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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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Harry P Erba, MD, PhD
Shaji K Kumar, MD
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EDITOR

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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

- Appraise the recent FDA approvals of ibrutinib, idelalisib and obinutuzumab, and discern how these agents can be appropriately integrated into clinical practice for patients with chronic lymphocytic leukemia and other B-cell neoplasms.
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors as therapeutic options for patients with chronic myeloid leukemia.
- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction, consolidation and maintenance treatment approaches for patients with multiple myeloma.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas.
- 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.
- Recognize the role of novel agents and regimens in the management of relapsed/refractory acute myeloid leukemia.
- 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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EDITOR

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INTERVIEW

Michael E Williams, MD, ScM

Dr Williams is Byrd S Leavell Professor of Medicine and Chief of the Hematology/Oncology Division at the University of Virginia Health System in Charlottesville, Virginia.

Tracks 1-16

Select Excerpts from the Interview

Tracks 1-3, 7

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

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

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

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

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

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

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

Tracks 5, 13

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

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

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

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

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

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

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

1.1

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

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

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

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

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

Track 6

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

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

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

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

Tracks 10-12

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

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

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

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

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

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

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

1.2

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

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

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

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

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

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

Track 14

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

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

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

SELECT PUBLICATIONS

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

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

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

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

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

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

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

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

INTERVIEW

Harry P Erba, MD, PhD

Dr Erba is Albert F LoBuglio Endowed Chair for Translational Cancer Research, Chair of the SWOG Leukemia Committee, Professor of Internal Medicine and Director of the Hematologic Malignancy Program at the University of Alabama at Birmingham in Birmingham, Alabama.

Tracks 1-13

Select Excerpts from the Interview

Tracks 5-9

DR LOVE: Are there any promising new agents or strategies in the treatment of acute myeloid leukemia (AML), particularly in terms of treatment for older patients?

DR ERBA: One strategy that I am excited by now in my role as chair of the SWOG Leukemia Committee is an Intergroup collaboration of translational and clinical scientists that we've convened to develop the next clinical trial for older patients with AML. ECOG is currently investigating "3 + 7" versus clofarabine and also asking a decitabine maintenance question. That study will end soon, and we're designing the next trial.

DR LOVE: Omacetaxine, which is an agent approved by the FDA for patients with chronic myeloid leukemia, also has reported activity in combination with low-dose

cytarabine for older patients with AML who are not fit enough for intensive chemotherapy (Kadia 2013). Have you administered this agent in the AML setting?

DR ERBA: Omacetaxine does have activity in AML, but I have not used it yet. However, it is one of the agents that we are considering for a randomized Phase II study for older patients with AML. Another promising agent is the polo-like kinase inhibitor volasertib.

Volasertib has been studied in a Phase II trial of low-dose cytarabine with or without volasertib for older patients with AML who were not believed to be candidates for intensive induction chemotherapy. Event-free survival was better in the volasertib arm, and a subset of patients with poor-risk cytogenetics experienced a superior response rate with the combination compared to low-dose cytarabine alone (Dohner 2014; [2.1]). Volasertib is now being evaluated in a larger, pivotal Phase III study (POLO-AML-2; NCT01721876), and we anticipate results in the near future.

DR LOVE: Are there any new developments in the management of AML with FLT3 mutations?

DR ERBA: Approximately 25% of patients with AML and a normal karyotype will have an FLT3 mutation, typically an internal tandem duplication (ITD) that's been associated with worse outcomes. Interestingly, FLT3 ITD has not been associated with a lower remission rate, but in adult AML it is associated with lower event-free and overall survival.

A number of agents are in development for AML with FLT3-activating mutations. None has yet been FDA approved for that indication. Sorafenib, which is FDA approved for hepatocellular carcinoma and renal cell carcinoma, also exhibits activity against FLT3 ITD, and Phase II data with sorafenib 400 mg twice daily in combination with azacitidine show biologic activity in patients with relapsed AML and FLT3-ITD mutations (Ravandi 2013).

2.1

Results of a Phase II Trial of Low-Dose Cytarabine (LDAC) with or without Volasertib for Patients with Acute Myeloid Leukemia Not Suitable for Induction Therapy

Efficacy	LDAC (n = 45)	LDAC + volasertib (n = 42)	Hazard ratio/ odds ratio	*p*-value
Median event-free survival	2.3 mo	5.6 mo	0.57	0.021
Median overall survival*	5.2 mo	8.0 mo	0.63	0.047
Overall response rate†	13.3%	31.0%	2.91	0.052
Select adverse events (Grade 3-5)	**LDAC**		**LDAC + volasertib**	
Febrile neutropenia	15.6%		54.8%	
Cellulitis	6.7%		4.8%	
Pneumonia	4.4%		21.4%	
Diarrhea	2.2%		9.5%	
Pyrexia	2.2%		7.1%	

* Estimate of 1-year overall survival rate = 36.8%; 9 (10%) patients were alive and followed for 23.7 to 34.1 months; † Responses in the LDAC/volasertib arm were observed across all genetic groups, including 5 of 14 patients with adverse cytogenetics.

Dohner H et al. *Blood* 2014;124(9):1426-33.

Single-agent quizartinib has demonstrated an approximately 50% response rate for patients with AML and FLT3-ITD mutations (Cortes 2013). A low response rate was also observed for patients with AML that was FLT3 ITD-negative, but the interesting aspect about the definition of *negative* is that the allelic burden would be less than 10%, so you can't rule out the possibility that the marrow simply had a low number of blasts and did express FLT3. In any case, quizartinib elicits responses and is being investigated further in FLT3-positive AML. The FDA is considering it as a single agent.

We are also eagerly awaiting the results of an ongoing CALGB/Alliance study for younger patients with AML and FLT3-ITD mutations. On this study patients are randomly assigned to standard 3 + 7 followed by high-dose cytarabine or the same chemotherapy in combination with the oral FLT3 inhibitor midostaurin during induction, consolidation and as maintenance therapy (CALGB-10603; NCT00651261). I like the design of this study because if you believe a drug will yield a benefit, why not administer it throughout the course of therapy? That's not always done.

Tracks 12-13

DR LOVE: What is your treatment approach for patients with low-risk myelodysplastic syndromes (MDS)?

DR ERBA: We now have more refined molecular analyses to define prognosis, and more information is on the way because we perform whole exome and genome sequencing for patients with MDS. But so far nothing has changed the outlook for these patients. We still have the same discussions about supportive care versus growth factors versus azacitidine or decitabine versus lenalidomide for low-grade or low-risk MDS.

For patients with higher-risk disease, the debate continues with regard to azacitidine or decitabine versus allogeneic stem cell transplantation as the only curative option. These are difficult clinical decisions we must make with our patients, with few randomized data to tell us the best option.

Patients should be considered for stem cell transplantation as soon as possible. Practically speaking, because it takes a while to find a donor and schedule a transplant, I don't see a downside to administering azacitidine or decitabine, especially considering that azacitidine compared to supportive care has been associated with a survival advantage for older patients. I believe that if the patient decides not to go through the transplant, you've done no harm by administering what would otherwise be standard therapy.

We are performing an Intergroup trial of interest in this patient population. We have rapidly enrolled 240 patients on this Phase II study. Patients with high-risk and intermediate-2 risk MDS are randomly assigned to azacitidine alone or azacitidine in combination with either lenalidomide or vorinostat (SWOG-S1117; NCT01522976). ■

SELECT PUBLICATIONS

Cortes JE et al. **Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status.** *J Clin Oncol* 2013;31(29):3681-7.

Kadia TM et al. **Results of omacetaxine plus low-dose cytarabine (LD-araC) in older patients with acute myeloid leukemia (AML).** *Proc ASCO* 2013;**Abstract 7068**.

Ravandi F et al. **Phase 2 study of azacitidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation.** *Blood* 2013;121(23):4655-62.

INTERVIEW

Shaji K Kumar, MD

Dr Kumar is Professor of Medicine and Consultant in the Division of Hematology and Blood and Marrow Transplantation at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-13

Track 1 Current status of minimal residual disease assessment in multiple myeloma (MM)

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Track 6 Activity, tolerability and ongoing trials of the oral proteasome inhibitor ixazomib in MM

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Track 8 Results of a meta-analysis of randomized trials evaluating lenalidomide maintenance therapy in MM

Track 9 Initial results of the Phase III FIRST trial of lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM

Track 10 Results of a meta-analysis evaluating second primary cancers with lenalidomide therapy for newly diagnosed MM

Track 11 Role of melphalan in the management of transplant-ineligible MM

Track 12 Clinical experiences with and tolerability of pomalidomide

Track 13 Activity, tolerability and ongoing evaluation of triplet regimens containing pomalidomide, carfilzomib or both for relapsed/refractory MM

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: The most commonly used induction regimen for multiple myeloma (MM) in the pretransplant setting is bortezomib/lenalidomide/dexamethasone (RVD). Would you discuss the emerging role of carfilzomib/lenalidomide/dexamethasone (CRd)?

DR KUMAR: Carfilzomib has some distinction from bortezomib in that it doesn't cause as much peripheral neuropathy (PN). Few data are available to compare the 2 regimens. The Phase II studies of CRd for high-risk smoldering, newly diagnosed or relapsed MM showed high efficacy (Jakubowiak 2012; Wang 2013). However, several questions are yet to be answered: Can we compare RVD to CRd head to head and show that one is more efficacious? Is one more convenient? Does a quality-of-life difference exist? These questions are being asked in the ongoing Phase III ECOG-E1A11 (ENDURANCE) trial. Patients with newly diagnosed MM are randomly assigned to receive

lenalidomide/dexamethasone with bortezomib or carfilzomib for 9 months followed by an indefinite duration versus 2 years of lenalidomide maintenance therapy.

DR LOVE: What has your experience been with issues such as dyspnea and cardiac dysfunction with carfilzomib?

DR KUMAR: All patients on early studies involving carfilzomib received aggressive hydration, so fluid overload may have occurred in some patients with this feeling of dyspnea. Also, some patients have received a number of other drugs, so their cardiac reserve may be relatively low. Finally, we need to keep in mind that some patients who live with myeloma for long periods can develop other conditions, like amyloidosis, which can also affect the heart.

The ongoing Phase III trials incorporate a concerted effort to better define who the people are who experience heart failure, what predisposes them to heart failure and which patients experience more of the primary dyspnea sensation and not really heart failure. For now this is something that practitioners should keep in mind when they are administering carfilzomib. If symptoms are present, doctors should follow up appropriately with cardiac biomarkers and echocardiograms.

DR LOVE: What kind of cardiac history would make you not want to use carfilzomib or absolutely preclude you from administering it?

DR KUMAR: A history of heart failure wouldn't stop me from administering carfilzomib, although I would watch those patients much more carefully. But if somebody were in congestive heart failure that was not well controlled with medications, I would be hesitant until we had better control of the heart failure.

Tracks 6-7

DR LOVE: Aside from the convenience factor, what else is known about the oral proteasome inhibitors, such as ixazomib, in MM?

DR KUMAR: Although ixazomib shares some properties with bortezomib, it is distinct in terms of how it binds and how fast it dissociates from the proteasome. It appears to have better distribution within the body and is better able to get outside the bloodstream. This may have implications for how we treat extramedullary disease. Also, the convenience of taking a pill once a week clearly opens up a new paradigm for patients needing proteasome inhibitor therapy.

We have evaluated the combination of ixazomib with lenalidomide/dexamethasone in newly diagnosed MM and demonstrated it to be effective (Kumar 2012). Ongoing Phase II studies are evaluating ixazomib in combination with cyclophosphamide/dexamethasone for newly diagnosed MM (NCT02046070) and previously untreated symptomatic MM (NCT01864018).

DR LOVE: What are your thoughts on oral proteasome inhibitors as maintenance therapy?

DR KUMAR: An oral agent as maintenance therapy will make a huge difference. This is important because many patients who need maintenance therapy have high-risk MM. These patients could gain significant benefit from proteasome inhibitor therapy. The availability of an oral agent would change the dynamics in that it could be conveniently administered to patients on a long-term basis. It's an exciting possibility that is

currently being explored in a Phase III trial evaluating ixazomib maintenance versus no maintenance therapy after stem cell transplant (SCT) (NCT02181413).

Tracks 8-10

DR LOVE: Your group presented a meta-analysis at ASH 2013 evaluating the existing outcomes data from Phase III randomized trials of maintenance lenalidomide. Would you discuss the current role of lenalidomide as maintenance therapy?

DR KUMAR: This is probably one of the most hotly debated topics these days. We must consider maintenance from the perspective of the ideal duration of therapy. It all boils down to continuous versus fixed-duration therapy. In the post-transplant setting this strategy has been referred to as maintenance therapy. However, in maintenance therapy for many other cancer types, patients receive a lower dose of treatment or a different kind of treatment after consolidation and induction therapy. So it may have different implications for a patient receiving SCT than for a transplant-ineligible patient.

For transplant-eligible patients, who receive 4 to 6 months of therapy and a single SCT, the question is whether to stop or continue treatment. The data are mixed in that setting. The US-based CALGB-100104 study reported a clear overall survival benefit with maintenance therapy. The more mature French IFM 2005-02 study, which did not allow crossover, reported no improvement in overall survival despite a similar improvement in progression-free survival to that in the US study (Singh 2013; [3.1]).

One of the fundamental differences in the design of the 2 studies is that patients on the control arm of the French study initially received 2 months of lenalidomide/dexamethasone consolidation. This raises the question of whether a group of patients exists who don't need continuous therapy and only need a couple of cycles of lenalidomide after SCT. The important aspect is to identify patients who would benefit the most from maintenance therapy.

In the transplant-ineligible population the story is different. Several trials have evaluated treatment continuation with thalidomide with or without bortezomib and showed an improvement in progression-free and overall survival. In this setting the debate is,

3.1

Meta-Analysis of Randomized Trials of Lenalidomide Maintenance Therapy in Multiple Myeloma

	Overall survival		PFS	
Phase III trial	HR*	*p*-value	HR*	*p*-value
IFM 2005-02	1.060	0.664	0.500	<0.001
CALGB-100104	0.610	0.008	0.480	<0.001
MM-015	0.790	0.251	0.340	<0.001
RV-MM-P1209	0.620	0.018	0.520	<0.001
Summary estimate	**0.767**	**0.071**	**0.491**	**<0.001**

* HR < 1 favors lenalidomide maintenance over no maintenance therapy.

PFS = progression-free survival; HR = hazard ratio

Singh PP et al. *Proc ASH* 2013;**Abstract 407**.

are we truly evaluating maintenance or are we trying to define what the duration of the ideal therapy should be?

DR LOVE: What are your thoughts on the results of the Phase III FIRST trial evaluating limited or continuous lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM (Benboubker 2014)?

DR KUMAR: The authors reported that overall survival was better with continuous Rd than with MPT. However, no difference was observed in overall survival between Rd administered continuously and Rd administered for 18 months. This suggests that early relapse after a patient stops receiving lenalidomide can be successfully salvaged by restarting lenalidomide or initiating a different therapy. The jury is still out on the ideal duration of therapy in this setting.

DR LOVE: You were also involved in a meta-analysis evaluating the incidence of second primary cancers with lenalidomide in newly diagnosed MM (Palumbo 2014; [3.2]). What were the study outcomes, and how do you approach this issue?

DR KUMAR: That analysis is important because it collected data from multiple institutions and asked a specific question: For patients initially receiving lenalidomide therapy, if that therapy is continued long term, is the risk of second primary cancer increased? The simple answer is no. However, the increase in second primary cancer with lenalidomide occurs in patients also receiving an alkylating agent, particularly melphalan.

I don't believe that lenalidomide is the cause of second primary cancer per se, but it's a facilitator. This is reassuring for patients with newly diagnosed MM who initially receive lenalidomide/dexamethasone and no alkylator. For a patient who achieved a good response to lenalidomide before SCT, I would strongly advocate for its use, but for a limited duration of 2 years. However, the decision should be made after a discussion of the risks and benefits. ■

3.2

Meta-analysis of Risk of Second Primary Cancer with Lenalidomide for Newly Diagnosed Multiple Myeloma

"Exposure to lenalidomide plus oral melphalan significantly increased haematological second primary malignancy risk versus melphalan alone (HR 4.86; $p<0.0001$). Exposure to lenalidomide plus cyclophosphamide … or lenalidomide plus dexamethasone … did not increase haematological second primary malignancy risk versus melphalan alone … These results suggest that alternatives, such as cyclophosphamide or alkylating-free combinations, should be considered instead of oral melphalan in combination with lenalidomide for myeloma."

Palumbo A et al. *Lancet Oncol* 2014;15(3):333–42.

SELECT PUBLICATIONS

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906–17.

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801–9.

Kumar SK et al. **A phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM).** *Proc ASH* 2012;**Abstract 332**.

Wang M et al. **Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma.** *Blood* 2013;122(18):3122–8.

INTERVIEW

Michelle A Fanale, MD

Dr Fanale is Associate Professor in the Department of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-13

Track 1 Approved indications and ongoing evaluation of brentuximab vedotin-based regimens in Hodgkin lymphoma (HL)

Track 2 CheckMate 205: An ongoing Phase II study of the anti-PD-1 agent nivolumab for patients with classical HL after failure of autologous stem cell transplant

Track 3 Management of brentuximab vedotin-associated peripheral neuropathy

Track 4 Incidence of brentuximab vedotin-associated pancreatitis

Track 5 Ongoing trials evaluating brentuximab vedotin in HL

Track 6 Management of early-stage HL with combined-modality treatment versus a nonradiation therapy-containing approach

Track 7 Novel agents and pathways under investigation in HL

Track 8 Differential management of T-cell lymphoma (TCL) subtypes

Track 9 ECHELON-2: A Phase III trial of brentuximab vedotin in combination with CHP versus CHOP as front-line therapy for CD30-positive mature TCL

Track 10 Correlation between CD30 positivity and benefit from brentuximab vedotin

Track 11 Rationale for combining romidepsin with the novel Aurora A kinase inhibitor alisertib for relapsed/refractory aggressive B-cell and T-cell lymphomas

Track 12 Sequencing of romidepsin, pralatrexate and belinostat in patients with TCL

Track 13 Activity of lenalidomide alone or in combination regimens in diffuse large B-cell lymphoma

Select Excerpts from the Interview

Tracks 1, 3-4, 9

DR LOVE: What are your thoughts on where we are and where we are heading with brentuximab vedotin in Hodgkin lymphoma (HL)?

DR FANALE: Brentuximab vedotin was approved a few years ago for relapsed classical HL in the third-line setting for patients who had further disease relapse after an autologous stem cell transplant. It was then evaluated in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) in the front line for advanced HL, but we had to drop bleomycin from the regimen because of pulmonary toxicity. The early PET scans from that study showed a high negativity rate with both ABVD/brentuximab and AVD/brentuximab (Younes 2013).

We have performed a retrospective study analyzing progression-free survival as a secondary endpoint of this trial, and the data are promising. We hope to present those findings at ASH 2014. Our institution is also a participating center for the Phase III trial comparing AVD/brentuximab vedotin to ABVD for classical HL.

DR LOVE: What has been your experience with brentuximab vedotin-associated PN?

DR FANALE: I haven't ever seen it become a problem to the point at which I've needed to stop treatment. When I've seen issues with neuropathy, it's generally been in someone who already had some baseline PN. Those patients seem to have a higher chance of developing Grade 2 or 3 PN. I will generally hold treatment, if necessary, and then I will deescalate the dose. I'll take them from 1.8 to 1.2 mg/kg, still at every 3 weeks. I've had an occasional patient for whom I spread it out to every 5 weeks or 6 weeks, but I've never needed to actually stop treatment because of PN.

DR LOVE: Have any of your patients receiving brentuximab vedotin experienced pancreatitis?

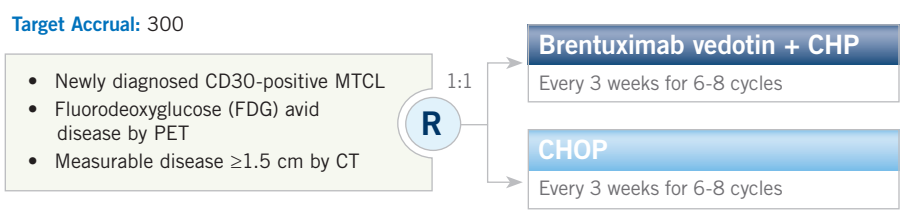
DR FANALE: Reports have been made of small numbers of patients developing pancreatitis (Gandhi 2013), but I've never seen any cases or had any patients experience issues with pancreatitis or even amylase lipase elevation.

DR LOVE: Would you also discuss the ECHELON-2 trial comparing brentuximab vedotin combined with CHP to CHOP chemotherapy for T-cell lymphoma (TCL)?

DR FANALE: ECHELON-2 is an ongoing front-line trial for patients with newly diagnosed TCL and lymph node involvement (4.1). Patients must have a level of CD30 expression on the surface of their cancer cells of 10% or more by IHC. Other upcoming trials will evaluate CHOP with belinostat and, internationally, CHOP with romidepsin.

4.1

ECHELON-2: An Ongoing Phase III Trial of Brentuximab Vedotin/CHP versus CHOP Chemotherapy in the Front-Line Treatment of CD30-Positive Mature T-Cell Lymphoma (MTCL)



Primary endpoint: Progression-free survival by independent review

CHP = cyclophosphamide/doxorubicin/prednisone

O'Connor OA et al. *Proc ASCO* 2013;**Abstract TPS8611**.

Tracks 11-12

DR LOVE: Would you discuss how you manage relapsed/refractory TCL?

DR FANALE: Right now we are focusing on single agents under evaluation or combinations of drugs that have already been approved as single agents. Romidepsin is approved for cutaneous TCL (CTCL) and peripheral TCL (PTCL), and I am involved in a trial that is administering romidepsin in combination with the oral Aurora A kinase inhibitor alisertib (NCT01897012). The thought behind that is that we know romidepsin generally yields response rates of approximately 30% (Coiffier 2012).

Initial data on alisertib from a Phase II trial for patients with PTCL indicated an overall response rate of approximately 50% (Friedberg 2014). The hope is that by administering the combination we can drive up the response rate. Typically, if I see a patient who has already received CHOP, ICE and ASCT, I consider this for the next line.

DR LOVE: How else has alisertib, which is orally bioavailable and also seems to be clinically active in aggressive B-cell lymphomas (Friedberg 2014), been studied, and how, if at all, do you see its role in the future?

DR FANALE: Alisertib is being compared to standard options, such as romidepsin or gemcitabine-based therapy, for patients with relapsed/refractory disease. It's an attractive agent from a patient perspective because it's oral. I am interested in seeing the final results of the large registration trial and whether alisertib can now follow those agents that have already been approved, like romidepsin, pralatrexate and, most recently, belinostat and brentuximab vedotin for patients with anaplastic large cell lymphoma.

DR LOVE: What is your approach to sequencing romidepsin, pralatrexate and belinostat for patients with TCL?

DR FANALE: Response rates with romidepsin, pralatrexate and belinostat are reasonably equivalent (Petrich 2013). Typically, for patients who have undergone ASCT, received 2 lines of therapy and do not meet the eligibility for or prefer not to participate in a trial, I consider romidepsin, pralatrexate or belinostat. Belinostat stands apart from romidepsin in that it results in a lower rate of significant thrombocytopenia (O'Connor 2013).

Another difference is in dosing. Romidepsin has a long infusion time, and it's administered once a week for 3 weeks. The infusion time for belinostat is significantly shorter, but it's administered for 5 days in a row. That choice is somewhat personal.

I also use pralatrexate, which is an effective agent, but the main issue to keep in mind is mucositis, especially if a patient is already debilitated from the disease itself. I can generally manage it by dose reducing or spreading out the doses in a CTCL-based schema, and some studies are evaluating leucovorin, which would be administered with methotrexate to try to decrease the mucositis. I don't know what the final word will be, but that would make it more palatable. ■

SELECT PUBLICATIONS

Coiffier B et al. **Therapeutic options in relapsed or refractory peripheral T-cell lymphoma.** *Cancer Treat Rev* 2014;40(9):1080-8.

Coiffier B et al. **Results from a pivotal, open-label, Phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.** *J Clin Oncol* 2012;30(6):631-6.

Friedberg JW et al. **Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas.** *J Clin Oncol* 2014;32(1):44-50.

Gandhi M et al. **Pancreatitis in patients treated with brentuximab vedotin: A previously unrecognized serious adverse event.** *Proc ASH* 2013;**Abstract 4380**.

O'Connor OA et al. **Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial.** *Proc ASCO* 2013;**Abstract 8507**.

Petrich AM, Rosen ST. **Peripheral T-cell lymphoma: New therapeutic strategies.** *Oncology (Williston Park)* 2013;27(9):878-84.

Younes A et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: A phase 1, open-label, dose-escalation study.** *Lancet Oncol* 2013;14(13):1348-56.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A Phase III study comparing idelalisib and rituximab to rituximab alone for relapsed CLL demonstrated a significant difference in favor of the idelalisib arm in terms of _____.**
   a. Overall response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above

2. **A recent study comparing obinutuzumab and chlorambucil to rituximab and chlorambucil for elderly patients with comorbidities demonstrated greater benefit with the rituximab combination for previously untreated CLL.**
   a. True
   b. False

3. **The Phase III LYM-3002 study, which evaluated R-CHOP versus VR-CAP for newly diagnosed, transplant-ineligible MCL, demonstrated significant increases in complete response rate, median duration of response and median progression-free survival with VR-CAP in comparison to R-CHOP.**
   a. True
   b. False

4. **A Phase II trial of low-dose cytarabine with or without volasertib for patients with AML not suitable for induction therapy reported an improvement in _____ with the combination.**
   a. Median event-free survival
   b. Median overall survival
   c. Overall response rate
   d. All of the above
   e. None of the above

5. **The ongoing Phase II/III SWOG-S1117 trial is evaluating azacitidine alone or in combination with _____ for patients with higher-risk MDS and chronic myelomonocytic leukemia.**
   a. Lenalidomide
   b. Vorinostat
   c. Either a or b
   d. Neither a nor b

6. **The ongoing Phase III ECOG-E1A11 (ENDURANCE) trial is randomly assigning patients with newly diagnosed symptomatic MM to receive either _____ or bortezomib in combination with lenalidomide and dexamethasone followed by limited or indefinite lenalidomide maintenance.**
   a. Ixazomib
   b. Oprozomib
   c. Carfilzomib

7. **A meta-analysis of individual patient data evaluating the incidence of second primary cancer with lenalidomide therapy for patients with newly diagnosed MM demonstrated that only patients who received lenalidomide in combination with an alkylating agent had an increased risk of developing a second primary cancer.**
   a. True
   b. False

8. **Results from the Phase III FIRST trial evaluating limited or continuous Rd versus standard MPT for transplant-ineligible patients with newly diagnosed MM demonstrated a statistically significant improvement in overall survival in favor of continuous Rd versus MPT.**
   a. True
   b. False

9. **ECHELON-2 is a Phase III trial evaluating _____/CHP versus CHOP as front-line therapy for CD30-positive mature TCL.**
   a. Pralatrexate
   b. Brentuximab vedotin
   c. Romidepsin

10. **Compared to romidepsin, the HDAC inhibitor belinostat is associated with a lower rate of thrombocytopenia.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 2014

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
Results of a Phase III trial of R-CHOP versus VR-CAP for newly diagnosed, transplant-ineligible MCL	4 3 2 1	4 3 2 1
Activity of volasertib with low-dose cytarabine in relapsed/refractory AML	4 3 2 1	4 3 2 1
Results of 2 separate meta-analyses evaluating the incidence of second primary cancer with lenalidomide for newly diagnosed disease and use of the agent as maintenance therapy in MM	4 3 2 1	4 3 2 1
ECHELON-2: A Phase III trial of brentuximab vedotin/CHP versus CHOP as front-line therapy for CD30-positive TCL	4 3 2 1	4 3 2 1
Rationale for combining romidepsin with the novel Aurora A kinase inhibitor alisertib for relapsed/refractory aggressive B-cell and T-cell lymphomas	4 3 2 1	4 3 2 1
ECOG-E1A11 (ENDURANCE): A Phase III trial of RVd versus CRd → lenalidomide maintenance for newly diagnosed symptomatic MM	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:

- Appraise the recent FDA approvals of ibrutinib, idelalisib and obinutuzumab, and discern how these agents can be appropriately integrated into clinical practice for patients with chronic lymphocytic leukemia and other B-cell neoplasms. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors as therapeutic options for patients with chronic myeloid leukemia. . . . 4 3 2 1 N/M N/A
- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction, consolidation and maintenance treatment approaches for patients with multiple myeloma.. . . . . 4 3 2 1 N/M N/A
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas. . . . . 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

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

- Recognize the role of novel agents and regimens in the management of relapsed/refractory acute myeloid leukemia. . . . . 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.
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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
Michael E Williams, MD, ScM	4 3 2 1	4 3 2 1
Harry P Erba, MD, PhD	4 3 2 1	4 3 2 1
Shaji K Kumar, MD	4 3 2 1	4 3 2 1
Michelle A Fanale, 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

Please recommend additional faculty for future activities:

. . . . . .

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