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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

Hematologic Oncology Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Over 45 pharmaceutical agents with more than 55 distinct FDA-approved indications are currently available for the management of the numerous types of hematologic cancer. This extensive armamentarium of treatment options poses a challenge to clinicians who must maintain up-to-date knowledge of optimal therapeutic algorithms for diverse tumor types. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading oncology investigators. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of state-of-the-art clinical management strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Apply emerging research results to effectively and safely integrate novel agents and regimens into the initial management of follicular lymphoma.
- Recall the emerging subtypes of diffuse large B-cell lymphoma and their implications for personalized therapy.
- Formulate optimal front-line and maintenance strategies for patients with acute promyelocytic leukemia.
- Describe the standard therapeutic approaches and investigational strategies for the treatment of newly diagnosed and relapsed Hodgkin lymphoma.
- Identify patients at high risk for tumor lysis syndrome (TLS), and incorporate recent research data into the prevention and management of TLS.
- Integrate innovative combination regimens into the management of multiple myeloma (MM), considering the benefits and risks of proteasome inhibitors and immunomodulatory agents.
- Evaluate consolidation and maintenance therapy approaches for patients with MM.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

John P Leonard, MD

Dr Leonard is Richard T Silver Distinguished Professor of Hematology and Medical Oncology, Professor of Medicine at Weill Cornell Medical College, Associate Director for Clinical Research at Weill Cornell Cancer Center, Clinical Director at the Center for Lymphoma and Myeloma and Attending Physician at New York Presbyterian Hospital in New York, New York.

Tracks 1-17

Track 1 **Case discussion:** A 58-year-old woman has low-risk follicular lymphoma (FL) initially managed with "watch and wait" for two years, followed by bendamustine/rituximab (BR) at disease progression

Track 2 German Phase III randomized trial comparing BR to R-CHOP in FL

Track 3 Bendamustine: A unique chemotherapeutic drug with evolving dosing recommendations

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Select Excerpts from the Interview

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DR LOVE: Would you discuss the data presented at ASH on the efficacy and safety of bendamustine/rituximab (BR) compared to R-CHOP for follicular lymphoma (FL)?

DR LEONARD: The Study Group Indolent Lymphomas (StiL) from Germany randomly assigned more than 500 patients to either BR or R-CHOP.

Not only were complete remissions increased but progression-free survival (PFS) was also improved with BR (Rummel 2009; [1.1]). BR is at least comparable in efficacy and is much better in terms of safety, with significantly less toxicity (Rummel 2009; [1.2]).

DR LOVE: In what situations would you use R-CHOP, and when would you use BR?

DR LEONARD: The data show improved safety and efficacy with BR. Despite this information, I continue to use R-CHOP when I am concerned about transformation because the role of bendamustine in the more aggressive subtype is not as clear.

1.1

Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas

	Overall response	Complete response	Progression-free survival	Time to next treatment
BR (n = 260)	93.8%	40.1%	54.8 months	Not reached
R-CHOP (n = 253)	93.5%	30.8%	34.8 months	40.7 months
p-value	—	0.0323	0.0002	0.0002

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

1.2

Safety Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas

	Grade III/IV neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Rash	Alopecia
BR (n = 260)	10.7%	36.5%	6.9%	6.2%	16.2%	15.0%
R-CHOP (n = 253)	46.5%	47.8%	28.8%	18.6%	9.1%	62.0%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	Not reported

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

In contrast, for an older patient or someone who is worried about side effects, administering BR makes complete clinical sense.

Tracks 8, 10

DR LOVE: What do we know about the PRIMA trial of postinduction therapy after front-line rituximab-containing regimens in FL?

DR LEONARD: PRIMA, the Primary RItuximab and MAintenance study, is the randomized Phase III trial examining rituximab maintenance therapy after rituximab-containing regimens for FL in the front-line setting. This study is being conducted primarily in Europe and has enrolled more than 1,000 patients. All patients received rituximab-containing initial induction and were then randomly assigned to observation or two years of maintenance rituximab.

A press release stated that the study reached the primary endpoint of improving PFS with maintenance rituximab in this setting. Most of these patients received R-CHOP as initial treatment. So when R-CHOP is used as up-front treatment for FL, maintenance rituximab can yield a PFS benefit. I anticipate that these data will be presented at ASCO 2010. So far, all of the maintenance studies have investigated rituximab. Because active oral agents such as lenalidomide are also being investigated in lymphoma, I believe that more data will emerge in the context of maintenance therapy for FL.

DR LOVE: What about consolidation therapy for patients with FL responding to initial induction therapy?

DR LEONARD: The only study that has been published in this setting is FIT, the First-line Indolent Trial. The study was a multinational, randomized Phase III trial that compared radioimmunotherapy with ibritumomab as first-line consolidation therapy to observation for advanced FL that had responded to initial induction therapy. The study showed a significant improvement in complete response rate and PFS on the ibritumomab arm, with acceptable safety (Morschhauser 2008; [1.3]). However, fewer than 20 percent of the patients received rituximab as part of initial induction therapy.

Tracks 12, 15

DR LOVE: What's new in the treatment of mantle-cell lymphoma (MCL)?

DR LEONARD: Bortezomib is clearly an active agent in MCL. It has been approved in the relapsed setting because of response rates of 30 percent and a PFS of nine months. Combination therapies with bortezomib are now being investigated in both front-line and relapsed MCL.

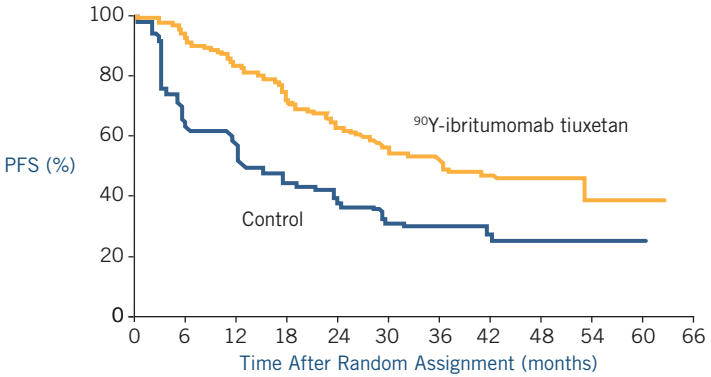
A Phase II study with the combination of bendamustine, bortezomib and rituximab (BVR) was reported at ASH 2009. The study included patients with heavily pretreated relapsed or refractory indolent lymphomas in addition to those with MCL. BVR is definitely active in both MCL and FL (Friedberg

2009; [1.4]). We need randomized trials of BR with or without bortezomib to investigate the benefit of adding bortezomib to the BR regimen.

Our group reported a Phase I/II study of R-CHOP with reduced-dose bortezomib as initial therapy for MCL. Among 32 evaluable patients, the overall response rate is 91 percent, with a complete response rate of 72 percent. The PFS for all 36 patients is 21 months, and the two-year overall survival rate is 86 percent (Ruan 2009).

1.3

Phase III Trial of Consolidation Therapy with Yttrium-90-Ibritumomab Tiuxetan versus No Additional Therapy After First Remission in Advanced Follicular Lymphoma: Progression-Free Survival (PFS)



	Ibritumomab tiuxetan (n = 208)	No additional therapy (n = 206)	Hazard ratio	*p*-value
Median PFS	36.5 months	13.3 months	0.465	<0.0001

Originally published by the American Society of Clinical Oncology. Morschhauser F et al. **Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.** *J Clin Oncol* 2008;26(32):5156-64.

1.4

Efficacy of Bendamustine/Bortezomib/Rituximab in Relapsed or Refractory Mantle-Cell Lymphomas (MCL) and Indolent Lymphomas

	Overall response
All patients (n = 29*)	79%
Relapsed or refractory FL (n = 16)	85%
Relapsed or refractory MCL (n = 7)	71%

FL = follicular lymphoma
* Remaining patients had marginal-zone non-Hodgkin lymphoma, small lymphocytic lymphoma or lymphoplasmacytic lymphomas

Friedberg JW et al. *Proc ASH* 2009;**Abstract 924**.

So bortezomib is clearly an exciting drug in MCL that warrants combination studies with various chemotherapeutic regimens in both the front-line and relapsed settings. ECOG is studying modified hyper-CVAD with bortezomib, and The University of Texas MD Anderson Cancer Center has examined full-dose hyper-CVAD with bortezomib in MCL.

DR LOVE: How do patients fare in terms of neuropathy when bortezomib is added to vincristine-containing regimens?

DR LEONARD: NCI Canada combined standard R-CVP with weekly bortezomib 1.3 mg/m^2 intravenously on days 1 and 8 every 21 days (Sehn 2009). None of the patients developed Grade IV neuropathy, and the incidence of Grade III neuropathy was 6.3 percent.

In the trial of reduced-dose bortezomib, 1 or 1.3 mg/m^2 intravenously on days 1 and 4 every 21 days with R-CHOP in MCL reported by my group (Ruan 2009), no patient developed Grade IV neuropathy and only one out of 36, or 2.7 percent, developed Grade III neuropathy. Neurotoxicity is primarily low grade, is reversible and does not limit the delivery of bortezomib or vincristine.

So the combination of bortezomib and vincristine can be administered, although dose modification of one or both agents may be needed. Nevertheless, the available data suggest that even with dose modification, the combination may be sufficiently active to affect patient outcomes. ■

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Goff L et al. **Quantitative PCR analysis for Bcl-2/IgH in a phase III study of yttrium-90 ibritumomab tiuxetan as consolidation of first remission in patients with follicular lymphoma.** *J Clin Oncol* 2009;27(36):6094-100.

Morschhauser F et al. **Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.** *J Clin Oncol* 2008;26(32):5156-64.

O'Connor OA et al. **Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: Results of a multicentre Phase 2 clinical trial.** *Br J Haematol* 2009;145(1):34-9.

Ruan J et al. **CHOP-R + bortezomib as initial therapy for mantle cell lymphoma (MCL).** *Proc ASH* 2009;**Abstract 2682**.

Rummel MJ et al. **B-R is superior in respect of PFS and CR rate when compared to CHOP-R 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**.

Sekeres MA et al. **A study comparing dosing regimens and efficacy of subcutaneous to intravenous azacitidine (AZA) for the treatment of myelodysplastic syndromes (MDS).** *Proc ASH* 2009;**Abstract 3797**.

Sehn LH et al. **Bortezomib added to CVP-R is safe and effective for previously untreated advanced stage follicular lymphoma: A Phase II study by the NCIC Clinical Trials Group.** *Proc ASH* 2009;**Abstract 407**.

INTERVIEW

David P Steensma, MD

Dr Steensma is Attending Physician at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-12

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you comment on the poster presented at ASH 2009 on the AVIDA registry that compared dosing regimens and the efficacy of subcutaneous versus intravenous azacitidine for myelodysplastic syndromes (MDS)?

DR STEENSMA: What I found interesting about the IV versus subcutaneous azacitidine comparison was that the response rates, in terms of hematologic improvement, were identical (Sekeres 2009). So although the AZA-001 study, which showed a survival advantage with azacitidine in high-risk MDS, used subcutaneous administration (Fenaux 2010), I believe that IV administration is acceptable and avoids some of the potential difficulties with subcutaneous administration, such as skin reactions.

The study also revealed that the vast majority of patients are not receiving the FDA-approved seven consecutive days of azacitidine. Perhaps that is not surprising, but what is alarming is that approximately 50 percent of patients are not even receiving this agent for a total of seven days per cycle. Many clinicians administer it for five days one week and two the next, but some administer it for only five days.

Data from the Spanish Azacitidine Compassionate Use Registry, also reported at ASH 2009, showed that the complete response rate was 12 percent for patients who received azacitidine on fewer than seven days per cycle and 22 percent for those who received it for seven days per cycle (Garcia 2009). It was a small retrospective study, but I believe that we should do our best to administer azacitidine for seven days.

DR LOVE: For how long should patients with MDS continue to receive treatment?

DR STEENSMA: We don't have clinical trial data to answer that question. For patients who demonstrate a complete response, I use maintenance therapy because it has been my experience that if I administer only two more cycles and then stop, as I do for lymphoma cases, the vast majority of patients experience relapse within six months. Varying opinions exist in terms of the best way to administer maintenance therapy. My practice with both azacitidine and decitabine is to wait six or seven weeks between cycles. Others decrease the dose, reducing azacitidine from 75 to 50 mg/m^2 or decitabine from 20 to 10 mg/m^2 and administering it for five days.

Tracks 5-6

DR LOVE: Would you discuss the data and clinical implications of the MDS-004 study that was presented at ASH 2009?

DR STEENSMA: This Phase III study compared five- or 10-mg lenalidomide to placebo for patients with low-risk or intermediate-1-risk MDS with 5q deletion. The complete cytogenetic response rate was more than twice as high on the 10-mg arm, and although the differences between the two doses weren't statistically different, the trend favored the higher dose (Fenaux 2009; [2.1]).

The incidence of cytopenias was approximately the same, with 58 percent of the patients who received the higher dose and 52 percent on the 5-mg arm requiring dose reduction. In most patients it is fairly well tolerated — certainly better than thalidomide. I believe that the starting dose of lenalidomide should be 10 mg, even for older patients.

Tracks 11-12

DR LOVE: What is the current approach to induction therapy for acute promyelocytic leukemia (APL)?

DR STEENSMA: Generally, the trend has been away from cytarabine and toward incorporating the three most active agents — arsenic trioxide, tretinoin and gemtuzumab — earlier in therapy. The Intergroup study in higher-risk APL, SWOG-S0535, is evaluating all three agents as induction therapy, which is an exciting approach.

DR LOVE: What is your initial approach to treating APL in practice?

DR STEENSMA: Outside a protocol setting, I believe the PETHEMA regimen or the older CALGB regimen that includes arsenic trioxide early, an anthracycline and then the incorporation of arsenic trioxide in one or more consolidation therapies is the best approach.

If I were diagnosed with APL, I would want to receive both tretinoin and arsenic trioxide at some point, and preferably — particularly with higher-risk disease — gemtuzumab, which is another active agent in APL. ■

2.1

MDS-004: Efficacy and RBC Transfusion Independence (TI) with Lenalidomide Five or 10 Mg versus Placebo in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndromes and the 5q Deletion

	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
Protocol RBC TI (≥26 weeks)	6%	41%[1]	56%[1]
IWG RBC TI (≥8 weeks)	8%	50%[1]	61%[1]
Median time to protocol TI (≥26 weeks)	0.3 weeks	3.3 weeks	4.3 weeks
Median maximum hemoglobin increase	2.3 g/dL	5.1 g/dL[2]	6.3 g/dL[3]
Complete CyR + partial CyR	0%	17%[1]	41%[1]
Complete CyR	0%	11%[3]	24%[1]

IWG = International Working Group consensus criteria; CyR = cytogenetic response
[1] $p < 0.001$ versus placebo; [2] $p < 0.05$ versus placebo; [3] $p = 0.01$ versus placebo

Fenaux P et al. *Proc ASH* 2009;**Abstract 944**.

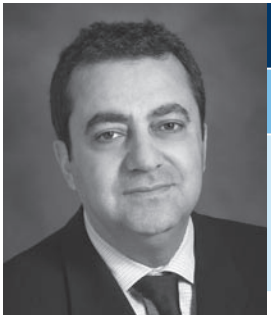
SELECT PUBLICATIONS

Fenaux P et al. **Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: Azacitidine compared with low dose ara-C.** *Br J Haematol* 2010;149(2):244-9.

Fenaux P et al. **RBC transfusion independence and safety profile of lenalidomide 5 or 10 mg in pts with low- or int-1-risk MDS with del5q: Results from a randomized Phase III trial (MDS-004).** ASH 2009;**Abstract 944**.

Garcia R et al. **Different clinical results with the use of different dosing schedules of azacitidine in patients with myelodysplastic syndrome managed in community-based practice: Effectiveness and safety data from the Spanish Azacitidine Compassionate Use Registry.** *Proc ASH* 2009;**Abstract 2773**.

Sekeres MA et al. **A study comparing dosing regimens and efficacy of subcutaneous to intravenous azacitidine (AZA) for the treatment of myelodysplastic syndromes (MDS).** *Proc ASH* 2009;**Abstract 3797**.



INTERVIEW

Anas Younes, MD

Dr Younes is Director of the Clinical and Translational Research Program and Professor of Medicine in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-16

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are some of the new agents or therapeutic strategies in the management of Hodgkin lymphoma (HL)?

DR YOUNES: A few novel classes of drugs are being investigated in HL. Brentuximab, or SGN-35, is an antibody-drug conjugate and a leading agent under investigation, and a pivotal trial has recently been completed (NCT00848926).

In addition, administration of the mTOR inhibitor everolimus resulted in response rates of approximately 50 percent, which is remarkable for heavily pretreated disease (Johnston 2010), and the data are being followed up with a large Phase II study from the Mayo Clinic (NCT00436618).

We also have a large randomized trial evaluating ABVD with or without rituximab, which is based on Phase II data from our group (Copeland 2009). The rationale for this approach is that cancer cells can be rendered more sensitive to ABVD chemotherapy by depleting reactive B lymphocytes in the microenvironment.

Another randomized trial in early-stage HL in Europe is evaluating ABVD with either rituximab or radiation therapy. The question is, can we replace radiation therapy with a less toxic drug such as rituximab?

Tracks 4-5

DR LOVE: Would you describe the risk factors and management of tumor lysis syndrome (TLS)?

DR YOUNES: TLS is not a common syndrome, but it is potentially fatal. It is characterized by metabolic derangements from the massive and abrupt release of cellular components in the blood after the rapid lysis of cancer cells.

Until recently, we did not have effective prophylaxis for TLS. The only management strategy available was allopurinol with aggressive hydration. Allopurinol inhibits the formation of uric acid but does not affect the existing uric acid. Now a new agent, rasburicase, is available. This is a recombinant enzyme that breaks down existing uric acid.

In a Phase I/II study evaluating the safety and efficacy of rasburicase in patients at risk for developing TLS, administration of rasburicase improved uric acid levels (Pui 2001; [3.1]). More importantly, significant decreases in serum creatinine levels occurred in patients both with and without hyperuricemia, and none of the patients required dialysis or developed other signs of TLS.

A panel recently provided guidelines on the risk stratification and optimal prophylactic management of TLS (Coiffier 2008; [3.2]). Patients with Burkitt's lymphoma, acute lymphocytic leukemia or AML with high white blood cell counts are in the high-risk category, and those with diffuse large B-cell lymphoma (DLBCL) are currently considered to be in the intermediate-risk category.

3.1

Improved Serum Uric Acid Levels with the Administration of Rasburicase in Patients at High Risk for TLS

	Median uric acid level at baseline	Median uric acid level four hours postrasburicase	*p*-value
All patients (n = 131)	5.7 mg/dL	0.5 mg/dL	<0.0001
Preexisting hyperuricemia (n = 65)	9.7 mg/dL	1.0 mg/dL	0.0001
Normal baseline uric acid levels (n = 66)	4.3 mg/dL	0.5 mg/dL	0.0001

Pui CH et al. *J Clin Oncol* 2001;19(3):697-704.

However, a patient with DLBCL and high-risk features such as high LDH or large masses should be monitored carefully, and rasburicase should be administered at the sign of early TLS.

3.2 **Guidelines for Management of TLS Individualized to Risk Category**

	Low risk for TLS	Intermediate risk for TLS	High risk for TLS
Guideline	Laboratory monitoring	Hydration and allopurinol or rasburicase	Hydration and rasburicase

Coiffier B et al. *J Clin Oncol* 2008;26(16):2767-78.

Tracks 11-12

DR LOVE: Would you describe some of the controversies and novel approaches in MCL?

DR YOUNES: The issue with MCL is that all available data are either from small single-arm Phase II trials or retrospective studies. The NCCN outcomes study showed equivalent benefit with R-hyper-CVAD and R-CHOP followed by transplant (LaCasce 2009), although the Phase II studies suggested that R-hyper-CVAD is better. In the absence of randomized trials, I believe that both of these approaches are fine.

Another agent that is moving up front is bortezomib. It is currently approved for relapsed MCL and is now being combined with R-CHOP, R-EPOCH or R-hyper-CVAD in the initial treatment of this lymphoma.

Lenalidomide is another interesting agent, with a response rate of approximately 30 percent as a single agent for relapsed MCL. Ongoing trials in relapsed MCL are evaluating the lenalidomide/rituximab combination. ■

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Coiffier B et al. **Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review.** *J Clin Oncol* 2008;26(16):2767-78.

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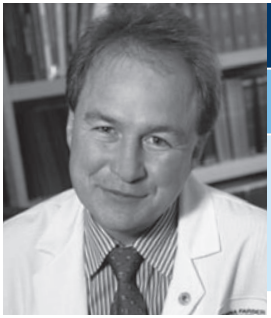
Johnston PB et al. **A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma.** *Am J Hematol* 2010;85(5):320-4.

LaCasce A et al. **R-CHOP followed by high dose therapy and autologous stem cell rescue and R-hyper-CVAD have equivalent PFS and are superior to R-CHOP alone in younger patients with MCL: A comparative effectiveness analysis from the NCCN NHL outcomes database project.** *Proc ASH* 2009;**Abstract 403**.

Pui CH et al. **Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma.** *J Clin Oncol* 2001;19(3):697-704.



INTERVIEW

Paul G Richardson, MD

Dr Richardson is Associate Professor of Medicine at Harvard Medical School and Clinical Director of the Jerome Lipper Center for Multiple Myeloma at the Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What were some of the important take-home messages from the ASH 2009 meeting related to the management of multiple myeloma?

DR RICHARDSON: Dr Mateos presented data from a large randomized trial that compared VMP to VTP as induction therapy in the older, transplant-

ineligible population, and she demonstrated equal activity but different toxicity profiles for the two regimens (Mateos 2009; [4.1]). She also showed that combined bortezomib and thalidomide maintenance therapy appeared to be superior to bortezomib maintenance with prednisone, and the take-home message is that the IMiD®/proteasome inhibitor combinations are attractive, which validates a lot of clinical and preclinical work in that context.

Another important data set presented at ASH was from the Palumbo trial, evaluating up-front melphalan/prednisone (MP) versus MP with lenalidomide (MPR) versus MPR with lenalidomide maintenance therapy.

It was no surprise that MPR with lenalidomide maintenance therapy was the winner, but it was surprising that MPR did not appear meaningfully different from MP at the 10-mg lenalidomide dose that was used, which is relatively low (Palumbo 2009). With early follow-up, the PFS differences between these two arms were superimposable.

My bet is that these results are a function of early follow-up and that with time the curves will separate, particularly because the response rates were different (4.2). Having said that, I believe the message is that lenalidomide maintenance therapy is important and should be continued.

The other message is that, frankly, we don't know whether MP is the best partner for lenalidomide. This echoes the publication of the landmark ECOG-4A03 trial, in which lenalidomide with low-dose dexamethasone was associated with better short-term overall survival and lower toxicity than lenalidomide with high-dose dexamethasone for patients with newly diagnosed myeloma (Rajkumar 2010).

4.1

Grade III/IV Adverse Events with Bortezomib/Melphalan/Prednisone (VMP) versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) versus Bortezomib/Prednisone (VP) in Elderly Patients with Untreated Multiple Myeloma

	Induction therapy		Maintenance therapy	
	VMP (n = 130)	VTP (n = 130)	VT (n = 91)	VP (n = 87)
Anemia	11%	8%	2%	2%
Neutropenia	39%	22%	3%	1%
Thrombocytopenia	27%	12%	1%	1%
Gastrointestinal toxicities	7%	2%	4%	1%
Peripheral neuropathy	5%	9%	5%	2%
Infections	7%	<1%	2%	1%
DVT/thromboembolism	<1%	2%	1%	—
Cardiologic events	—	8%	2%	1%

Mateos MV et al. *Proc ASH* 2009;**Abstract 3**.

The ECOG data clearly show that high-dose dexamethasone is the wrong partner for lenalidomide, and it's my sense, from Palumbo's presentation, that MP is not the correct partner either because myelosuppression was a problem.

I also believe these data suggest that up-front lenalidomide — but perhaps not MP — is important, if that isn't too heretical. I expect that lenalidomide will be approved on the basis of this trial.

4.2

Response Rates in a Phase III Study Evaluating Melphalan/Prednisone (MP) versus MP with Lenalidomide (MPR) versus MPR Followed by Lenalidomide Maintenance (MPR-R) for Elderly Patients with Multiple Myeloma

Best overall response[1]	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)	*p*-value (MPR-R vs MP)
Overall response rate	77%	67%	49%	<0.001
CR rate[2]	18%	13%	5%	<0.001
≥VGPR rate[3]	32%	33%	11%	<0.001
PR rate	45%	34%	37%	—

[1] As measured using EBMT criteria (Blade 1998)
[2] Immunofixation-negative with or without bone marrow confirmation
[3] VGPR: >90% reduction in M-protein

CR = complete response; VGPR = very good partial response; PR = partial response

Palumbo A et al. *Proc ASH* 2009;**Abstract 613**; Blade J et al. *Br J Haematol* 1998;102:1115-23.

Track 4

DR LOVE: Would you comment on the studies presented at ASH 2009 on maintenance therapy after transplant?

DR RICHARDSON: We participated in the CALGB-100104 trial, which randomly assigned patients to lenalidomide versus placebo maintenance therapy after single autologous stem cell transplant (ASCT). At ASH we were able to report that it was feasible from a safety perspective (McCarthy 2009), but shortly after the meeting the CALGB announced that the interim analysis was strikingly positive in favor of lenalidomide.

Also presented were preliminary data from the French randomized study (IFM 2005 02) in which patients, after ASCT, received consolidation treatment with lenalidomide followed by maintenance therapy with placebo or lenalidomide until relapse (Attal 2009).

In January 2010 the investigators announced that with a median follow-up of three years, PFS for lenalidomide maintenance therapy was 70 percent and in the control arm it was substantially lower at 35 percent. I believe this will be updated further at ASCO and presented in full form.

DR LOVE: What did you take away from the pretransplant induction therapy data presented at ASH?

DR RICHARDSON: The EVOLUTION trial showed the four-drug regimen of bortezomib, dexamethasone, cyclophosphamide and lenalidomide to be extremely active, and it validated the three-drug platform, but treatment-related mortality occurred with the four-drug combination (Kumar 2009). The pretransplant three-drug platform seems to be standard, and the use of a proteasome inhibitor before transplant also appears to be standard.

In addition, the role of the IMiDs continues to be strong both in the pretransplant setting and in the post-transplant setting as maintenance therapy. For the older population, Dr Mateos showed striking evidence that bortezomib maintenance therapy is feasible and, at least in combination with the IMiD, apparently important (Mateos 2009).

For patients who are transplant candidates, our institutional standard is a three-drug regimen, and our favorite is RVD — lenalidomide/bortezomib/dexamethasone — because we find that the neurotoxicity associated with this regimen is rarely severe. ■

SELECT PUBLICATIONS

Attal M et al. **Lenalidomide after autologous transplantation for myeloma: First analysis of a prospective, randomized study of the Intergroupe Francophone du Myelome (IFM 2005 02).** *Proc ASH* 2009;**Abstract 529**.

Dimopoulos MA et al. **VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: Cohort analysis of the Phase III VISTA study.** *J Clin Oncol* 2009;27(36):6086-93.

Kumar S et al. **Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: Encouraging results from the multi-center, randomized, Phase 2 EVOLUTION study.** *Proc ASH* 2009;**Abstract 127**.

Mateos MV et al. **Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the phase III VISTA trial.** *J Clin Oncol* 2010;28(13):2259-66.

Mateos MV et al. **A prospective, multicenter, randomized trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years.** *Proc ASH* 2009;**Abstract 3**.

McCarthy PL et al. **Phase III Intergroup study of lenalidomide (CC-5013) versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma (CALGB 100104): Initial report of patient accrual and adverse events.** *Proc ASH* 2009;**Abstract 3416**.

Palumbo A et al. **A Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma.** *Proc ASH* 2009;**Abstract 613**.

Rajkumar SV et al. **Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial.** *Lancet Oncol* 2010;11(1):29-37.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a Phase III study, bendamustine/rituximab (BR) resulted in significant improvements in _____ compared to R-CHOP for patients with follicular lymphoma (FL).**
   a. Complete response rate
   b. Progression-free survival
   c. Safety
   d. All of the above

2. **What was the two-year overall survival rate for patients with highly pretreated mantle-cell lymphomas (MCL) or indolent lymphomas who received the R-CHOP with reduced-dose bortezomib regimen?**
   a. 86 percent
   b. 70 percent
   c. 55 percent

3. **Sekeres and colleagues reported data from a study evaluating the efficacy of subcutaneous versus intravenous azacitidine for myelodysplastic syndromes (MDS), which showed superior hematologic improvement with which route of administration?**
   a. Subcutaneous
   b. Intravenous
   c. Neither — the hematologic improvement was equivalent

4. **An interim analysis of the AVIDA registry, examining the dosing schedule of azacitidine for MDS, revealed that more than _____ percent of patients overall are not receiving azacitidine for a total of seven days per cycle.**
   a. 10
   b. 30
   c. 50

5. **Data from MDS-004, the Phase III study comparing lenalidomide five or 10 mg to placebo for patients with low- or intermediate-1-risk MDS and the 5q deletion, included a complete cytogenetic response rate of _____ with the higher dose and 11 percent with the lower dose.**
   a. 12 percent
   b. 15 percent
   c. 24 percent

6. **Which of the following is an associated risk factor for development of tumor lysis syndrome (TLS)?**
   a. Highly proliferative tumor
   b. Chemosensitive tumor with high LDH level
   c. Uric acid elevation
   d. All of the above

7. **Patients at high risk for TLS, such as those with Burkitt's lymphoma, should receive rasburicase as primary prophylaxis during the first cycle of chemotherapy.**
   a. True
   b. False

8. **In the Phase III trial reported by Mateos and colleagues evaluating VMP versus VTP as induction therapy followed by maintenance VT versus VP for elderly patients with multiple myeloma, which induction therapy resulted in a significantly higher overall response rate?**
   a. VMP
   b. VTP
   c. Neither — the response rates were not significantly different

9. **In the Phase III study evaluating melphalan/prednisone (MP) versus MP with lenalidomide (MPR) versus MPR followed by lenalidomide maintenance (MPR-R) for elderly patients with multiple myeloma, which regimen resulted in the highest overall response rate?**
   a. MP
   b. MPR
   c. MPR-R

10. **Data released after the 2009 ASH meeting from the CALGB-100104 trial, which randomly assigned patients with multiple myeloma to maintenance lenalidomide versus placebo after single autologous stem cell transplant, failed to show an efficacy benefit with maintenance therapy.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2010

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
Phase III trial of BR versus R-CHOP for low-grade lymphomas	4 3 2 1	4 3 2 1
Consolidation ibritumomab versus observation after initial induction therapy for FL	4 3 2 1	4 3 2 1
Clinical research with bortezomib in FL and MCL	4 3 2 1	4 3 2 1
Activity of lenalidomide in MDS-004, a randomized Phase III trial in del(5q) MDS	4 3 2 1	4 3 2 1
Studies of arsenic trioxide in initial and relapsed acute promyelocytic leukemia	4 3 2 1	4 3 2 1
Guidelines for the use of rasburicase in patients at risk for TLS	4 3 2 1	4 3 2 1
Phase III studies presented at ASH 2009 on lenalidomide maintenance therapy for 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:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ 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:

- Apply emerging research results to effectively and safely integrate novel agents and regimens into the initial management of follicular lymphoma..... 4 3 2 1 N/M N/A
- Recall the emerging subtypes of diffuse large B-cell lymphoma and their implications for personalized therapy..... 4 3 2 1 N/M N/A
- Formulate optimal front-line and maintenance strategies for patients with acute promyelocytic leukemia..... 4 3 2 1 N/M N/A
- Describe the standard therapeutic approaches and investigational strategies for the treatment of newly diagnosed and relapsed Hodgkin lymphoma..... 4 3 2 1 N/M N/A
- Identify patients at high risk for tumor lysis syndrome (TLS), and incorporate recent research data into the prevention and management of TLS..... 4 3 2 1 N/M N/A
- Integrate innovative combination regimens into the management of multiple myeloma (MM), considering the benefits and risks of proteasome inhibitors and immunomodulatory agents..... 4 3 2 1 N/M N/A
- Evaluate consolidation and maintenance therapy approaches for patients with MM..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

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
John P Leonard, MD	4 3 2 1	4 3 2 1
David P Steensma, MD	4 3 2 1	4 3 2 1
Anas Younes, MD	4 3 2 1	4 3 2 1
Paul G Richardson, 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:

.....

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UPDATE

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