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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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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 research developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to effectively integrate novel agents and regimens into the management of myelodysplastic syndromes.
- Identify early mortality in acute promyelocytic leukemia (APL), and formulate optimal management strategies for APL.
- Optimize the management of chronic lymphocytic leukemia through the rational integration of prospective Phase III and Phase II data.
- Outline the classification of T-cell lymphomas, and incorporate recent research results into the management of T-cell lymphoma.
- Summarize the rational use of proteasome inhibitors and immunomodulatory agents in the management of multiple myeloma.
- Discuss recently presented Phase III data on induction and maintenance therapy in the management of follicular lymphoma.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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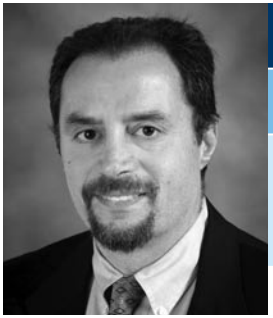


INTERVIEW

Hagop M Kantarjian, MD

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

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on the recent advances in the management of MDS?

DR KANTARJIAN: In MDS, the two drugs that are FDA approved and provide benefit to patients are azacitidine and decitabine. Of these two drugs, only azacitidine has shown a survival advantage in a randomized study (Fenaux 2009; [1.1]).

Once patients fail on the hypomethylating agents, the median survival is brief — approximately four to five months. We are studying several agents in this

setting, including clofarabine. A recent publication from our group showed that response rates are in the range of 30 to 40 percent in patients who have failed on azacitidine or decitabine (Faderl 2010).

DR LOVE: What are your thoughts on the alternative dosing schedules of azacitidine and the duration of therapy?

DR KANTARJIAN: We must remember that the survival advantage with azacitidine is with the seven-day regimen. The five-day regimen has been compared to the seven-day regimen, but only the response rates and hematologic improvements were reported and the study did not address survival (Lyons 2009).

If, because of logistical issues, the standard seven-day schedule is not possible during the weekend, my preference is to make up the other two days on the next Monday and Tuesday rather than truncate the schedule to five days because no evidence supports the equivalence of the survival outcome.

Regarding the duration of therapy, I usually offer two years. After two years, I would give the patient the option of either watching and waiting or continuing at the lower-dose schedule or a more infrequent schedule, such as every five to six weeks instead of every four weeks.

1.1

Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk Myelodysplastic Syndromes: Efficacy Data

	Azacitidine (n = 179)	CCR (n = 179)	Hazard ratio	*p*-value
Median overall survival	24.5 months	15 months	0.58	0.0001
Median time to AML	17.8 months	11.5 months	0.50	<0.0001

AML = acute myeloid leukemia

Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

Track 3

DR LOVE: What do we know about lenalidomide in MDS or acute myeloid leukemia (AML)?

DR KANTARJIAN: Lenalidomide is an established treatment for patients with del 5q low-risk MDS. The transfusion independence rate of 60 to 70 percent and a complete cytogenetic response rate of approximately 40 percent have been reported in this subset.

The more pertinent issue is to understand the role of lenalidomide in higher-risk MDS or AML. My hope is that clinical trials will also demonstrate a role in higher-risk MDS in combination with azacitidine and, perhaps, for subsets of AML, particularly patients with 5q abnormalities. At this time, it is reasonable to use lenalidomide in combination with growth factors for transfusion-

dependent lower-risk MDS, in which growth factors alone have not worked well and the blasts are still low.

Track 8

DR LOVE: Any new data sets in CLL we should know about?

DR KANTARJIAN: The latest update from the German CLL8 trial shows that FCR improves progression-free survival and overall survival in up-front CLL when compared to FC (Hallek 2009; [1.2]). This has been in the making for many years because the initial pilot studies from MD Anderson reported excellent activity with this regimen in CLL.

1.2

Phase III Study Evaluating Fludarabine, Cyclophosphamide and Rituximab (FCR) versus FC as Initial Therapy for Advanced CLL

	OS at 37.7 months	Median PFS	CR	ORR
FCR	87.2%	51.8 mo	44.1%	95.1%
FC	82.5%	32.8 mo	21.8%	88.4%
p-value	0.012	<0.001	<0.01	<0.01

OS = overall survival; PFS = progression-free survival; CR = complete remission; ORR = overall response rate

Hallek M et al. *Proc ASH* 2009;**Abstract 535**.

Tracks 9, 11

DR LOVE: What about bendamustine in CLL?

DR KANTARJIAN: The studies of bendamustine with rituximab (BR) in the front-line setting are showing a high overall response rate of approximately 90 percent, with a complete response rate in one third of the patients (Fischer 2009; [1.3]). Clearly, this combination is effective in front-line CLL. The question is whether BR is as good as FCR or whether it can rescue patients who have failed on FCR therapy.

DR LOVE: What about bendamustine for elderly patients with CLL or those with comorbidities?

DR KANTARJIAN: I believe this is an important question because, although the FCR data have shown a significant advantage for progression-free survival and for survival, most of the FCR studies enrolled patients younger than age 70 or 75. In fact, at least one German study compared fludarabine to chlorambucil and did not show an advantage with fludarabine in patients older than age 65 (Eichhorst 2009). So, among this subset, BR might have equivalent efficacy to FCR and might be a gentler regimen. We should conduct comparative studies of BR versus FCR among patients with CLL who are older than age 70. In

general, among patients who are older than the age range accrued in the FCR studies, BR is a reasonable approach in the up-front setting.

1.3

Phase II Multicenter Trial of Bendamustine/Rituximab in Advanced Untreated Chronic Lymphocytic Leukemia (N = 117)

OR	CR	PR/nodular PR	SD
90.9%	32.7%	58.2%	9.1%

OR = overall response; CR = complete response; PR = partial response; SD = stable disease

Fischer K et al. *Proc ASH* 2009;**Abstract 205**.

Track 13

DR LOVE: Would you discuss the use of lenalidomide in CLL?

DR KANTARJIAN: Lenalidomide, either as a single agent or in combination with rituximab, has good activity in CLL (Ferrajoli 2009). The responses are slow to occur, so the therapy must be continued. A study from MD Anderson of front-line lenalidomide for elderly patients with CLL was reported at ASCO 2010 (Badoux 2010; [1.4]).

In this study, lenalidomide was started at five mg per day, and approximately 60 patients, all older than age 65, have received treatment so far. The overall response rate is 62 percent with the survival at two years being estimated at 90 percent, which appears to be as good as the FCR regimen.

I believe the lenalidomide/rituximab combination could be interesting, particularly for older patients with CLL because the toxicity of lenalidomide-based regimens can be controlled by starting with a lower dose. Lenalidomide either alone or in combination with rituximab could carve out a possible role in the setting of elderly patients with CLL.

1.4

Phase II Study of Lenalidomide as Initial Treatment of Chronic Lymphocytic Leukemia in Elderly Patients

	NCI Working Group 2008 response (N = 60)	
	Patients, n	%
Complete response (CR)	6	10
CR with incomplete blood cell count recovery	3	5
Partial response (PR)	25	42
Nodular PR	3	5
Overall response rate	37	62

Badoux X et al. *Proc ASCO* 2010;**Abstract 6508**.

Tracks 14, 16

DR LOVE: Would you discuss recent advances in the management of acute promyelocytic leukemia (APL)?

DR KANTARJIAN: Recently, a Phase III Intergroup study was published and showed in a randomized fashion that arsenic trioxide consolidation administered during a short period of two months in the setting of APL provides a survival benefit (Powell 2010; [1.5]). In the clinical setting, I favor the AIDA regimen, which is mostly a combination of ATRA and arsenic trioxide. I believe that of all of the drugs for APL, arsenic trioxide is the most potent. ■

1.5

CALGB-C9710 Phase III Intergroup Study in Acute Promyelocytic Leukemia: Efficacy Outcome (N = 481)

	Standard induction followed by standard consolidation	Standard induction followed by arsenic consolidation and standard consolidation	*p*-value
Three-year EFS	63%	80%	<0.0001
Three-year OS	81%	86%	0.059

EFS = event-free survival; OS = overall survival

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

SELECT PUBLICATIONS

Badoux X et al. **A phase II study of lenalidomide as initial treatment of elderly patients with chronic lymphocytic leukemia.** *Proc ASCO* 2010;**Abstract 6508**.

Eichhorst BF et al. **First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia.** *Blood* 2009;114(16):3382-91.

Faderl S et al. **Oral clofarabine in the treatment of patients with higher-risk myelodysplastic syndrome.** *J Clin Oncol* 2010;28(16):2755-60.

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.

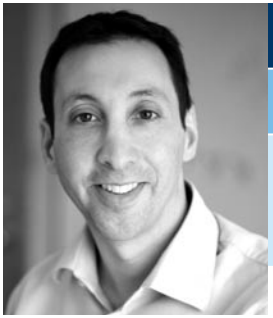
Ferrajoli A et al. **Combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;**Abstract 206**.

Fischer K et al. **Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter Phase II trial of the German CLL Study Group (GCLLSG).** *Proc ASH* 2009;**Abstract 205**.

Hallek M et al. **First-line treatment with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) improves overall survival (OS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a randomized Phase III trial on behalf of an international group of investigators and the German CLL Study Group.** *Proc ASH* 2009;**Abstract 535**.

Lyons RM et al. **Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes.** *J Clin Oncol* 2009;27(11):1850-6.

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.



INTERVIEW

Steven M Horwitz, MD

Dr Horwitz is Assistant Attending in the Lymphoma Service, Division of Hematologic Oncology at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 3, 7

DR LOVE: Would you discuss the efficacy and safety of pralatrexate and romidepsin in T-cell lymphomas?

DR HORWITZ: I have been involved with trials evaluating the novel agents pralatrexate and romidepsin in T-cell lymphomas, and I would say that at a minimum the quality of the data that have been generated with these agents is much better than the historical data. Pralatrexate received FDA approval for relapsed or refractory peripheral T-cell lymphoma (PTCL) on the basis of

the Phase II PROPEL study, which had 109 patients who were evaluable for efficacy. Aside from these two new agents, no other study has enrolled more than 25 or 30 patients. In view of this, I believe that confidence is higher in the recent data sets.

In a single-center study initially conducted at Memorial Sloan-Kettering Cancer Center, the response rate with pralatrexate in relapsed or refractory PTCL was approximately 40 percent. When pralatrexate was investigated in the Phase II PROPEL study at more than 20 centers worldwide, the response rate by formal central review was determined to be 28 percent, with some of the responses being complete responses. The median duration of response was approximately 10 months (O'Conner 2009).

Pralatrexate is easy to administer as an intravenous push for three to five minutes. The approved dose and schedule is 30 mg/m^2 weekly for six out of seven weeks. It does not cause much nausea, and premedication with prochlorperazine may suffice.

The main side effect we noted with earlier studies was severe oral stomatitis, which limited administration. Subsequently, pralatrexate dosing was reduced and patients received presupplementation with folic acid and vitamin B12. Since these modifications, we see much less incidence of severe mucositis.

Tracks 5-6

DR LOVE: What are your thoughts on romidepsin, the other new agent for T-cell lymphomas?

DR HORWITZ: Romidepsin is a histone deacetylase inhibitor and is approved for cutaneous T-cell lymphoma (CTCL). We recently finished a 130-patient study for aggressive PTCL, similar in design to the pralatrexate PROPEL study. The central review for response rates is ongoing, and we should have the response data soon.

The National Cancer Institute experience looks good, reporting response rates of more than 30 percent across a number of different subtypes (Piekarz 2008; [2.1]). The standard dosing approved for CTCL is 14 mg/m^2, administered intravenously weekly, for three out of four weeks. The drug is administered as a four-hour infusion. In PTCL studies, the same dose and schedule are being used. The toxicities are not cumulative, so patients can continue receiving romidepsin as long as it provides a benefit.

The main issue, historically, has been a worry about QTc prolongation. If patients with known arrhythmias and those receiving concomitant medications that can cause QTc prolongation are excluded, then we do not see any changes in the QTc interval. This has been much less of a concern once people have been aware of the risk.

In the clinical studies, EKG monitoring was conducted before and after treatment. I also check electrolytes at baseline before the first cycle and make sure

that the potassium and magnesium levels are okay. If they are below normal, then I supplement them.

I also check an EKG postantiemetic and postromidepsin during the first cycle. If I don't see any QTc prolongation, then I don't conduct additional EKG monitoring. I simply make sure that the electrolytes are in the normal range before starting each cycle.

We also observe malaise with romidepsin and sometimes nausea and vomiting. High-grade fatigue, with which patients might lose weight or experience severe nausea or vomiting, is not common. For most patients the fatigue is lower grade and they experience some tiredness with a loss of appetite. The main hematologic side effect is thrombocytopenia, and occasionally we might have to hold the drug because of low platelet counts. If the drug is skipped for a week, thrombocytopenia resolves right away. ■

2.1

Phase II National Cancer Institute Multicenter Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma (n = 43)

Overall response	Complete response	Partial response
38%	15%	23%

"This study demonstrates tolerability and durable clinical benefit...of romidepsin in pts with recurrent or refractory PTCL."

Piekarz R et al. *Proc ASH* 2008;**Abstract 1567**.

SELECT PUBLICATIONS

Coiffier B et al. **Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy.** *Proc ASH* 2010;**Abstract 114**.

Goy A et al. **Pralatrexate is effective in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with prior ifosfamide, carboplatin, and etoposide (ICE)-based regimens.** *Proc ASH* 2010;**Abstract 1753**.

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**.

Horwitz SM et al. **Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial.** *Proc ASH* 2009;**Abstract 919**.

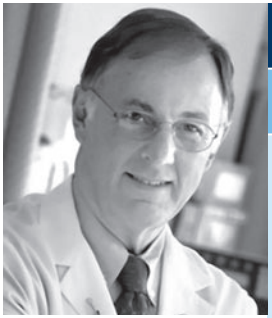
O'Conner O et al. **PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).** *Proc ASCO* 2009;**Abstract 8561**.

Piekarz RL et al. **Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma.** *J Clin Oncol* 2009;27(32):5410-7.

Piekarz R et al. **Results of a Phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2008;**Abstract 1567**.

Pinter-Brown L et al. **Safety and management of pralatrexate treatment in relapsed or refractory peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2009;**Abstract 1675**.

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

Richard I Fisher, MD

Dr Fisher is Samuel E Durand Professor of Medicine, Director of the James P Wilmot Cancer Center, Director of the University of Rochester Medical Faculty Group, Senior Associate Dean for Clinical Affairs and Vice President of the University of Rochester Medical Center in Rochester, New York.

Tracks 1-19

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the data from the PRIMA trial evaluating rituximab maintenance after initial rituximab/chemotherapy induction in follicular lymphoma (FL)?

DR FISHER: A number of studies suggested the value of maintenance rituximab in relapsed FL. However, the question remains whether maintenance

rituximab after initial rituximab/chemotherapy induction in FL provides a real benefit versus waiting and then re-treating later. In the PRIMA study, patients with FL received up-front rituximab/chemotherapy and were then randomly assigned to maintenance rituximab versus observation. The results show an absolute benefit of 16 percent in two-year progression-free survival in favor of the maintenance arm (Salles 2010; [3.1]).

Rituximab was administered every two months for two years, and clearly it delays recurrence. Although no survival benefit has been observed yet, that may come with longer follow-up. We need to put the PRIMA data in the context of all available data for maintenance rituximab. In the relapsed setting, some of the data sets have shown a survival advantage with longer follow-up. It's clear to me that maintenance rituximab should be considered as up-front therapy for FL.

The side effects of two years of maintenance rituximab were minimal, with no catastophic infections, but I believe that outside of a clinical protocol we should not go beyond two years at this time. I believe prolonged immunosuppression and the absence of B cells will ultimately deplete new antigen reactivity and might have adverse consequences. Ongoing trials examining longer rituximab maintenance, such as four or five years, will eventually indicate whether longer maintenance might be of further benefit.

We are starting to observe some immunodeficiency in terms of lower immunoglobulin levels in patients who have undergone extensive treatment with rituximab, and some of these patients are developing signs of pulmonary infections. My guess is that there is an inflection point and a tipping point, such that an optimal duration of maintenance exists beyond which toxicity will overcome the benefits. Currently, we don't know that tipping point.

With the overwhelming weight of evidence from the PRIMA study, I am comfortable now with two years of maintenance in the up-front setting.

3.1

Phase III PRIMA Study: Efficacy Results with Maintenance Rituximab for Previously Untreated Follicular Lymphoma

	Observation (n = 513)	Maintenance rituximab (n = 505)	Hazard ratio	*p*-value
Two-year PFS	66%	82%	0.50	<0.0001

PFS = progression-free survival

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

Tracks 3, 5

DR LOVE: Does a role exist for radioimmunotherapy (RIT) consolidation as part of initial therapy for patients with FL?

DR FISHER: Next year we might have an answer on the role of RIT as part of initial therapy. An Intergroup trial, S0016, comparing R-CHOP to CHOP followed by tositumomab for the initial treatment of FL, is ongoing (3.2). This is a large trial that is maturing, and hopefully we will have an abstract at ASCO 2011.

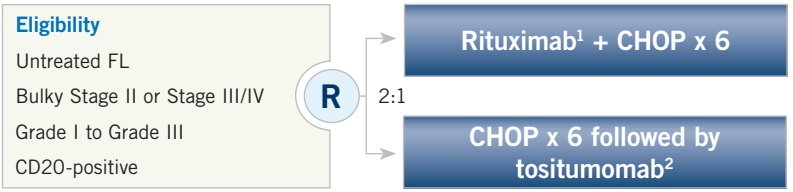
The results are currently blinded by the Data and Safety Monitoring Board. However, the study is pivotal in the sense that it may "make or break" RIT as an option as consolidation for up-front FL. RIT has been slow to take off in popularity for a number of reasons, and we look forward to the results of S0016. Then we will have to decide where to go from there.

I believe RIT is in danger of disappearing soon if these studies are not positive, although RIT is active and physicians who have used it know that it is active. We would like to see it used, and hopefully within a year we will know the answer to that.

3.2

Randomized Phase III Trial Comparing R-CHOP to CHOP Followed by Tositumomab for the Initial Treatment of Follicular Lymphoma

Protocol ID: SWOG-S0016 **Target Accrual:** 500



[1] A total of six doses of rituximab are administered. Two doses are administered before CHOP cycle 1, a third and a fourth dose of rituximab are administered with CHOP cycle 3 and cycle 5, respectively, and the last two rituximab doses are administered after CHOP cycle 6.
[2] Two doses of tositumomab are administered after CHOP cycle 6.

www.clinicaltrials.gov. Identifier NCT00006721.

Tracks 7-8

DR LOVE: Would you discuss bendamustine/rituximab in the treatment of FL?

DR FISHER: Bendamustine is an extremely active agent. I don't believe anyone in the United States predicted that this drug would have this kind of activity. It has properties of both an alkylating agent and a purine analog.

The study comparing R-CHOP to BR presented at ASH 2009 looks good, and we use BR extensively (Rummel 2009; [3.3]). The data are not published in a peer-reviewed journal yet, so we don't have a lot of knowledge of how the statistics were obtained and how the follow-ups were performed.

Overall, I believe it is interesting and worthy of consideration, particularly when contraindications to anthracycline-based chemotherapy are present. Even for patients without contraindications, such as a healthy 60-year-old, I believe it is a reasonable option and would be appropriate for use. In our center we still use R-CHOP as the standard, but we also use BR a great deal.

The toxicity profile is different, and not much hair loss occurs. Some marrow toxicity is still present along with significant fatigue. The Rummel data suggest that BR is significantly less toxic than R-CHOP (Rummel 2009; [3.4]). We have not administered BR to enough patients with good performance status or to those in great health to know how it compares. We are using it for a preselected population that, by definition, is less healthy, and that makes it difficult for me to make the comparison — my database is skewed against BR because I am using it for the less healthy people. ■

3.3

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

	Overall response	Complete response	Progression-free survival	Median time to next treatment
BR (n = 260)	92.7%	39.6%	54.9 months	Not reached
R-CHOP (n = 253)	91.3%	30.0%	34.8 months	46.7 months
p-value	—	0.0262	0.00012	0.0281

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

3.4

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

	Grade 3 or 4 neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Drug-related rash	Alopecia
BR	10.7%	36.5%	6.9%	6.2%	16.2%	15%
R-CHOP	46.5%	47.8%	28.8%	18.6%	9.1%	62%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	—

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

SELECT PUBLICATIONS

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.

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**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.

INTERVIEW

Michele Cavo, MD

Professor Cavo is Professor of Hematology in the Institute of Hematology and Medical Oncology "Seràgnoli" at S Orsola's University Hospital's Bologna University School of Medicine in Bologna, Italy.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: How do you approach the choice of induction regimen for patients with multiple myeloma (MM) who are eligible for transplant?

PROF CAVO: Transplant-eligible patients should receive an induction regimen containing at least one novel agent. We divide the induction regimens into those that are bortezomib based, those that are IMiD® based and a third class that includes both bortezomib and an IMiD. A three-drug regimen is clearly superior to a two-drug regimen in terms of a higher rate of complete response or very good partial response before autotransplant, and these responses are further improved after the autologous stem cell transplant. I believe that the best induction regimen for a younger transplant-eligible patient is probably a three-drug regimen incorporating both bortezomib and an IMiD, such as

lenalidomide. Such a combination seems to offer the highest complete response rate before transplant (Richardson 2010; [4.1]).

4.1

Prospective Phase I/II Study of Bortezomib, Lenalidomide and Dexamethasone (RVD) in Newly Diagnosed Multiple Myeloma

	All patients (n = 66)	Phase II patients (n = 35)
Complete response (CR)/near-CR	40%	57%
Very good partial response or better	67%	74%
Partial response or better	100%	100%

"This phase 1/2 study, the first prospective investigation of the regimen of lenalidomide-bortezomib-dexamethasone in newly diagnosed MM, has shown the combination to have favorable tolerability during a lengthy period, with no treatment-related mortality. This regimen is the first of its kind to result in a 100% response rate."

Richardson PG et al. *Blood* 2010;116(5):679–86.

Track 3

DR LOVE: What are your thoughts on induction therapy for older patients or those who are ineligible for transplant?

PROF CAVO: For patients with myeloma who are transplant ineligible, the standard combinations so far include melphalan/prednisone/thalidomide (MPT) and melphalan/prednisone/bortezomib (MPV). At ASH 2009 results were presented of a Phase III three-arm study evaluating standard MP, MP combined with lenalidomide (MPR) and MPR followed by maintenance lenalidomide (Palumbo 2009; [4.2]). The results reported that MPR followed by maintenance lenalidomide improves the clinical outcome significantly in comparison to standard MP. This provides us with a third combination for transplant-ineligible myeloma and demonstrates the role of maintenance lenalidomide for such patients.

Tracks 4, 10

DR LOVE: Where are we in terms of the schedule of bortezomib in the management of MM?

PROF CAVO: In my view, the most important issue in the nontransplant setting regarding the use of bortezomib is the recognition that changing from a twice-weekly schedule to a once-weekly schedule does not reduce the efficacy but significantly lowers the incidence of neurological toxicity (Bringhen 2010; [4.3]). It is also important to explain clearly to patients the symptoms of neuropathy and to advise them that at the first onset of one of the symptoms they should call the doctor and ask for a consultation. Physicians

will then be able to appropriately reduce the bortezomib dose or even stop the treatment in cases of neurological toxicity. Bortezomib dose modification is mandatory for achieving resolution or a decrease in the grade of neurological toxicity. ■

4.2

Response Rates and Progression-Free Survival (PFS) in a Phase III Study Evaluating MP versus MPR versus MPR-R for Elderly Patients with Multiple Myeloma

Efficacy	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)	*p*-value (MPR-R vs MP)
Overall response rate[1]	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%	—
Median PFS	Not reached	13.2 months	13.0 months	<0.001

[1] As measured using EBMT criteria (Blade 1998); [2] Immunofixation-negative with or without bone marrow confirmation; [3] VGPR: >90% reduction in M-protein
M = melphalan; P = prednisone; R = lenalidomide; 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(5):1115-23.

4.3

Efficacy and Peripheral Neuropathy (PN) with Once-Weekly versus Twice-Weekly Bortezomib for Elderly Patients with Newly Diagnosed Multiple Myeloma

	Weekly bortezomib regimen (n = 372)	Twice-weekly bortezomib regimen (n = 139)
Median progression-free survival	33.1 months	31.7 months
Three-year survival	88%	89%
Overall response	85%	86%
Complete response	30%	35%
PN at 18 months (all grades)	40%	72%
PN at 18 months (Grade 3 or 4)	9%	36%

Bringhen S et al. *Blood* 2010;116(23):4745-53.

SELECT PUBLICATIONS

Bringhen S et al. **Efficacy and safety of once weekly bortezomib in multiple myeloma patients.** *Blood* 2010;116(23):4745-53.

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**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

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

2. **In MDS, the alternate five-day dosing schedules of azacitidine have shown comparable _____ to the standard seven-day dosing.**
   a. Response rates
   b. Hematological improvement
   c. Response rates and hematological improvement
   d. Overall survival

3. **Which of the following regimens has shown an improvement in overall survival in the up-front management of chronic lymphocytic leukemia?**
   a. Alemtuzumab
   b. Bendamustine/rituximab
   c. FCR
   d. R-CHOP

4. **In a Phase III Intergroup study, the addition of arsenic trioxide as consolidation therapy for APL improved _____.**
   a. Overall survival
   b. Event-free survival
   c. Event-free survival and overall survival

5. **In a Phase III study comparing bendamustine/rituximab (BR) to R-CHOP as front-line treatment for patients with indolent lymphomas, which of the following were observed significantly less frequently with the BR regimen?**
   a. Grade 3 to 4 neutropenia
   b. Infectious complications
   c. Peripheral neuropathy
   d. Stomatitis
   e. All of the above

6. **In the Phase III PRIMA study, patients with previously untreated FL who received maintenance rituximab experienced a _____ percent improvement in two-year progression-free survival compared to those who were observed after initial treatment.**
   a. Zero
   b. 25
   c. 50

7. **Which of the following drugs is FDA approved for relapsed or refractory peripheral T-cell lymphoma?**
   a. Pralatrexate
   b. Romidepsin
   c. Vorinostat
   d. None of the above

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

9. **What is the mechanism of action of romidepsin?**
   a. Antimetabolite
   b. Alkylating agent
   c. Histone deacetylase inhibitor
   d. None of the above

10. **Which of the following regimens has ever shown an overall response rate of 100 percent in multiple myeloma?**
    a. VAD
    b. RVD
    c. Rd
    d. None of the above

11. **A weekly bortezomib regimen has _____ when compared to a twice-weekly bortezomib regimen in the treatment of multiple myeloma in elderly patients.**
    a. Similar efficacy and toxicity
    b. Similar efficacy and reduced toxicity
    c. Reduced efficacy and toxicity

Post-test answer key: 1a, 2c, 3c, 4c, 5e, 6c, 7a, 8b, 9c, 10b, 11b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 4

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
Activity of lenalidomide in acute myeloid leukemia and high-risk myelodysplastic syndromes	4 3 2 1	4 3 2 1
CLL8: A Phase III trial comparing FCR to FC as initial treatment of chronic lymphocytic leukemia	4 3 2 1	4 3 2 1
PRIMA trial: Maintenance rituximab after initial immunochemotherapy in follicular lymphoma	4 3 2 1	4 3 2 1
Studies of arsenic trioxide in the initial treatment of acute promyelocytic leukemia	4 3 2 1	4 3 2 1
Efficacy and safety of weekly versus biweekly bortezomib in MM	4 3 2 1	4 3 2 1
PROPEL: A pivotal Phase II study of pralatrexate in peripheral T-cell lymphoma	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 the results of emerging clinical research to effectively integrate novel agents and regimens into the management of myelodysplastic syndromes. .... 4 3 2 1 N/M N/A
- Identify early mortality in acute promyelocytic leukemia (APL), and formulate optimal management strategies for APL. .... 4 3 2 1 N/M N/A
- Optimize the management of chronic lymphocytic leukemia through the rational integration of prospective Phase III and Phase II data. .... 4 3 2 1 N/M N/A
- Outline the classification of T-cell lymphomas, and incorporate recent research results into the management of T-cell lymphoma. .... 4 3 2 1 N/M N/A
- Summarize the rational use of proteasome inhibitors and immunomodulatory agents in the management of multiple myeloma. .... 4 3 2 1 N/M N/A
- Discuss recently presented Phase III data on induction and maintenance therapy in the management of follicular lymphoma. .... 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
Hagop M Kantarjian, MD	4 3 2 1	4 3 2 1
Steven M Horwitz, MD	4 3 2 1	4 3 2 1
Richard I Fisher, MD	4 3 2 1	4 3 2 1
Michele Cavo, 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

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

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UPDATE

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UPDATE

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