HOU | 2012 VOL 5 | ISSUE 1

Hematologic Oncology™ UPDATE

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

FACULTY INTERVIEWS

Paul G Richardson, MD
Srdan Verstovsek, MD, PhD
Jonathan W Friedberg, MD, MMSc
Jerald P Radich, MD

EDITOR

Neil Love, MD

CONTENTS

2 Audio CDs
Monograph

CME Certified

Hematologic Oncology Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of evidence-based and current therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Use case-based learning to formulate individualized treatment strategies for the care of patients with hematologic cancer.
- Appraise recent data on therapeutic advances and changing practice standards in follicular lymphoma, and apply this information to clinical practice.
- Compare and contrast the benefits and risks of imatinib, nilotinib and dasatinib to guide the selection of initial therapy for patients with chronic myeloid leukemia.
- Integrate recent findings with proteasome inhibitors and immunomodulatory agents in developing individualized induction and maintenance treatment strategies for patients with multiple myeloma.
- Develop an understanding of the mechanisms of action and emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform patients about protocol and nonprotocol options.
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

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

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph, complete the Post-test with a score of 70% or better and fill out the Educational Assessment and Credit Form located in the back of this monograph or on our website at **ResearchToPractice.com/HOU112/CME**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/HOU112** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in **blue, bold text**.

This activity is supported by educational grants from Allos Therapeutics, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva.

Last review date: April 2012; Release date: April 2012; Expiration date: April 2013

TABLE OF CONTENTS

FACULTY INTERVIEWS

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

EDITOR

Neil Love, MD
Research To Practice
Miami, Florida

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — **Dr Verstovsek** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Richardson** — Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Keryx Biopharmaceuticals Inc, Millennium: The Takeda Oncology Company, Nereus Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation. **Dr Friedberg** — Advisory Committee: Cephalon Inc, Genentech BioOncology; Consulting Agreement: Mundipharma International Limited; Data and Safety Monitoring Board: Lilly USA LLC; Paid Research: Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc. **Dr Radich** — Advisory Committee: ARIAD Pharmaceuticals Inc, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc.

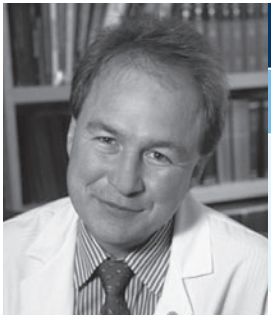
EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abbott Laboratories, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Inctye Corporation, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

Have Questions or Cases You Would Like Us to Pose to the Faculty?

Submit them to us via Facebook or Twitter
and we will do our best to get them answered for you

Facebook.com/ResearchToPractice or Twitter @DrNeilLove



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 Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-22

Track 1 Updated survival analysis from the VISTA trial of VMP versus MP for patients with untreated multiple myeloma (MM) — Further evidence for use of triplet therapy as initial systemic therapy

Track 2 Immediate versus delayed autologous transplantation after immunomodulatory agent-based induction therapy in patients with newly diagnosed MM

Track 3 Improved survival and response with bortezomib-containing induction regimens versus nonbortezomib-containing induction regimens in transplant-eligible patients with MM

Track 4 A Phase III trial evaluating conventional-dose therapy with lenalidomide, bortezomib and dexamethasone (RVD) versus high-dose treatment with stem cell transplant in MM

Track 5 Duration of lenalidomide maintenance therapy in MM

Track 6 Use of lenalidomide maintenance and potential incorporation of subcutaneous bortezomib into this approach for patients with MM and abnormal cytogenetics

Track 7 Perspective on the risk of second primary cancers with post-transplant maintenance lenalidomide in MM

Track 8 Subcutaneous versus weekly intravenous administration of bortezomib in MM

Track 9 Use of an attenuated RVD regimen in older patients with MM

Track 10 Management of myeloma-associated renal dysfunction in the era of novel therapies

Track 11 Attenuated neurotoxicity with the second-generation proteasome inhibitors carfilzomib and marizomib

Track 12 Care of patients with newly diagnosed MM and acute renal failure

Track 13 Final results from a Phase I/II study of carfilzomib, lenalidomide and low-dose dexamethasone (CRd) as first-line therapy in MM

Track 14 Carfilzomib-associated toxicities

Track 15 Development of carfilzomib as an orally administered agent

Track 16 Toward incorporating carfilzomib into the treatment algorithm for MM

Track 17 Initial Phase I/II study results with the novel proteasome inhibitor MLN9708 as a single agent in relapsed/refractory MM and in combination with lenalidomide and dexamethasone in previously untreated MM

Track 18 Mechanism of action and activity of elotuzumab, a humanized monoclonal immunoglobulin G1 antibody targeting CS1

Track 19 MRC Myeloma IX study: Zoledronic acid in patients with MM with or without bone disease

Track 20 **Case discussion:** An 88-year-old woman has IgA lambda monoclonal gammopathy and ISS Stage III MM with 80% involvement of plasma cells in the bone marrow and widespread diffuse bony lesions

Track 21 Clinical use of bortezomib/dexamethasone in elderly patients with high-risk MM and bone disease

Track 22 Salvage therapy with an attenuated RVD regimen after disease progression in elderly patients with MM

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: What are your thoughts on using a 3-drug combination as initial systemic therapy for multiple myeloma (MM) rather than opting for a 2-drug regimen and keeping the third agent in reserve?

DR RICHARDSON: That may be one of the most fundamentally important questions in MM treatment today. The VISTA trial demonstrates that holding additional agents in reserve may be the wrong approach in symptomatic MM. In the 5-year follow-up presented at ASH 2011, the authors reported a highly significant 13.3-month increase in median overall survival with the 3-drug regimen of bortezomib/melphalan/prednisone (VMP) compared to MP even though the trial allowed for substantial crossover with salvage treatments such as bortezomib and IMiDs for patients receiving MP (San

1.1

Phase III VISTA Trial: 5-Year Overall Survival Analyses of Patients with Previously Untreated Multiple Myeloma

Patient population	VMP	MP	Hazard ratio	*p*-value
Intent to treat (n = 344, 338)	56.4 mo	43.1 mo	0.69	0.0004
Patients (pts) receiving subsequent therapy (n = 215, 246)	55.7 mo	46.4 mo	0.75	0.016
Pts receiving VMP vs pts receiving first-line MP + pts receiving MP and salvage bortezomib (n = 344, 237)	56.4 mo	45.4 mo	0.71	0.0029

V = bortezomib; M = melphalan; P = prednisone

San Miguel JF et al. *Proc ASH* 2011;**Abstract 476**.

1.2

Meta-Analysis of Phase III Trials of Bortezomib-Containing Induction Regimens (BCIR) versus Nonbortezomib-Containing Induction Regimens (NBCIR) for Transplant-Eligible Patients with Multiple Myeloma

	BCIR versus NBCIR	
Response rate (n = 4)*	Pooled odds ratio	*p*-value
Postinduction Overall response rate	2.619	<0.000
Post-ASCT Overall response rate	1.907	<0.000
Response rate (n = 4)*	Pooled hazard ratio	*p*-value
Three-year progression-free survival	0.723	0.000
Three-year overall survival	0.789	0.016

ASCT = autologous stem cell transplant
* Number of Phase III randomized, controlled trials analyzed
$p \leq 0.000$ or $p = 0.016$ indicates that bortezomib-based induction regimens result in improved efficacy and demonstrates the superiority of BCIR over NBCIR.

Nooka AK et al. *Proc ASH* 2011;**Abstract 3994**.

Miguel 2011; [1.1]). The response rates were robust and the clinical benefit derived from the salvage strategies appeared to be durable, which is unprecedented. These data inform community clinicians that administering the best drug combinations up front carries "no penalty" to clinical benefit later. The best combinations can be used up front to generate optimal response by intensifying consolidation and maintenance treatments and then salvage therapies later.

Another interesting data set at ASH 2011 from a meta-analysis of randomized trials reported that bortezomib-based therapy in transplant-eligible patients is associated with a response rate advantage. In addition, bortezomib as a part of pretransplant therapy was associated with improved overall survival (Nooka 2011; [1.2]).

Tracks 13-15

DR LOVE: Would you discuss results recently reported with carfilzomib, lenalidomide and low-dose dexamethasone (CRd) as first-line therapy in MM?

DR RICHARDSON: This study provides validation of the concept that combining a proteasome inhibitor and an immunomodulator provides synergy. The authors reported an overall response rate of 94% and a dramatic reduction in neurotoxicity with an emergent rate of peripheral neuropathy of 24% (Jakubowiak 2011; [1.3]). A higher signal for neuropathy was previously reported with RVD. That's why I believe these results are such an important step forward, because the rate of neurotoxicity reported with CRd is dramatically reduced but at the same time the regimen has similar response outcomes compared to RVD.

Significant rates of hyperglycemia and shortness of breath associated with infusions, which were ascribed to fluid hydration required for the CRd combination, were reported. Even though carfilzomib treatment has the potential for renal impact, this can be managed by hydration together with the use of dexamethasone. Essentially, the CRd regimen was well tolerated, but we have to be aware of the potential side effects.

I am excited about the evolution of the CRd regimen, particularly if and when oral carfilzomib becomes available. This will circumvent the inconvenience associated with

1.3

Responses in a Front-Line Phase I/II Study of Carfilzomib, Lenalidomide and Low-Dose Dexamethasone for Patients with Multiple Myeloma

Parameter	ORR	CR/nCR	≥VGPR
No. of treatment cycles			
1+ (n = 49)	94%	53%	65%
4+ (n = 35)	100%	71%	89%
8+ (n = 28)	100%	75%	89%
12+ (n = 19)	100%	79%	100%
CFZ dose (mg/m^2)			
20 (n = 4)	100%	75%	100%
27 (n = 13)	100%	85%	100%
36 (n = 32)	91%	38%	47%

ORR = overall response rate; CR = complete response; nCR = near CR; VGPR = very good partial response; CFZ = carfilzomib

Jakubowiak AJ et al. *Proc ASH* 2011;**Abstract 631**.

intravenous administration. Although oral carfilzomib is not quite ready for prime time, it is under evaluation in clinical trials (NCT01129349).

Track 17

DR LOVE: Would you discuss what is currently known about the oral proteasome inhibitor MLN9708?

DR RICHARDSON: Oral MLN9708 is a boronate peptide that has undergone Phase I/II testing as a single agent (NCT00963820) and in combination with lenalidomide/dexamethasone. In the up-front setting, the lenalidomide/dexamethasone/MLN9708 combination produced a response rate of 100% in evaluable patients with MM (Berdeja 2011; [1.4]). Except for the occurrence of manageable Grade 2 or lower skin rashes, it was well tolerated. As a single agent in the relapsed setting, we have observed clear responses even after bortezomib failure.

MLN9708 has qualitative differences from bortezomib, making it attractive. Unlike bortezomib, it does not appear to induce neurotoxic effects. Presently, 4 proteasome inhibitors have the potential to be therapeutic choices in the future: bortezomib, carfilzomib, MLN9708 and marizomib. ■

1.4

Efficacy and Safety of Oral MLN9708 in Combination with Lenalidomide and Dexamethasone for Patients with Previously Untreated Multiple Myeloma

Preliminary response*	Patients (n = 15)
≥Partial response through 4 cycles	100%
Complete response	27%
Very good partial response	33%
Partial response	40%
Select adverse events (AEs)	
Any AE/drug-related AEs	15/13
Grade ≥3 AEs/drug-related Grade ≥3 AEs	11/9
Peripheral neuropathy (PN)	
Grade 1 drug-related PN	3
Grade >1 PN	0

* IMWG uniform criteria and minimal response and near-complete response
AEs were transient and manageable with standard supportive care or dose reduction/discontinuation.

Berdeja JG et al. *Proc ASH* 2011;**Abstract 479**.

SELECT PUBLICATIONS

Jakubowiak AJ et al. **Final results of a frontline phase 1/2 study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in multiple myeloma (MM).** *Proc ASH* 2011;**Abstract 631**.

Nooka AJ et al. **The improved efficacy of bortezomib containing induction regimens (BCIR) versus non-bortezomib containing induction regimens (NBCIR) in transplant-eligible patients with multiple myeloma (MM): Meta-analysis of phase III randomized controlled trials (RCTs).** *Proc ASH* 2011;**Abstract 3994**.

San Miguel JF et al. **Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with previously untreated multiple myeloma, and no increased risk of second primary malignancies: Final results of the phase 3 VISTA trial.** *Proc ASH* 2011;**Abstract 476**.

INTERVIEW

Srdan Verstovsek, MD, PhD

Dr Verstovsek is Associate Professor, Chief of the Section of Myeloproliferative Neoplasms and Director of the Clinical Research Center for Myeloproliferative Neoplasms at The University of Texas MD Anderson Cancer Center's Department of Leukemia in Houston, Texas.

Tracks 1-9

Track 1 **Case discussion:** A 63-year-old man initially observed for low-risk myelofibrosis (MF) with no JAK2 or BCR-ABL mutation receives ruxolitinib after worsening of his disease

Track 2 Symptomatology and pathophysiology of MF

Track 3 Activity of JAK2 inhibitors in JAK mutation-positive and mutation-negative MF

Track 4 Improved quality of life and duration of ruxolitinib therapy in MF

Track 5 Volumetric MRI as a research tool for evaluating splenic response to JAK2 inhibitors

Track 6 **Case discussion:** A 74-year-old woman with IPSS high-risk, JAK2 mutation-positive MF receives an investigational JAK2 inhibitor on a clinical trial

Track 7 Potential role of pomalidomide in the treatment of MF

Track 8 **Case discussion:** A 55-year-old woman initially diagnosed with MF is determined upon reexamination to have chronic myeloid leukemia (CML) with fibrosis

Track 9 Early clinical trial results and dose-limiting toxicities with novel dual FLT3/JAK2 inhibitors in MF

Select Excerpts from the Interview

Tracks 1-5

Case discussion

A 63-year-old man initially observed for low-risk myelofibrosis (MF) with no JAK2 or BCR-ABL mutation receives ruxolitinib after worsening of his disease

DR VERSTOVSEK: This patient was initially prescribed hydroxyurea as standard first-line therapy for his worsening symptoms. Hydroxyurea can decrease spleen size but does not affect blood count. Some improvement occurred, but eventually a referral was made to our center. I saw the patient about a year and a half ago. His spleen was enlarged and he had all the constitutional symptoms.

He was enrolled in the Phase I/II study of ruxolitinib and, like the vast majority of patients in the more recent Phase III COMFORT-I trial, he experienced benefit (Verstovsek 2012; [2.1, 2.2]). His spleen markedly decreased in size, he regained weight and he didn't have any major problems with blood cell count. He started enjoying life on a stable dose of ruxolitinib.

One noteworthy point is that this patient did not have the JAK2 mutation. Patients do

not need to be tested for the presence of the JAK2 mutation to receive JAK2 inhibitors because they inhibit JAK2 whether it's normal or not. All patients with MF have a high activity of JAK2 and should benefit.

DR LOVE: When is the optimal time to introduce a JAK2 inhibitor, and is there a rationale for treating asymptomatic patients?

DR VERSTOVSEK: The COMFORT-II study compared ruxolitinib to best available therapy, which in most cases was hydroxyurea. No benefit was reported with best available therapy (Harrison 2012; [2.1]), so one could argue that the correct way to care for patients who are symptomatic and/or have an enlarged spleen is to start with a JAK2 inhibitor. Administering a JAK2 inhibitor in patients who are at an early stage of the disease and asymptomatic seems reasonable, but we don't have data to substantiate that.

Many patients with MF are older and retired, and after treatment with ruxolitinib they improve so much that they can perform activities they have missed for years. Ruxolitinib controls the symptoms of the disease and prolongs survival, but it is not curative. The duration of the benefits of ruxolitinib is variable. The signs and symptoms will come back, at which point one can try different options. Patients feel so much better on the agent, they can consider a bone marrow transplant to attain cure.

We don't know if patients with MF can have their disease controlled indefinitely with ruxolitinib. We may be able to slowly discontinue therapy over time. The longest follow-up now is about 5 years since the initial studies were performed.

DR LOVE: Is there a role for the tools used in the COMFORT-I study for monitoring patients, or can they just be followed clinically?

DR VERSTOVSEK: In the COMFORT-1 study spleen volumes were assessed with MRI. We also used an electronic patient questionnaire called the Myelofibrosis Symptom Assessment Form (MFSAF). Patients receiving ruxolitinib showed improvement across the board, regardless of spleen shrinkage. The waterfall plot showed that all patients except 2 had some spleen shrinkage (2.2).

2.1

Phase III Trial Results with the JAK1/JAK2 Inhibitor Ruxolitinib for Patients with Myelofibrosis

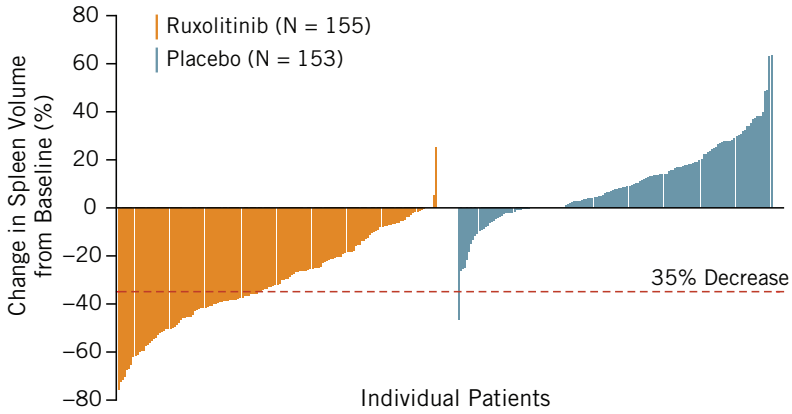
	COMFORT-I[1]		COMFORT-II[2]	
Efficacy — Primary endpoint	Ruxolitinib (n = 155)	Placebo (n = 153)	Ruxolitinib (n = 144)	Best available therapy (n = 72)
Patients with ≥35% decrease in spleen volume at 24 wk[1] and 48 wk[2]	41.9%	0.7%	28.0%	0%
	$p < 0.001$		$p < 0.001$	
Change in symptom score — Secondary endpoint	Ruxolitinib (n = 145)	Placebo (n = 145)		
Patients with ≥50% decrease in symptom score at 24 wk	45.9%	5.3%	—	—
	$p < 0.001$		—	

Symptom score = sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the left ribs and early satiety (from the Myelofibrosis Symptom Assessment Form)

[1] Verstovsek S et al. *N Engl J Med* 2012;366(9):799-807; [2] Harrison C et al. *N Engl J Med* 2012;366(9):787-98.

2.2

COMFORT-I Study: Percent Change in Spleen Volume from Baseline in Response to Ruxolitinib versus Placebo in Patients with Myelofibrosis



Verstovsek S et al. *N Engl J Med* 2012;366(9):799-807. Copyright © 2012 Massachusetts Medical Society.

We recommend neither MRI nor the MFSAF for use in daily practice because focusing on these tools may complicate optimal delivery of therapy. Patients can be asked how they feel. This approach along with physical exam of the spleen is enough to assess utility of ruxolitinib in practice.

Track 7

DR LOVE: What is known about pomalidomide and other IMiDs in MF, and is it possible to combine them with JAK2 inhibitors?

DR VERSTOVSEK: Pomalidomide is an IMiD used in the treatment of some hematologic cancers. It is a derivative of thalidomide that has a different toxicity profile compared to the other 2 IMiDs — thalidomide and lenalidomide. It is associated with lower levels of neuropathy and myelosuppression than the levels observed with thalidomide and lenalidomide, respectively. At a low dose of 0.5 mg, it has the potential to improve the red blood cell count (Tefferi 2009). It does not have an impact on any other aspects of the disease. Its efficacy is now being tested in a randomized Phase III study for patients with MF who are red blood cell transfusion dependent (NCT01178281). If pomalidomide is found to be beneficial in this Phase III study, I would definitely like to combine it with JAK2 inhibitors. This would allow a dual effect of the JAK2 inhibitors on the spleen and symptoms and an improvement in anemia by pomalidomide. ■

SELECT PUBLICATIONS

Harrison C et al. **JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.** *N Engl J Med* 2012;366(9):787-98.

Tefferi A et al. **Pomalidomide is active in the treatment of anemia associated with myelofibrosis.** *J Clin Oncol* 2009;27(27):4563–9.

Verstovsek S et al. **A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis.** *N Engl J Med* 2012;366(9):799-807.

INTERVIEW

Jonathan W Friedberg, MD, MMSc

Dr Friedberg is Professor of Medicine and Oncology and Chief of the Hematology/Oncology Division at the University of Rochester's James P Wilmot Cancer Center in Rochester, New York.

Tracks 1-17

Track 1 ECOG-E4402: RESORT trial comparing 2 rituximab dosing regimens for low tumor burden indolent non-Hodgkin lymphoma (NHL)

Track 2 SAKK-35/98: Long-term follow-up from a randomized trial of prolonged versus short-course rituximab for follicular lymphoma (FL)

Track 3 SWOG-S0016: Results from a Phase III study of R-CHOP versus CHOP in combination with ^{131}I-tositumomab for patients with newly diagnosed FL

Track 4 SWOG-S0801: A Phase II trial of induction R-CHOP → radioimmunotherapy (RIT) consolidation → rituximab maintenance for patients with previously untreated Stage II to IV FL

Track 5 Role of RIT as initial treatment and as consolidation therapy in FL

Track 6 Barriers to the use of RIT in FL

Track 7 Clinical trial results with RIT in combination with R-CHOP in mantle-cell lymphoma (MCL)

Track 8 Obinutuzumab (GA101) — a third-generation, anti-CD20 monoclonal antibody for the treatment of B-cell lymphomas

Track 9 GAUSS: Preliminary analysis of a Phase II study of obinutuzumab versus rituximab for patients with relapsed CD20 indolent B-cell NHL

Track 10 Activity of novel tyrosine kinase inhibitors (TKIs) in NHL

Track 11 Brentuximab vedotin for relapsed/refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma

Track 12 Consideration of brentuximab vedotin therapy as a bridge to allogeneic transplant

Track 13 Promising role of brentuximab vedotin in CD30-expressing lymphomas

Track 14 Management of brentuximab vedotin-related peripheral neuropathy

Track 15 Safety of brentuximab vedotin with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD in newly diagnosed advanced HL

Track 16 Proposed study of ABVD versus AVD in combination with brentuximab vedotin in advanced-stage HL

Track 17 **Case discussion:** An 80-year-old man with CD5-positive, CD23-negative, t(11;14) translocated MCL receives 6 cycles of rituximab/bendamustine and is now considering rituximab maintenance

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you comment on the data from the RESORT trial recently presented at ASH 2011?

DR FRIEDBERG: The RESORT trial evaluated patients with low tumor burden indolent lymphoma. Patients who did not require treatment by formal criteria received

4 weekly doses of rituximab. Responding patients were then randomly assigned to 2 therapy approaches — rituximab maintenance continuously once every 3 months until progression or rituximab weekly times 4 at disease progression. The primary study endpoint was time to failure of rituximab. The presentation at ASH was limited to the subgroup of patients with follicular lymphoma (FL).

Both groups had reasonably long progression-free survival (PFS), and no difference was seen in time to failure of rituximab with the 2 different dosing strategies (Kahl 2011). The ECOG group concluded that both strategies were active but more rituximab was administered in the maintenance arm with slightly more toxicity, so they favored the scheduled re-treatment approach rather than the maintenance approach.

These findings affect my practice because it's challenging to interpret RESORT and reconcile those data with the SAKK results. The SAKK-35/98 study was conducted in 1998, but the 10-year follow-up results are now available. This study enrolled patients with a variety of histologies of both newly diagnosed and rituximab-naïve, relapsed lymphoma. The study evaluated 2 schedules of rituximab — weekly times 4 versus weekly times 4 followed by 4 doses of rituximab 2 months apart. Some people consider that maintenance, and others consider it an extended schedule. It's really 8 doses of rituximab versus 4 doses of rituximab.

For patients with FL, the preliminary results published in 2004 reported a doubling in time to progression for those who received 8 doses of rituximab, and that benefit was durable at 10 years of follow-up (Martinelli 2010; [3.1]). Of patients with newly diagnosed disease who received 8 doses of rituximab, 45% have not experienced progression. A borderline survival advantage was observed in the patients who received 8 doses versus 4 doses of rituximab.

Those results were hypothesis generating for me and suggest that if you're using single-agent rituximab, administering it on a more prolonged schedule may provide further durability. That approach wasn't formally studied in the RESORT trial, but I believe it does suggest some benefit to the extended schedule. In my practice, if I'm administering single-agent rituximab to a patient, I use the SAKK schedule of 8 doses, and I don't feel at all concerned that administering additional maintenance rituximab makes a difference based on the RESORT results.

3.1

SAKK-35/98 Study: Long-Term Follow-Up of Prolonged versus Short-Course Rituximab for Patients with Follicular Lymphoma

	Short-course rituximab (n = 78)	Prolonged rituximab (n = 73)	*p*-value
Median event-free survival (EFS)	13 months	24 months	<0.001
EFS*, all patients			
At 5 years	13%	27%	
At 8 years	5%	27%	—
EFS in chemotherapy-naïve patients (n = 38)			
At 8 years	22%	45%	0.045

* EFS: Time until progression, relapse, second tumor or death

Martinelli G et al. *J Clin Oncol* 2010;28(29):4480-4.

Tracks 3, 5

DR LOVE: Would you discuss the results your group presented at ASH 2011 on R-CHOP versus CHOP in combination with ^{131}I-tositumomab for patients with newly diagnosed FL?

DR FRIEDBERG: The SWOG-S0016 trial initially randomly assigned patients to 3 arms — CHOP alone, R-CHOP or CHOP followed by ^{131}I-tositumomab. After the first year when data became available that R-CHOP was better than CHOP, the CHOP alone arm was dropped, making this trial a head-to-head comparison of R-CHOP versus CHOP followed by ^{131}I-tositumomab. One important conclusion is that both arms performed better than we anticipated when we designed the study.

That having been said, no difference was observed between the 2 arms with regard to PFS or overall survival. Some mild toxicity differences occurred, as would be expected — slightly higher neutropenia in the group who received rituximab and some hypothyroidism in patients who received radioimmunotherapy (RIT). Some cases of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and toxic deaths occurred on the RIT arm (Press 2011; [3.2]). For people who were hoping that up-front RIT would provide a benefit, this was disappointing.

Another important study that evaluated RIT was the FIT trial, in which patients were randomly assigned to ibritumomab tiuxetan consolidation versus observation. The patients who received RIT consolidation experienced prolonged PFS. Longer-term follow-up of that study presented at ASH 2010 suggested increased numbers of MDS and AML in the patients who received ibritumomab tiuxetan (Hagenbeek 2010; [3.3]).

3.2

SWOG-S0016: A Phase III Study of R-CHOP versus CHOP Followed by ^{131}I-Tositumomab for Patients with Newly Diagnosed Follicular Lymphoma

	R-CHOP	CHOP → ^{131}I-tositumomab	*p*-value
Overall response rate (n = 264, 260)	85%	86%	0.90
Two-year PFS (n = 267, 265)	76%	80%	0.11
Two-year overall survival (n = 267, 265)	97%	93%	0.08
Treatment-related mortality (n = 263, 263)	0.4%	1.5%	0.37
AML/MDS (n = 267, 265)	1.1%	2.7%	0.34

PFS = progression-free survival; AML = acute myeloid leukemia; MDS = myelodysplastic syndromes

Press OW et al. *Proc ASH* 2011;**Abstract 98**.

Tracks 8-9

DR LOVE: What are your thoughts on the novel agent obinutuzumab (GA101) under investigation in non-Hodgkin lymphoma (NHL)?

DR FRIEDBERG: A preliminary analysis we presented at ASH 2011 was designed to compare the third-generation anti-CD20 monoclonal antibody obinutuzumab to rituximab head to head in patients with rituximab-sensitive, relapsed NHL. The primary

3.3

FIT: A Phase III Trial of Consolidation Therapy with Yttrium-90 Ibritumomab Tiuxetan After First Remission in Advanced Follicular Lymphoma

	Ibritumomab tiuxetan (n = 207)	No additional therapy (n = 202)	Hazard ratio	*p*-value
Median progression-free survival (PFS)	49 mo	14 mo	NR	NR
Five-year PFS	47%	29%	0.51	<0.0001
Secondary cancer Cases of MDS/AML	7.7% 2.9%	4.5% 0.5%	— —	0.19 0.063

Median follow-up = 66.2 months (5.5 years)
MDS = myelodysplastic syndrome; AML = acute myeloid leukemia

Hagenbeek A et al. *Proc ASH* 2010;**Abstract 594**.

endpoint of the study was response rate, and obinutuzumab produced a higher response rate than did rituximab (Sehn 2011; [3.4]).

However, essentially no difference in PFS was noted between the 2 study arms. Despite the disappointing PFS result, 3 large randomized Phase III trials are under way to determine whether this agent can beat rituximab. These studies are being performed in up-front FL, relapsed FL and up-front diffuse large B-cell lymphoma with a bold international goal of enrolling more than 2,000 patients.

3.4

GAUSS Study: Preliminary Analysis* of a Phase II Trial of Obinutuzumab (GA101) versus Rituximab for Patients with Relapsed CD20-Positive Indolent B-Cell Non-Hodgkin Lymphoma

	Obinutuzumab (n = 74)	Rituximab (n = 75)
Overall response rate (by investigator assessment)	43.2%	38.7%
Progression-free survival	79.7%	82.7%

* Primary efficacy analysis conducted after induction in patient population with FL

Sehn LH et al. *Proc ASH* 2011;**Abstract 269**.

Tracks 11, 15-16

DR LOVE: Would you talk about what's been reported recently with brentuximab vedotin and what new directions we're heading in with this agent?

DR FRIEDBERG: I was involved in the pivotal study of brentuximab vedotin and I've seen many patients with no other therapeutic options who were approaching hospice care have remarkable turnaround in their performance status and impressive durability of response with this agent (3.5).

When you have an active single agent that probably has the highest response rate in relapsed Hodgkin lymphoma, you want to try to move it up front so more patients can benefit. A study reported at ASH 2011 evaluated the addition of brentuximab vedotin to the ABVD regimen for patients with newly diagnosed advanced-stage Hodgkin lymphoma. The authors reported increased pulmonary toxicity that they felt

3.5

Response and Maximum Tumor Reduction with Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma (HL) and Systemic Anaplastic Large Cell Lymphoma (sALCL)*

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

* By independent review facility

[1] Younes A et al. *J Clin Oncol* 2012;[Epub ahead of print].
[2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

was secondary to the combination of bleomycin and brentuximab vedotin. The rate of pulmonary toxicity was as high as 40%. They elected to drop bleomycin and continue with brentuximab vedotin and AVD.

Patients who received AVD in combination with brentuximab vedotin did not exhibit pulmonary toxicity. For a single-arm study the response rate was high, suggesting that this is an approach that could move forward in a randomized trial (Younes 2011; [3.6]). A proposed global randomized study will evaluate ABVD versus AVD in combination with brentuximab vedotin, and the cooperative groups in the United States are in final stages of discussions planning our next Intergroup study in advanced-stage Hodgkin lymphoma. I am certain that brentuximab vedotin will be part of that study too. ■

3.6

Front-Line Therapy with Brentuximab Vedotin (B-Vedotin) and ABVD or AVD for Patients with Newly Diagnosed Advanced-Stage Hodgkin Lymphoma

	ABVD + B-vedotin* (n = 25)	AVD + B-vedotin (n = 19)
Complete response	60%	Not yet reported
Pulmonary toxicity	40%	0%

* Fifteen of 25 patients have completed front-line therapy and have response results.
Toxicity resembling that of bleomycin alone led to its discontinuation in 10 patients. Seven of 10 continued treatment with AVD and brentuximab vedotin.
A = doxorubicin; B = bleomycin; V = vinblastine; D = dacarbazine

Younes A et al. *Proc ASH* 2011;**Abstract 955**.

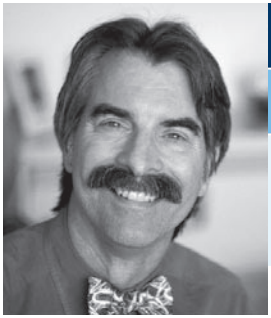
SELECT PUBLICATIONS

Hagenbeek A et al. **90Y-ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, Phase III First-Line Indolent Trial (FIT) in 414 patients.** *Proc ASH* 2010;**Abstract 594**.

Kahl BS et al. **Results of Eastern Cooperative Oncology Group protocol E4402 (RESORT): A randomized Phase III study comparing two different rituximab dosing strategies for low tumor burden follicular lymphoma.** *Proc ASH* 2011;**Abstract LBA-6**.

Martinelli G et al. **Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98.** *J Clin Oncol* 2010;28(29):4480-4.

Sehn LH et al. **Randomized Phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: Preliminary analysis of the GAUSS study.** *Proc ASH* 2011;**Abstract 269**.



INTERVIEW

Jerald P Radich, MD

Dr Radich is a Member of the Clinical Research Division at Fred Hutchinson Cancer Research Center and Professor of Medicine at the University of Washington in Seattle, Washington.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-4, 6

DR LOVE: Would you discuss the role of second-generation tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML)?

DR RADICH: Imatinib is successful in achieving cytogenetic remissions. After a year, nearly 70% of patients will be in cytogenetic remission (Kantarjian 2010). However, 10% to 15% of patients have resistance to this agent. In patients who do experience a response it is maintained for a long time (Deininger 2009), but some patients are lost because of drug intolerance or late relapse. Follow-up of the imatinib trials reports that only about 50% of patients are still receiving the agent.

Even though imatinib is an effective agent, it has room for improvement. Enter the second-generation TKIs — nilotinib and dasatinib. These agents have now been approved for newly diagnosed chronic-phase CML and seem to be more effective than imatinib.

DR LOVE: How does the efficacy of the first- and second-generation TKIs compare clinically?

DR RADICH: A series of trials have consistently reported an advantage of dasatinib and nilotinib compared to imatinib. With imatinib about 70% of patients will go into a complete cytogenetic remission at 12 months, whereas for both nilotinib and dasatinib more than 80% of patients do so. If you evaluate major molecular response (MMR), which is a 1,000-fold reduction in the BCR-ABL mRNA, about 20% to 30% of patients achieve MMR with imatinib at 12 months. The rate of MMR is almost doubled with nilotinib or dasatinib (Saglio 2010; Kantarjian 2010).

The most important surrogate for long-term response is progression to accelerated phase or blast crisis. That is the worst outcome for patients because these agents don't work well in accelerated phase or blast crisis. In virtually all the trials to date, dasatinib and nilotinib have been associated with far less progression than imatinib.

At 1 to 2 years, approximately 1% progress to accelerated phase or blast crisis on second-generation TKIs as compared to 3% to 5% on imatinib (Kantarjian 2011, 2012; [4.1]). The follow-up on dasatinib and nilotinib isn't as long as it is with imatinib, and so far no difference in overall survival has been recorded.

DR LOVE: How would you compare the toxicity of imatinib, nilotinib and dasatinib?

DR RADICH: Long-term data exist regarding toxicity with imatinib. We don't have these data for dasatinib and nilotinib, although we've seen no signal so far that they would be any different. Imatinib causes a lot of gastrointestinal problems, such as nausea and diarrhea, and peripheral edema. Dasatinib and nilotinib don't have those issues.

These agents are remarkable because they both display cross-intolerance. If someone develops a specific toxicity with imatinib, he or she will probably not experience that with nilotinib or dasatinib. With dasatinib the main concern is pleural effusion, whereas with nilotinib the major worry is pancreatitis. Nilotinib also has a black box warning for cardiac events. However, it is not clear that cardiac events are associated with nilotinib administration.

DR LOVE: If a patient who is receiving dasatinib presents with pleural effusion, how do you manage it?

4.1

Results from the ENESTnd[1] and DASISION[2] Studies Comparing Nilotinib or Dasatinib to Imatinib for Patients with Newly Diagnosed Chronic Myeloid Leukemia

	ENESTnd study		DASISION study	
Response at 12 and 24 months	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg qd (n = 283)	Dasatinib 100 mg qd (n = 259)	Imatinib 400 mg qd (n = 260)
MMR (%)	43, 67	22, 44	46, 64	28, 46
	$p < 0.001$, $p < 0.0001$		$p < 0.0001$, $p < 0.0001$	
CCR (%)	78, 85	65, 77	77, 86	66, 82
	$p < 0.001$, $p = 0.0160$		$p = 0.007$, $p = 0.0002$	
Progression to AP/BC (%)	<1, 1.9	4, 4.8	1.9, 2.3	3.5, 5.0
	$p < 0.004$, $p = 0.0196$		—	—

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

[1] Kantarjian HM et al. *Lancet Oncol* 2011;12(9):841-51; [2] Kantarjian HM et al. *Blood* 2012;119(5):1123-9.

DR RADICH: If the patient presents with mild pleural effusion, usually it's sufficient to interrupt the dose and ascertain whether the symptoms resolve. You can also administer diuretics, and some centers also administer steroids. Unless a compelling reason exists to keep the patient on dasatinib, I believe the most common approach now is simply to switch to nilotinib.

Track 9

DR LOVE: Would you discuss the possibility of discontinuation of imatinib therapy in CML?

DR RADICH: The thought process has been that patients with CML will have to remain on TKI therapy forever, but that doesn't seem to be the case. One trial evaluating this issue is the STIM trial (Mahon 2011). This trial studied patients who were in sustained complete molecular remission, which means undetectable PCR for BCR-ABL, for at least 2 years. Imatinib therapy was discontinued and the patients were monitored. Of the patients who discontinued imatinib therapy, 60% experienced disease relapse within 7 months.

They all responded to rechallenge with imatinib, however, and approximately 40% of the patients have remained PCR-negative for more than 2 years. This is shocking to most of us who study CML biology. Patients who were able to come off imatinib are those who present with low Sokal scores.

Although these data are encouraging, discontinuation of therapy has to be performed on a clinical trial. Even though all the patients who have discontinued therapy and experienced relapse have responded on rechallenge, they haven't all gone back to being PCR-negative. If you believe that unopposed BCR-ABL is what drives progression, you've given a person a few months of unopposed BCR-ABL. They may respond, but they may have developed clones that down the road lead to progression. I don't believe we will know the fate of those patients until 3 to 5 years from now. ■

SELECT PUBLICATIONS

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

Kantarjian HM et al. **Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION).** *Blood* 2012;119(5):1123-9.

Kantarjian HM et al. **Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.** *Lancet Oncol* 2011;12(9):841-51.

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

Mahon F et al. **Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular response: Updated results of the STIM.** *Proc ASH* 2011;**Abstract 604**.

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

Takahashi N et al. **Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia.** *Haematologica* 2011;[Epub ahead of print].

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III VISTA trial for patients with previously untreated MM reported an increase in median overall survival of _____ after a follow-up period of 5 years for patients who received VMP in comparison to MP therapy.**
   a. 13.3 months
   b. 43.1 months
   c. 60 months
2. **In a Phase I/II trial, CRd as first-line therapy for patients with MM generated high-quality responses but was associated with which of the following side effects?**
   a. Hyperglycemia
   b. Anorexia
   c. Proteinuria
   d. All of the above
3. **In a Phase I/II trial by Berdeja and colleagues, the administration of MLN9708 in combination with lenalidomide and dexamethasone produced a response rate of 100% in evaluable patients.**
   a. True
   b. False
4. **The RESORT trial demonstrated that rituximab re-treatment upon disease progression was as effective as rituximab maintenance in terms of time to treatment failure for patients with previously untreated, low tumor burden FL.**
   a. True
   b. False
5. **In the Phase III FIT trial of consolidation therapy with yttrium-90 ibritumomab tiuxetan after first remission in patients with advanced FL, patients who received consolidation therapy experienced a median progression-free survival advantage of approximately ____ versus patients who received no additional therapy.**
   a. 10 months
   b. 22 months
   c. 35 months
6. **The SAKK-35/98 clinical trial, which evaluated a short course (4 weekly doses) of rituximab versus prolonged rituximab for patients with newly diagnosed or relapsed FL, did not report a prolonged event-free survival rate for patients who received prolonged rituximab.**
   a. True
   b. False
7. **The GAUSS study is evaluating obinutuzumab (GA101) versus _____ for patients with relapsed CD20-positive indolent B-cell NHL.**
   a. Bortezomib
   b. Brentuximab vedotin
   c. Rituximab
8. **The Phase III COMFORT-I and COMFORT-II trials of ruxolitinib versus placebo and ruxolitinib versus best available therapy for MF did not demonstrate statistically significant and sustained reduction in spleen size in patients on the ruxolitinib study arms.**
   a. True
   b. False
9. **Study data with brentuximab vedotin presented at ASH 2010 demonstrated an overall response rate of 75% or higher for patients with _____.**
   a. Hodgkin lymphoma
   b. Systemic anaplastic large T-cell lymphoma
   c. Both a and b
10. **Which of the following is an approved treatment for CML?**
    a. Dasatinib
    b. Imatinib
    c. Nilotinib
    d. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 1, 2012

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 1 — 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 and toxicity of brentuximab vedotin in relapsed Hodgkin lymphoma and potential role in other CD30-expressing lymphomas	4 3 2 1	4 3 2 1
Efficacy, toxicity and duration of treatment with the JAK2 inhibitor ruxolitinib in MF	4 3 2 1	4 3 2 1
Improved survival and response with bortezomib-containing induction regimens versus nonbortezomib-containing induction regimens in transplant-eligible patients with MM	4 3 2 1	4 3 2 1
CRd as first-line therapy in MM	4 3 2 1	4 3 2 1
Effectiveness and depth of responses of first- (imatinib) and second-generation (nilotinib and dasatinib) TKIs in CML	4 3 2 1	4 3 2 1
Ongoing evaluation of obinutuzumab (GA101) in NHL	4 3 2 1	4 3 2 1
Role of RIT as initial treatment and as consolidation therapy in FL	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Use case-based learning to formulate individualized treatment strategies for the care of patients with hematologic cancer. . . . . 4 3 2 1 N/M N/A
- Appraise recent data on therapeutic advances and changing practice standards in follicular lymphoma, and apply this information to clinical practice. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of imatinib, nilotinib and dasatinib to guide the selection of initial therapy for patients with chronic myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Integrate recent findings with proteasome inhibitors and immunomodulatory agents in developing individualized induction and maintenance treatment strategies for patients with multiple myeloma.. . . . . 4 3 2 1 N/M N/A
- Develop an understanding of the mechanisms of action and emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform patients about protocol and nonprotocol options. . . . . 4 3 2 1 N/M N/A
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.. . . . . 4 3 2 1 N/M N/A

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

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

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

PART 2 — 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
Paul G Richardson, MD	4 3 2 1	4 3 2 1
Srdan Verstovsek, MD, PhD	4 3 2 1	4 3 2 1
Jonathan W Friedberg, MD, MMSc	4 3 2 1	4 3 2 1
Jerald P Radich, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

Street Address:..... Box/Suite:.....

City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the 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:.....

The expiration date for this activity is April 2013. To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/HOU112/CME.

QID 974

Hematologic Oncology™ UPDATE

PRSRT STD
U.S. POSTAGE
PAID
MIAMI, FL
PERMIT #1317

Neil Love, MD
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

This activity is supported by educational grants
from Allos Therapeutics, Genentech BioOncology/Biogen Idec,
Incyte Corporation, Millennium: The Takeda Oncology Company,
Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc,
Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva.

Research To Practice®

Sponsored by Research To Practice.

Last review date: April 2012
Release date: April 2012
Expiration date: April 2013
Estimated time to complete: 3 hours

This program is printed on MacGregor XP paper, which is manufactured in accordance with the world's leading forest management certification standards.