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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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CME Certified

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Hematologic Oncology Update
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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

- Optimize the management of chronic lymphocytic leukemia through the rational integration of prospective pivotal data sets.
- Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment.
- Apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes.
- Develop a treatment approach for younger and older patients with mantle-cell lymphoma based on recent clinical trial data.
- Outline the classification of T-cell lymphomas, and formulate up-to-date treatment strategies for patients with diverse subtypes of the disease.
- Summarize the critical factors in selecting patients with chronic myelogenous leukemia for treatment with first- and second-generation tyrosine kinase inhibitors.
- Employ an understanding of recent findings with proteasome inhibitors and immunomodulatory agents in individualized induction and maintenance therapy for patients with multiple myeloma.
- Describe the biologic rationale, efficacy and toxicity of novel agents targeting CD30-positive Hodgkin lymphoma and anaplastic large cell lymphoma.
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.

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INTERVIEW

Brad S Kahl, MD

Dr Kahl is Associate Professor and Director of the Lymphoma Service at the University of Wisconsin School of Medicine and Public Health and Associate Director for Clinical Research at UW Carbone Cancer Center in Madison, Wisconsin.

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Select Excerpts from the Interview

Track 5

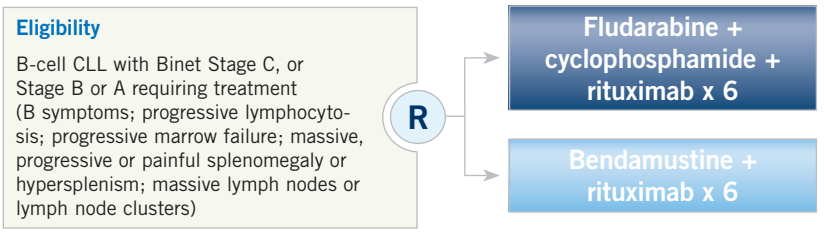
DR LOVE: What is your approach to first-line therapy for an older patient with chronic lymphocytic leukemia (CLL)?

DR KAHL: At present, I might be more inclined to start with bendamustine in combination with rituximab. Fludarabine is an active drug in CLL but has a number of potential problems — cytopenias and infectious complications — as folks get older. A presentation at ASH 2010 of a head-to-head comparison of bendamustine/rituximab (BR) to fludarabine/rituximab (FR) reported better performance with BR in patients with relapsed indolent lymphoma (Rummel 2010). If you extrapolate that to the CLL population, it may end up being a better choice for patients of all ages. An ongoing randomized trial is evaluating that question, although the comparison is BR versus fludarabine/cyclophosphamide/rituximab (FCR) (1.1).

For younger patients, the choice would be between BR and FCR. FCR is an effective therapy, but it's hard on the stem cells, bone marrow and blood counts, which sometimes makes it difficult to administer subsequent therapies. I'm eagerly awaiting the data from the randomized trial (1.1), with the expectation that BR will at least be equivalent if not superior to FCR because I believe BR will be better tolerated.

1.1 **Combined Immunochemotherapy versus Bendamustine and Rituximab as Up-Front Treatment for Chronic Lymphocytic Leukemia (CLL)**

Protocol IDs: GCLLSG-CLL10, EUDRACT-2007-007587-21, EU-20883
Target Accrual: 550



www.clinicaltrials.gov. Identifier NCT00769522.

Track 12

DR LOVE: Would you discuss the PRIMA study, which evaluated two years of rituximab maintenance for patients with follicular lymphoma (FL) responding to immunochemotherapy?

DR KAHL: The PRIMA study evaluated approximately 1,000 patients with FL. The immunochemotherapy regimen was the center's choice between R-CHOP, R-CVP and a third fludarabine-based arm, which few centers chose.

Patients who did not experience progression were then randomly assigned to observation or maintenance rituximab. A profound progression-free survival benefit was reported with maintenance rituximab (Salles 2011; [1.2]). At three years, approximately 60 percent of the patients not receiving maintenance are still in remission, but that number is closer to 80 percent for those who did receive maintenance. That's quite a striking absolute difference. No overall survival difference was observed between the two groups.

From a toxicity standpoint, immunoglobulin levels did not drop in the patients receiving maintenance rituximab. The infection rates were slightly higher, but the infections were generally not serious.

1.2

Rituximab (R) Maintenance for Patients with Follicular Lymphoma Responding to Immunochemotherapy: Survival and Adverse Events (AEs) in the PRIMA Study at 36 Months Median Follow-Up

	R maintenance (n = 501)	Observation (n = 508)	Hazard ratio (HR) or risk ratio (RR)	*p*-value
Three-year PFS	74.9%	57.6%	0.55 (HR)	<0.0001
Grade 3 or 4 AEs	24%	17%	1.46 (RR)	0.0026
Grade 2 to 4 infections	39%	24%	1.62 (RR)	<0.0001
Treatment discontinued due to AE	4%	2%	2.41 (RR)	0.029

PFS = progression-free survival

Salles G et al. *Lancet* 2011;377(9759):42-51.

Track 13

DR LOVE: Would you update us on the ECOG RESORT trial of which you are the principal investigator, which is evaluating long-term rituximab maintenance?

DR KAHL: The RESORT trial is evaluating long-term rituximab dosing strategies. Patients with previously untreated low tumor burden indolent lymphoma receive four weekly doses of single-agent rituximab. The first group of responding patients receives rituximab re-treatment on an as-needed basis upon disease recurrence. As long as disease remissions are lasting at least six months, patients continue to be re-treated at each progression until they stop responding to rituximab.

The other group of patients receives a single dose of rituximab every three months as maintenance. As long as they remain in remission, they continue to

receive the agent indefinitely. Our primary endpoint is time to rituximab resistance. We're trying to determine if one strategy is better for controlling disease. We are hoping to report our first data soon, maybe at this year's ASH meeting.

Track 15

DR LOVE: What are your thoughts on the Intergroup study of rituximab versus watch and wait in advanced-stage, nonbulky FL?

DR KAHL: This was a large trial conducted in the United Kingdom, evaluating the same patient population that we have in the RESORT trial — patients with low tumor burden, indolent lymphoma — but their question is different than ours. This study evaluated rituximab versus a watch-and-wait strategy. The presumption is that when patients with indolent lymphoma move on to chemotherapy, they experience a detriment in quality of life. If you could apply a nontoxic strategy that could delay the time it takes for patients to get to chemotherapy, that should translate into a quality-of-life benefit.

The results were presented at ASH 2010, and the authors reported that the time it takes to move to chemotherapy is substantially longer for the patients who started out receiving rituximab treatment compared to the watch-and-wait group (Ardeshna 2010). No overall survival difference was reported.

Many physicians are struggling with how to apply this information to their practice. We don't know if quality of life is being affected in a clinically meaningful manner. We have to appreciate that every patient is different and a one-size-fits-all approach is not appropriate. Some patients derive great psychological comfort from knowing their disease is in remission, whereas others are comfortable living with their disease and not receiving therapy.

This study hasn't yet changed my practice. For several years I have been having long discussions with my patients who have low tumor burdens. I tell them my recommendation is to watch and wait, but for patients who are uncomfortable with that approach we focus on rituximab monotherapy or rituximab with chemotherapy and try to make a decision together.

Tracks 17-19

DR LOVE: Would you comment on what's going on right now in mantle-cell lymphoma (MCL) research and practice?

DR KAHL: A number of active questions are being pursued for younger patients with MCL. For example, if stem cell transplant is part of your initial treatment strategy, how important is choice of induction therapy? In other words, does the induction therapy matter?

A large European trial in which patients were randomly assigned to either R-CHOP or R-CHOP with alternating R-DHAP was presented at ASH 2010. The authors reported a significant advantage in terms of progression-free survival for the patients who received high-dose cytarabine (Hermine 2010).

I believe some merit exists for trying to build that into your induction strategy, whether it be R-CHOP alternating with R-DHAP or whether it be hyper-CVAD, which has high-dose cytarabine. That's a reasonable course. Once a younger patient is in remission, it's a reasonable approach to then consolidate that remission with stem cell transplant.

Options for older patients are tougher. They can't tolerate these intensive strategies, so treatment options are more limited. We're hopeful that BR will prove to be an effective induction strategy for older patients with MCL.

A planned US cooperative group trial with a target accrual of approximately 300 patients with MCL will evaluate induction BR with or without bortezomib followed by rituximab with or without lenalidomide as maintenance therapy.

A large European trial for older patients with MCL recently reported a major benefit with rituximab maintenance after initial therapy. The Data Safety Monitoring Board closed this trial early because the rituximab maintenance group was performing substantially better (Kluin-Nelemans 2011; [1.3]). So for the first time, good evidence supports the use of rituximab maintenance in older patients with MCL. ■

1.3

Rituximab (R) Maintenance After Induction Therapy with R-CHOP or R-FC for Elderly Patients with Mantle-Cell Lymphoma: First Results from the European MCL Network Study

Response	R maintenance	IFN maintenance	Hazard ratio	*p*-value
Median remission duration	51 months	24 months	0.56	0.0117
Three-year overall survival with R-CHOP induction	85%	70%	—	0.0375

Kluin-Nelemans H et al. *Proc EHA* 2011;**Abstract 0504**.

SELECT PUBLICATIONS

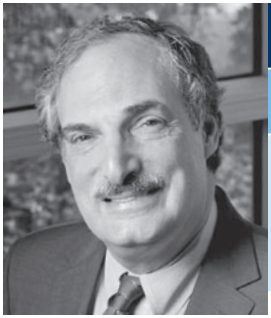
Ardeshna KM et al. **An Intergroup randomised trial of rituximab versus a watch and wait strategy in patients with Stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (Grades 1, 2 and 3a). A preliminary analysis.** *Proc ASH* 2010;**Abstract 6**.

Hermine O et al. **Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net).** *Proc ASH* 2010;**Abstract 110**.

Kluin-Nelemans HC, Doordujin JK. **Treatment of elderly patients with mantle cell lymphoma.** *Semin Hematol* 2011;48(3):208-13.

Rummel MJ et al. **Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas — Final results of the randomized Phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2010;**Abstract 856**.

Salles G et al. **Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial.** *Lancet* 2011;377(9759):42-51.



INTERVIEW

David J Straus, MD

Dr Straus is Attending Physician in the Department of Medicine at Memorial Sloan-Kettering Cancer Center and Professor of Clinical Medicine at Weill Medical College of Cornell University in New York, New York.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-5

DR LOVE: Would you discuss SGN-35, or brentuximab vedotin, and its use in relapsed/refractory Hodgkin lymphoma (HL)?

DR STRAUS: SGN-35 is an immunotoxin — a fusion molecule of a monoclonal antibody directed against CD30, which is expressed on the Reed-Sternberg cells of classic HL. The anti-CD30 monoclonal antibody is attached to auristatin, a mitotic spindle inhibitor. The data presented at ASH 2010 from a Phase II study with this agent were spectacular. The overall response rate was 75 percent, with 34 percent complete responses — and this was in a group of patients with heavily pretreated disease, all of whom had already undergone autologous stem cell transplants (Chen 2010; [2.1]). Approximately 70 percent of the patients had primary refractory disease and did not experience responses to front-line treatment.

Side effects are similar to those of the vinca alkaloids, specifically neuropathy. Sensory neuropathy was observed in 47 percent of patients. Grade III

neuropathy was observed in eight percent, but Grade 1 and Grade 2 fatigue and nausea were also reported.

A companion study was also reported at ASH of SGN-35 in anaplastic large cell lymphoma (ALCL), which is a subgroup of peripheral T-cell lymphoma (PTCL). In this lymphoma, tumor cells also express CD30, which is in common with the Reed-Sternberg cells of HL, although the Reed-Sternberg cells are not T cells. The study reported an impressive overall response rate of approximately 80 percent (Shustov 2010; [2.1]). CD30 is also expressed in some B-cell non-Hodgkin lymphomas, particularly in primary mediastinal diffuse large B-cell lymphomas. They are CD20-positive B-cell lymphomas, but they often express CD30 also, and I believe some data suggest a relationship between this particular non-Hodgkin lymphoma and HL.

2.1

Response and Maximum Tumor Reduction with Brentuximab Vedotin (SGN-35) in Relapsed/Refractory Hodgkin Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL)*

	HL[1] (n = 102)	ALCL[2] (n = 58)
Overall response rate	75%	86%
Complete remission	34%	53%
Partial remission	40%	33%
Maximum tumor reduction (n = 96, 57)	94%	97%

* By independent review facility

[1] Chen R et al. *Proc ASH* 2010;**Abstract 283**; [2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

Tracks 8-9

DR LOVE: What are your thoughts on pralatrexate and romidepsin, which were recently approved for the treatment of advanced T-cell lymphomas?

DR STRAUS: Pralatrexate is newly approved for the treatment of PTCL. It is an antifolate agent with a high affinity for the reduced folate carrier type 1 and is designed to accumulate preferentially in tumor cells. In preclinical studies it is polyglutamated more than agents such as methotrexate, and therefore it is pumped out of the cell less avidly. The PROPEL study reported a 29 percent overall response rate with pralatrexate in relapsed or refractory PTCL, which was enough to obtain approval (O'Connor 2011; [2.2]). Studies are beginning to move pralatrexate into the front-line setting, perhaps with CEOP (NCT01336933).

Romidepsin is an HDAC inhibitor and has an indication in cutaneous T-cell lymphoma (CTCL), with approximately a 30 percent response rate, but I believe it will be approved in PTCL also (Demierre 2009). Romidepsin is administered intravenously, whereas some of the other HDAC inhibitors are oral. This agent can cause fatigue and diarrhea, and in some of the earlier

studies, reports arose of cardiac arrhythmias, although in more recent studies with dose adjustments this has not been a problem. The prospect of having a second agent approved for use in this setting is exciting.

DR LOVE: Outside of a protocol setting, how do you currently use HDAC inhibitors in CTCL?

DR STRAUS: The HDAC inhibitors romidepsin and vorinostat are approved for CTCL that requires systemic treatment, and these are among a longer list of agents that are active in advanced CTCL, including most chemotherapy agents. Almost every class of chemotherapy agent has a 20 to 40 percent response rate in this setting, as do romidepsin and vorinostat. The problem is that, unlike the other non-Hodgkin lymphomas and HL, in which you can treat for some time and expect durable unmaintained remissions, the remissions in CTCL last as long as you're administering treatment. So when you stop treatment, the disease recurs fairly quickly.

DR LOVE: How do side effects factor into the decision to administer the various available agents?

DR STRAUS: The side effects are important because all of the agents have similar activity. Bexarotene tends to be popular because it's an oral agent, as does vorinostat, which is an oral HDAC inhibitor. Denileukin diftitox, which was one of the first immunotoxins to come on the market about 10 years ago, also has a role in this area. ■

2.2

PROPEL Study: Single-Agent Pralatrexate in Relapsed or Refractory Peripheral T-Cell Lymphoma

Efficacy (n = 109)

Complete response	Partial response	Overall response
11%	18%	29%

Grade 3 or 4 adverse events

Thrombocytopenia	32%	Neutropenia	22%
Mucositis	22%	Anemia	18%

O'Connor OA et al. *J Clin Oncol* 2011;29(9):1182-9.

SELECT PUBLICATIONS

Chen R et al. **Results of a pivotal Phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASH* 2010;**Abstract 283**.

Demierre M et al. **Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL).** *Proc ASCO* 2009;**Abstract 8546**.

Shustov AR et al. **Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2010;**Abstract 961**.

INTERVIEW

Elias Jabbour, MD

Dr Jabbour is Assistant Professor and Internist in the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-13

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is your approach to selection of first-line therapy for a patient with chronic-phase chronic myelogenous leukemia (CML)?

DR JABBOUR: Three options have been approved by the FDA — imatinib, nilotinib and dasatinib. The question is, which therapy do you start with? One question I receive from community oncologists is, "Can I start patients on imatinib and switch to one of the newer agents if the patient is not responding

well?" My answer is, "You may never have a second chance. You go to the war with the best weapons you have."

At eight years of follow-up with imatinib, 35 percent of patients either responded and lost their response or never responded (Deininger 2009). If you administer second-line salvage therapy with either nilotinib or dasatinib, only 50 percent of patients will respond, so why wait until the second line to go to these agents?

Nilotinib and dasatinib both have shown increased rates of complete cytogenetic response (CCyR) by 12 months (Saglio 2010; Kantarjian 2010). Why is that important? If you can improve the rate of CCyR by 12 months, then you can improve survival. That correlation needs to be shown in the future, but at least we have a surrogate endpoint. Major molecular response — another secondary endpoint — is also improved with these agents compared to imatinib.

Nilotinib has also been reported to improve transformation-free survival significantly (Saglio 2010). Patients with CML die only if their disease transforms, so if nilotinib can reduce the rate of transformation, patients can survive with chronic-phase CML for a long time. We are no longer administering imatinib in a front-line setting based on this evidence.

How to best select among the second-generation agents is a hard decision as we administer both of these agents. The DASISION trial did not show the rate of improvement in transformation with dasatinib that was reported with nilotinib in the ENESTnd trial. However, nilotinib is administered twice daily and dasatinib once a day, so one aspect to consider is the patient's rhythm of life. If a patient is traveling all the time, for example, I tend to opt for dasatinib.

Comorbidities should also be considered. If I have a patient who is a smoker and who has hypertension, I avoid dasatinib because of the risk of pleural effusion.

DR LOVE: How often do you have patients referred to you with intolerance to imatinib, and if you're going to switch to one of the other available agents, how do you make that decision at that point?

DR JABBOUR: We're seeing more patients with intolerance. In the past, switching was rare because we had no other options. In my experience, if a patient was responding to imatinib and then becomes intolerant, a switch to either nilotinib or dasatinib will be effective. If the patient has not experienced a response to imatinib, the likelihood of experiencing a response to a second-generation tyrosine kinase inhibitor is not as great.

Generally, if I have a patient who has a major problem with intolerance to imatinib, it's occurring as a result of pancytopenia. In this case, I would prefer switching to nilotinib.

Given a patient with an imatinib-related skin rash, I may opt for dasatinib because skin rash has been observed with nilotinib. Overall, cross intolerances between imatinib and nilotinib or imatinib and dasatinib are extremely rare.

Track 12

DR LOVE: Can you discuss the recent *Journal of Clinical Oncology* publication from your group on orally administered azacitidine in myelodysplastic syndromes (MDS)?

DR JABBOUR: Oral azacitidine is promising, and we're administering it up front for patients with MDS (Garcia-Manero 2011; [3.1]).

We have observed increased platelet counts in these patients, which could be a result of the azacitidine therapy. So high platelets at the beginning of therapy should not be a discouraging sign. It could be an effect caused by the therapy because after approximately a month of treatment, the platelet count decreases and a response begins to appear. ■

3.1

Phase I Study of Oral Azacitidine* for Patients with Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia or Acute Myeloid Leukemia†

Response	First line (n = 15)	Previously treated (n = 17)
Overall response (excluding mCR)	73%	35%
Complete remission‡	40%	0%
Hematologic improvement	56%	38%
Erythroid	50%	30%
Neutrophil	29%	0%
Platelet	33%	36%
Bone marrow complete remission (mCR)	33%	67%

* One cycle of subcutaneous azacitidine (75 mg/m^2) on the first seven days of cycle one followed by oral azacitidine daily (120 to 600 mg) on the first seven days of each additional 28-day cycle
† No patients with acute myeloid leukemia experienced a response
‡ Patients achieving complete remission were not included in any other categories

Garcia-Manero G et al. *J Clin Oncol* 2011;29(18):2521-7.

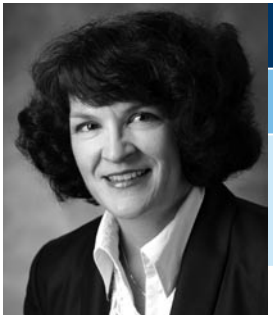
SELECT PUBLICATIONS

Deininger M et al. **International Randomized Study of Interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib.** *Proc ASH* 2009;**Abstract 1126**.

Garcia-Manero G et al. **Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia.** *J Clin Oncol* 2011;29(18):2521-7.

Kantarjian H et al. **Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2260-70.

Saglio G et al. **Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2251-9.



INTERVIEW

Carol Ann Huff, MD

Dr Huff is Director of the Myeloma Program and Associate Professor of Oncology and Medicine at Johns Hopkins University in Baltimore, Maryland.

Tracks 1-18

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the recent study by Mateos and colleagues on lenalidomide in high-risk smoldering multiple myeloma (MM)?

DR HUFF: The question under evaluation in this study was, is it possible to change the natural history of smoldering myeloma? Until now we have not been able to consider that with any agents because of their side-effect profiles. However, with the immunomodulatory agents and, in particular, lenalidomide — which is well tolerated by most patients — we can begin to address this question.

Mateos and colleagues reported a decreased risk of progression to symptomatic disease in the patients who received lenalidomide versus those who did not (Mateos 2010).

This isn't completely unexpected because patients are receiving treatment, so their disease markers are changing. We do not yet have long-term data or know if we've affected overall survival. A currently ongoing study is randomly assigning patients with smoldering myeloma who meet high-risk criteria to single-agent treatment with lenalidomide or observation.

DR LOVE: Outside of a clinical trial, if a patient with smoldering myeloma requested treatment with lenalidomide, would you administer it?

DR HUFF: No. Even with this decreased risk of progression we still do not know how it would affect long-term overall survival. I would encourage interested patients to participate in the clinical trial.

Track 7

DR LOVE: Would you comment on the ASH 2010 presentation, which has now been published in *Lancet Oncology*, on subcutaneous administration of bortezomib in relapsed MM?

DR HUFF: A Phase III trial was presented on subcutaneous versus intravenous bortezomib on the same standard schedule of twice weekly. Investigators reported a significantly lower incidence of neurotoxicity from subcutaneous versus intravenous bortezomib, and it seemed to be associated with lower peak levels of the drug, with equal efficacy (Moreau 2011; [4.1]). Subcutaneous administration of bortezomib is appealing, and I hope it will move forward, perhaps even administered on a once-weekly basis.

In general, with bortezomib I use once-weekly IV dosing for patients with underlying neuropathy due to their disease, diabetes or a comorbid illness. In the absence of that, I initiate treatment at the full dose and administer it twice weekly. If warranted, the first dose reduction is typically to once-weekly administration versus changing the dose and maintaining it on a twice-weekly basis.

It's a more patient-friendly schedule in terms of traveling to the office once a week versus twice a week, and it works nicely in ameliorating the severity of the neuropathy. I have used it enough that clinically it syncs up with what I've read in the literature.

4.1

MMY-3021: A Phase III Trial of Subcutaneous (SC) versus Intravenous Administration of Bortezomib in Relapsed Multiple Myeloma

	Bortezomib SC (n = 145)	Bortezomib IV (n = 73)
Overall response rate[1]	42%	42%
Complete response	6%	8%
Partial response	36%	34%
≥Very good partial response	17%	16%

[1] Relative risk of overall response rate is 0.99 with 95% confidence interval of 0.71-1.37

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Track 9

DR LOVE: What are your thoughts on the third-generation IMiD pomalidomide?

DR HUFF: Pomalidomide is highly active in patients for whom lenalidomide is not. In the data from Lacy and colleagues, more than 40 percent of patients with disease progression on lenalidomide responded to pomalidomide (Lacy 2011; [4.2]), similar to how patients who experience disease progression while receiving thalidomide respond to lenalidomide. We don't have data on the converse — if the patients whose disease didn't respond to pomalidomide will respond to the other agents — but this agent is active and promising.

The toxicity seems to be predominantly hematologic but it does not appear to cause neuropathy and the other toxicities we've observed with thalidomide and, to some degree, lenalidomide. So if pomalidomide were available, I would consider it.

4.2

Pomalidomide in Myeloma Refractory to Bortezomib and Lenalidomide

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Objective response rate	49%	43%
Confirmed response (≥partial response)	26%	28%
Time to response (median)	1 month	1.7 months
Survival rate at six months	78%	67%

≥Minimal response rate for patients from both subgroups considered to be at high risk (N = 62) was 33%.

Lacy MQ et al. *Blood* 2011;[Epub ahead of print].

Track 10

DR LOVE: What do we know about the second-generation proteasome inhibitor carfilzomib?

DR HUFF: Carfilzomib has a slightly different mechanism of action and is administered a little differently than bortezomib. Carfilzomib is administered two days in a row intravenously. It's an hour-long infusion, and it seems to have a slightly different side-effect profile with perhaps less neuropathy, more asthenia and more fatigue. I believe it's an active agent that will likely become available for patients with myeloma, but I'm not convinced it will replace bortezomib.

DR LOVE: What are your thoughts on the presentation from ASH 2010 on carfilzomib/lenalidomide/dexamethasone (CRd) for patients with newly diagnosed MM?

DR HUFF: Andrzej Jakubowiak presented data on CRd at ASH showing high response rates and complete response rates (Jakubowiak 2010; [4.3]). It's a tantalizing combination. All of the new triple regimens are demonstrating such high response rates that it will be difficult to compare one to the other. Unfortunately, we have no head-to-head comparisons in terms of survival differences, and they would be difficult to conduct because many patients proceed to transplant or maintenance therapy. ■

4.3

Carfilzomib/Lenalidomide/Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma

Clinical response	CRd (n = 19)
≥Partial response (PR)	100%
≥Very good PR	63%
Complete response (CR) or near CR	37%

Jakubowiak AJ et al. *Proc ASH* 2010;**Abstract 862**.

SELECT PUBLICATIONS

Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of Phase I/II MMRC trial.** *Proc ASH* 2010;**Abstract 862**.

Lacy MQ et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Blood* 2011;[Epub ahead of print].

Mateos MV et al. **Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: A Phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (len-dex) as induction therapy followed by maintenance therapy with len alone vs no treatment.** *Proc ASH* 2010;**Abstract 1935**.

Moreau P et al. **Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study.** *Lancet Oncol* 2011;12(5):431-40.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III German CLL-10 trial is evaluating combined immunochemotherapy with FCR versus _____ for patients with previously untreated CLL.**
   a. FR with lenalidomide
   b. R-CHOP
   c. BR

2. **In an Intergroup randomized trial of rituximab versus watch and wait for patients with Stage II to Stage IV asymptomatic, nonbulky FL, patients receiving rituximab experienced a longer time to initiation of next treatment.**
   a. True
   b. False

3. **A trial evaluating maintenance rituximab after induction therapy with R-CHOP or R-FC for elderly patients with MCL reported that remission duration was more than doubled for patients receiving rituximab maintenance versus IFN maintenance.**
   a. True
   b. False

4. **A planned US cooperative group trial with a target accrual of approximately 300 patients with MCL will evaluate induction BR with or without _____ followed by maintenance therapy.**
   a. Bortezomib
   b. Bendamustine
   c. Lenalidomide

5. **Study data with brentuximab vedotin presented at ASH 2010 demonstrated an overall response rate of 75 percent or higher for patients with_____.**
   a. Hodgkin lymphoma
   b. Anaplastic large T-cell lymphoma
   c. Both a and b

6. **The antifolate agent pralatrexate is FDA approved for the treatment of PTCL.**
   a. True
   b. False

7. **Which of the following are approved treatments for patients with chronic-phase CML?**
   a. Dasatinib
   b. Imatinib
   c. Nilotinib
   d. All of the above

8. **In a Phase I study of oral azacitidine for patients with MDS, chronic myelomonocytic leukemia and acute myeloid leukemia, an increase in platelet counts was sometimes observed during initiation of therapy in patients who subsequently experienced disease response.**
   a. True
   b. False

9. **Investigators of a Phase III trial found a significantly lower incidence of neurotoxicity with the use of subcutaneous versus intravenous bortezomib, with the same efficacy results.**
   a. True
   b. False

10. **In data reported by Lacy and colleagues at the 2010 American Society of Hematology meeting, approximately 10 percent of patients with myeloma that was refractory to bortezomib and lenalidomide responded to the third-generation IMiD pomalidomide.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2011

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 ONE — 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
BR versus FR or FCR as first-line therapy for CLL	4 3 2 1	4 3 2 1
PRIMA and RESORT trials of maintenance rituximab in FL	4 3 2 1	4 3 2 1
Activity of brentuximab vedotin in heavily pretreated HL and ALCL	4 3 2 1	4 3 2 1
Study results with orally administered azacitidine in MDS	4 3 2 1	4 3 2 1
Subcutaneous versus IV bortezomib in relapsed myeloma	4 3 2 1	4 3 2 1
Carfilzomib, lenalidomide and dexamethasone versus RVD in myeloma	4 3 2 1	4 3 2 1
Pomalidomide after progression on lenalidomide in myeloma	4 3 2 1	4 3 2 1

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; no changes will be made
☐ 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 one 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:

- Optimize the management of chronic lymphocytic leukemia through the rational integration of prospective pivotal data sets. . . . . 4 3 2 1 N/M N/A
- Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment. . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes. . . . . 4 3 2 1 N/M N/A
- Develop a treatment approach for younger and older patients with mantle-cell lymphoma based on recent clinical trial data. . . . . 4 3 2 1 N/M N/A
- Outline the classification of T-cell lymphomas, and formulate up-to-date treatment strategies for patients with diverse subtypes of the disease. . . . . 4 3 2 1 N/M N/A
- Summarize the critical factors in selecting patients with chronic myelogenous leukemia for treatment with first- and second-generation tyrosine kinase inhibitors. . . . . 4 3 2 1 N/M N/A
- Employ an understanding of recent findings with proteasome inhibitors and immunomodulatory agents in individualized induction and maintenance therapy for patients with multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Describe the biologic rationale, efficacy and toxicity of novel agents targeting CD30-positive Hodgkin lymphoma and anaplastic large cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities. . . . . 4 3 2 1 N/M N/A

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

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

☐ Yes, I am willing to participate in a follow-up survey.

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

PART TWO — 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
Brad S Kahl, MD	4 3 2 1	4 3 2 1
David J Straus, MD	4 3 2 1	4 3 2 1
Elias Jabbour, MD	4 3 2 1	4 3 2 1
Carol Ann Huff, 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:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

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Hematologic Oncology™
UPDATE

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