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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Bruce D Cheson, MD
Steven D Gore, MD
Francine Foss, MD
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CME Certified

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

- 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.
- Efficiently apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes and acute myeloid leukemia.
- Recall the expanding body of evidence for the use of arsenic trioxide in the management of acute promyelocytic leukemia, and incorporate this agent, when appropriate, into evidence-based treatment algorithms.
- Outline the classification of T-cell lymphomas, and formulate up-to-date treatment strategies for patients with diverse subtypes of the disease.
- 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

Bruce D Cheson, MD

Dr Cheson is Professor of Medicine, Head of Hematology and Director of Hematology Research at the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-18

Tracks 1-2, 5-6

DR LOVE: What are the current evidence-based treatment options for up-front management of chronic lymphocytic leukemia (CLL)?

Select Excerpts from the Interview

DR CHESON: Bendamustine was recently evaluated versus chlorambucil in a Phase III trial in newly diagnosed CLL, and it resulted in a higher overall response rate and a higher complete response rate. More importantly, the primary endpoint of progression-free survival was significantly improved with bendamustine (Knauf 2009), leading to approval by the FDA.

A potential advantage of bendamustine is that data do not suggest that it's associated with an increased incidence of secondary cancer, at least in lymphoma (Rummel 2009). It remains to be seen in randomized trials whether that's true in CLL.

DR LOVE: Are any up-front trials in CLL ongoing that you'd like to comment on or that you're enrolling patients on?

DR CHESON: I believe the most important ongoing study right now is the German CLL-10 trial, which is evaluating fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR). The results of that trial may revolutionize how we approach this disease (1.1). An Intergroup study in the United States is evaluating FCR versus fludarabine/rituximab (FR) versus FR followed by lenalidomide maintenance for at least six months. In fact, we have administered FR → lenalidomide to more than 20 patients at our institution, and a few of the responses after FR have converted from partial responses to complete responses.

Lenalidomide is another potentially interesting drug in CLL. In the relapsed setting, two studies have taken place — one from MD Anderson (Ferrajoli 2008) with a response rate of approximately 35 percent and the other from Roswell Park (Chanan-Kahn 2006) with a response rate of approximately 45 percent. It has some unique adverse effects — notably, tumor lysis syndrome (TLS) and a tumor flare reaction.

1.1

Phase III Trial of 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

Eligibility

B-cell CLL with Binet Stage C or Stage B or A requiring treatment (B symptoms; progressive lymphocytosis; progressive marrow failure; massive, progressive or painful splenomegaly or hypersplenism; massive lymph nodes or lymph node clusters)

R

- Fludarabine + cyclophosphamide + rituximab x 6
- Bendamustine + rituximab x 6

Primary Endpoint: Progression-free survival rate after 24 months

www.clinicaltrials.gov. Identifier NCT00769522.

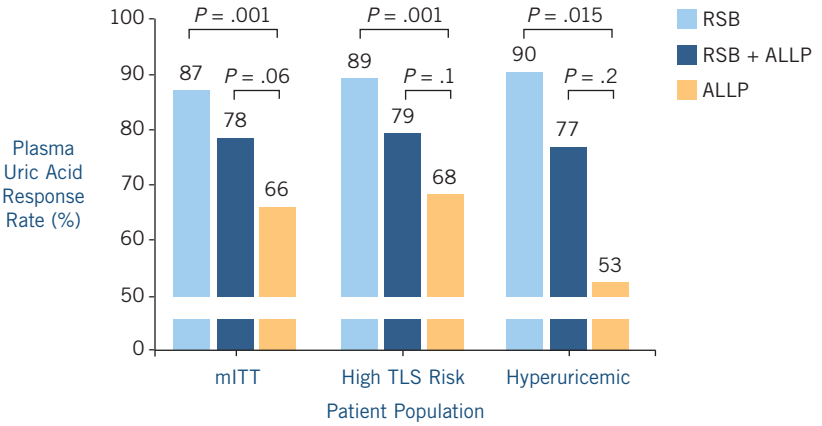
DR LOVE: What's your experience with tumor lysis in CLL and in general?

DR CHESON: In the past, TLS was uncommon with fludarabine, but now with more effective drugs such as lenalidomide we're seeing it more often — fortunately not always clinical TLS, sometimes just chemical. The more potent the drugs, the more likely you are to encounter tumor lysis (Cheson 2009).

For patients at higher risk for TLS it becomes a question of prevention: Is it fluids? Is it allopurinol or rasburicase (Cortes 2010; [1.2])? We tend to use rasburicase in patients at high risk who we believe may experience rapid tumor lysis from therapy. I have had no toxicity issues with that agent at all.

1.2

Control of Plasma Uric Acid in Adults at Risk for Tumor Lysis Syndrome (TLS): Rasburicase (RSB), RSB Followed by Allopurinol (ALLP) or ALLP Alone



Cortes J et al. *J Clin Oncol* 2010;28(27):4207-13. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

Track 11

DR LOVE: Would you talk about the ASH 2010 presentation on "watch and wait" versus rituximab monotherapy in follicular lymphoma (FL)?

DR CHESON: The study reported a significantly higher rate of disease progression in the watch-and-wait population. Time to next treatment, which was the primary endpoint, was significantly longer in the patient population who received treatment with rituximab, but no survival difference was evident (Ardeshna 2010).

I hope we will learn from the ongoing RESORT trial — which is evaluating four weekly doses of rituximab and then re-treatment upon relapse versus four weekly doses and indefinite maintenance — what the role of continuous treatment is in this setting.

Some older studies suggest that you can use rituximab again and the benefit may be equivalent to what you obtained from maintenance. Issues arise with rituximab maintenance — the expense, the nuisance, the risk of late infections and cytopenias and the risk of impairing responsiveness to subsequent treatments.

This has been seen in the transplant arena when patients who received rituximab previously had worse outcomes than patients who didn't. I believe we need longer follow-up on these data to ascertain if more toxicity occurs or if any survival benefit manifests itself. I'm not changing my practice currently.

Tracks 14-15

DR LOVE: What new treatment approaches for mantle-cell lymphoma (MCL) are being evaluated in clinical trials?

DR CHESON: We are planning an Intergroup study evaluating R-hyper-CVAD followed by transplant versus BR followed by transplant for younger patients who require treatment. The BR data in up-front MCL show a response rate of more than 90 percent and a progression-free survival significantly better than R-CHOP with considerably less toxicity (Rummel 2009).

For older patients, *the* standard regimen is R-CHOP, and it's a terrible standard. It has a median time to progression of approximately 18 months. So we are also planning a study for elderly patients evaluating a BR-based regimen followed by a few nontransplant maintenance options.

Track 18

DR LOVE: Over the past six months or year, throughout the field of hematologic oncology, have any other data sets caught your eye?

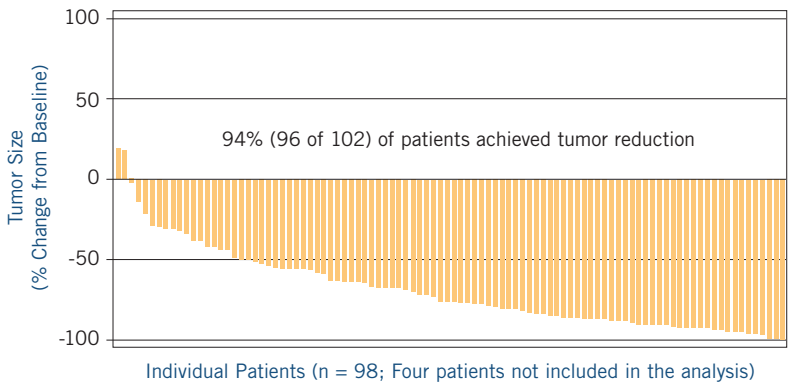
DR CHESON: One of the most exciting drugs out there is brentuximab vedotin (SGN-35). Previously, we had an anti-CD30 antibody, SGN-30, which was basically inactive in the treatment of Hodgkin lymphoma and had a little bit of activity in anaplastic large cell lymphoma (ALCL). However, when the antibody is conjugated with monomethyl auristatin E, which is a tubulin poison, what do you get?

In Hodgkin lymphoma, you obtain a response rate of 75 percent in patients with relapsed/refractory disease with a fair number of complete remissions (Chen 2010; [1.3]).

In relapsed/refractory ALCL, you obtain a response rate of 86 percent, most of which are complete remissions (3.3, page 14). We've never seen results of this magnitude before. ■

1.3

Maximum Tumor Reduction from Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL)



"Brentuximab vedotin was associated with manageable adverse events and, based on investigator assessment, demonstrated encouraging activity in heavily pretreated patients with relapsed or refractory HL. Tumor shrinkage was observed in 95%* of patients and the B symptom resolution rate was 83%."

* Original data from abstract, updated to 94% in final presentation

With permission from Chen R et al. *Proc ASH* 2010;**Abstract 283**.

SELECT PUBLICATIONS

Ardeshna M 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**.

Chanan-Khan A et al. **Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: Results of a phase II study.** *J Clin Oncol* 2006;24(34):5343-9.

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**.

Cheson BD. **Etiology and management of tumor lysis syndrome in patients with chronic lymphocytic leukemia.** *Clin Adv Hematol Oncol* 2009;7(4):263-71.

Cortes J et al. **Control of plasma uric acid in adults at risk for tumor lysis syndrome: Efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone — Results of a multicenter phase III study.** *J Clin Oncol* 2010;28(27):4207-13.

Ferrajoli A et al. **Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia.** *Blood* 2008;111(11):5291-7.

Knauf WU et al. **Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia.** *J Clin Oncol* 2009;27(26):4378-84.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

INTERVIEW

Steven D Gore, MD

Dr Gore is Professor of Oncology at Johns Hopkins University in Baltimore, Maryland.

Tracks 1-14

Select Excerpts from the Interview

Tracks 5-9

DR LOVE: How are you generally approaching patients with higher-risk myelodysplastic syndromes (MDS) or those with chromosome 5q deletion?

DR GORE: My first question is always, is this patient now or could this patient ever be a candidate for a potentially curable allogeneic stem cell transplant? That always needs to be kept in mind. We perform nonablative transplants up through age 75, so it's not a trivial question. That's not to say that every 75-year-old should undergo a transplant, but it could be considered for

appropriate patients up through that age. Patients at higher risk should start a nucleoside analog, and the only one that has been proven to improve survival is azacitidine (Fenaux 2009).

For patients at lower risk whose disease has failed to respond to or who are not candidates for erythropoietin-stimulating agents and who have deletion of chromosome 5q, lenalidomide is the treatment of choice. For patients who don't have that abnormality, lenalidomide can be considered if they are not thrombocytopenic.

DR LOVE: What are your thoughts on the issue of duration of treatment with hypomethylating agents?

DR GORE: A recently published analysis of the AZA-001 data evaluated time to first response and best response and reported that it may take as long as 12 months to see your first hematologic response, and responses do continue to improve with continued azacitidine therapy (Silverman 2011). For patients with high-risk disease, the current recommendation remains to continue therapy as long as the disease is responding and the patient is tolerating the drug.

Data from four independent cohorts were analyzed with regard to outcomes of patients whose disease either failed to respond to azacitidine or responded and then ceased to respond (Prebet 2010). Patients whose disease stops responding or doesn't respond to azacitidine have a limited life expectancy, so it seems that the longer patients continue to receive it, the better off they are.

Tracks 11-12

DR LOVE: What new developments have occurred recently in acute promyelocytic leukemia (APL)?

DR GORE: The main event this past year was the publication of data from the CALGB-C9710 trial, which randomly assigned patients with APL to standard induction followed by consolidation therapy with or without two cycles of arsenic trioxide (ATO). Survival was markedly improved in the patients

2.1

Intergroup Study C9710: Arsenic Trioxide (ATO) with Standard Induction/Consolidation Therapy* for Acute Promyelocytic Leukemia

Endpoint	Induction → consolidation (n = 237)	Induction → consolidation + ATO† (n = 244)	*p*-value
Three-year event-free survival	63%	80%	<0.0001
Three-year overall survival	81%	86%	0.07
Three-year disease-free survival	70%	90%	<0.0001

* Induction (ATRA, Ara-C, daunorubicin) → two courses consolidation (ATRA, daunorubicin)
† Two 25-day courses of ATO consolidation immediately after induction

Powell BL et al. *Blood* 2010;116(19):3751-7.

receiving ATO (Powell 2010; [2.1]). The CALGB-C9710 study has been criticized because event-free survival on the control arm was only about 60 percent, which is not great compared to results from the Spanish PETHEMA group trial (Ades 2008; Gore 2010). With that said, this was a well-done randomized clinical trial consistent with other recent APL studies (2.2), and I believe these are real data that illustrate the importance of ATO in this setting.

Another interesting aspect is that ATO seems to overcome the negative effect of high-risk APL. The outcomes for patients on the CALGB-C9710 trial with high-risk APL who receive ATO, once they're in remission, are comparable to the outcomes for patients with low-risk APL. Virtually no relapses occur in patients who survive APL and receive arsenic-based therapy (Powell 2010). ■

2.2 **Comparison of Outcomes in Recent Trials for Acute Promyelocytic Leukemia**

	Gore 2010[1] (n = 45)	C9710 ATO arm[2] (n = 243)	PETHEMA LPA99[3] (n = 410)	APL2000 Ara-C arm[4] (n = 178)	Shanghai[5] (n = 85)	MD Anderson[6] (n = 82)
OS	88%	86%	93.7%	90.5%	91.7%	84.1%
DFS	90%	90%	NR	NR	94.8%	90.6%
EFS	76%	80%	86%	85.6%	89.2%	82.9%
Follow-up	2.7 y	2.4 y	5.6 y	5.2 y	5.8 y	1.9 y

[1] ATRA + DNR → cytarabine + DNR → 30 doses ATO beginning on day 8; [2] (ATRA, Ara-C, DNR) → two courses (ATRA, DNR) → two 25-day courses ATO; [3] ATRA, high cumulative dose idarubicin and mitoxantrone; [4] Ara-C + ATRA + lower cumulative dose DNR; [5] ATRA/ATO-based therapy; [6] ATRA, ATO, gem

ATO = arsenic trioxide; OS = overall survival; DFS = disease-free survival; NR = not reported; EFS = event-free survival; ATRA = all-trans retinoic acid; DNR = daunorubicin; gem = gemtuzumab

Gore SD et al. *J Clin Oncol* 2010;28(6):1047-53; Powell BL et al. *Blood* 2010;116(19):3751-7.

SELECT PUBLICATIONS

Ades L et al. **Treatment of newly diagnosed acute promyelocytic leukemia (APL): A comparison of French-Belgian-Swiss and PETHEMA results.** *Blood* 2008;111(3):1078-84.

Fenaux P et al. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study.** *Lancet Oncol* 2009;10(3):223-32.

Gore SD et al. **Single cycle of arsenic trioxide-based consolidation chemotherapy spares anthracycline exposure in the primary management of acute promyelocytic leukemia.** *J Clin Oncol* 2010;28(6):1047-53.

Powell BL et al. **Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup study C9710.** *Blood* 2010;116(19):3751-7.

Prebet T et al. **Outcome of patients (pts) treated for myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (s AML) after azacitidine (AZA) failure.** *Proc ASH* 2010;**Abstract 443**.

Silverman LR et al. **Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes.** *Cancer* 2011;[Epub ahead of print].

INTERVIEW

Francine Foss, MD

Dr Foss is Professor of Medicine and Director of Clinical Investigation of Hematological Malignancies at Yale Cancer Center in New Haven, Connecticut.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-5, 9

Case discussion

A 34-year-old woman with a history of patch-plaque mycosis fungoides and erythroderma undergoes treatment with CHOP x 6 but experiences relapse within six months of completing therapy and receives romidepsin.

DR FOSS: Like many patients with cutaneous T-cell lymphoma (CTCL) who receive CHOP, she had a very good clinical response but experienced

a quick relapse. When she presented to me she had extensive plaques, areas of erythema and multiple tumors, some of which were five centimeters in diameter on her trunk and interior chest wall.

This patient illustrates an interesting point about how mycosis fungoides can evolve. Many patients who present with patches and plaques may remain free of progression for a long time. However, when the disease progresses to tumor-stage disease, you need to be concerned that it is declaring itself as a disease with a more aggressive clinical course.

It is important to rebiopsy these tumors to determine whether the histology has changed and evolved into a large cell transformation because that portends a much different prognosis for the patient. Fortunately, this patient's disease did not transform.

DR LOVE: How do you decide on the sequence of treatments to use for these patients and for this woman?

DR FOSS: This patient had previously received CHOP chemotherapy from another physician. Clinicians who are not that familiar with CTCL may view this disease as similar to other lymphomas and jump right to CHOP as a reflex reaction. So she is different from the de novo patient I would be caring for from the outset of her diagnosis. Generally speaking, for a patient with extensive patch-plaque disease, my first treatment would be a skin-based therapy along with one of the oral therapies — bexarotene or vorinostat.

Because this patient already received CHOP and experienced relapse with fairly aggressive clinical disease, a number of options are available, depending on the long-term plan for this patient.

In terms of the big picture for this patient, she's a young woman with aggressive, refractory disease. I am increasingly considering the use of allogeneic stem cell transplant in this setting, but we know that these patients need to be in remission and we need to administer effective salvage chemotherapy. If one were considering single-agent chemotherapy, liposomal doxorubicin and gemcitabine have demonstrated activity in this setting. Romidepsin, which is FDA approved for CTCL (Whittaker 2010; [3.1]), and pralatrexate, which is approved for peripheral T-cell lymphoma (PTCL), are also both options.

3.1

Final Results of a Multicenter, International Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

All (N = 96)		Stage IIB to IVA (n = 68)			
ORR (CR + PR)	CR	ORR (CR + PR)	CR	Median TTR	Median DOR
34%	6%	38%	7%	2 mo	15 mo

ORR = overall response rate; CR = complete response; PR = partial response; TTR = time to response; DOR = duration of response

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

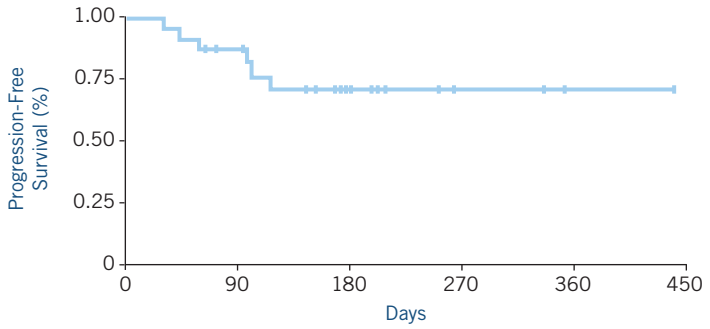
A study presented by Dr Horwitz at ASH 2010 involved more than 50 patients with relapsed or refractory CTCL, and that study showed a high response rate for pralatrexate administered at a slightly lower dose and on a different schedule than in PTCL (Horwitz 2010; [3.2]).

I decided to administer romidepsin to this patient, and she experienced a partial response for about four months before recurrence. She did not experience a response to denileukin diftitox, and we could not obtain coverage for pralatrexate. She experienced a very good partial response, if not complete response, to gemcitabine, and I am hoping to move forward with an allogeneic stem cell transplant.

A couple of clinical issues are worth considering. Once a patient is in remission, how do you keep that patient in remission? No studies address maintenance therapy, although we administer agents such as romidepsin, and even bexarotene or vorinostat, until patients experience relapse. For this patient, I decided to treat with vorinostat because it's an agent that's relatively well tolerated in this setting and I planned to administer radiation therapy to consolidate her response before the transplant.

3.2

PDX-010 Study: Progression-Free Survival with the Optimal Dose and Schedule of Pralatrexate in Relapsed or Refractory Cutaneous T-Cell Lymphoma



	n	Response rate
Response 15 mg/m^2 (3/4 weeks)	29	45%

With permission from Horwitz SM et al. *Proc ASH* 2010;**Abstract 2800**.

Tracks 9, 11

DR LOVE: Returning to the biopsy for this patient, how would your approach have changed if her disease had transformed?

DR FOSS: If the rebiopsy had shown a large cell transformation, then I probably would have been more aggressive. If you examine our clinical trials

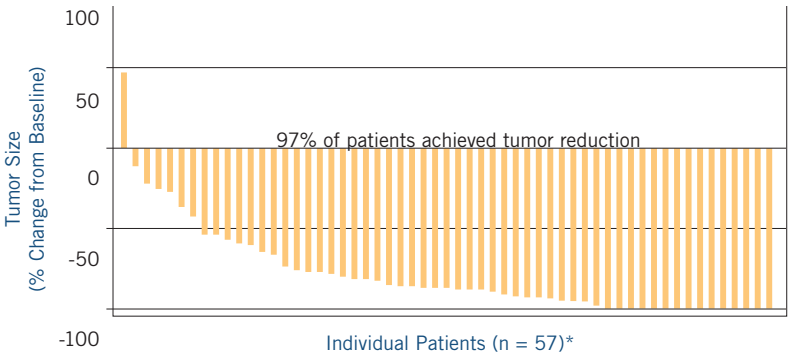
with approved agents — denileukin diftitox, bexarotene and romidepsin — we excluded patients with large cell transformation. The only study that addressed those patients was with pralatrexate. So my choice for her would probably have been pralatrexate or perhaps a more aggressive chemotherapy approach.

DR LOVE: Would you have tried to enroll her on a trial of SGN-35?

DR FOSS: SGN-35, or brentuximab vedotin, is an antibody conjugated with a toxin, and it is an active agent. Data were recently presented at ASH in ALCL with this agent that showed a high response rate in these patients who had previously treated, refractory disease (Shustov 2010; [3.3]). It was an astounding response rate in that setting. It's also well tolerated with minimal side effects. So if it were available and she had CD30-positive disease, I would have administered SGN-35, and we'd love to have clinical trials for these patients. ■

3.3

Response and Maximum Tumor Reduction in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma Treated with Brentuximab Vedotin (SGN-35)



* 57 of 58 patients with postbaseline CT assessments

Response	Independent review facility	Investigator
Overall response rate	86%	81%
Complete remission	53%	59%
Partial remission	33%	22%

With permission from Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

SELECT PUBLICATIONS

Horwitz SM et al. **Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL): Final results of a multicenter dose-finding study.** *Proc ASH* 2010;**Abstract 2800**.

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**.

Whittaker SJ et al. **Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.** *J Clin Oncol* 2010;28(29):4485-91.

INTERVIEW

Ruben Niesvizky, MD

Dr Niesvizky is Associate Professor of Medicine at Weill Cornell Medical College and Director of the Multiple Myeloma Service at NewYork-Presbyterian Hospital in New York, New York.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the work you recently presented at ASH on the UPFRONT study in newly diagnosed multiple myeloma?

DR NIESVIZKY: UPFRONT is a randomized Phase IIIb study for patients who are not eligible for stem cell transplant, and therefore patients older than age 65 are significantly represented. The goal is to evaluate a bortezomib-containing induction regimen — bortezomib/melphalan/prednisone (VMP), bortezomib/thalidomide/dexamethasone (VTD) or bortezomib/dexamethasone (VD) — followed by a bortezomib-containing maintenance regimen. This is the first time such an approach is being used for elderly patients.

Peripheral neuropathy was common, with the lowest rates on the VD arm and the highest rates on the VTD arm. Overall, the responses were higher on the VTD arm when compared to VMP or VD, although the difference was not

statistically significant (Niesvizky 2010; [4.1]). An interesting observation is that the group of patients receiving VD is performing as well as the other groups. It is possible, at least in this elderly population, that we can administer two agents and still maintain the same efficacy with perhaps even less toxicity.

4.1

UPFRONT Study: Bortezomib-Based Induction (I) Followed by Weekly Bortezomib Maintenance (M) for Elderly Patients with Newly Diagnosed Multiple Myeloma

	VD (n = 167)		VTD (n = 168)		VMP (n = 167)	
Efficacy endpoints*						
Median PFS	13.8 mo		18.4 mo		17.3 mo	
	I	**I + M**	**I**	**I + M**	**I**	**I + M**
ORR	68%	71%	78%	79%	71%	73%
CR + nCR	24%	31%	36%	38%	31%	34%
Peripheral neuropathy (PN)						
Grade ≥3 PN	15%	5%	26%	6%	20%	2%
Grade ≥3 PN resulting in discontinuation of all study drugs	4%	4%	13%	0%	14%	0%

V = bortezomib; D = dexamethasone; T = thalidomide; M = melphalan; P = prednisone; PFS = progression-free survival; ORR = overall response rate; CR = complete response; nCR = near CR

* No statistically significant differences were identified between treatment arms.

Niesvizky R et al. *Proc ASH* 2010;**Abstract 619**.

Track 6

DR LOVE: How do you approach induction and long-term therapy for patients in the transplant setting?

DR NIESVIZKY: In both the transplant and nontransplant settings, achieving a complete remission is one of the most important goals that will be reflected in long-term survival and long-term progression-free survival. I believe the bar for complete response should be 40 percent, and I would reject any regimen that does not reach it.

Lenalidomide, dexamethasone and clarithromycin, or the BiRD regimen, yields more than a 90 percent overall response rate with an approximately 40 percent complete response rate (Niesvizky 2008). Similar results have been observed with lenalidomide/bortezomib/dexamethasone (Richardson 2010b). If we do not achieve a complete response or very good partial response with lenalidomide/dexamethasone, I add bortezomib to the regimen, either in combination with lenalidomide or in combination with cyclophosphamide and dexamethasone in a CyBorD approach.

With the new data coming from the CALGB and the French group, many physicians are considering continuation of maintenance lenalidomide after stem cell transplant (4.2).

4.2

Post-Transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	**Placebo** (n = 307)	**Lenalidomide** (n = 231)	**Placebo** (n = 229)
Median PFS[1] or TTP[2]	42 mo	24 mo	42 mo	22 mo
Deaths	NR	NR	8%	12%

PFS = progression-free survival; TTP = time to progression; NR = not reported

[1] Attal M et al. *Proc ASH* 2010;**Abstract 310**; [2] McCarthy PL et al. *Proc ASH* 2010;**Abstract 37**.

Tracks 6-8

DR LOVE: Do you have any experience with the novel proteasome inhibitor carfilzomib or the new IMiD pomalidomide?

DR NIESVIZKY: At ASH, we heard the promising results of the Phase I/II study of front-line carfilzomib/lenalidomide and dexamethasone, with a 100 percent response rate when used for at least four cycles (Jakubowiak 2010). What is also significant is the reduction in neuropathy and the potential for long-term use. Pomalidomide has an excellent toxicity profile with less neuropathy, minimal thrombogenicity and improved responses when paired with dexamethasone (Lacy 2010). It also has the ability to overcome resistance to lenalidomide (Richardson 2010a). We're excited about this agent not only because of its efficacy but also because of its high level of tolerability. ■

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 M et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Proc ASH* 2010;**Abstract 863**.

Niesvizky R et al. **BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naïve symptomatic multiple myeloma.** *Blood* 2008;111(3):1101-9.

Richardson PG et al. **A Phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib.** *Proc ASH* 2010a;**Abstract 864**.

Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010b;116(5):679-86.

QUESTIONS (PLEASE CIRCLE ANSWER):

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

2. **Which of the following hypomethylating agents has shown a survival advantage in the initial management of MDS?**
   a. Azacitidine
   b. Decitabine
   c. Both of the above
   d. None of the above

3. **In a Phase III Intergroup study — CALGB-C9710 — the addition of ATO as consolidation therapy for patients with APL improved _____.**
   a. Overall survival
   b. Event-free survival
   c. Disease-free survival
   d. All of the above

4. **A study by Gore and colleagues of single-cycle ATO-based consolidation therapy in the primary management of APL reported an estimated disease-free survival of 90 percent.**
   a. True
   b. False

5. **Emerging data with the antibody-drug conjugate brentuximab vedotin (SGN-35) reported at ASH 2010 indicated encouraging activity with the agent for patients with _____.**
   a. Relapsed/refractory Hodgkin lymphoma
   b. Relapsed/refractory systemic ALCL
   c. Both of the above

6. **Which of the following tendencies typically characterizes romidepsin-associated QTc interval prolongation?**
   a. Tends to be transient and not associated with clinical symptoms
   b. Tends to be persistent and associated with clinical symptoms
   c. QTc interval prolongation is not a side effect of romidepsin

7. **Which of the following is a dose-limiting side effect with pralatrexate?**
   a. Hypertension
   b. Mucositis
   c. Fatigue

8. **The Phase III UPFRONT study demonstrated a statistically superior rate of response with which of the following bortezomib-based regimens?**
   a. VMP
   b. VTD
   c. VD
   d. None of the above

9. **Data from the CALGB-100104 and IFM 2005-02 trials show that lenalidomide maintenance therapy is effective in patients with multiple myeloma.**
   a. True
   b. False

10. **Treatment with both carfilzomib and pomalidomide results in low rates of _____ among patients with multiple myeloma.**
    a. Fatigue
    b. Mucositis
    c. Neuropathy

Post-test answer key: 1a, 2a, 3d, 4a, 5c, 6a, 7b, 8d, 9a, 10c

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 1, 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
Rituximab versus watch and wait in patients with Stage II to IV asymptomatic, nonbulky FL	4 3 2 1	4 3 2 1
Planned clinical trials with BR-based induction therapy for MCL	4 3 2 1	4 3 2 1
Brentuximab vedotin (SGN-35) in Hodgkin lymphoma and ALCL	4 3 2 1	4 3 2 1
ECOG-E1905 study: Azacitidine with or without the histone deacetylase inhibitor entinostat in MDS	4 3 2 1	4 3 2 1
Intergroup study C9710: ATO in APL	4 3 2 1	4 3 2 1
Systemic treatment options for mycosis fungoides/Sézary syndrome	4 3 2 1	4 3 2 1
UPFRONT study: Bortezomib-based induction followed by bortezomib maintenance therapy for elderly patients	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
- Efficiently apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes and acute myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Recall the expanding body of evidence for the use of arsenic trioxide in the management of acute promyelocytic leukemia, and incorporate this agent, when appropriate, into evidence-based treatment algorithms. . . . . 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
- 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
Bruce D Cheson, MD	4 3 2 1	4 3 2 1
Steven D Gore, MD	4 3 2 1	4 3 2 1
Francine Foss, MD	4 3 2 1	4 3 2 1
Ruben Niesvizky, 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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Hematologic Oncology™
UPDATE

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