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 up-to-date therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES
• Describe the biologic rationale for and emerging roles of novel and approved antibody-drug conjugates — alone and in combination with chemotherapy — in the treatment of Hodgkin lymphoma and other CD30- or CD20-positive lymphomas.
• Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with multiple myeloma.
• Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors as therapeutic options for patients with chronic myeloid leukemia.
• 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 options in and outside of the research setting.
• Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment.
• Recall ongoing clinical trials evaluating innovative investigational approaches for diverse hematologic cancers, and consent or refer appropriate patients for study participation.

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**FACULTY INTERVIEWS**

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<th>Page</th>
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<td>3</td>
<td>Bruce D Cheson, MD</td>
<td>Professor of Medicine, Deputy Chief, Division of Hematology-Oncology, Head of Hematology, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC</td>
</tr>
<tr>
<td>7</td>
<td>Andrzej J Jakubowiak, MD, PhD</td>
<td>Professor of Medicine, Director, Myeloma Program, The University of Chicago, Chicago, Illinois</td>
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<td>11</td>
<td>Elias Jabbour, MD</td>
<td>Assistant Professor and Internist, Leukemia Department, The University of Texas MD Anderson Cancer Center, Houston, Texas</td>
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<td>15</td>
<td>Mathias J Rummel, MD, PhD</td>
<td>Head, Department for Hematology, Hospital of the Justus-Liebig University, Giessen, Germany</td>
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**18 POST-TEST**

**19 EDUCATIONAL ASSESSMENT AND CREDIT FORM**

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Tracks 1-16

Track 1 Current indications and emerging roles for the antibody-drug conjugate brentuximab vedotin in Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL)

Track 2 Doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) versus AVD in combination with brentuximab vedotin in advanced-stage HL: Pilot study results, safety and future directions

Track 3 Promising role of brentuximab vedotin in CD30-expressing lymphomas

Track 4 Therapeutic strategies with brentuximab vedotin-based up-front therapy in ALK-negative ALCL

Track 5 Clinical experiences with brentuximab vedotin

Track 6 Romidepsin and pralatrexate in relapsed/refractory T-cell lymphomas

Track 7 Results from a Phase II trial of the novel Aurora A kinase inhibitor alisertib (MLN8237) in patients with aggressive B- and T-cell non-Hodgkin lymphoma (NHL)

Track 8 SWOG-S0016: Results from a Phase III study of R-CHOP versus CHOP in combination with 131I-tositumomab for patients with newly diagnosed follicular lymphoma (FL)

Track 9 Barriers in clinical practice to the use of radioimmunotherapy in FL

Track 10 Novel agents under investigation in B-cell lymphomas — the PI3 kinase inhibitor GS-1101 (CAL-101) and the Bruton’s tyrosine kinase inhibitor (TKI) ibrutinib (PCI-32765)

Track 11 Obinutuzumab (GA101) — a third-generation, anti-CD20 monoclonal antibody for the treatment of B-cell lymphomas

Track 12 CALGB-50401: A Phase II trial of lenalidomide alone versus lenalidomide in combination with rituximab for patients with recurrent FL

Track 13 Perspective on lenalidomide-associated tumor lysis and tumor flare reaction and the need to refine clinical endpoints in chronic lymphocytic leukemia (CLL)

Track 14 Prevention and management of tumor lysis syndrome in patients with CLL: Role of rasburicase

Track 15 Updated results from the StiL NHL1 study: A Phase III trial of bendamustine in combination with rituximab (BR) versus R-CHOP as first-line treatment for patients with indolent and mantle-cell lymphomas (MCL)

Track 16 Rapid incorporation of BR into clinical practice and its effect on current and future clinical trials in FL

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the current indications and future directions for brentuximab vedotin in Hodgkin lymphoma and systemic anaplastic large cell lymphoma (sALCL)?
DR CHESON: Brentuximab vedotin is approved for patients with Hodgkin lymphoma for whom an autologous stem cell transplant has failed and for relapsed or refractory sALCL (1.1). Forty to 50% of patients develop mostly Grade 1 or Grade 2 peripheral neuropathy with this agent. Most of the Grade 3 neuropathy is reversible. Some myelosuppression can also occur. The drug is now available, and we are trying to move it toward up-front therapy.

The standard up-front treatment for Hodgkin lymphoma is doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD). In a Phase I study of ABVD with brentuximab vedotin, investigators had to eliminate bleomycin because of pulmonary toxicity (Younes 2011; [1.2]). Approximately 90% of those patients achieved negative PET scan results after doxorubicin/brentuximab vedotin/vinblastine/dacarbazine (A^2VD) therapy. A trial evaluating A^2VD versus standard ABVD has been initiated.

The management of peripheral T-cell lymphoma (PTCL) has been challenging. The standard up-front regimen is CHOP, but the long-term disease-free survival of 10% to 15% is poor and relapse is common. Approximately 30% of PTCL is CD30-positive and can be targeted with brentuximab vedotin. We now have agents in addition to brentuximab vedotin that are active in the relapsed setting: romidepsin, an HDAC inhibitor, and pralatrexate, an antifolate, yield response rates in the range of 30 to 50%.
25% to 30%. Patients tend to receive one drug followed by the other because they are seriously ill. I’m excited by a new agent, an Aurora A kinase inhibitor, that produced a response in 5 out of 8 patients with T-cell lymphomas (Friedberg 2011).

**Tracks 8-9**

**DR LOVE:** Would you talk about the SWOG-S0016 study of R-CHOP versus CHOP with radioimmunotherapy (RIT) for patients with newly diagnosed follicular lymphoma (FL)?

**DR CHESON:** The initial results of the S0016 study were presented at ASH 2011, and no difference in overall response rates or survival was reported between R-CHOP and CHOP/RIT (Press 2011; [1.3]). A subgroup analysis of patients by factors such as FLIPI score was presented at ASCO 2012, and the only factors that seemed to stand out were LDH and ß2M (Press 2012). The role for RIT in that context is not clear. Yttrium-90 ibritumomab tiuxetan is approved as consolidation therapy after induction therapy in FL, but I don’t believe this approach has penetrated much into the community or into academic centers.

RIT is the most effective, least used therapy for FL. The reasons why it is not being used include cost, complexity, loss of income and the potential for secondary cancer. RIT is a simple therapy administered for 8 days. I’ve seen patients who have experienced 5-year responses with RIT after disease progression on a couple of lines of treatment.

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

<table>
<thead>
<tr>
<th>R-CHOP</th>
<th>CHOP 131I-tositumomab</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (n = 263, 260)</td>
<td>85%</td>
<td>86%</td>
</tr>
<tr>
<td>Two-year PFS (n = 267, 265)</td>
<td>76%</td>
<td>80%</td>
</tr>
<tr>
<td>Two-year overall survival (n = 267, 265)</td>
<td>97%</td>
<td>93%</td>
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<tr>
<td>Treatment-related mortality (n = 263, 263)</td>
<td>0.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>AML/MDS (n = 267, 265)</td>
<td>1.1%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

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


**Track 12**

**DR LOVE:** Would you discuss the role of lenalidomide in FL?

**DR CHESON:** Lenalidomide is active against a broad range of lymphoid cancers. I proposed the R² regimen of lenalidomide and rituximab in 2008. For patients with untreated FL, the response rate is higher than 90%. The CALGB-50401 trial evaluated lenalidomide alone or in combination with rituximab for patients with FL that had relapsed on rituximab. The overall response rate and progression-free survival strongly favored the combination (Leonard 2012; [1.4]). Surprisingly, fewer cases of phlebitis and thromboembolism occurred in the combination arm.
Tracks 13-14

**DR LOVE:** Would you discuss lenalidomide-associated tumor lysis syndrome and tumor flare reaction in chronic lymphocytic leukemia?

**DR CHESON:** The more effective your therapy is, the more likely you are to encounter tumor lysis syndrome. It is of particular concern with lenalidomide and does not appear to be dose related. If you’re combining lenalidomide with rituximab, it may be better to administer the rituximab before the lenalidomide.

Clinicians also need to be aware of tumor flare reaction. A week or two after the first dose of lenalidomide the lymphocyte count increases, which can suggest that the disease is rapidly progressing. Some people believe that this predicts a more favorable outcome. In a recent publication in the *Journal of Clinical Oncology* we contend that high lymphocyte count can be ignored unless some other parameter is also signaling deterioration (Cheson 2012).

**DR LOVE:** Which patients are more at risk for tumor lysis syndrome, and how do you monitor and treat it?

**DR CHESON:** Patients at high risk are those who before the treatment have extensive tumor bulk, abnormal renal function, high initial uric acid or abnormalities of calcium, potassium and phosphorus. These patients should receive either allopurinol or a single dose of rasburicase a few hours before treatment to prevent the development of what can be a life-threatening complication. I have administered rasburicase a number of times and have not observed any toxicity with this agent.

**SELECT PUBLICATIONS**


Friedberg J et al. *Phase 2 trial of alisertib (MLN8237), an investigational, potent inhibitor of aurora A kinase (AAK), in patients (pts) with aggressive B- and T-cell non-Hodgkin lymphoma (NHL).* *Proc ASH* 2011;Abstract 95.

Leonard J et al. *CALGB 50401: A Randomized Phase II Trial of Lenalidomide Alone versus Lenalidomide with Rituximab for Patients with Recurrent Follicular Lymphoma* 


Tracks 1-15

Track 1  Efficacy, toxicity profile and duration of response with the novel proteasome inhibitor MLN9708 in multiple myeloma (MM)

Track 2  Activity of single-agent carfilzomib in patients with relapsed/refractory MM

Track 3  Background and design of a Phase I/II study of carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) as front-line treatment for MM

Track 4  Stringent complete response in patients with newly diagnosed MM treated with CRd

Track 5  Carfilzomib-associated side effects

Track 6  Attenuated rates of peripheral neuropathy and evolving role of carfilzomib for patients with MM and renal dysfunction

Track 7  ASPIRE: A Phase III trial evaluating CRd versus lenalidomide and dexamethasone (Rd) in patients with relapsed MM

Track 8  Underlying considerations for a proposed clinical trial evaluating CRd versus RVD in patients with MM

Track 9  Toward incorporating CRd into the therapeutic algorithm for MM

Track 10  Role of transplant in the era of novel agents

Track 11  Critical appraisal of available clinical trial data with thalidomide, lenalidomide or bortezomib as post-transplant maintenance or consolidation therapy

Track 12  Practical considerations — optimal therapeutic duration, cost and chronic disease versus “cure” — with lenalidomide maintenance therapy

Track 13  Subcutaneous versus intravenous administration of bortezomib in MM

Track 14  Single-agent MLN9708 in relapsed/refractory MM and in combination with lenalidomide/dexamethasone in newly diagnosed MM

Track 15  Phase II study of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory MM

Select Excerpts from the Interview

Tracks 1-7, 9, 14

DR LOVE: What are your thoughts on some of the new proteasome inhibitors under evaluation in multiple myeloma (MM)?

DR JAKUBOWIAK: The top 2 next-generation proteasome inhibitors are carfilzomib and MLN9708, which is similar to bortezomib but administered orally. These are agents with proven efficacy, and we’ve learned during the past few years that these newer agents are potentially useful not only because of their different toxicity profiles but also because they work in different patient subpopulations and can overcome resistance.
We know that a major limitation to prolonged bortezomib use is the development of peripheral neuropathy. Although recent evidence that subcutaneous administration of bortezomib maintains efficacy while decreasing the incidence of peripheral neuropathy by about 50% is good news (Arnulf 2012), MLN9708 is associated with a lack or limited incidence of this side effect.

Rates of nausea, gastrointestinal toxicities and skin rashes are higher with MLN9708, but they are easily manageable. As we move forward to combination therapies with this agent, steroids will be incorporated, so those side effects should potentially be less of a problem. An update at ASCO reported that MLN9708 is active as a single agent in patients with advanced MM (Lonial 2012). This agent also has excellent activity when combined with lenalidomide and dexamethasone for patients with previously untreated MM (Richardson 2012; [2.1]). Even if MLN9708 ends up not being superior to bortezomib, it is still one of the most exciting developments in myeloma treatment because of its toxicity profile and convenience.

Another exciting new proteasome inhibitor that doesn’t cause significant toxicity is carfilzomib. Carfilzomib has single-agent activity in patients with relapsed or refractory MM previously treated with bortezomib (Vij 2012b) and in patients not exposed to bortezomib (Vij 2012a).

› DR LOVE: Would you discuss the results of your Phase I/II study of carfilzomib, lenalidomide and low-dose dexamethasone (CRd), which were recently presented at ASCO and subsequently published in Blood (Jakubowiak 2012)?

› DR JAKUBOWIAK: This study did not focus only on elderly patients or transplant candidates — we took all patients. For patients eligible for transplant, we collected stem cells during CRd induction. For CRd maintenance therapy we initially planned an indefinite period, but we ended up finishing treatment at 24 months for practical reasons.

This combination is powerful. The rapidity of response is among the best I have observed. We reported a 67% reduction of disease after 1 cycle and an 81% reduction of disease after 2 cycles. We observed a continuous decline of the slope of the curve of M protein if plotted from day 1 to cycle 12, approaching undetectable levels in many patients.

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

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<td>Complete response</td>
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<td>Very good partial response</td>
<td>21%</td>
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<tr>
<td>Partial response</td>
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<table>
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<tr>
<td>Serious drug-related AE</td>
<td>26%</td>
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<tr>
<td>Any grade drug-related peripheral neuropathy (PN)</td>
<td>21%</td>
</tr>
<tr>
<td>Grade 2 PN with pain</td>
<td>11%</td>
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Richardson PG et al. Proc ASCO 2012; Abstract 8033.
When we continue patients on treatment with a median of 12 cycles of treatment, our overall response rate is close to 100%, but very good partial response is more than 80%, near-complete response is 62% and stringent complete response for the entire patient population is 42%, meaning that we cannot detect disease by any means, including immunofixation and serum free light chain assays, in these patients who received CRd.

Analysis of patients who had been receiving treatment longer — 8 or more cycles — reached unmatched levels of response. Near-complete response was 78% for this group of patients, and stringent complete response was 61%. These numbers compare favorably to those with any regimen previously studied, including combination treatments with an initial 3-drug regimen followed by transplant and consolidation.

**DR LOVE:** What side effects have been observed with carfilzomib?

**DR JAKUBOWIAK:** Dyspnea has been noted in a few cases, mostly in patients with advanced disease. It is believed to some extent to be related to tumor lysis syndrome or some other rapid cytoreduction-related effects. In our study, dyspnea was observed in few cases — only a small proportion of patients experienced this problem.

We did not observe any pattern other than occasional fatigue in some patients. We did not observe any pneumonitis. Reports exist of some increase in creatinine and decrease of renal function in patients with relapsed disease. That has not necessarily been observed in our study, which is for patients with newly diagnosed disease. The most common toxicities were mild — Grade 1 or Grade 2 — decreases of hemoglobin and white blood cells and thrombocytopenia. The most common nonhematologic toxicities were hyperphosphatemia and hyperglycemia. Those 2 are clearly dexamethasone related.

Peripheral neuropathy was observed in about 20% of patients, but it was all Grade 1 with the exception of 2 cases that were borderline Grade 2. In all cases except one we attributed this to lenalidomide, and we noted improvement of this neuropathy after lenalidomide was reduced without reducing the dose of carfilzomib.

We are now anxiously awaiting results from the Phase III ASPIRE trial, which is evaluating CRd versus lenalidomide/dexamethasone in approximately 700 patients with relapsed MM. Interestingly, patients who experienced disease progression on maintenance lenalidomide were allowed to be enrolled on both arms of this study. I hope to see first results from this trial sometime early next year.

**DR LOVE:** Given all the recent favorable data with carfilzomib and the anticipation that it will soon be approved by the FDA (2.2), how many clinicians, including yourself, do you believe will opt to simply go ahead and start administering up-front CRd?

**DR JAKUBOWIAK:** We will have to respect the FDA label if and when carfilzomib is approved, but we know that to some extent in the United States we have the ability to access agents off label for some indications. So this is with the clear disclosure that I am now sharing my personal opinion and experience from administering a variety of these agents in combinations. If I would like to begin with the best treatment strategy, I definitely would choose CRd. I would have a hard time deciding whether I should break the treatment and administer transplant in the middle for a transplant candidate and then resume CRd treatment. That question needs to be answered. But I believe that between RVD followed by transplant followed by RVD and CRd without a transplant, we see patients faring well with CRd. And why not, to try something which I believe will end up being a better therapy?
**SELECT PUBLICATIONS**

Arnulf B et al. *Updated survival analysis of a randomized, phase 3 study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma.* *Haematologica* 2012;[Epub ahead of print].


Lonial S et al. *Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM).* *Proc ASCO* 2012;Abstract 8017.


Tracks 1-14

Track 1  PACE: Results from a Phase II trial of ponatinib in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to dasatinib or nilotinib or with the T315I mutation

Track 2  Defining the goals of TKI treatment in CML

Track 3  Overview of the side-effect profiles of first- (imatinib) and second- (dasatinib and nilotinib) generation TKIs

Track 4  Selection of second-generation TKIs nilotinib or dasatinib for initial treatment of CML

Track 5  Monitoring and switching patterns in patients with CML treated with imatinib

Track 6  Mechanism of action, efficacy and side effects of the novel protein translation inhibitor omacetaxine alone and in combination with low-dose Ara-C in patients with acute myeloid leukemia (AML) or CML

Track 7  Role of allogeneic stem cell transplantation for patients with TKI-resistant CML

Track 8  Perspective on potential discontinuation of imatinib after sustained complete molecular remission in patients with CML

Track 9  Initial diagnosis and staging of myelofibrosis (MF)

Track 10  Overview of JAK2 inhibitors: Durations of response, mechanisms of action and activity in JAK mutation-positive and mutation-negative MF

Track 11  Role of immunomodulatory drugs in the treatment of MF

Track 12  Initial ruxolitinib dosing and clinical impact of JAK2 mutational status on outcome in MF

Track 13  Patient stratification in AML and risk factors that influence therapeutic approach

Track 14  Promising early results with novel antibodies inotuzumab ozogamicin and blinatumomab in acute lymphocytic leukemia

Select Excerpts from the Interview

Tracks 2-5

**DR LOVE:** Is it your perception that in the community, treatment of newly diagnosed chronic myeloid leukemia (CML) has shifted to second-generation tyrosine kinase inhibitors (TKIs), or is imatinib still used commonly?

**DR JABBOUR:** Based on surveys in the United States, 60% of physicians still prescribe imatinib in the front line (Mauro 2011), and that’s in contrast to almost no CML investigators. Although community physicians usually follow academia, this is not the case in CML. Most of them have used imatinib. My colleagues say, “Oh, I had a great experience with it. Why take a chance with something else?”
DR LOVE: Would you discuss the monitoring of patients with CML?

DR JABBOUR: We presented an abstract at ASCO on monitoring CML in the community, and the results were not good (Chen 2012). The difference between Europe and the United States is large because in Europe CML is generally managed in academia. In America it’s managed more in the community.

Forty percent of physicians are not aware of the recommendations about what to monitor and when. We also noted confusion with regard to the importance of reaching a molecular response and whether it should result in a change of therapy — some physicians are switching therapies at 6 months in patients who don’t attain a molecular response, which is not a good practice (Saglio 2012).

We must make the recommended approach simple now with the availability of second-generation TKIs. We published a study in the *Journal of Clinical Oncology* showing that early responses are important, so with any TKI patients should be monitored at 3 months, 6 months and then 1 year with levels of optimal response, suboptimal response or failure being assessed (Jabbour 2011).

In addition, mutation testing should only be ordered in a setting of disease progression, when you decide to switch therapy. This is when mutations are relevant because they can help you select which agent to use next. We don’t order mutation testing when the disease is responding to therapy.

DR LOVE: What factors do you use to choose between nilotinib and dasatinib?

DR JABBOUR: Several factors must be considered — for smokers or those with COPD or lung injuries, I avoid dasatinib. I avoid nilotinib for patients with a history of pancreatitis or liver dysfunction and in the case of barely controlled diabetes, although hyperglycemia may not be an issue in front-line therapy. I recently saw a patient for whom I avoided dasatinib because he’s receiving a blood thinner. He had a stroke and a low platelet count, so I’m concerned about dasatinib in terms of a higher risk of bleeding.

DR LOVE: What’s the difference in side-effect profiles between second-generation TKIs and imatinib?

DR JABBOUR: Common side effects observed with imatinib are fluid retention, periorbital edema, nausea, myalgia/arthralgia and fatigue. These aren’t severe but can affect daily life and may lead to a drop in the use of the drug for a patient who experiences all of these side effects. With nilotinib more rashes occur, although not Grade 3 or 4, and migraines. Dasatinib can cause pleural effusion. With both of these agents the side effects are less frequent, but they may be severe.

Track 1

DR LOVE: What are some of the interesting CML data from the recent ASCO meeting?

DR JABBOUR: Jorge Cortes presented longer follow-up from his trial evaluating the promising new TKI ponatinib in CML (Cortes 2012; [3.1]). Responses are impressive in T315I and non-T315I disease — approximately 50%. Ponatinib is good for patients whose disease has progressed on several TKIs.
We’re learning more about safety, and we have a front-line trial launching in the United States and across the world randomly assigning patients to ponatinib or imatinib (NCT01650805).

The incidence of myelosuppression is approximately 30%, which is similar to the pivotal Phase II trial of nilotinib and dasatinib with a 35% incidence of thrombocytopenia. The issue with ponatinib eventually is abdominal pain and pancreatitis, with an incidence of approximately 7%. We need to manage the side effects and confirm that ponatinib is safe with longer follow-up in another trial.

| Tracks 9-10, 12 |

**DR LOVE:** Would you discuss the initial diagnosis and staging of myelofibrosis and where we are with the JAK2 inhibitors?

**DR JABBOUR:** I want to remind community physicians that myeloproliferative neoplasms are a group of highly malignant diseases, the primary of which is myelofibrosis. These patients come to us because they have enlarged spleens and anemia, sometimes requiring blood transfusions. We always test the patient’s bone marrow to confirm a myelofibrosis diagnosis. Patients can have CML and fibrosis in the bone marrow, which does not equal a myelofibrosis diagnosis. Several criteria, major and minor, must be considered to rule out other causes.

Once you come to a definitive diagnosis of myelofibrosis, the disease must be staged to distinguish how aggressive it is and to develop a treatment strategy. The Dynamic International Prognostic Scoring System for myelofibrosis (DIPSS) factors in age, systemic symptoms, white blood cell count and degree of anemia to distinguish low risk versus high risk. We treat high-risk myelofibrosis with transplant and/or chemo-
therapy. For patients at low risk, we start with growth factors, steroids, and this is where JAK2 inhibitors fit in.

Because patients with myelofibrosis sometimes have low platelet counts and splenomegaly, physicians may be afraid to start with a full dose of JAK2 inhibitor. One option is to start with the lower dose and increase the dose while controlling the platelets. I use 5 mg daily or 5 mg twice daily until I reach 20 mg.

Several JAK2 inhibitors are being tested, and some are more specific than others. Most have minimal activity in the bone marrow. Most of the effect is peripheral, through the blockage of interleukin/cytokine flare more than in the bone marrow.

In the future we must use a combination. It’s a first step, targeting the symptom of the disease without touching much of the marrow. We must combine this kind of therapy to target the bone marrow and the spleen. Patients from the COMFORT trials are still responding (3.2), but they eventually experience disease progression. The median duration of initial therapy is a year or more.

» DR LOVE: What kind of treatment do you generally use next?

» DR JABBOUR: Nothing is approved. We administer clofarabine with low-dose Ara-C, hypomethylating agents with low-dose Ara-C or, if the patient is young, chemotherapy. If the patient has a low blast percent, I consider clinical trials. If the blasts are 10% or higher, usually platelet counts are low and JAK2 inhibitors are not appropriate. In that case we use epigenetic therapy or more aggressive chemotherapy, clofarabine or twice-daily fludarabine and cytarabine. ■

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

<table>
<thead>
<tr>
<th></th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy — Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥35% decrease in spleen volume at 24 wk and 48 wk</td>
<td>41.9% (n = 155)</td>
<td>0.7% (n = 154)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Change in symptom score — Secondary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥50% improvement in symptom score at 24 wk</td>
<td>45.9% (n = 145)</td>
<td>5.3% (n = 145)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>—</td>
</tr>
</tbody>
</table>

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


### SELECT PUBLICATIONS


### Tracks 1-10

<table>
<thead>
<tr>
<th>Track</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Background for the design of the StiL NHL1 trial of BR versus R-CHOP</td>
</tr>
<tr>
<td>2</td>
<td>Lead investigator’s perspective on the updated results from the StiL NHL1 study</td>
</tr>
<tr>
<td>3</td>
<td>StiL NHL1: Subset analysis of progression-free survival by histologic subtype</td>
</tr>
<tr>
<td>4</td>
<td>StiL NHL1: Incidence of second cancers</td>
</tr>
<tr>
<td>5</td>
<td>StiL NHL1: Stem cell mobilization in patients receiving BR</td>
</tr>
<tr>
<td>6</td>
<td>Debate on the current and future role of R-CHOP versus BR in up-front management of FL</td>
</tr>
<tr>
<td>7</td>
<td>Rationale for the design of the ongoing Phase III MAINTAIN trial evaluating the significance of duration of rituximab maintenance therapy after BR induction in NHL</td>
</tr>
<tr>
<td>8</td>
<td>Investigations of rituximab maintenance therapy in MCL</td>
</tr>
<tr>
<td>9</td>
<td>Therapeutic options for patients with transformed FL or relapsed/refractory diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>10</td>
<td>Investigation of novel agents and pathways in lymphoma</td>
</tr>
</tbody>
</table>

### Select Excerpts from the Interview

**Tracks 1-4**

*DR LOVE:* Would you discuss the updated results of the Phase III StiL NHL1 trial?

*DR RUMMEL:* The StiL trial was initiated in 2003 with the intention to challenge the standard treatment approach for patients with indolent lymphoma. Although R–CHOP was frequently used for patients with indolent lymphomas, its use was not based on evidence. Because indolent lymphoma is not curable with R–CHOP, patients eventually experience relapse. Therefore, we compared a newer regimen to R–CHOP because it was important to question whether a less intensive treatment would have the same clinical benefit. Based on a Phase I/II trial that demonstrated high activity and low toxicity with bendamustine/rituximab (BR), we initiated the Phase III StiL trial.

Surprisingly, we found that BR was less toxic and more effective. The initial results were presented at ASH 2009 (Rummel 2009) and the updated follow-up results at ASCO 2012 (Rummel 2012; [4.1]). The difference in progression-free survival between BR and R–CHOP was statistically significant at 69 versus 31 months and clinically relevant, making the StiL trial results important for physicians and patients. Even though the hazard ratio in 2012 was the same as in 2009, the updated results were more pronounced.
The updated results demonstrated no overall survival benefit but suggested, albeit
immaturely, that the overall survival curves may split with a longer follow-up period.
In evaluating the mature points of the curves at 5 years, it is not surprising to find no
overall survival advantage. First, the study was not powered for survival. Second, a
longer follow-up period was required. Notably, the study protocol did not define the
salvage regimen for the time of relapse. The treating physician’s choice certainly influ-
enced the survival data.

› DR LOVE: Because the study included patients with FL, marginal-zone lymphoma
(MZL) and mantle-cell lymphoma (MCL), would you discuss the subset analysis of the
data in terms of progression-free survival?

› DR RUMMEL: For patients with FL a statistically significant advantage was evident with
BR. A subset analysis showed that BR was superior to R-CHOP for patients in the
subgroups with low-risk and high-risk FLIPI scores. In the subset of patients with high
FLIPI scores, although progression-free survival was not statistically significant, BR was
not inferior to R-CHOP.

Interestingly, BR was also more effective than R-CHOP for patients with MCL.
However, both R-CHOP and BR results were discouraging for MCL, suggesting that
patients with MCL need additional therapy. A comparison of BR to R-CHOP demon-

### 4.1 Updated Safety and Efficacy Results from the Phase III STiL NHL1 Trial
of Bendamustine/Rituximab (BR) versus R-CHOP as First-Line Therapy
for Patients with Indolent and Mantle-Cell Lymphomas

<table>
<thead>
<tr>
<th>Median progression-free survival</th>
<th>BR</th>
<th>R-CHOP</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 514)</td>
<td>69.5 mo</td>
<td>31.2 mo</td>
<td>0.58</td>
<td>0.0000148</td>
</tr>
<tr>
<td>Mantle-cell lymphoma (n = 93)</td>
<td>35.4 mo</td>
<td>22.1 mo</td>
<td>0.50</td>
<td>0.0061</td>
</tr>
<tr>
<td>Marginal-zone lymphoma (n = 67)</td>
<td>57.2 mo</td>
<td>47.2 mo</td>
<td>0.70</td>
<td>0.3249</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>69.5 mo</td>
<td>28.1 mo</td>
<td>0.33</td>
<td>0.0033</td>
</tr>
<tr>
<td>FLIPI low (n = 152)</td>
<td>Not reached</td>
<td>Not reached</td>
<td>0.61</td>
<td>0.0072</td>
</tr>
<tr>
<td>FLIPI high (n = 127)</td>
<td>53.4 mo</td>
<td>40.9 mo</td>
<td>0.56</td>
<td>0.0428</td>
</tr>
<tr>
<td>Not reached</td>
<td>46.6 mo</td>
<td>34.9 mo</td>
<td>0.63</td>
<td>0.0679</td>
</tr>
<tr>
<td>Not reached</td>
<td>53.4 mo</td>
<td>40.9 mo</td>
<td>0.61</td>
<td>0.0072</td>
</tr>
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<td>0.61</td>
<td>0.0072</td>
<td></td>
</tr>
<tr>
<td>46.6 mo</td>
<td>34.9 mo</td>
<td>0.63</td>
<td>0.0679</td>
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</tr>
<tr>
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<td>0.0072</td>
<td></td>
</tr>
<tr>
<td>46.6 mo</td>
<td>34.9 mo</td>
<td>0.63</td>
<td>0.0679</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma (n = 279)</td>
<td>Not reached</td>
<td>Not reached</td>
<td>0.62</td>
<td>0.0022</td>
</tr>
<tr>
<td>FLIPI low (n = 152)</td>
<td>53.6 mo</td>
<td>31.5 mo</td>
<td>0.62</td>
<td>0.0022</td>
</tr>
<tr>
<td>FLIPI high (n = 127)</td>
<td>71.6 mo</td>
<td>30.9 mo</td>
<td>0.52</td>
<td>0.0022</td>
</tr>
<tr>
<td>Age  ≥61 years (n = 315)</td>
<td>53.6 mo</td>
<td>31.5 mo</td>
<td>0.62</td>
<td>0.0022</td>
</tr>
<tr>
<td>≤60 years (n = 199)</td>
<td>71.6 mo</td>
<td>30.9 mo</td>
<td>0.52</td>
<td>0.0022</td>
</tr>
<tr>
<td>Overall survival</td>
<td>BR</td>
<td>R-CHOP</td>
<td>Hazard ratio</td>
<td>p-value</td>
</tr>
<tr>
<td>Five-year overall survival</td>
<td>80.1%</td>
<td>77.8%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Select adverse events</td>
<td>BR (n = 261)</td>
<td>R-CHOP (n = 253)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesias</td>
<td>7%</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>6%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>16%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary cancer</td>
<td>BR (n = 260)</td>
<td>R-CHOP (n = 253)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>8%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = not reported
Follow-up: 45 months; deaths: BR (n = 43), R-CHOP (n = 45)

strated that BR therapy is preferred for elderly patients who cannot tolerate R-CHOP. Although no statistically significant difference in progression-free survival between BR and R-CHOP was recorded for patients with MZL, a huge difference in progression-free survival in favor of BR was observed for patients with Waldenström macroglobulinemia. Also, because BR is a relatively new regimen, its association with secondary cancer is of concern. With a median follow-up of 4 years, no difference was evident in the incidence of secondary cancer between BR and R-CHOP (4.1).

**Track 7**

**DR LOVE:** What are your thoughts on rituximab maintenance therapy in indolent lymphoma?

**DR RUMMEL:** Maintenance therapy with rituximab is globally approved and currently administered by many physicians despite uncertainties about the survival benefit. The PRIMA trial reported no survival advantage (Salles 2011).

As suggested by the results of the PRIMA trial, rituximab maintenance is more beneficial for patients with complete responses than for those with partial responses. In other words, one can only maintain what has been achieved. So it makes more sense to add maintenance to the BR regimen because the quality and the depth of responses after BR are better and even more profound than those after R-CHOP.

If we accept the fact that a good response is the best indication for maintenance, then maintenance therapy should be added after BR therapy. Because the standard approach in Germany already includes 2 years of maintenance therapy after BR, the ongoing randomized Phase II/III MAINTAIN trial will ask the question of whether 2 or 4 years’ duration is optimal for rituximab maintenance (4.2).

**SELECT PUBLICATIONS**


Rummel MJ et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Proc ASH* 2009; Abstract 405.

1. Studies evaluating brentuximab vedotin reported 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

2. The CALGB-50401 study demonstrated a higher overall response rate and longer event-free survival with lenalidomide and ____________ compared to lenalidomide alone for patients with rituximab-refractory FL.
   a. Rituximab
   b. Bortezomib
   c. Obinutuzumab

3. The SWOG-S0016 study evaluating R-CHOP versus CHOP with RIT for patients with newly diagnosed FL reported a significant difference in overall response rate and survival for patients receiving CHOP/RIT.
   a. True
   b. False

4. In a Phase I/II trial by Richardson and colleagues, the administration of MLN9708 in combination with lenalidomide and dexamethasone produced a response rate of 100% among evaluable patients.
   a. True
   b. False

5. A Phase II study evaluating 2 different doses of elotuzumab with lenalidomide/dexamethasone for patients with relapsed or refractory MM reported an overall response rate of 92% for patients who received lenalidomide/dexamethasone and elotuzumab 10 mg/kg.
   a. True
   b. False

6. The Phase III ASPIRE trial is evaluating ____________ versus lenalidomide and dexamethasone for patients with relapsed MM.
   a. CRd
   b. RVD
   c. Both of the above

7. The Phase III COMFORT-I and COMFORT-II trials of ruxolitinib versus placebo and ruxolitinib versus best available therapy for patients with myelofibrosis demonstrated statistically significant and sustained reduction in spleen size in patients on the ruxolitinib study arms.
   a. True
   b. False

8. Common side effects associated with nilotinib include which of the following?
   a. Headache
   b. Skin rash
   c. Both a and b
   d. Neither a nor b

9. The updated results of the Phase III StiL NHL1 trial demonstrated that the BR regimen was statistically superior to R-CHOP in terms of ____________ for patients with indolent and mantle-cell lymphomas.
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

10. The ongoing Phase II/III MAINTAIN trial will evaluate 2 years versus ________ of maintenance therapy with rituximab after BR induction therapy for patients with non-Hodgkin lymphoma.
    a. Eight years
    b. Four years
    c. One year
**PART 1 — Please tell us about your experience with this educational activity**

**How would you characterize your level of knowledge on the following topics?**

<table>
<thead>
<tr>
<th>Topic</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of peripheral neuropathy associated with the use of brentuximab vedotin for Hodgkin lymphoma and ALCL</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Alternative dosing strategies with ruxolitinib for patients with MF</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>CRd as first-line therapy for MM</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>SWOG-S0016: A Phase III study of R-CHOP versus CHOP followed by 131I-tositumomab for patients with newly diagnosed FL</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Long-term efficacy and toxicity data from the StiL NHL1 trial of BR versus R-CHOP in patients with indolent lymphomas</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Rasburicase in the management of tumor lysis syndrome</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

**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:**

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a result of this activity, I will be able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Describe the biologic rationale for and emerging roles of novel and approved antibody-drug conjugates — alone and in combination with chemotherapy — in the treatment of Hodgkin lymphoma and other CD30- or CD22-positive lymphomas.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with multiple myeloma.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors as therapeutic options for patients with chronic myeloid leukemia.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 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 options in and outside of the research setting.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recall ongoing clinical trials evaluating innovative investigational approaches for diverse hematologic cancers, and consent or refer appropriate patients for study participation.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce D Cheson, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Andrzej J Jakubowiak, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Elias Jabbour, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Mathias J Rummel, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Editor</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neil Love, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

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

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

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

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

FACULTY INTERVIEWS
Bruce D Cheson, MD
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Mathias J Rummel, MD, PhD

EDITOR
Neil Love, MD

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