case discussion:** An 89-year-old woman with CLL and multiple comorbidities who responds to single-agent obinutuzumab
- Track 7** Management of obinutuzumab-associated infusion reactions
- Track 8** Similarities and differences between rituximab and obinutuzumab
- Track 9** Rates of minimal residual disease (MRD) with obinutuzumab/chlorambucil versus rituximab/chlorambucil on the pivotal Phase III CLL11 trial
- Track 10** Clinical experience with obinutuzumab monotherapy in CLL
- Track 11** Brentuximab vedotin in CD30-positive lymphomas

Select Excerpts from the Interview

Track 3

► **DR LOVE:** Recently, the FDA granted accelerated approval to idelalisib for the treatment of relapsed follicular lymphoma (FL) or small lymphocytic lymphoma (SLL) for patients who have received at least 2 prior systemic therapies. What is your clinical experience with idelalisib, and how does it fit into your practice?

► **DR SHARMAN:** I generally administer idelalisib prior to ibrutinib for patients with relapsed FL. Idelalisib was approved based on a trial for patients with indolent non-Hodgkin lymphoma refractory to both rituximab and alkylating agents (Gopal 2014). These patients received single-agent idelalisib at 150 mg BID.

In the study that led to the labeled indication for idelalisib in chronic lymphocytic leukemia (CLL), patients did not have disease that was rituximab refractory and received idelalisib with rituximab or rituximab with placebo (Furman 2014). Hence, in CLL I use idelalisib in combination with rituximab, and in FL or SLL I administer it as a single agent.

The most significant toxicity issues are elevated transaminases, diarrhea and colitis. Elevated transaminases tend to occur quite early, almost exclusively within the first 3 months. Patients who are receiving idelalisib need to have their liver function tests monitored every other week during this time. The likelihood of a transaminase elevation goes down quite a bit after that 3-month period, and you can then check once monthly at that point. Once the patient recovers from elevated transaminases, it usually does not recur.

Diarrhea and colitis tend to occur later in the course of therapy, with a median time frame closer to 6 months. When diarrhea occurs, it's more of an inflammatory phenomenon than typical pill-based diarrhea. The label information suggests management with dose interruption or discontinuation. Diarrhea can be significant and lead to hospitalizations.

So as long as you know how to use the drug, what to look for and when to look for it, I've found it to be quite easy to use. Once the patient recovers from elevated transaminases, diarrhea or colitis, it is possible to reinitiate therapy depending on what the other options are, how severe the side effects were and how well the patient is performing at that point.

Tracks 7-10

▶ **DR LOVE:** Would you describe the differences between rituximab and obinutuzumab?

▶ **DR SHARMAN:** The key clinical difference between the 2 agents is that obinutuzumab has been demonstrated to be superior to rituximab in CLL, and no other anti-CD20 antibody can make that claim. Importantly, obinutuzumab was approved in combination with chlorambucil for patients with untreated CLL on the basis of the German Phase III CLL11 trial that included arms comparing it to rituximab/chlorambucil and chlorambucil alone (Goede 2014; [1.1]).

▶ **DR LOVE:** Would you discuss some of the key findings of the CLL11 trial?

▶ **DR SHARMAN:** Patients on the CLL11 trial had previously untreated CLL with comorbidities, and overall, obinutuzumab/chlorambucil improved efficacy in this population that might be considered inappropriate for cytotoxic chemotherapy. The study also evaluated MRD negativity. MRD in the bone marrow is more difficult to achieve than it is in the blood. Essentially, MRD negativity was not achieved with chlorambucil alone but was achieved to a small degree in the bone marrow with rituximab/chlorambucil, and with obinutuzumab/chlorambucil approximately 20% of patients were MRD-negative.

▶ **DR LOVE:** How do you administer obinutuzumab, and what are the toxic effects associated with its use?

▶ **DR SHARMAN:** I administer obinutuzumab as monotherapy, not in combination with chlorambucil. I recognize this is an off-label use, but I believe that chlorambucil adds relatively little to the overall efficacy and there are practical challenges with its use. Unfortunately, the CLL11 study did not include obinutuzumab with or without chlorambucil, which would have teased out the effect of chlorambucil.

Most patients who receive obinutuzumab experience considerable infusion-related reactions (IRRs) in the first cycle. The first 1,000-mg dose of obinutuzumab can be administered intravenously at a split dose of 100 mg on day 1 and 900 mg on day 2.

Final Stage II Results of the Phase III CLL11 Trial of Obinutuzumab/Chlorambucil (O-C1b) versus Rituximab/Chlorambucil (R-C1b) for Patients with Chronic Lymphocytic Leukemia and Comorbidities

Efficacy (all patients)	O-C1b	R-C1b
Overall response rate (ORR) (n = 333, 329)	78.4%	65.1%
Complete response	20.7%	7.0%
Partial response	57.7%	58.1%
Median progression-free survival (PFS) (n = 333, 330)	26.7 mo	15.2 mo
Death rates (n = 333, 330)	8%	12%
Minimal residual disease (MRD) negativity	O-C1b	R-C1b
Bone marrow (BM) (n = 133, 114)	19.5%	2.6%
Peripheral blood (PB) (n = 231, 243)	37.7%	3.3%
Select Grade ≥ 3 adverse events	O-C1b (n = 241)	R-C1b (n = 225)
Infusion-related reactions	21%	4%
Neutropenia	35%	27%
Anemia	5%	4%
Thrombocytopenia	11%	4%
Infections	11%	13%

ORR: O-C1b versus R-C1b, $p < 0.001$; PFS: O-C1b versus R-C1b, hazard ratio (HR) = 0.39, $p < 0.001$

Death rates: O-C1b versus R-C1b, HR = 0.66, $p = 0.08$

MRD negativity (BM or PB): O-C1b versus R-C1b, $p < 0.001$

Negative test results for MRD in blood after O-C1b therapy were associated with a favorable disease course during follow-up.

Goede V et al. *N Engl J Med* 2014;370(12):1101-10.

I've administered obinutuzumab to approximately 50 patients, and it appears that the kinetics of the IRRs are different from those with rituximab, with "obinutuzumab being more like lightning and rituximab like thunder." Obinutuzumab causes early and significant IRRs, which, once settled down, don't reoccur. On the other hand, with rituximab, every time you increase the dose, patients experience more IRRs.

With obinutuzumab IRRs are generally experienced during the administration of the first 25 mg, so it's imperative to discontinue the infusion as soon as a reaction is observed. Early interruption after administering 5 mg to 10 mg of the agent seems to offset some of the acuity of the infusion, although I can't say that I have strong data to support this. We have become quite comfortable with obinutuzumab at our institution since we started working with it in our own clinical trial and gained familiarity with IRRs and how to manage them. ■

SELECT PUBLICATIONS

Furman RR et al. **Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.** *N Engl J Med* 2014;370(11):997-1007.

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. **PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma.** *N Engl J Med* 2014;370(11):1008-18.



INTERVIEW

Jonathan L Kaufman, MD

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

Tracks 1-15

- Track 1** Interim results of the Phase III ASPIRE trial: Improvement in progression-free survival with the addition of carfilzomib to lenalidomide/dexamethasone for relapsed multiple myeloma (MM)
- Track 2** Importance of MRD detection in MM
- Track 3** RVD consolidation and maintenance therapy for patients with high-risk MM
- Track 4** Mechanism of action of the recently FDA-approved pan-deacetylase inhibitor panobinostat in relapsed/refractory MM
- Track 5** Results of the Phase II PANORAMA 2 and Phase III PANORAMA 1 trials of panobinostat in combination with bortezomib/dexamethasone for relapsed/refractory MM
- Track 6** Clinical experience with and dosing of panobinostat
- Track 7** Ongoing investigation of panobinostat in combination with carfilzomib for patients with relapsed/refractory MM
- Track 8** Combining the oral proteasome inhibitor ixazomib with lenalidomide/dexamethasone in relapsed/refractory MM
- Track 9** Investigation of ixazomib as maintenance therapy
- Track 10** Tolerability of single-agent oprozomib, an oral, selective, irreversible proteasome inhibitor, for relapsed/refractory MM
- Track 11** Safety of carfilzomib for patients with previously treated systemic light-chain amyloidosis
- Track 12** Carfilzomib-associated cardiopulmonary adverse events and use of carfilzomib in patients with a history of heart disease
- Track 13** Mechanism of action and efficacy of elotuzumab in combination with lenalidomide/dexamethasone in relapsed/refractory MM
- Track 14** Activity of daratumumab alone or in combination regimens for relapsed/refractory MM
- Track 15** **Case discussion:** A 44-year-old man with high-risk, ISS Stage III MM receives triplet induction therapy followed by autologous stem cell transplant (ASCT) and RVD maintenance and remains in CR 3 years later

Select Excerpts from the Interview

Tracks 1, 12

► **DR LOVE:** Would you discuss the results of the Phase III ASPIRE trial evaluating the addition of carfilzomib to lenalidomide/dexamethasone for relapsed multiple myeloma (MM) that were presented at ASH 2014 and subsequently published in *The New England Journal of Medicine*?

► **DR KAUFMAN:** ASPIRE was a randomized trial for patients with relapsed MM who had received 1 to 3 prior lines of therapy. Response rates and deep responses were much higher with the addition of carfilzomib and ultimately translated into a significant improvement in progression-free survival (Stewart 2015; [2.1]). We observed the

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

Efficacy	CRd (n = 396)	Rd (n = 396)	Hazard ratio	p-value
Median progression-free survival	26.3 mo	17.6 mo	0.69	0.0001
Median overall survival	Not estimable	Not estimable		
2-year overall survival rates	73.3%	65.0%	0.79	0.04
Overall response rate	87.1%	66.7%	—	<0.001
Complete response or better	31.8%	9.3%	—	<0.001
Very good partial response or better	69.9%	40.4%	—	<0.001
Clinical benefit rate	90.9%	76.3%	—	<0.001
	CRd (n = 392)		Rd (n = 389)	
Select adverse events	All grades	Grade ≥3	All grades	Grade ≥3
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%
Ischemic heart disease	5.9%	3.3%	4.6%	2.1%

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

beginning of what appeared to be an improvement in overall survival. Because it's not a final analysis, they're not calling it statistically significant yet.

We've known for a long time in the up-front setting that combination therapy is the way to go, but this is the first confirmation that the same approach is also preferable in the relapsed setting.

► **DR LOVE:** What are your thoughts on the issue of carfilzomib and patients experiencing dyspnea? How much of this do you think has to do with hydration?

► **DR KAUFMAN:** It is rare, but I'd say that the cardiac toxicity rate is somewhere on the order of 3% to 5% in the several hundred patients to whom I've administered carfilzomib. Most of the time, if a patient has a decrease in their ejection fraction you can stop the drug and the patient will recover with time. On the ASPIRE study, we saw a 2% to 5% increase in cardiac toxicity such as heart failure and ischemic events in the carfilzomib/lenalidomide/dexamethasone arm compared to the lenalidomide/dexamethasone arm (2.1).

I don't believe fluid is the entire answer. In large part, we've minimized fluid administration for patients who are not at risk for tumor lysis. A real dyspnea signal is observed, and I believe it's drug related. When patients do experience dyspnea it usually lasts a day or two, but that's not heart failure.

► **DR LOVE:** How would you think through using carfilzomib in a patient with heart disease or heart failure? And do you perform cardiac screening in patients about to receive carfilzomib?

► **DR KAUFMAN:** If a patient had a history of heart disease and had coronary disease but received appropriate treatment, it would not deter me from treating, but if someone came in and had an ejection fraction of 40% and symptomatic heart failure, I probably would avoid carfilzomib in that situation. Conversely, we do not monitor ejection

fraction in younger patients. When we've run into problems with issues like heart failure, it's almost uniformly been in the older patient population.

Track 5

► **DR LOVE:** Would you review the data that led to the recent FDA approval of panobinostat in relapsed or refractory MM?

► **DR KAUFMAN:** It's important to first review the Phase II study. It provided proof of principle that we can overcome bortezomib resistance. In this relatively small study for patients with relapsed and bortezomib-refractory myeloma who received bortezomib/dexamethasone and panobinostat, a 35% response rate was reported (Richardson 2013).

The Phase III trial was not conducted in the bortezomib-refractory setting, however. Patients were relatively early in the course of therapy — 1 to 3 prior lines — and they may or may not have been exposed to bortezomib and IMiDs previously. We reported a numerical but not statistical improvement in overall response rate, a statistical improvement in deep responses and an improvement in progression-free survival from 8 months on the bortezomib/dexamethasone arm compared to approximately 12 months with the combination of bortezomib/dexamethasone and panobinostat (San-Miguel 2014; [2.2]). No significant increase in overall survival was observed at the time of analysis.

One of the challenges with all pan-deacetylase inhibitors is toxicity. The biggest issues I have encountered with these agents are diarrhea, nausea, fatigue and thrombocytopenia (2.3). Typically, thrombocytopenia does not cause us to stop treatment. We use dose delays or reductions. A 25% incidence of Grade 3 or 4 diarrhea was observed in the Phase III trial. If we recognize it early and it's managed aggressively, we can prevent patients coming off study. The biggest problem that I've observed that causes patients to come off study is fatigue or asthenia. It can be quite debilitating. We don't have tools to overcome that as we do for diarrhea.

2.2

PANORAMA 1: Efficacy Results of a Phase III Trial of Panobinostat with Bortezomib/Dexamethasone (VD) versus Placebo/VD in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma

Overall analysis	Panobinostat + VD (n = 387)	Placebo + VD (n = 381)	Hazard ratio	p-value
Median progression-free survival (PFS)	11.99 mo	8.08 mo	0.63	<0.0001
Median overall survival*	33.64 mo	30.39 mo	0.87	0.26
Overall response rate	60.7%	54.6%	—	0.09
CR/nCR	27.6%	15.7%	—	0.00006
PFS subgroup analysis (hazard ratio <1.0 favors panobinostat + VD)			Hazard ratio	
Prior exposure to bortezomib (n = 336)			0.58	
Prior exposure to immunomodulatory drugs (IMiDs) (n = 485)			0.54	
Prior exposure to bortezomib and IMiDs (n = 198)			0.53	

* Data not yet mature

CR/nCR = complete response/near complete response

San-Miguel JF et al. *Lancet Oncol* 2014;15(11):1195-206.

PANORAMA 1: Select Adverse Events with Panobinostat and Bortezomib/Dexamethasone (VD) versus Placebo/VD

	Panobinostat + VD (n = 381)		Placebo + VD (n = 377)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	68%	25%	42%	8%
Peripheral neuropathy	61%	18%	67%	15%
Asthenia or fatigue	57%	24%	41%	13%
Nausea	36%	6%	21%	<1%
Thrombocytopenia	98%	68%	84%	31%

San-Miguel JF et al. *Lancet Oncol* 2014;15(11):1195-206.

Consequently, when ODAC reviewed these Phase III data, they were concerned about the risk-benefit ratio. The FDA then evaluated the patient subpopulations with a specific focus on those patients who'd been exposed to both IMiDs and bortezomib. In this group of patients a much stronger risk-benefit ratio was observed (2.2), and that's ultimately where the approval was granted. I believe that's appropriate.

Track 8

► **DR LOVE:** Would you review some of the research you've been involved with evaluating the oral proteasome inhibitor ixazomib in MM?

► **DR KAUFMAN:** We previously reported that ixazomib is effective in combination with dexamethasone for patients with relapsed disease. We've also studied this agent in combination with lenalidomide/dexamethasone for patients with newly diagnosed MM and demonstrated a response rate of more than 90% (Kumar 2014b). What was interesting about this study was that after up to a year's worth of induction therapy, we administered maintenance ixazomib and showed that we could increase response depth in 48% of patients (Kumar 2014a).

Common toxicities associated with ixazomib are rash, nausea and diarrhea. We observe less peripheral neuropathy than with bortezomib, and, importantly, even if peripheral neuropathy occurs, it's rarely the typical painful sort we observe with bortezomib and few patients have to discontinue ixazomib because of it. ■

SELECT PUBLICATIONS

Kumar S et al. **Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients (pts) with previously untreated multiple myeloma (MM): Phase 2 study results.** *Proc ASH* 2014a; **Abstract 82.**

Kumar SK et al. **Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: An open-label phase 1/2 study.** *Lancet Oncol* 2014b;15(13):1503-12.

Richardson PG et al. **PANORAMA 2: Panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma.** *Blood* 2013;122(14):2331-7.

Stewart AK et al. **Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.** *N Engl J Med* 2015;372(2):142-52.



INTERVIEW

Elias Jabbour, MD

Dr Jabbour is Associate Professor in the Department of Leukemia of the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-12

- Track 1 Case discussion:** A 51-year-old man with chronic-phase chronic myeloid leukemia (CML) with disease progression on dasatinib is found to harbor a rare F317L mutation and receives ponatinib
- Track 2** Mitigating ponatinib-related side effects with dose reductions or discontinuation
- Track 3** Rational placement of omacetaxine in the treatment algorithm for CML
- Track 4 Case discussion:** A 48-year-old man with hydroxyurea-resistant polycythemia vera (PV) receives ruxolitinib
- Track 5** Duration and rapidity of response with ruxolitinib in PV versus myelofibrosis (MF)
- Track 6** Activity and toxicities of novel JAK inhibitors — pacritinib, momelotinib — in myeloproliferative disorders
- Track 7** Approach to ruxolitinib dosing in patients with anemia and thrombocytopenia
- Track 8** Diagnostic and prognostic roles of JAK and other mutations in MF
- Track 9 Case discussion:** A 95-year-old woman with intermediate-2 myelodysplastic syndrome with abnormal karyotype experiences a prolonged complete cytogenetic response to azacitidine
- Track 10** SORAML: Results of a Phase II trial of sorafenib versus placebo in addition to standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)
- Track 11** Activity and incidence of tumor lysis syndrome with the novel second-generation Bcl-2 inhibitor venetoclax (ABT-199) in AML
- Track 12 Case discussion:** A 25-year-old woman with high-risk acute promyelocytic leukemia receives gemtuzumab ozogamicin on a compassionate use program

Select Excerpts from the Interview

Tracks 1-3

► **DR LOVE:** What is your approach to the choice of tyrosine kinase inhibitor (TKI) for first-line therapy in chronic myeloid leukemia (CML)?

► **DR JABBOUR:** Imatinib, nilotinib and dasatinib are available for front-line therapy. For patients with low-risk disease, I would recommend imatinib because the advantage of the second-generation TKIs dasatinib or nilotinib is marginal and yields no effect on survival. I start with imatinib and switch therapy at 3 to 6 months if the response is not good.

For patients who are young and have high-risk features, I would consider dasatinib or nilotinib up front. My choice would be based on comorbidities. I would avoid dasatinib for patients who are at risk for pleural effusion and offer them nilotinib instead. In contrast, for patients with diabetes or cardiovascular issues, I would opt for dasatinib.

In the future, the cost of these agents will also dictate our choice of therapy, especially when generic imatinib becomes available.

► **DR LOVE:** Ponatinib is a potent TKI used for patients who are resistant/intolerant to dasatinib or nilotinib or those with the T315I mutation. What is known about the cardiovascular side effects with ponatinib?

► **DR JABBOUR:** Ponatinib is associated with a higher incidence of cardiovascular events compared to other TKIs. Arterial events are observed at a rate of approximately 13% per year of therapy. This does not increase with time on therapy. Both venous and arterial events are observed. When these events occur, the drug must be discontinued.

Based on the PACE trial, patients with certain risk factors at baseline, such as cardiac disease, diabetes or advanced age, are at higher risk of developing vascular events (Cortes 2013). We try to optimize risk factors before starting patients on ponatinib. Because the agent is potent and you can minimize side effects by reducing the dose, in our practice we administer 30 mg per day and reduce to 15 mg.

► **DR LOVE:** What are your thoughts on the role of omacetaxine, another drug approved for CML?

► **DR JABBOUR:** Omacetaxine inhibits protein translation and has shown activity in patients who are resistant or intolerant to multiple TKIs and those with the T315I mutation. In a pivotal trial that led to the approval in chronic phase, 23% of patients achieved a major cytogenetic response (Cortes 2012). For patients in blast phase, the combination of omacetaxine and a TKI is attractive. It can be considered off label with a TKI in patients for whom you want to stop therapy.

As induction therapy, the drug is administered subcutaneously twice daily for 2 weeks. It can now be administered at home, which is more practical for patients. In my practice, I administer it for 1 week at the start and then for 3 days later to minimize the risk of myelosuppression.

Tracks 5-7

► **DR LOVE:** What is your clinical experience with ruxolitinib for polycythemia vera (PV)?

► **DR JABBOUR:** The main goal is to achieve hematocrit control and improve symptoms in patients with PV. The response to ruxolitinib in PV is rapid because myelosuppression is not as much of a concern as it is with myelofibrosis (MF). I have found it to be a well-tolerated agent. The blood counts must be closely monitored early on and the dose adjusted if necessary. Patients usually receive 10 mg BID and experience a dramatic improvement in quality of life. In the RESPONSE trial, assessing ruxolitinib versus best available therapy in patients with PV who had an inadequate response to or unacceptable side effects from hydroxyurea, the probability that a response to ruxolitinib would be maintained for 1 year was approximately 90% (Vannucchi 2015; [3.1]).

► **DR LOVE:** How do you approach dosing of ruxolitinib in patients with anemia and thrombocytopenia?

► **DR JABBOUR:** For patients who have platelet counts on the order of 100 or 110 x 10⁹/L, I usually start with a 10-mg dose and titrate upward. A dose of 10 mg BID or higher is necessary to have an effect on the spleen. I will monitor blood counts on a

RESPONSE: Efficacy Results of a Phase III Trial of Ruxolitinib (RUX) versus Best Available Therapy (BAT) for Polycythemia Vera (PV)

Response	RUX (n = 110)	BAT (n = 112)	p-value
Composite primary endpoint	20.9%	0.9%	<0.001
≥35% reduction in spleen volume	38.2%	0.9%	—
Hematocrit control	60.0%	19.6%	—

- Composite primary endpoint: Hematocrit control and >35% reduction in spleen volume at week 32
- Significantly more patients in the RUX group than in the BAT group had a complete hematologic response: 23.6% vs 8.9%, $p = 0.003$
- Treatment with RUX was associated with greater and clinically meaningful improvements in PV-related symptom burden and quality-of-life measures compared to standard therapy
- The probability that a primary response to ruxolitinib would be maintained for 1 year from the time of the initial response was 94%

Vannucchi A et al. *N Engl J Med* 2015;372(5):426–35; Mesa R et al. *Proc ASH* 2014; **Abstract 709**.

weekly basis and escalate every 4 weeks to reach 20 mg BID or higher. The goal is to avoid discontinuing therapy. If therapy is stopped, the benefits are lost within 7 days and patients start experiencing symptoms again. Drugs like danazol can be used in combination with ruxolitinib to manage the anemia.

► **DR LOVE:** What do we know about the novel agent pacritinib in the treatment of myeloproliferative neoplasms?

► **DR JABBOUR:** Pacritinib is a JAK2 inhibitor that has similar efficacy to ruxolitinib. The main advantage of pacritinib versus ruxolitinib is that it doesn't cause as much myelosuppression. If pacritinib were available, I would consider it for patients who have baseline anemia or thrombocytopenia. The main side effects are gastrointestinal toxicities like diarrhea, nausea and vomiting, which can be managed with dose reductions. The drug is promising and is also being evaluated in patients with low counts compared to best available therapy, including ruxolitinib.

► **DR LOVE:** What other novel agents are being investigated in MF?

► **DR JABBOUR:** A number of new agents are being evaluated. They include histone deacetylase inhibitors and antifibrotic agents. With histone deacetylase inhibitors, more side effects are encountered. A promising therapy for patients who have the mixed syndrome of myelodysplastic syndrome/myeloproliferative neoplasm is the combination of azacitidine and ruxolitinib, which can be considered sequentially instead of concurrently to improve outcomes and reduce the risk of side effects.

Track 10

► **DR LOVE:** Would you discuss the results of the SORAML trial of sorafenib in addition to standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)?

► **DR JABBOUR:** In the SORAML study, an advantage was observed overall with sorafenib versus placebo among patients with AML in the front-line setting, independent of FLT3-ITD status (Rollig 2014; [3.2]). It cannot be determined from the study

SORAML: Results of a Phase II Trial of Sorafenib versus Placebo with Standard Therapy for Younger Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

Outcome	Sorafenib	Placebo	p-value
Complete response (CR)	60%	59%	0.764
Median event-free survival (EFS)* 3-year EFS rate	20.5 mo 40%	9.2 mo 22%	0.013
Median relapse-free survival (RFS) 3-year RFS rate	NYR 56%	23 mo 38%	0.017
Median overall survival (OS) 3-year OS rate	NYR 63%	NYR 56%	0.382

NYR = not yet reached

* An event is defined as failure to achieve CR after induction, relapse or death.

- The most common reported Grade ≥ 3 adverse events were fever (40%), infections (22%) and bleeding events (2%).
- The risk of fever, bleeding events and hand-foot syndrome was significantly higher on the sorafenib arm.
- The incidence of all other adverse events showed no significant difference between arms.

Rollig C et al. *Proc ASH* 2014;Abstract 6.

if sorafenib increases overall survival. Although sorafenib has not been approved in this setting, it can be considered in combination with chemotherapy for patients with AML who have the FLT3-ITD mutation.

Track 11

► **DR LOVE:** What are your thoughts on the use of the novel Bcl-2 inhibitor venetoclax (ABT-199), an agent for which breakthrough therapy designation was recently granted by the FDA for patients with CLL and deletion 17p, for patients with AML?

► **DR JABBOUR:** Venetoclax is one of the most promising agents under investigation for patients with AML. A study presented at ASH 2014 demonstrated encouraging activity with this agent in patients with heavily treated AML (Konopleva 2014). Ongoing trials are evaluating the combination of venetoclax with decitabine or azacitidine.

I have 3 patients with AML who were unfit for chemotherapy to whom I administered venetoclax in combination with decitabine. They achieved a remission after 1 course, which is unheard of. One major toxicity with this therapy is neutropenia. Tumor lysis syndrome is a concern, but it is not a major problem. I employ dose escalation with venetoclax and monitor patients carefully. ■

SELECT PUBLICATIONS

Cortes JE et al. **A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias.** *N Engl J Med* 2013;369(19):1783-96.

Cortes JE et al. **Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation.** *Blood* 2012;120(13):2573-80.

Konopleva M et al. **A Phase 2 study of ABT-199 (GDC-0199) in patients with acute myelogenous leukemia (AML).** *Proc ASH* 2014;Abstract 118.



INTERVIEW

Bruce D Cheson, MD

Dr Cheson is Professor of Medicine, Deputy Chief of the Division of Hematology-Oncology and Head of Hematology at Georgetown University Hospital Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-11

- Track 1** **Case discussion:** A 73-year-old woman under observation since 2009 for CLL with adverse cytogenetics presents with symptomatic anemia and splenomegaly and receives ibrutinib
- Track 2** Monitoring lymphocytosis in patients responding to ibrutinib
- Track 3** Management of bleeding risks in patients receiving ibrutinib
- Track 4** Balancing “watch and wait” with the need for active treatment in CLL
- Track 5** Venetoclax-associated tumor lysis syndrome
- Track 6** Clinical experience with idelalisib in indolent and aggressive lymphomas
- Track 7** Efficacy of bortezomib, lenalidomide and ibrutinib for relapsed/refractory mantle-cell lymphoma (MCL)
- Track 8** Therapeutic options for younger patients with MCL
- Track 9** Rationale for the ongoing Phase III RELEVANCE trial of R² versus rituximab-based chemotherapy → rituximab maintenance for previously untreated FL
- Track 10** **Case discussion:** A 36-year-old woman with recurrent limited-stage nodular sclerosing Hodgkin lymphoma (HL) receives brentuximab vedotin as a bridge to ASCT
- Track 11** Activity of the immune checkpoint inhibitors pembrolizumab and nivolumab in relapsed/refractory HL

Select Excerpts from the Interview

Tracks 1-3

► **DR LOVE:** Would you discuss your approach to considering “watch and wait” versus initiating active treatment for a patient with CLL? Does your approach differ based on cytogenetics?

► **DR CHESON:** My approach is the same regardless of any of the prognostic factors. I have one patient with CLL with deletion 17p whom I have been following for 5 years. It's not the risk factors. It's the eventual symptoms and laboratory findings that will compel us to treat.

Patients can remain on observation for a long time. We sometimes see a rapid increase in the lymphocyte count that will then plateau for months or years, so a single number doesn't compel us to treat. It's the patient who tells us when treatment is indicated.

► **DR LOVE:** How do you manage lymphocytosis in patients responding to ibrutinib?

► **DR CHESON:** Lymphocytosis is a demargination phenomenon. The lymphocyte count can go up several-fold, up to the hundreds of thousands, and even some of my colleagues start to become concerned.

We've seen no correlation between whether it goes up or doesn't and the patient's eventual response. It's simply something that you shouldn't let scare you in and of itself. In fact, we published a paper a couple of years ago after a workshop that I held to make it clear that a number of agents are associated with what appears to be progressive disease — for example, the flare reaction with lenalidomide and this lymphocytosis (Cheson 2014). We are now starting to see it with the checkpoint inhibitors in solid tumors in addition to the lymphomas.

It appears as though the patient's disease is progressing in some areas, but everything else seems like it's improving. So, in these cases, you have to give the patients and the drug the benefit of the doubt, follow them carefully, repeat the appropriate tests and come to a good clinical decision as to whether the patient is experiencing disease progression or not. Lymphocytosis alone is not considered progressive disease in patients who are receiving these agents for CLL.

► **DR LOVE:** Would you also talk more specifically about what you've observed in terms of bleeding or bruising with ibrutinib?

► **DR CHESON:** Bruising and bleeding are a couple of unusual adverse effects of ibrutinib. In most of my patients who have experienced these sorts of complications with ibrutinib, they've been cutaneous. I've seen a couple of nosebleeds. I had a patient who had a conjunctival hemorrhage. I have had 2 patients who were receiving ibrutinib and experienced intracranial hemorrhages. To one of them I had been administering treatment for 20 years, and he died from the bleeding event.

Just because ibrutinib is a pill and is generally well tolerated, you can't assume that everything is going to be easy. You still have to exercise care.

► **DR LOVE:** Is it a relative or absolute contraindication to administer ibrutinib to a patient on anticoagulation?

► **DR CHESON:** If I didn't have alternatives, it would be more difficult. But we have idelalisib, which is also an effective agent. I'm uncomfortable administering a drug that predisposes patients to bleeding when they are already receiving anticoagulants. I don't know what to do with an atrial fibrillation. I have a patient with cutaneous CLL who has had a nice response to ibrutinib but developed atrial fibrillation. It came and went. He didn't have it the last time I saw him, and because he recently received his month's supply, we're going to see what happens in the next month. If he starts fibrillating again, we'll probably switch him to idelalisib.

Track 7

► **DR LOVE:** How have you incorporated bortezomib, lenalidomide and ibrutinib, which are now all approved, into the treatment of relapsed/refractory mantle-cell lymphoma (MCL)?

► **DR CHESON:** I administer ibrutinib first because it has a higher response rate, and then I administer lenalidomide. I've observed some durable responses to lenalidomide in MCL. I have a patient who received lenalidomide after a stem cell transplant failed who has been in remission for 3 years now.

► **DR LOVE:** What are your thoughts on the use of bortezomib as a component of up-front therapy for MCL, specifically the recent data comparing R-CHOP to

bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) for transplant-ineligible patients with newly diagnosed MCL?

► **DR CHESON:** Those data initially presented by Franco Cavalli at ASCO 2014 and subsequently published in *The New England Journal of Medicine* were interesting and led to bortezomib being approved in this setting (Robak 2015; [4.1]). However, we must consider that the comparator arm was R-CHOP on this trial. If you review the NCCN guidelines, it's the “sick puppy” of all the treatments for MCL, unless it is followed by a stem cell transplant. We have other good options for these patients — BR, R-hyper-CVAD, R-hyper-CVAD/transplant and even R² appear to be better.

So again, the comparator is the problem in many of these clinical trials. Once a new regimen becomes available, you have to ask, how did it win? What was the patient population? What was the comparator? And what other options are out there?

4.1

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	HR	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 = 229, 228)	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

HR = hazard ratio; NR = not reached

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

Tracks 10-11

► **DR LOVE:** What are your thoughts on the results of the Phase III AETHERA trial of brentuximab vedotin for patients with Hodgkin lymphoma (HL) and high risk of disease progression after autologous stem cell transplant (ASCT) presented at ASH 2014 and subsequently published in *The Lancet*?

► **DR CHESON:** We had not yet had many opportunities to use brentuximab vedotin after ASCT, but those results were compelling and will influence my practice. Post-transplant brentuximab vedotin was effective compared to placebo (Moskowitz 2015; [4.2]).

How will this approach fare with more people now using brentuximab vedotin either prior to transplant or as part of initial treatment? The Phase III ECHELON-1 study is

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

Progression-free survival (PFS)	Per independent review		Per investigator	
	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	
	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%

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

now evaluating ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) versus A²VD (brentuximab vedotin/doxorubicin/vinblastine/dacarbazine) as front-line therapy for classical HL (NCT01712490). That's an important study because the preliminary Phase I/II data appear exceptionally promising (Connors 2014).

However, just when we thought you couldn't get better than brentuximab vedotin, along come nivolumab and pembrolizumab. For patients with relapsed/refractory disease, response rates are higher than 80% with nivolumab, and adverse events were mostly low grade (Ansell 2015). The response rate was not quite as high with pembrolizumab, but the patient populations were a bit different and it was a small number of patients (Moskowitz 2014), so those variables could have influenced that.

The question is what to do with these agents. Do you want to save them for the end? I would think not. We are now developing an up-front trial for older patients with HL who don't fare well with ABVD evaluating brentuximab vedotin with nivolumab. When you take 2 drugs with 80% response rates and you put them together up front, instead of after transplant, hopefully they will be more effective and well tolerated. ■

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.

Cheson BD et al. **Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification.** *J Clin Oncol* 2014;32(27):3059-68.

Connors JM et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed advanced stage Hodgkin lymphoma: Long term outcomes.** *Proc ASH* 2014; **Abstract 292.**

Moskowitz CH et al; AETHERA Study Group. **Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2015;[Epub ahead of print].

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.**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The final Stage II results from the German Phase III CLL11 trial for patients with CLL and coexisting medical conditions demonstrated that obinutuzumab/chlorambucil was significantly superior to rituximab/chlorambucil in terms of _____.
 - a. Overall response rate
 - b. Median progression-free survival
 - c. MRD negativity in the bone marrow
 - d. MRD negativity in the peripheral blood
 - e. All of the above
2. Interim results of the Phase III ASPIRE trial of lenalidomide and dexamethasone with or without carfilzomib for patients with relapsed MM demonstrated a statistically significant improvement in _____ with the addition of carfilzomib.
 - a. Median progression-free survival
 - b. Overall response rate
 - c. Both a and b
3. 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
4. Common side effects associated with treatment with panobinostat include _____.
 - a. Diarrhea
 - b. Asthenia/fatigue
 - c. Nausea
 - d. Thrombocytopenia
 - e. All of the above
5. The major side effect of the novel JAK2 inhibitor pacritinib is _____.
 - a. Myelosuppression
 - b. Gastrointestinal toxicities
 - c. Tumor lysis syndrome
6. In the Phase II SORAML trial, the sequential addition of sorafenib to standard chemotherapy in younger patients with newly diagnosed AML resulted in a significant improvement in event-free survival.
 - a. True
 - b. False
7. Patients with PV on the RESPONSE study of ruxolitinib versus best available therapy experienced which of the following with ruxolitinib?
 - a. A higher rate of complete hematologic response
 - b. Reduction in spleen volume
 - c. Improvement in symptoms
 - d. All of the above
8. 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 progression-free survival with VR-CAP compared to R-CHOP.
 - a. True
 - b. False
9. In the Phase III AETHERA trial evaluating brentuximab vedotin versus placebo after ASCT for patients with HL, the rate of 2-year progression-free survival with brentuximab vedotin, the primary endpoint, was approximately _____.
 - a. 40%
 - b. 65%
 - c. 90%
10. Which of the following immune checkpoint inhibitors has demonstrated promising antitumor activity in patients with relapsed/refractory HL?
 - a. Nivolumab
 - b. Pembrolizumab
 - c. Both a and b
 - d. Neither a nor b

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

	BEFORE	AFTER
Interim results of the Phase III ASPIRE trial evaluating the addition of carfilzomib to lenalidomide/dexamethasone for relapsed MM	4 3 2 1	4 3 2 1
Kinetics and management of obinutuzumab-associated infusion reactions	4 3 2 1	4 3 2 1
Phase II/III trial results and ongoing investigation of the newly FDA-approved pan-deacetylase inhibitor panobinostat in 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
SORAML: Results of a Phase II trial of sorafenib versus placebo in addition to standard therapy for younger patients with newly diagnosed AML	4 3 2 1	4 3 2 1
AETHERA: Results of a Phase III trial of brentuximab vedotin as consolidation therapy after ASCT in patients with HL at risk of relapse or progression	4 3 2 1	4 3 2 1

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 Other (please explain):

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- 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 management approach to patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

- 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
- 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

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Jonathan L Kaufman, MD	4	3	2	1	4 3 2 1
Elias Jabbour, MD	4	3	2	1	4 3 2 1
Bruce D Cheson, MD	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

Other comments about the faculty and editor for this activity:

.....

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U P D A T E

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