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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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Hematologic Oncology Update
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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

- Appraise the use of cytogenetics for individualizing the clinical management of hematologic cancer.
- Develop evidence-based treatment algorithms for frequently encountered adult chronic leukemia.
- Summarize emerging data with novel agents/combinations and treatment approaches for newly diagnosed or relapsed/refractory indolent or aggressive B-cell non-Hodgkin lymphoma (NHL).
- Tailor up-front/induction therapy based on individual and disease characteristics for patients with multiple myeloma.
- Evaluate consolidation and maintenance therapy approaches for patients with multiple myeloma.
- Describe the standard therapeutic approaches and investigational strategies for the treatment of newly diagnosed and relapsed acute promyelocytic leukemia (APL).
- Recall the efficacy and side effects of hypomethylating and immunomodulating agents in the treatment of myelodysplastic syndromes (MDS).
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

Susan M O'Brien, MD

Dr O'Brien is Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about the Phase III trial of nilotinib versus imatinib in CML, presented at the recent ASH meeting?

DR O'BRIEN: The ENESTnd trial was a front-line trial that compared standard-dose imatinib to two different doses of nilotinib — 300 mg or 400 mg twice daily. The primary endpoint was the major molecular response — determined by PCR — at 12 months. Results showed that the endpoint was

significantly in favor of nilotinib (Saglio 2009; [1.1]). The endpoint chosen was based on the data from the IRIS trial, which initially showed that a major molecular response at 12 months was associated with superior progression-free survival (PFS). However, with longer follow-up, it does not appear to be as significant as previously thought. As of now, the data on association of molecular responses with PFS are still evolving. Clinically, I believe the most interesting observation was the significant difference between the groups in transformation rate — with less than one percent of patients in each of the nilotinib groups experiencing disease transformation to accelerated/blast phase by 12 months compared to four percent in the imatinib group. Clearly, everyone can relate to the transformation rate as a clinically relevant endpoint compared to the 12-month molecular response.

DR LOVE: Reimbursement and cost issues aside, what would be your treatment choice in this setting?

DR O'BRIEN: I would probably choose nilotinib.

1.1

ENESTnd Trial: An International Phase III Trial Comparing Nilotinib to Imatinib for Patients with Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
MMR	57%	54%	30%
CCR (by 12 mo)	80% $p < 0.0001$	78% $p = 0.0005$	65%
Progression to AP/BC (12 mo)	<1% $p = 0.0095$	<1% $p = 0.0037$	4%

MMR = major molecular response; CCR = complete cytogenetic response; AP/BC = accelerated phase/blast crisis

Saglio G et al. *Proc ASH* 2009;**Abstract LBA-1**.

Track 5

DR LOVE: Would you discuss data from the international study of fludarabine/cyclophosphamide/rituximab (FCR) versus fludarabine/cyclophosphamide (FC) in CLL?

DR O'BRIEN: This Phase III study showed that FCR was associated with superior survival in addition to higher complete response rates, overall response rates and PFS (Hallek 2009; [1.2]) compared to FC. This is the first time a survival advantage has been shown in front-line CLL.

Another trial comparing fludarabine to chlorambucil in the front-line setting reported a survival advantage with fludarabine (Rai 2009). Clearly because we have better therapies, we are now affecting survival in this disease.

1.2

Phase III Study Evaluating Fludarabine, Cyclophosphamide and Rituximab (FCR) versus FC for Initial Therapy in Advanced Chronic Lymphocytic Leukemia

	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 remissions; ORR = overall response rate

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

Tracks 10-11

DR LOVE: Would you discuss the data with lenalidomide in elderly patients with CLL?

DR O'BRIEN: We presented data at ASH 2008 (Ferrajoli 2008) from a Phase II trial of single-agent lenalidomide in patients older than age 65 with CLL requiring treatment. Early results indicated that lenalidomide administered as continuous therapy is safe and well tolerated as initial therapy for elderly patients with CLL.

No complete remissions were observed, though about two thirds responded. The median time on the study was nine months at the time of reporting. Because lenalidomide has no direct cytotoxicity to CLL cells, complete responses are not expected before 12 months. This should be taken into consideration when evaluating the results of this study.

In another front-line trial of lenalidomide in patients of all ages with CLL (Chen 2008), the response rates were similar to ours, and with no CRs in early follow-up. The main side effect was neutropenia in both trials, so we need to be more aggressive with growth factors to maintain patients on therapy.

Tracks 13, 15

DR LOVE: What are some of the recent developments in MDS that you think oncologists in practice need to know about?

DR O'BRIEN: In MDS the most important recent study was the comparison of azacitidine to best supportive care because this is the first study that actually showed a significant survival advantage for the use of azacitidine (Fenaux 2009). I don't know how practice changing it is, because many physicians are already using azacitidine, but it's good to know that it's not just a palliative type of treatment. Rather, it's affecting survival.

Having said that, if I had a young patient with MDS — even if he or she is faring well on azacitidine — that patient should be considered for a transplant because nobody is cured with any of our systemic therapies. Our newer agents are relatively well tolerated and may produce durable remissions, but we still do not have a curative therapeutic strategy in MDS other than allogeneic transplant.

DR LOVE: Could you comment on lenalidomide in MDS?

DR O'BRIEN: Lenalidomide has impressive data on patients with 5q deletion MDS. About two thirds of patients with 5q deletion MDS are at lower risk, and lenalidomide is quite effective in this population. The response rate, including cytogenetic remissions, is approximately 70 percent, and patients become transfusion independent for prolonged periods.

Response rates for patients with 5q deletion MDS with higher-risk disease (Adès 2009) were 27 percent. Other high-risk features, including additional cytogenetic abnormalities and platelet counts of less than 100,000/mm^3 at baseline, were further correlated with decreased efficacy.

DR LOVE: What are your thoughts about the use of lenalidomide in patients with MDS without 5q deletion?

DR O'BRIEN: The response rate with lenalidomide is approximately 20 percent for patients without 5q deletion. Response rates have varied from 10 percent to 40 percent with azacitidine or decitabine. Therefore, lenalidomide clearly has responses in a similar range and can be quite effective in this group also. ■

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Chen C et al. **A phase II study of lenalidomide in previously untreated, symptomatic chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 44**.

Cortes JE et al. **Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase.** *J Clin Oncol* 2010;28(3):392-7.

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. **Lenalidomide as initial treatment of elderly patients with chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 45**.

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Rai K et al. **Long-term survival analysis of the North American Intergroup study C9011 comparing fludarabine and chlorambucil in previously untreated patients with CLL.** *Proc ASH* 2009;**Abstract 536**.

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INTERVIEW

Peter McLaughlin, MD

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

Tracks 1-20

Track 1 **Case discussion:** A 46-year-old man with Grade IIIA follicular lymphoma (FL)

Track 2 R-FND followed by radioimmunotherapy for high-risk FL

Track 3 FIT: Consolidation therapy with yttrium-90-ibritumomab tiuxetan compared to no additional therapy after first remission in advanced FL

Track 4 PRIMA: Maintenance rituximab after chemotherapy/rituximab in FL

Track 5 Efficacy and tolerability of bendamustine/rituximab compared to R-CHOP as first-line treatment in FL, indolent lymphoma and mantle-cell lymphoma (MCL)

Track 6 Therapeutic options for the initial treatment of FL

Track 7 Consolidation yttrium-90-ibritumomab tiuxetan in patients with FL

Track 8 Initial treatment of FL with radioimmunotherapy alone or after chemotherapy

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Track 12 Phase II trial of bortezomib in combination with R-hyper-CVAD/methotrexate and cytarabine for untreated MCL

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Track 16 Lenalidomide and rituximab as front-line therapy for indolent B-cell non-Hodgkin lymphoma

Track 17 Bendamustine/bortezomib and rituximab in indolent lymphoma

Track 18 Lenalidomide salvage therapy for diffuse large B-cell lymphoma (DLBCL)

Track 19 **Case discussion:** A 61-year-old man with a vallecular mass and neck and abdominal adenopathy is diagnosed with Stage IIIE DLBCL

Track 20 Dose-dense R-CHOP-14 versus R-CHOP-21 for DLBCL

Tracks 2-3, 7

DR LOVE: Would you describe the results of the recent radioimmunotherapy (RIT) trials for patients with high-risk FL?

DR MCLAUGHLIN: At ASH 2008, we reported interim results from a Phase II study for patients with high-risk FL according to FLIPI.

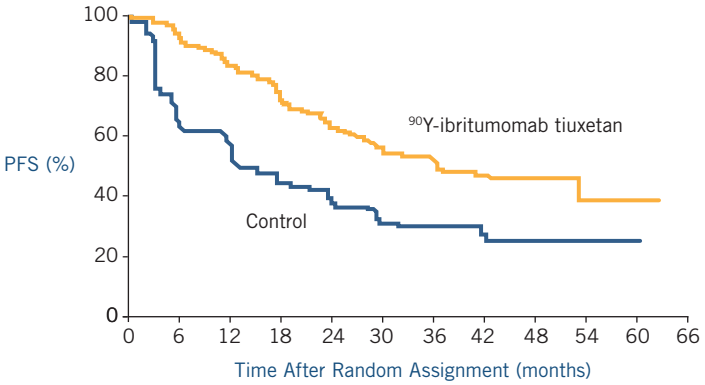
The induction regimen in this study included rituximab, fludarabine, mitoxantrone and dexamethasone (R-FND). After induction, patients received consolidation RIT with ibritumomab tiuxetan and then maintenance rituximab for one year (McLaughlin 2008). The complete remission rate was 83 percent, and the Kaplan-Meier curve showed a 20 percent improvement compared to the expected three-year disease-free survival.

DR LOVE: Where are we in general in terms of consolidation RIT?

DR MCLAUGHLIN: In addition to our Phase II study, the results of the Phase III FIT trial showed that the PFS was significantly improved on the consolidation arm — 36 months versus 13 months (Morschhauser 2008; [2.1]).

2.1

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



	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

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. Reprinted with permission.

Tracks 5-6, 11

DR LOVE: Can you review the data we have on the use of rituximab/bendamustine (R-B) as first-line treatment for follicular, indolent and mantle-cell lymphomas?

DR MCLAUGHLIN: The Study Group Indolent Lymphomas, or StIL, presented data at ASH 2009 that indicated that not only is R-B much better tolerated than R-CHOP, but it also appears to be superior in terms of disease control (Rummel 2009; [2.2]). In view of these intriguing data (Rummel 2009), I am already talking to my patients with FL about front-line R-B as an acceptable alternative to R-CHOP.

DR LOVE: What about trials evaluating bortezomib as part of the initial treatment of mantle-cell lymphoma (MCL)?

DR MCLAUGHLIN: Bortezomib is an effective agent for MCL, and I find it attractive to incorporate bortezomib into front-line regimens. However, adding another agent to the backbone of R-CHOP or R-CVP may be troublesome, as it may lead to unacceptable neuropathy. However, we presented a Phase I study (Romaguera 2008) of bortezomib with R-hyper-CVAD, which also includes vincristine, and we did not observe increased neuropathy in this study.

2.2 **Phase III Trial Evaluating First-Line Rituximab/Bendamustine (R-B) versus R-CHOP for Advanced Follicular, Indolent and Mantle-Cell Lymphomas**

Final analysis (median follow-up of 32 months)

Efficacy	R-B (n = 260)	R-CHOP (n = 253)	Hazard ratio	*p*-value
Overall response rate	94%	94%	—	—
Complete response rate	40%	31%	—	0.0323
Median PFS	55 months	35 months	0.5765	0.0002
Median EFS	54 months	31 months	0.6014	0.0002
Adverse events				
Alopecia	15%	62%	—	—
Infection	37%	48%	—	0.0403
Erythematous skin reaction	16%	9%	—	0.0122
Grade III/IV neutropenia	11%	47%	—	<0.0001
Peripheral neuropathy	7%	29%	—	<0.0001
Stomatitis	6%	19%	—	<0.0001

PFS = progression-free survival; EFS = event-free survival

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

Track 16

DR LOVE: Would you discuss the results of lenalidomide/rituximab as front-line therapy for indolent B-cell non-Hodgkin lymphoma (NHL)?

DR MCLAUGHLIN: The interim analysis of the Phase II trial (Fowler 2009) showed excellent overall and complete response rates in patients with indolent B-cell lymphomas. The combination was well tolerated, with a manageable toxicity profile (Fowler 2009; [2.3]).

DR LOVE: Cost and reimbursement issues aside, is this combination an option in terms of clinical therapy in this setting?

DR MCLAUGHLIN: Yes, I believe that it's a legitimate consideration. ■

2.3

Phase II Trial Evaluating Front-Line Lenalidomide/Rituximab in Indolent B-Cell Non-Hodgkin Lymphoma: Interim Efficacy Data

	ORR	CR	CR/CRu
All patients (n = 20)	84%	79%	58%/21%
Patients with FL (n = 10)*	100%	100%	NR

* By the completion of six cycles of therapy
ORR = overall response rate; CR = complete response; CRu = complete response unconfirmed; FL = follicular lymphoma; NR = not reported

Fowler N et al. *Proc ASH* 2009;**Abstract 1714**.

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Rummel M 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

Farhad Ravandi, MD

Dr Ravandi is Associate Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-12

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the current approach to patients with acute promyelocytic leukemia (APL)?

DR RAVANDI: APL represents a medical emergency with a high rate of early mortality, often because of hemorrhage from a characteristic coagulopathy. Even if the diagnosis is only a possibility, the patient should be admitted and undergo a workup as an inpatient. It is critical to start all-trans retinoic acid (ATRA) as soon as the diagnosis is suspected based on histopathologic criteria and before definitive cytogenetic confirmation is made.

Long-term leukemia-free survival is now in the range of 80 percent, and the majority of deaths still occur in the first few days or in the first week. ATRA is a relatively nontoxic oral agent, and early therapy can mean reducing early mortality. ATRA differentiates the immature promyelocytes and leukemic

blasts, and the procoagulant properties of these cells are lost. If the diagnosis is not confirmed, ATRA can be discontinued and treatment changed to that which is used for other types of AML.

Tracks 5-7

DR LOVE: How about other agents for APL?

DR RAVANDI: Up to 30 percent of patients who receive ATRA-based regimens may experience relapse. Arsenic trioxide should be the first choice in this setting and can result in up to an 80 percent clinical response and a 60 percent molecular response.

DR LOVE: What about research evaluating arsenic trioxide in the first-line setting for APL?

DR RAVANDI: The randomized Phase III study that addresses this question in the consolidation setting is the North American Intergroup protocol C9710 (Powell 2007; [3.1]). This study is complete and should be available in a publication soon. The addition of two courses of arsenic trioxide consolidation after remission induction therapy significantly improved event-free survival and overall survival in patients with APL despite no significant effect on response rates. In the induction setting, a Phase II trial evaluating the combination of ATRA and arsenic trioxide with or without gemtuzumab has shown acceptable long-term outcomes (Ravandi 2009; [3.2]). This combination could clearly be used if patients are deemed unfit for chemotherapy, such as patients with cardiac disease or those who wish to avoid chemotherapy.

3.1

North American Intergroup C9710: A Phase III Study Evaluating Consolidation Therapy with Arsenic Trioxide in Newly Diagnosed Acute Promyelocytic Leukemia

	Arsenic consolidation	No arsenic consolidation	*p*-value
Event-free survival at three years	81%	66%	0.0007
Overall survival at three years	86%	79%	0.063

Powell BL et al. *Proc ASCO* 2007;**Abstract 2**.

3.2

Clinical and Molecular Response Rates to All-Trans Retinoic Acid and Arsenic Trioxide with and without Gemtuzumab in Front-Line Induction Therapy for Patients with Acute Promyelocytic Leukemia (N = 82)

Response rate	Molecular response rate	Three-year survival	Three-year event-free survival
92%	73%	85%	83%

Ravandi F et al. *J Clin Oncol* 2009;27(4):504-10.

DR LOVE: What are the clinical options for APL in the front-line setting?

DR RAVANDI: I believe that ATRA and arsenic trioxide will be the way of the future. We have used this regimen successfully with a variety of patients in all risk groups, and I would recommend it off protocol in the front-line setting.

Tracks 10-11

DR LOVE: What are some of the major recent clinical research data sets that have emerged in MDS?

DR RAVANDI: The recent findings from the AZA-001 study (Fenaux 2009; [3.3]) showed a significant survival benefit in favor of azacitidine versus conventional care. A similar Phase III study conducted by the EORTC with decitabine in patients with higher-risk MDS was negative for survival, though the study was poorly designed (Wijermans 2008).

DR LOVE: What about the duration of administration of azacitidine?

DR RAVANDI: For responding patients, I continue administration of azacitidine as long as the patient tolerates it, which is often 12 to 24 cycles and sometimes up to 36 cycles. This translates to approximately two to three years of therapy. ■

3.3

Phase III Study Evaluating Azacitidine versus Conventional Care Regimens (CCR) for Higher-Risk Myelodysplastic Syndromes

	Azacitidine (n = 179)	CCR (n = 179)	Hazard ratio	*p*-value
Median overall survival	24.5 mo	15 mo	0.58	0.0001
Two-year survival	50.8%	26.2%	NR	<0.0001
Time to AML/death	17.8 mo	11.5 mo	0.50	<0.0001

NR = not reported; AML = acute myeloid leukemia

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

SELECT PUBLICATIONS

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Wijermans P et al. **Low dose decitabine versus best supportive care in elderly patients with intermediate or high risk MDS not eligible for intensive chemotherapy: Final results of the randomized phase III study (06011) of the EORTC Leukemia and German MDS Study Groups.** *Proc ASH* 2008;**Abstract 226**.

INTERVIEW

Keith Stewart, MBChB

Dr Stewart is Professor of Medicine at Mayo Clinic in Scottsdale, Arizona.

Tracks 1-12

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: How do you approach induction therapy for a patient with high-risk multiple myeloma (MM)?

DR STEWART: The options include regimens containing bortezomib and lenalidomide/dexamethasone. We have published (Reeder 2009b) results of a three-drug combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD) in patients with newly diagnosed MM. Responses were rapid, with a mean 80 percent decline in the M-protein at the end of two cycles. We believe that bortezomib offers assistance in overcoming poor prognoses in patients with MM and high-risk cytogenetics.

Lenalidomide/dexamethasone is another alternative and might be more suitable for patients with long distances to travel to receive therapy, in addition to those who don't want to or can't stop working and those with relatively normal renal function.

DR LOVE: What about the recent data related to the schedule of administration of bortezomib and peripheral neuropathy?

DR STEWART: This question was studied in a prospective randomized Phase II trial (Reeder 2009a) by administering bortezomib either once or twice weekly. The once-weekly regimen was shown to be a much more convenient schedule with identical response rates and fewer Grade III/IV adverse events, including Grade III peripheral neuropathy. Overall rates of peripheral neuropathy were comparable.

Track 4

DR LOVE: What is the role of novel three- and four-drug combinations in newly diagnosed MM?

DR STEWART: Interim results from the EVOLUTION study (Kumar 2009; [4.1]) were presented at ASH 2009. The study included the triplet and quadruplet combinations of VDR (bortezomib/dexamethasone/lenalidomide), VDC (bortezomib/dexamethasone/cyclophosphamide) and VDCR (bortezomib/dexamethasone/cyclophosphamide/lenalidomide).

All of these regimens yielded high rates of OR, CR or VGPR. Although, as one might expect, with the addition of more drugs, adverse event profiles increased. Almost three fourths of the patients experienced at least one serious adverse event. However, if a patient experiences a need for rapid control of symptoms, these three- and four-drug combinations will fill that niche.

4.1

EVOLUTION: A Multicenter, Randomized Phase II Study of Novel Three- and Four-Drug Combinations of Bortezomib (V), Dexamethasone (D), Lenalidomide (R) and Cyclophosphamide (C) for Newly Diagnosed Multiple Myeloma

Best unconfirmed response

Regimen	Evaluable patients	ORR %	CR (sCR) %	VGPR* (nCR) %	PR %
VDR	42	90	12	33 (10)	45
VDC	31	87	6	35	45
VDCR	33	94	15 (3)	42 (3)	36

* Patients categorized as having a VGPR include those who have no measurable M-protein but have not yet had follow-up bone marrow assessments to confirm CR/nCR status.

ORR = overall response rate; CR = complete response; sCR = stringent complete response; VGPR = very good partial response; nCR = near CR; PR = partial response

Kumar S et al. ASH 2009;**Abstract 127**.

Tracks 7-8

DR LOVE: Would you comment on the recent press release on maintenance therapy with lenalidomide in the CALGB-100104 trial?

DR STEWART: This Intergroup trial was evaluating lenalidomide maintenance after high-dose melphalan and stem cell transplantation in patients with multiple myeloma. The independent data review committee halted the trial after an interim analysis confirmed a highly significant improvement in the PFS in favor of the maintenance arm.

Despite several unanswered questions in the press release, two facts are apparent: patients need to continue to be in remission, and they need to be receiving some kind of maintenance therapy, particularly if they have high-risk disease.

DR LOVE: Do data exist on lenalidomide maintenance therapy for patients who do not undergo transplants?

DR STEWART: A randomized, double-blind, placebo-controlled, Phase III study with 459 patients (Palumbo 2009; [4.2]) compared melphalan/prednisone (MP) to melphalan/prednisone/lenalidomide (MPR) versus melphalan/prednisone/lenalidomide followed by lenalidomide maintenance therapy (MPR-R) for elderly patients with MM.

MPR-R was shown to be better than both MP and MPR. The PFS was improved on the MPR-R arm when compared to MP or MPR. This is a practice-changing trial in a couple of ways. It will add to the choice of MPR for elderly patients with MM, and the most important take-home message is the option of maintenance lenalidomide therapy in a nontransplant setting.

4.2 **Lenalidomide (R) Maintenance in Elderly Patients with MM**

	MP	MPR-R	Hazard ratio	*p*-value
Overall response	49%	77%	Not reported	<0.001
Progression-free survival	13 mo	Not reached	0.499	<0.001

Palumbo A et al. ASH 2009;**Abstract 613**.

Track 9

DR LOVE: How do you approach younger patients with MM?

DR STEWART: For younger patients with standard-risk cytogenetics, it may be reasonable to tell them that they will likely live 10 years or longer with modern therapy. Up-front aggressive therapy may not be needed for them. Lenalidomide/dexamethasone or a triplet may be appropriate as indicated,

and maintenance therapy should be used for those who are not in complete remission.

Patients with high-risk cytogenetics will fare poorly without aggressive measures. With these patients, we want to use all of the drugs that are available. In general, we use a triplet that includes bortezomib in initial induction in addition to transplant and maintenance therapy for everyone.

Track 11

DR LOVE: Would you comment on prevention and the risk of thrombosis associated with IMiD therapy?

DR STEWART: The thrombosis rate with IMiD therapy, especially in combination with higher doses of dexamethasone, is 20 to 25 percent. With aspirin alone, the risk of thrombosis drops to the five to 10 percent range. So we tend to recommend aspirin alone unless additional risk factors for thrombosis are present, such as smoking, factor V Leiden mutation, history of thrombosis or physical inactivity.

In these circumstances, full anticoagulation with enoxaparin or warfarin is prudent. ■

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**.

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.** ASH 2009;**Abstract 127**.

Magarotto V, Palumbo A. **Evolving role of novel agents for maintenance therapy in myeloma.** *Cancer J* 2009;15(6):494-501.

Martin MG, Vij R. **Arterial thrombosis with immunomodulatory derivatives in the treatment of multiple myeloma: A single-center case series and review of the literature.** *Clin Lymphoma Myeloma* 2009;9(4):320-3.

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.** ASH 2009;**Abstract 613**.

Palumbo A et al. **Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.** *Leukemia* 2008;22(2):414-23.

Rajkumar SV, Sonneveld P. **Front-line treatment in younger patients with multiple myeloma.** *Semin Hematol* 2009;46(2):118-26.

Reeder CB et al. **A Phase II trial comparison of once versus twice weekly bortezomib in CYBORD chemotherapy for newly diagnosed myeloma: Identical high response rates and less toxicity.** ASH 2009a;**Abstract 616**.

Reeder CB et al. **Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial.** *Leukemia* 2009b;23(7):1337-41.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the ENESTnd trial of imatinib or nilotinib in patients with newly diagnosed, chronic phase CML, nilotinib was associated with _____.**
   a. More major molecular responses
   b. More complete cytogenetic responses
   c. Less progression to accelerated phase/blast crisis
   d. All the above
2. **A Phase III trial of fludarabine/cyclophosphamide with or without rituximab found that the addition of rituximab was associated with greater overall survival among patients with untreated, advanced CLL.**
   a. True
   b. False
3. **In a Phase II study, the addition of rituximab to lenalidomide in patients with relapsed CLL was associated with an overall response rate of _____.**
   a. 16 percent
   b. 51 percent
   c. 68 percent
4. **In the Phase III FIT study of consolidation therapy with yttrium-90-ibritumomab tiuxetan after first remission in advanced follicular lymphoma, ibritumomab tiuxetan resulted in an approximate _____ improvement in median progression-free survival compared to no additional therapy.**
   a. Eight-month
   b. 16-month
   c. 24-month
   d. 30-month
5. **Prophylactic aspirin has shown a reduction in the incidence of thrombosis in patients with MM receiving lenalidomide.**
   a. True
   b. False
6. **In the Phase III study comparing rituximab/bendamustine to R-CHOP in follicular, indolent and mantle-cell lymphomas, all of the following were more common in the R-CHOP group except _____.**
   a. Infections
   b. Alopecia
   c. Erythematous skin reactions
   d. Neutropenia
   e. Peripheral neuropathy
   f. Stomatitis
7. **In the Intergroup C9710 trial, the addition of arsenic as consolidation therapy for patients with APL resulted in all of the following except _____.**
   a. Improved overall survival
   b. Improved event-free survival
   c. Improved response rate
8. **Lenalidomide maintenance therapy has been reported to improve event-free survival for patients with MM who have undergone prior stem cell transplants.**
   a. True
   b. False
9. **The German Study Group Indolent Lymphomas (StIL) reported a Phase III trial comparing rituximab/bendamustine to R-CHOP in follicular, indolent and mantle-cell lymphomas at ASH 2009. Which of the following is true regarding the reported results of the study?**
   a. Overall response rates were equivalent
   b. Median progression-free and event-free survival were significantly improved with rituximab/bendamustine
   c. Both a and b
10. **In the Phase II trial comparing once- versus twice-weekly bortezomib in cyclophosphamide/bortezomib/dexamethasone chemotherapy for newly diagnosed MM, the rates of Grade III peripheral neuropathy were significantly reduced when bortezomib was administered once weekly.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 1, 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
ENESTnd: Nilotinib versus imatinib in newly diagnosed CML in chronic phase	4 3 2 1	4 3 2 1
Improvement in overall survival with first-line FCR in advanced CLL	4 3 2 1	4 3 2 1
Lenalidomide as initial treatment for elderly patients with CLL	4 3 2 1	4 3 2 1
Efficacy of hypomethylating agents and lenalidomide in MDS	4 3 2 1	4 3 2 1
Radioimmunotherapy in FL	4 3 2 1	4 3 2 1
Prolonged and maintenance rituximab therapy in NHL	4 3 2 1	4 3 2 1
Emerging data and ongoing studies of arsenic trioxide in APL	4 3 2 1	4 3 2 1
Role of proteasome inhibitors and immunomodulatory agents in multiple 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:

- Appraise the use of cytogenetics for individualizing the clinical management of hematologic cancer. . . . . 4 3 2 1 N/M N/A
- Develop evidence-based treatment algorithms for frequently encountered adult chronic leukemia. . . . . 4 3 2 1 N/M N/A
- Summarize emerging data with novel agents/combinations and treatment approaches for newly diagnosed or relapsed/refractory indolent or aggressive B-cell non-Hodgkin lymphoma (NHL) . . . . . 4 3 2 1 N/M N/A
- Tailor up-front/induction therapy based on individual and disease characteristics for patients with multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Evaluate consolidation and maintenance therapy approaches for patients with multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Describe the standard therapeutic approaches and investigational strategies for the treatment of newly diagnosed and relapsed acute promyelocytic leukemia (APL) . . . . . 4 3 2 1 N/M N/A
- Recall the efficacy and side effects of hypomethylating and immuno-modulating agents in the treatment of myelodysplastic syndromes (MDS) . . . . . 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
Susan M O'Brien, MD	4 3 2 1	4 3 2 1
Peter McLaughlin, MD	4 3 2 1	4 3 2 1
Farhad Ravandi, MD	4 3 2 1	4 3 2 1
Keith Stewart, MBChB	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: Specialty:

Professional Designation:
☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other

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

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Hematologic Oncology™
UPDATE

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