HOU | 2014 VOL 7 | ISSUE 2

Hematologic Oncology™ UPDATE

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

FACULTY INTERVIEWS

Stephen M Ansell, MD, PhD
Philip L McCarthy, MD
Ann S LaCasce, MD
Martin S Tallman, 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 individual 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 therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Develop an algorithm for the risk-stratified induction treatment of follicular lymphoma, diffuse large B-cell lymphoma and mantle-cell lymphoma.
- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction, consolidation and maintenance treatment approaches for patients with multiple myeloma.
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients.
- Appreciate the recent FDA approvals of ibrutinib and obinutuzumab, and discern how these agents can be appropriately integrated into clinical practice for patients with chronic lymphocytic leukemia.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas.
- Recognize the role of novel agents and regimens in the management of relapsed/refractory acute myeloid leukemia.
- Appraise recent clinical research findings on the efficacy and safety of novel proteasome inhibitor- and/or BTK inhibitor-based therapeutic strategies for Waldenström macroglobulinemia, and consider this information when caring for these patients.

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/HOU214/CME**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/HOU214** 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 Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Seattle Genetics and Teva Oncology.

Release date: October 2014; Expiration date: October 2015

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 LaCasce** 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 Ansell** — Research Funding: Bristol-Myers Squibb Company, Celldex Therapeutics. **Dr McCarthy** — Advisory Committee: Celgene Corporation, Janssen Pharmaceuticals Inc, Millennium: The Takeda Oncology Company, Sanofi. **Dr Tallman** — Advisory Committee: Agios Pharmaceuticals, BioLineRx, Seattle Genetics; Other Remunerated Activities: Boehringer Ingelheim Pharmaceuticals 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: AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc, Teva Oncology and VisionGate Inc.

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

Stephen M Ansell, MD, PhD

Dr Ansell is Professor of Medicine in the Division of Hematology at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-12

Track 1 "Watch and wait" for patients with follicular lymphoma (FL)

Track 2 Perspective on the role of rituximab (R) maintenance therapy in FL

Track 3 Efficacy of the R^2 regimen (lenalidomide and R) for newly diagnosed FL

Track 4 Genetic factors and pathogenesis of B-cell lymphomas

Track 5 Mechanism of action of ibrutinib

Track 6 Heightened response rates with R-CHOP and lenalidomide (R^2-CHOP) for patients with newly diagnosed ABC subtype diffuse large B-cell lymphoma (DLBCL)

Track 7 Approved indications and ongoing evaluation of brentuximab vedotin-based regimens in Hodgkin lymphoma (HL)

Track 8 Management of brentuximab vedotin-associated toxicities

Track 9 Activity of brentuximab vedotin in relapsed/refractory systemic anaplastic large cell lymphoma

Track 10 Therapeutic approach for patients with peripheral T-cell lymphoma (PTCL) not otherwise specified

Track 11 Treatment options and sequencing of systemic agents in PTCL

Track 12 Efficacy of novel therapeutic strategies for Waldenström macroglobulinemia

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your recent editorial "Follicular lymphoma: Watch and wait is watch and worry" relating to the results of the Phase III trial reported by Ardeshna and colleagues comparing rituximab to the watch and wait approach for patients with low tumor burden follicular lymphoma (FL) (Ansell 2014)?

DR ANSELL: As rituximab has become a standard treatment for FL, the question arose as to whether rituximab therapy was an appropriate approach for patients with low tumor burden disease. The trial by Ardeshna and colleagues initially had 3 arms — patients were randomly assigned to a watch and wait approach or 4 doses of rituximab followed by observation or 4 doses of rituximab followed by rituximab maintenance therapy for 2 years. The second arm was closed early because other studies showed a benefit with maintenance rituximab compared to the watch and wait approach after rituximab induction.

Time to next therapy and progression-free survival were improved with rituximab therapy, but there was no difference in overall survival between the arms. The rationale for stating that watch and wait is watch and worry in the editorial is that patients

on the watch and wait arm experienced a poorer quality of life compared to those who received rituximab (Ardeshna 2014; [1.1]). Patients were more concerned about their disease and visits to their physicians in part because of anxiety about whether their disease had progressed and would require therapy.

DR LOVE: How do you care for patients with FL in your practice outside a protocol setting?

DR ANSELL: My approach in clinical practice is to have a comprehensive conversation with patients because I believe it is important that they participate in the decision-making process. Some patients are comfortable with watching and waiting and monitoring the disease to see what happens, but another population of patients are anxious, and those patients would benefit from receiving rituximab.

In my practice, however, I tend to follow a re-treatment approach for patients with low disease burden receiving rituximab, based on the results of the RESORT trial: I generally administer 4 doses of rituximab, and then at any time the disease looks as if it is beginning to progress, re-treat with 4 more doses at that point.

Patients with bulky disease who have significant constitutional symptoms require chemotherapy. I generally treat those cases with bendamustine/rituximab (BR), based on the fact that the StiL and BRIGHT trials comparing R-CHOP chemotherapy to BR demonstrated good outcomes with BR (Rummel 2013; Flinn 2014).

DR LOVE: How do you approach the issue of rituximab maintenance after rituximab-based chemotherapy for FL?

DR ANSELL: Data suggest that this practice improves time to disease progression and overall outcome, and that is a valid reason for considering it. The optimal duration of rituximab maintenance is still unclear and would require more robust, long-term data for us to make definite conclusions. Toxicities may be exacerbated with a longer duration of rituximab therapy, and the benefit needs to be weighed against potential side effects.

1.1

Phase III Trial of Rituximab versus Watch and Wait for Advanced, Asymptomatic, Nonbulky Follicular Lymphoma

Efficacy	Rituximab maintenance (n = 192)	Watch and wait (n = 187)	Hazard ratio	*p*-value
Median time to start of new treatment	NR	31.1 mo	0.21	<0.0001
Patients who did not need new treatment at 3 years	88%	46%		
Median progression-free survival	NR	24.1 mo	0.23	<0.0001
Three-year overall survival	97%	94%	0.73	0.4

- The rituximab induction arm (n = 84) was closed early.
- Compared to the watchful waiting group, patients in the maintenance rituximab group had significant improvements in the Mental Adjustment to Cancer Scale score ($p = 0.0004$) and Illness Coping Style score ($p = 0.0012$) between baseline and month 7.

NR = not reached

Ardeshna KM et al. *Lancet Oncol* 2014;15(4):424-35.

Tracks 7-9

DR LOVE: Would you discuss the clinical trial findings with brentuximab vedotin in Hodgkin lymphoma (HL)?

DR ANSELL: Brentuximab vedotin has become a key player in the management of HL, particularly in the relapsed setting. In the pivotal Phase II trial of brentuximab vedotin for patients with HL whose disease had progressed after autologous stem cell transplantation (ASCT), the overall response rate was 75% and approximately one third of patients experienced a complete remission (Younes 2012). Long-term follow-up shows that a subgroup of approximately 15% to 20% of patients remain in remission 3 to 4 years later. It is approved for patients after failure of ASCT or multiple chemotherapy regimens and is an appropriate approach in that setting.

It is exciting that this agent is being investigated as front-line therapy for HL. The combination of AVD (doxorubicin, vinblastine, dacarbazine) with brentuximab vedotin was highly effective, with a complete response rate of 96% and a lack of serious pulmonary toxicity (Younes 2013). There is a lot of enthusiasm for this active regimen. The question is whether it will perform better than ABVD alone. An ongoing randomized Phase III trial is comparing AVD with brentuximab vedotin to ABVD as front-line therapy in patients with advanced HL (NCT01712490).

DR LOVE: What do we know about the side effects of brentuximab vedotin?

DR ANSELL: We're still learning about the potential toxicities of brentuximab vedotin. Peripheral neuropathy is a significant side effect and becomes more pronounced with longer administration. Dermatologic toxicities are not common. Infusion reactions have been reported but can be easily managed with the addition of premedication and steroids.

DR LOVE: Would you comment on the efficacy of brentuximab vedotin in systemic anaplastic large cell lymphoma (sALCL)?

DR ANSELL: The treatment of sALCL with brentuximab vedotin has been a huge success story. CD30 is expressed at high levels in sALCL, and response rates have been good. Patients with relapsed or refractory sALCL show continued benefit over time. It is now being investigated in the front-line setting for sALCL. Randomized trials are comparing brentuximab vedotin with CHP — CHOP without vincristine — to standard therapy (NCT01777152).

Track 11

DR LOVE: What are your thoughts on the roles of histone deacetylase (HDAC) inhibitors and pralatrexate in the treatment of peripheral T-cell lymphoma (PTCL)?

DR ANSELL: HDAC inhibitors like belinostat have shown promising efficacy in the relapsed/refractory setting and are being evaluated up front. These agents can be used in combination with standard CHOP or CHOEP — CHOP with etoposide. The combination of belinostat and CHOP, or BelCHOP, is being investigated as first-line treatment for PTCL (NCT01839097).

Romidepsin is an agent that has a real benefit and is being studied in combination with CHOP in patients with untreated PTCL (NCT01796002). Hopefully the data will show that it provides additional benefit to patients in the long term.

The addition of pralatrexate to CHOP-like chemotherapy has proven to be challenging because of potential toxicities. The T-cell Consortium recently reported the results of a study of CEOP — cyclophosphamide, etoposide, vincristine and prednisone — alternating with pralatrexate. The data were not as promising as what one might have hoped.

DR LOVE: How do you approach the sequencing of pralatrexate and romidepsin outside of a protocol setting?

DR ANSELL: They are both useful agents, and I would commonly use them in the relapsed setting. The choice between the 2 agents would mainly depend on discussions with the patient about the risks and benefits, because they have similar efficacies but different toxicities.

Editor's note: On July 3, 2014, the US Food and Drug Administration (FDA) granted accelerated approval to belinostat for the treatment of relapsed or refractory PTCL.

Track 12

DR LOVE: Would you discuss emerging data with some of the novel therapeutic strategies for Waldenström macroglobulinemia (WM)?

DR ANSELL: The discovery of mutations in the MyD88 adaptor protein, which is present in more than 90% of patients with WM, is interesting and provides us with opportunities to target that pathway. Ibrutinib has shown a high level of activity in initial studies and is a promising agent in WM (Treon 2013; [1.2]). In the future, hopefully combining ibrutinib with other effective agents will be beneficial for patients.

We reported on the lenalidomide, rituximab, cyclophosphamide and dexamethasone (LR-CD) combination at ASH 2013 (Rosenthal 2013; [1.3]). Lenalidomide had been shown to be effective, but patients experienced some issues with anemia. Our goal in this study was to see if combining lenalidomide with a standard regimen would be beneficial. The results were promising, so the hope is in the future to continue to add effective agents to yield a better overall result.

1.2

Prospective Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Ibrutinib in Relapsed or Refractory Waldenström Macroglobulinemia

Efficacy	(n = 63)
Overall response rate	81.0%
Very good partial response	6.3%
Partial response	50.8%
Minor responses	23.8%

- Grade >2 toxicities included neutropenia (19.1%), thrombocytopenia (14.3%), atrial fibrillation (1.6%) and herpes zoster (1.6%).
- Rapid reductions in serum IgM were observed in most patients.
- Attainment of major responses to ibrutinib was affected by mutations in CXCR4 but not MYD88 L265P.

Treon SP et al. *Proc ASH* 2013;**Abstract 251**.

1.3

Phase II Study of Lenalidomide, Rituximab, Cyclophosphamide and Dexamethasone (LR-CD) for Untreated Low-Grade Non-Hodgkin Lymphoma: Waldenström Macroglobulinemia Cohort

Efficacy	(n = 15)
Overall response rate	80.0%
Complete response	6.7%
Partial response	73.3%

- The most common Grade 3 or 4 adverse events were neutropenia (13% Grade 3, 33% Grade 4), anemia (27% Grade 3, 13% Grade 4), and leukopenia (13% Grade 3, 20% Grade 4).
- Grade ≥3 nonhematologic toxicity: 40%
- LR-CD can be safely administered for newly diagnosed symptomatic Waldenström macroglobulinemia.

Rosenthal AC et al. *Proc ASH* 2013;**Abstract 4352**.

1.4

Phase II Study of Carfilzomib, Rituximab and Dexamethasone for Symptomatic Waldenström Macroglobulinemia

Efficacy	(n = 31)
Overall response rate	87.1%
Complete response	3.2%
Very good partial response	32.3%
Partial response	32.3%
Minimal responses	19.3%

- Grade ≥2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), cardiomyopathy (3.2%) and peripheral neuropathy (3.2%).

Treon SP et al. *Blood* 2014;124(4):503-10.

Proteasome inhibitors are also effective in WM. They elicit good responses and lower IgM levels. The lower incidence of peripheral neuropathy with carfilzomib, compared to bortezomib, makes it an appealing agent (Treon 2014; [1.4]). If we can find the optimal agent with low toxicity, that would be a welcome addition to the armamentarium for treating this disease. ■

SELECT PUBLICATIONS

Ansell SM. **Follicular lymphoma: Watch and wait is watch and worry.** *Lancet Oncol* 2014;15(4):368-9.

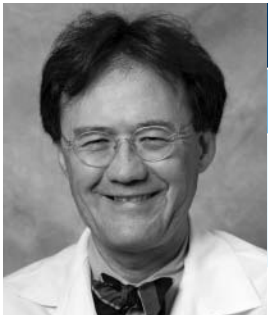
Ansell SM et al. **Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma.** *Proc ASH* 2012;**Abstract 798**.

Flinn IW et al. **Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study.** *Blood* 2014;123(19):2944-52.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial.** *Lancet* 2013;381(9873):1203-10.

Younes A et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: A phase 1, open-label, dose-escalation study.** *Lancet Oncol* 2013;14(13):1348-56.

Younes A et al. **Results of a pivotal Phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma.** *J Clin Oncol* 2012;30(18):2183-9.



INTERVIEW

Philip L McCarthy, MD

Dr McCarthy is Professor of Oncology and Internal Medicine at the Roswell Park Cancer Institute and State University of New York at Buffalo in Buffalo, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on the current role of transplantation in the management of multiple myeloma (MM)?

DR MCCARTHY: Patients who require a transplant need some form of induction therapy. In the past we've used the "CRAB" criteria to help us decide when to initiate therapy. Once you've decided that the patient needs treatment, you should administer therapy until the best response is reached and collect stem cells. We typically offer patients single ASCT.

A current topic of investigation is the use of up-front versus delayed transplant. Some registry data seem to indicate not much difference between the 2 strategies, but other data suggest a benefit with early transplant, so this is an open question. A number of studies are ongoing, and we're anxiously awaiting those results. One such study is a joint French

and American venture called DETERMINATION (NCT01208662), spearheaded by Dr Paul Richardson. Patients receive RVD (lenalidomide/bortezomib/dexamethasone) induction therapy, have their stem cells collected with cyclophosphamide mobilization and are then randomly assigned to either an autotransplant or continued RVD. Patients who undergo autotransplant then receive RVD consolidation. The trial organizers discussed at length the duration of lenalidomide maintenance therapy. The French decided to administer a year of maintenance, and in the United States it was decided that a year was short so US patients will receive maintenance therapy until disease progression.

Track 5

DR LOVE: What do we know about the oral proteasome inhibitor ixazomib in the treatment of MM, and where do you think it's heading?

DR MCCARTHY: Shaji Kumar recently published data in *Blood* on once-weekly ixazomib, and Paul Richardson published data on the twice-weekly schedule in relapsed/refractory MM (2.1). It appears as though the weekly schedule will be preferred with lenalidomide/dexamethasone. Some rashes and gastrointestinal toxicity occur, but this schedule seems to be efficacious and fairly well tolerated. The likely scenario is a completely oral administration of lenalidomide and weekly ixazomib.

An upcoming trial will evaluate maintenance ixazomib versus placebo after a single autotransplant (NCT02181413), although I don't know if that will be used much in the United States. The trial will be limited to 2 years, which may not be long enough. The duration of maintenance therapy is a current debate. I would have been more interested in a placebo-controlled trial of lenalidomide versus lenalidomide/ixazomib.

2.1

Weekly versus Twice-Weekly Ixazomib for Patients with Relapsed and/or Refractory Multiple Myeloma

Efficacy	Weekly ixazomib[1] (N = 50)	Twice-weekly ixazomib[2] (N = 55)
Complete response	0%	1 (2%)
Partial response	18%	6 (11%)
Stable disease	30%	33 (60%)
Progressive disease	50%	18%
Adverse events (Grade ≥3)	**Weekly ixazomib[1] (N = 60)**	**Twice-weekly ixazomib[2] (N = 60)**
Thrombocytopenia	33%	37%
Neutropenia	18%	17%
Skin/subcutaneous skin disorders	3%	8%
Peripheral neuropathy	2%	0%

[1] Kumar SK et al. *Blood* 2014;124(7):1047-55. [2] Richardson PG et al. *Blood* 2014;124(7):1038-46.

Track 6

DR LOVE: Would you review what we know about the use of carfilzomib/lenalidomide/dexamethasone (CRd) as up-front therapy in MM?

DR MCCARTHY: The NCI reported deep responses with CRd (Korde 2013), and the Jakubowiak data are certainly encouraging as well (Jakubowiak 2012). ECOG also has a trial evaluating CRd versus RVD followed by limited versus indefinite maintenance therapy with lenalidomide for patients newly diagnosed with symptomatic standard-risk MM (NCT01863550).

I believe carfilzomib is reasonable as a single agent for relapsed or refractory disease, but it's probably better when combined with an immunomodulatory agent. Up front our group is not using it much. For someone with severe neuropathy you could petition the insurance company by saying that the patient won't tolerate bortezomib. Or if neuropathy worsens after 1 cycle of bortezomib — for example, in a patient with diabetes — you might want to use carfilzomib up front. But right now we still use bortezomib.

Some cardiac toxicity occurs with carfilzomib also, and we don't know which patients will be affected by it. We've observed a couple of idiosyncratic cases that arose suddenly, without a clear reason, in patients with no cardiac history, who then developed congestive heart failure. Any marker for this effect remains to be discovered. Not all patients need an echocardiogram, but with an older patient you might want to consider that when you initiate therapy.

Tracks 13-14

DR LOVE: What are your thoughts on the impact of brentuximab vedotin on transplant decisions in HL?

DR MCCARTHY: We've been using it off label for patients with HL who experience relapse after primary therapy. If their disease is not well controlled with chemotherapy, we administer brentuximab vedotin as salvage therapy prior to autologous transplant. We also administer this agent after transplant for patients who experience relapse, according to the FDA label. And we will consider brentuximab vedotin as a bridge to allogeneic transplant for younger patients.

DR LOVE: How does ruxolitinib affect transplant decisions in myelofibrosis?

DR MCCARTHY: In the past, if they had a suitable donor patients often received allogeneic transplant early, especially if they were transfusion dependent. Now ruxolitinib has changed everything. Ruxolitinib provides a survival benefit, and it makes people feel much better. So if it can control a patient's disease, we hold the transplant. Ruxolitinib may not be the "home run" that imatinib was for CML, but I believe it's a great first step because now we have something to offer patients, especially if we can decrease their transfusion requirements and make them feel better. All the systemic symptoms seem to disappear with it. Unfortunately many patients experience disease breakthrough, and then we have to consider other options, such as transplant. ■

SELECT PUBLICATIONS

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801-9.

Korde N et al. **Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients.** *Proc ASH* 2013;**Abstract 538**.

Kumar S et al. **Phase I study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma.** *Blood* 2014;124(7):1047-55.

INTERVIEW

Ann S LaCasce, MD

Dr LaCasce is Program Director of the Fellowship Program in Hematology/Oncology at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the results of the Phase III CLL10 trial comparing fludarabine, cyclophosphamide and rituximab (FCR) to BR for patients with previously untreated advanced chronic lymphocytic leukemia (CLL)?

DR LACASCE: FCR resulted in a somewhat longer progression-free survival compared to BR in this study. In addition, there were more complete remissions with FCR (Eichhorst 2013; [3.1]). We know an alkylator is important for patients whose disease carries a deletion 11q, so that would be another setting in which we would prefer FCR. BR is a good option for older patients, but I believe it is inferior to FCR.

Track 2

DR LOVE: Can you talk about obinutuzumab, which was recently approved by the FDA in combination with chlorambucil for previously untreated CLL?

DR LACASCE: Obinutuzumab is a good option in CLL, for which rituximab doesn't seem to be as active as it is in other subtypes of non-Hodgkin lymphoma (NHL). Significant infusional toxicities do seem to be associated with obinutuzumab (Goede 2014; [3.2]). They must be carefully monitored, particularly when starting the drug for a patient with a high white blood cell count.

I've seen patients with severe reactions because not as much published experience is available with this agent. This is something that people need to be aware of and perhaps premedicate patients more than they might expect, even with rituximab. It appears that

3.1

CLL10: Interim Analysis of a Phase III Trial of Fludarabine, Cyclophosphamide and Rituximab (FCR) versus Bendamustine and Rituximab (BR) for Physically Fit Patients with Previously Untreated Advanced Chronic Lymphocytic Leukemia

Efficacy	FCR (n = 282)	BR (n = 279)	Hazard ratio	*p*-value
Two-year progression-free survival rate	85.0%	78.2%	1.385	0.041
Overall response rate (n = 274, 273)	97.8%	97.8%	—	1.0
Complete response rate (n = 274, 273)	47.4%	38.1%	—	0.031
Select Grade 3-5 adverse events (AEs)	**FCR**	**BR**	***p*-value**	
Severe hematologic AEs	90.0%	66.9%	<0.001	
Severe neutropenia	81.7%	56.8%	<0.001	
Severe infections	39.0%	25.4%	0.001	
Treatment-related death	3.9%	2.1%	Not reported	

Eichhorst B et al. *Proc ASH* 2013;**Abstract 526**.

3.2

Results of the Phase III CLL11 Trial of Obinutuzumab/Chlorambucil (O-Clb) versus Rituximab/Chlorambucil (R-Clb) or Chlorambucil Alone for Patients with Chronic Lymphocytic Leukemia and Comorbidities

Efficacy	O-Clb	R-Clb
Overall response rate (n = 333, 329) Complete response Partial response	78.4% 20.7% 57.7%	65.1% 7.0% 58.1%
Median progression-free survival (n = 333, 330)	26.7 mo	15.2 mo
Death rates (n = 333, 330)	8%	12%
Select Grade ≥3 adverse events	**O-Clb (n = 336)**	**R-Clb (n = 321)**
Infusion-related reaction	20%	4%
Neutropenia	33%	28%
Anemia	4%	4%
Thrombocytopenia	10%	3%
Infection	12%	14%

Overall response rate, O-Clb versus R-Clb: $p < 0.001$; progression-free survival, O-Clb versus R-Clb: hazard ratio (HR) = 0.39, $p < 0.001$; death rates, O-Clb versus R-Clb: HR = 0.66, $p = 0.08$

Goede V et al. *N Engl J Med* 2014;370(12):1101-10.

if the patient experiences a significant infusion reaction with the first dose, it does not seem to recur on subsequent doses, as we sometimes see with rituximab. But that first one can be quite severe.

DR LOVE: What is your approach for administering obinutuzumab to a patient with a high white blood cell count?

DR LACASCE: In the CLL11 study the dose was divided, so the patients received a small proportion on day 1 and the balance on day 2. But even in a patient with a particularly high white blood cell count, no substantial decrease will become apparent in 1 day, so I would delay longer if the patient experienced a severe reaction to the first infusion. Then I'd probably premedicate for several days with dexamethasone and diphenhydramine and add H1 and H2 blockers before administration of the next cycles.

Track 3

DR LOVE: How are you using ibrutinib in your practice now that its approval has been expanded to CLL (Byrd 2014; [3.3])?

DR LACASCE: Ibrutinib is a great agent with minimal toxicity. I have administered ibrutinib to a number of patients since it was approved and have been extremely impressed with the rapidity with which people respond and feel better.

You can observe their white count go up and kind of peak and then start to slowly come down as their hematocrit and platelets improve. Patients tolerate it well and are receiving it for a long period of time, even if they have persistent lymphocytosis.

3.3

RESONATE: Results of a Phase III Trial of Ibrutinib versus Ofatumumab for Previously Treated Chronic Lymphoid Leukemia

Efficacy	Ibrutinib (n = 195)	Ofatumumab (n = 196)	Hazard ratio	*p*-value
Median progression-free survival*	Not reached	8.1 mo	0.22	<0.001
Median overall survival	Not reached	Not reached	0.43	0.005
One-year overall survival	90%	81%		
Overall response rate	42.6%	4.1%	—	<0.001
	Ibrutinib (n = 195)		**Ofatumumab** (n = 191)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	48%	4%	18%	2%
Fatigue	28%	2%	30%	2%
Nausea	26%	2%	18%	0%
Pyrexia	24%	2%	15%	1%
Cough	19%	0%	23%	1%
Infusion-related reaction	0%	0%	28%	3%

* Median follow-up = 9.4 months

Byrd JC et al; RESONATE Investigators. *N Engl J Med* 2014;371(3):213-23.

The one aspect that has been a little challenging is in patients who are receiving anticoagulation therapy. There is an increased risk of bleeding, and all of the studies excluded patients who were receiving warfarin. So we worry about that a little. But in general, the toxicity has been quite minimal.

Track 6

DR LOVE: Would you discuss the mechanisms of action, efficacy and tolerability of idelalisib and ABT-199 in CLL also?

DR LACASCE: Idelalisib is a PI3 kinase delta inhibitor, and that is downstream of the BTK enzyme, which is the target of ibrutinib. Idelalisib has been studied in both indolent B-cell lymphomas and CLL and yields good response rates, though I believe the response rates are probably a little lower than with ibrutinib in CLL. It is also associated with the same phenomenon of peripheral lymphocytosis when you initiate therapy.

The toxicity profile is a little different. You see a fair number of cases of pneumonitis and LFT abnormalities, but we are able to administer treatment to most patients through those. Cases of colitis have also been reported recently in patients who've received idelalisib for a period of time. But it is an active drug, and I believe we'll be seeing other PI3 kinase inhibitors being studied in CLL.

The second-generation BCL2 inhibitor ABT-199 is also an interesting agent. The first-generation agent also inhibited BCL-XL and thus caused significant thrombocytopenia. That is not an issue with ABT-199, however. The major issue with ABT-199 is that it's associated with tumor lysis, so studies of this agent have used careful dose escalation. I've observed patients in whom LDH rose within a short time after starting ABT-199 therapy, so it's simply a matter of prophylaxis for tumor lysis.

But it is an active and well-tolerated agent in CLL and NHL, based on data from Matt Davids at our institution (Davids 2013, 2014). Combining it with antibodies and other agents will be interesting. I believe a study is planned of ABT-199 with R-CHOP in large cell lymphoma, and because of their favorable toxicity profiles, these agents are perfect to study in combination with chemotherapy. ■

Editor's note: On July 23, 2014, the US FDA approved idelalisib for the treatment of relapsed CLL, in combination with rituximab, for patients in whom rituximab alone would be considered appropriate therapy because of comorbidities.

The FDA also granted accelerated approval to idelalisib for the treatment of relapsed FL or relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies.

SELECT PUBLICATIONS

Davids MS et al. **Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): Responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses.** *Proc ASCO* 2014;**Abstract 8522**.

Davids MS et al. **Overcoming stroma-mediated treatment resistance in chronic lymphocytic leukemia through BCL-2 inhibition.** *Leuk Lymphoma* 2013;54(8):1823-5.

Eichhorst B et al. **Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a planned interim analysis of the CLL10 trial, an international, randomized study of the German CLL Study Group (GCLLSG).** *Proc ASH* 2013;**Abstract 526**.

INTERVIEW

Martin S Tallman, MD

Dr Tallman is Chief of the Leukemia Service at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-8

Select Excerpts from the Interview

Track 4

DR LOVE: Would you review what we know about the use of targeted therapy in FMS-like kinase 3 internal tandem duplication (FLT3-ITD)-positive acute myeloid leukemia (AML)?

DR TALLMAN: FLT3-ITD occurs in 20% to 25% of patients with AML and confers an unfavorable prognosis. Interestingly, it occurs at a frequency of 35% to 40% in the acute promyelocytic leukemia (APL) subtype of AML, where it appears to have less importance because patients fare so well in APL despite its presence. FLT3 inhibitors are one of the most studied and active areas for drug discovery in AML. One group of inhibitors were effective in the laboratory but not particularly effective in vitro. But then the drug quizartinib, or AC220, came along.

Quizartinib inhibits FLT3. It demonstrated single-agent activity in a Phase II trial for relapsed or refractory AML, with a composite complete remission (CR) rate of approximately 50%, which includes CR with incomplete platelet recovery and incomplete hematologic recovery (Cortes 2013; [4.1]). However, the true CR rate was low.

There's tremendous interest in moving quizartinib up front, particularly in combination with chemotherapy. We're anxious for the results of studies that have been initiated evaluating induction chemotherapy with or without quizartinib (NCT01390337).

4.1

Efficacy and Safety Results of a Phase II Trial of Quizartinib (AC220) in FLT3-ITD-Positive Relapsed or Refractory Acute Myeloid Leukemia

Best response	30 mg/d (n = 38)	60 mg/d (n = 38)
Composite complete remission (CR)	47%	47%
CR	5%	3%
CR with incomplete platelet recovery	0%	3%
CR with incomplete hematologic recovery	42%	42%
Partial response	13%	24%
Survival outcome	30 mg/d (n = 38)	60 mg/d (n = 38)
Median overall survival	20.7 weeks	25.4 weeks
Select Grade 3 or 4 adverse events	30 mg/d (n = 38)	60 mg/d (n = 36)
Anemia	39%	8%
Febrile neutropenia	26%	36%
Pyrexia	8%	8%
Diarrhea	3%	3%
Fatigue	3%	6%

Cortes JE et al. *Proc ASH* 2013;**Abstract 494**.

Track 5

DR LOVE: Volasertib recently received FDA breakthrough designation for the treatment of AML. What are your thoughts on the activity and safety of this agent?

DR TALLMAN: Volasertib is a polo-like kinase inhibitor. It's particularly involved in the regulation of the mitotic spindle function. The FDA breakthrough designation was based on the results of a randomized Phase II study of volasertib/low-dose cytarabine (LDAC) versus LDAC alone for patients with previously untreated AML who are ineligible for intensive therapy (Dohner 2014). The objective response rate was 31% with volasertib/LDAC and 13.3% with LDAC alone. Also, a trend was evident toward an improvement in overall survival (OS). Volasertib is an interesting and promising agent that has a unique mechanism of action. We need a prospective randomized Phase III trial to confirm its activity (4.2).

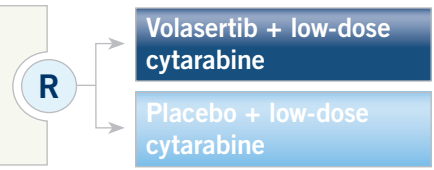
4.2

POLO-AML-2: A Phase III Trial of Volasertib and Low-Dose Cytarabine for Patients with Previously Untreated Acute Myeloid Leukemia

Protocol ID: NCT01721876 **Target Accrual:** 660

Eligibility

- Ineligible for intensive remission induction therapy
- Age ≥65 years
- ECOG PS ≤2
- No acute promyelocytic leukemia



www.clinicaltrials.gov. Accessed September 2014.

Track 6

DR LOVE: Would you discuss the results of the Phase III APL0406 trial for patients with newly diagnosed, nonhigh-risk APL?

DR TALLMAN: As remarkably effective as all-trans retinoic acid (ATRA) is, arsenic trioxide (ATO) is even more active. It's the single most active agent in this disease. The APL0406 trial compared ATRA with anthracycline-based chemotherapy, a more conventional approach, to ATRA and ATO with no provision for chemotherapy except for some hydroxyurea if the white count rises (Lo-Coco 2013; [4.3]). This study confirmed an important benefit in OS: 99% of patients appear to be cured of their disease with ATO-ATRA.

DR LOVE: Where are we today and what are the current issues requiring improvements in the management of APL?

DR TALLMAN: We have had a remarkable triumph in the treatment of APL in recent decades. The most remarkable change has been the movement away from chemotherapy. The APL0406 study included patients aged 18 to 71 years. It's an important study that established ATO in combination with ATRA as a new standard therapy for APL. It has been fascinating, as most patients with APL appear to be cured.

The major limitation to cure in most subtypes of AML is relapse and resistance. In contrast, the major limitation to cure for all patients with APL is early death, primarily due to CNS bleeding and some bleeding in the gastrointestinal tract and lungs. It's remarkable to have a subtype of AML in which resistant disease is not a major problem. In APL, there is no primary resistance. We are putting major efforts into reducing the risk of early death from APL. If we can reduce that risk and administer ATO-ATRA without chemotherapy to most patients, we will be close to curing all patients. ■

4.3

APL0406: A Phase III Trial Comparing Arsenic Trioxide (ATO) in Combination with All-Trans Retinoic Acid (ATRA) to Standard ATRA and Idarubicin-Based Chemotherapy in Newly Diagnosed, Nonhigh-Risk Acute Promyelocytic Leukemia

Response rate	ATO-ATRA	ATRA-chemotherapy	*p*-value
Hematologic complete response (n = 77, 79)	100%	95%	0.12
Two-year survival outcome	ATO-ATRA	ATRA-chemotherapy	*p*-value
Event-free survival (n = 74, 76)	97%	86%	<0.001* 0.02†
Overall survival (n = 77, 79)	99%	91%	0.02
Disease-free survival (n = 76, 73)	97%	90%	0.11

- Compared to ATRA-chemotherapy, ATO-ATRA was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity.

* Noninferiority of ATO-ATRA; † superiority of ATO-ATRA

Lo-Coco F et al. *N Engl J Med* 2013;369(2):111-21.

SELECT PUBLICATION

Dohner H et al. **Randomized, phase 2 trial comparing low-dose cytarabine with or without volasertib in AML patients not suitable for intensive induction therapy.** *Blood* 2014;124(9):1426-33.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A comparison by Ardeshna and colleagues of rituximab maintenance therapy to the watch and wait approach for patients with advanced, asymptomatic, nonbulky FL demonstrated a significant benefit with rituximab maintenance in which of the following parameters?**
   a. Time to start of new treatment
   b. Mental Adjustment to Cancer Scale score
   c. Overall survival
   d. Both a and b
   e. All of the above

2. **The combination of AVD with brentuximab vedotin was shown to be highly effective but is associated with a high rate of pulmonary toxicity in the front-line treatment of Hodgkin lymphoma.**
   a. True
   b. False

3. **A Phase II study of carfilzomib, rituximab and dexamethasone for symptomatic WM demonstrated _____.**
   a. An overall response rate of more than 80%
   b. A low rate (3.2%) of peripheral neuropathy
   c. Activity independent of MYD88 and CXCR4 mutation status
   d. All of the above

4. **Recent data on the use of the oral proteasome inhibitor ixazomib administered either weekly or twice weekly in the treatment of relapsed and/or refractory multiple myeloma demonstrated low rates of peripheral neuropathy with both dosing schedules.**
   a. True
   b. False

5. **Results of the prospective multicenter study of the Bruton tyrosine kinase inhibitor ibrutinib in relapsed or refractory WM demonstrated _____.**
   a. A high overall response rate
   b. Rapid reductions in serum IgM levels
   c. That the toxic effects include neutropenia and thrombocytopenia
   d. All of the above

6. **An interim analysis of the Phase III CLL10 trial for physically fit patients with previously untreated advanced CLL demonstrated that BR was _____ to FCR in terms of median progression-free survival.**
   a. Inferior
   b. Noninferior
   c. Superior

7. **The final Stage II results of the Phase III CLL11 trial for patients with CLL and coexisting medical conditions demonstrated that obinutuzumab/chlorambucil was superior to rituximab/chlorambucil in terms of _____.**
   a. Progression-free survival
   b. Overall response rate
   c. Both a and b

8. **The Phase III RESONATE trial, which evaluated ibrutinib versus ofatumumab for patients with relapsed or refractory CLL or SLL, reported statistically significant improvement(s) in _____ among patients who received ibrutinib.**
   a. Progression-free survival
   b. Overall survival
   c. Overall response rate
   d. All of the above

9. **The results of the Phase III APL0406 trial demonstrated that the combination of ATRA with ATO is noninferior to ATRA in combination with chemotherapy in the treatment of newly diagnosed, nonhigh-risk acute promyelocytic leukemia.**
   a. True
   b. False

10. **_____ is a polo-like kinase inhibitor that is particularly involved in the regulation of the mitotic spindle function that recently received FDA breakthrough designation for the treatment of acute myeloid leukemia.**
    a. Quizartinib
    b. Volasertib
    c. Sorafenib

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2014

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 of the Bruton tyrosine kinase inhibitor ibrutinib in relapsed or refractory Waldenström macroglobulinemia	4 3 2 1	4 3 2 1
Activity, tolerability and ongoing trials of the oral proteasome inhibitor ixazomib in multiple myeloma	4 3 2 1	4 3 2 1
Response and survival outcomes for patients with untreated CLL and comorbidities on the Phase III CLL11 trial evaluating obinutuzumab/chlorambucil or rituximab/chlorambucil versus chlorambucil alone	4 3 2 1	4 3 2 1
Results of the Phase III APL0406 trial of ATRA and arsenic trioxide versus ATRA and idarubicin-based chemotherapy for newly diagnosed, nonhigh-risk acute promyelocytic leukemia	4 3 2 1	4 3 2 1
Activity and tolerability of the polo-like kinase inhibitor volasertib in combination with low-dose cytarabine in relapsed/refractory AML	4 3 2 1	4 3 2 1

Practice Setting:

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice
☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

Approximately how many new patients with hematologic cancer do you see per year? ..... patients

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:

- Develop an algorithm for the risk-stratified induction treatment of follicular lymphoma, diffuse large B-cell lymphoma and mantle-cell lymphoma..... 4 3 2 1 N/M N/A
- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction, consolidation and maintenance treatment approaches for patients with multiple myeloma..... 4 3 2 1 N/M N/A
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients..... 4 3 2 1 N/M N/A
- Appreciate the recent FDA approvals of ibrutinib and obinutuzumab, and discern how these agents can be appropriately integrated into clinical practice for patients with chronic lymphocytic leukemia..... 4 3 2 1 N/M N/A
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas..... 4 3 2 1 N/M N/A
- Recognize the role of novel agents and regimens in the management of relapsed/refractory acute myeloid leukemia..... 4 3 2 1 N/M N/A

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

- Appraise recent clinical research findings on the efficacy and safety of novel proteasome inhibitor- and/or BTK inhibitor-based therapeutic strategies for Waldenström macroglobulinemia, and consider this information when caring for these patients. . . . . 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
Stephen M Ansell, MD, PhD	4 3 2 1	4 3 2 1
Philip L McCarthy, MD	4 3 2 1	4 3 2 1
Ann S LaCasce, MD	4 3 2 1	4 3 2 1
Martin S Tallman, 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 October 2015. 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/HOU214/CME.

QID 1304

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 Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Seattle Genetics and Teva Oncology.

Research To Practice®

Sponsored by Research To Practice.

Release date: October 2014
Expiration date: October 2015
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.