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Hematologic Oncology™ UPDATE

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

FACULTY INTERVIEWS

Craig Moskowitz, MD
Nikhil C Munshi, MD
John O Mascarenhas, MD
B Douglas Smith, MD
Nathan H Fowler, MD

EDITOR

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OVERVIEW OF ACTIVITY

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

LEARNING OBJECTIVES

- Incorporate new therapeutic strategies into the best-practice management of Hodgkin lymphoma.
- 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.
- Recall potentially practice-changing clinical research on the care of patients with newly diagnosed and relapsed/refractory acute myeloid leukemias.
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors and protein translation inhibitors as therapeutic options for patients with chronic myeloid leukemia.
- Appropriately incorporate ruxolitinib into the treatment of JAK2 mutation-positive or mutation-negative myelofibrosis, with consideration of dosing based on platelet counts.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under investigation for indolent and aggressive B-cell non-Hodgkin lymphomas.

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EDITOR

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INTERVIEW

Craig Moskowitz, MD

Dr Moskowitz is Clinical Director of the Division of Hematologic Oncology at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Medical College of Cornell University in New York, New York.

Tracks 1-16

Select Excerpts from the Interview

Track 4

DR LOVE: In what settings do you administer brentuximab vedotin for Hodgkin lymphoma (HL) in your own practice?

DR MOSKOWITZ: I use it as the label directs. I administer brentuximab vedotin for patients with HL after failure of autologous stem cell transplant, but I also use it for patients who are ineligible for transplant. This agent can be administered on first relapse. Some clinicians believe they need to administer multiagent chemotherapy to these patients, but brentuximab vedotin is approved for patients who are in first relapse

and ineligible for transplant. It is my belief that brentuximab vedotin also will be approved within the next year as part of salvage treatment for HL.

We recently reported data from a Phase II trial of PET-adapted sequential therapy with brentuximab vedotin and augmented ICE for patients with relapsed/refractory HL. Only about a third of patients achieved a PET-negative state with brentuximab vedotin alone, but the sequential treatment has been remarkable — approximately 85% of patients were in remission at the time of transplant with little toxicity (Moskowitz 2013).

Tracks 10, 13

DR LOVE: The novel B-cell receptor inhibitors ibrutinib and idelalisib are being studied in chronic lymphocytic leukemia (CLL), but what has been presented with these agents recently in indolent non-Hodgkin lymphoma (NHL)?

DR MOSKOWITZ: Idelalisib seems to be an active agent in follicular lymphoma (FL) based on data presented at ASCO 2013, and I am convinced that it will be approved in FL (Leonard 2013; [1.1]). Idelalisib causes liver function test abnormalities, which has been a bit of a problem on study because the drug must be held if patients experience Grade 3 AST or ALT abnormalities. I've observed few side effects with ibrutinib, although it can cause some diarrhea.

DR LOVE: A number of reports have come out recently evaluating these 2 agents in combination with various regimens. What's your global take on this approach?

DR MOSKOWITZ: You can imagine that the addition of a novel agent to rituximab would not be all that great for patients with heavily pretreated, rituximab-refractory NHL, but it's critical to see those results to make sure that additive toxicity doesn't occur because these agents will be moved up in the armamentarium and combined with an anti-CD20 antibody (Younes 2013; [1.2]).

With regard to diffuse large B-cell lymphoma (DLBCL), it is interesting that ibrutinib has selective activity in the activated B-cell (ABC) subtype. A Phase I/II study we participated in reported a 41% response rate to single-agent ibrutinib in patients with the ABC subtype of DLBCL but little to no activity in any of the other subtypes (deVos 2013). A large Phase III study of R-CHOP with or without ibrutinib for patients with the ABC subtype of DLBCL has been initiated (NCT01855750).

1.1 **Phase I Study of Idelalisib with Rituximab (R) and/or Bendamustine (B) in Previously Treated Indolent Non-Hodgkin Lymphoma**

	Idelalisib + R (n = 32)	Idelalisib + B (n = 33)	Idelalisib + BR (n = 14)	Idelalisib + all combinations (n = 79)
Overall response rate	72%	85%	71%	78%

For all cohorts, select Grade 3 or higher adverse events included pneumonia (15%), diarrhea (8%), rash (8%), fatigue (4%) and pyrexia (3%). Idelalisib was generally well tolerated in combination therapy for a period of 2.5 years.

Leonard J et al. *Proc ASCO* 2013;**Abstract 8500**.

1.2

Phase Ib Study of Ibrutinib with R-CHOP for Patients with Treatment-Naïve, CD20-Positive B-Cell Non-Hodgkin Lymphoma

	Ibrutinib + R-CHOP (n = 15)
Overall response rate	100%

Dose expansion study: 280 mg (n = 6), 420 mg (n = 4), 560 mg (n = 5) in patients with diffuse large B-cell lymphoma (n = 7), follicular lymphoma (n = 3) and mantle-cell lymphoma (n = 5)

Younes A et al. *Proc ASCO* 2013;**Abstract 8502**.

Track 11

DR LOVE: What are your thoughts on the new data being reported on the efficacy of the anti-CD20 antibody obinutuzumab in CLL?

DR MOSKOWITZ: Stage I results from the Phase III CLL11 study were presented at ASCO 2013. The study evaluated chlorambucil alone versus chlorambucil with either rituximab or obinutuzumab. Both anti-CD20 antibody-containing arms were superior to chlorambucil alone, and that arm was closed (Goede 2013; [1.3]). The investigators are now expanding the remaining 2 cohorts of patients to ascertain which of the remaining treatments is superior. If the obinutuzumab arm is superior, that could lead to approval of this agent in CLL. (Editor's note: Subsequent to this interview additional important findings from this study were reported in a press release [1.3]). ■

1.3

Stage I Results from the Phase III CLL11 Trial of Obinutuzumab (GA101) with Chlorambucil (Clb) or Rituximab (R) with Clb versus Clb Alone in Previously Untreated Chronic Lymphocytic Leukemia

	Stage Ia		Stage Ib	
Efficacy[1]	GA101 + Clb	Clb	R + Clb	Clb
Overall response rate (n = 212, 106, 217, 110)	75.5%	30.2%	65.9%	30.0%
Median progression-free survival (n = 238, 118, 233, 118)	23.0 mo	10.9 mo	15.7 mo	10.8 mo
	HR = 0.14; $p < 0.0001$		HR = 0.32; $p < 0.0001$	

Press release (July 24, 2013): At a preplanned interim analysis, an independent data monitoring committee determined that the study met its primary endpoint, showing that GA101 with chlorambucil helped people live significantly longer without their disease worsening (progression-free survival) compared to rituximab with chlorambucil. Final data from the CLL11 study will be submitted to the American Society of Hematology's 55th Annual Meeting in December 2013.[2]

[1] Goede V et al. *Proc ASCO* 2013;**Abstract 7004**; [2] Available at: **http://www.roche.com/media/media_releases/med-cor-2013-07-24.htm**.

SELECT PUBLICATIONS

DeVos S et al. **The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the activated B cell-like (ABC) subtype of relapsed/refractory (R/R) DLBCL: Interim Phase 2 results.** *Proc EHA* 2013;**Abstract S1180**.

Moskowitz AJ et al. **PET-adapted sequential therapy with brentuximab vedotin and augmented-ICE induces FDG-PET normalization in 92% of patients with relapsed and refractory Hodgkin lymphoma.** *Proc ICML* 2013;**Abstract 141**.

INTERVIEW

Nikhil C Munshi, MD

Dr Munshi is Associate Professor of Medicine at Harvard Medical School and Associate Director at Dana-Farber Cancer Institute's Jerome Lipper Multiple Myeloma Center in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 5, 12

DR LOVE: Would you discuss the existing data on the use of carfilzomib or pomalidomide up front and any thoughts you have about ongoing trials evaluating these agents?

DR MUNSHI: Data with the combination of carfilzomib, lenalidomide and low-dose dexamethasone for newly diagnosed multiple myeloma are excellent. Patients experience rapid responses with this 3-drug combination (Jakubowiak 2012; [2.1, 2.2]). I

2.1

Phase I/II Trial of Carfilzomib in Combination with Lenalidomide and Low-Dose Dexamethasone as Front-Line Therapy for Transplant-Eligible and Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Parameter	≥PR	≥VGPR	≥nCR	sCR
All patients (n = 53)	98%	81%	62%	42%
Treatment duration				
≥4 cycles (n = 49)	100%	88%	67%	45%
≥8 cycles (n = 36)	100%	92%	78%	61%
≥12 cycles (n = 29)	100%	86%	72%	62%
Cytogenetics*				
Normal/favorable (n = 34)	100%	76%	59%	38%
Unfavorable (n = 17)	94%	76%	65%	53%

* Unfavorable: Del(13) by metaphase, hypodiploidy, t(4;14), t(14;16) or del(17p); normal/favorable: All others
PR = partial response; VGPR = very good PR; nCR = near complete response; sCR = stringent complete response

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

2.2

Select Adverse Events During Induction with Carfilzomib/Lenalidomide/ Low-Dose Dexamethasone in Patients with Multiple Myeloma

Adverse events (n = 53)	Any grade	Grade 3 or 4
Nonhematologic		
Hyperglycemia	72%	23%
Hypophosphatemia	45%	25%
Fatigue	38%	2%
Muscle cramping	32%	0%
Peripheral neuropathy	23%	0%
Hematologic		
Thrombocytopenia	68%	17%
Anemia	60%	21%
Neutropenia	30%	17%

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

would especially consider administering carfilzomib up front for a patient with significant preexisting neuropathy of an extent prohibiting bortezomib.

Pomalidomide is also a powerful and active agent, but we have fewer data with that agent in the newly diagnosed setting. We do not yet have enough data for me to say that I would administer it in the front-line setting. The fact that pomalidomide works when lenalidomide has stopped working (San Miguel 2013; [2.3]) tells us that it has different, if not better, activity compared to lenalidomide. In terms of the chemical structure, pomalidomide is like a combination of thalidomide and lenalidomide. I would predict that at some point studies will be conducted and pomalidomide will be used in the newly diagnosed setting.

DR LOVE: How do you choose between carfilzomib and pomalidomide in the relapsed or refractory setting?

DR MUNSHI: For patients with mild neuropathy carfilzomib is not much of a problem, but because it's a proteasome inhibitor I lean more toward pomalidomide in that

setting. For disease initially responsive to lenalidomide, I would administer pomalidomide if lenalidomide had been stopped without disease progression for about 6 months, although that's arbitrary. If the patient experienced relapse while receiving lenalidomide maintenance therapy, I would administer carfilzomib and save pomalidomide for the next relapse.

2.3

MM-003 Study: Pomalidomide (POM) and Low-Dose Dexamethasone (LoDEX) in Patients with Relapsed/Refractory Multiple Myeloma (MM)

Outcome	POM + LoDEX (n = 302)	HiDEX (n = 153)	HR	*p*-value
Intent-to-treat population				
Median PFS	4.0 mo	1.9 mo	0.48	<0.001
Median OS	12.7 mo	8.1 mo	0.74	0.028

	HR	
Subgroup (POM + LoDEX vs HiDEX)	**PFS**	**OS**
Lenalidomide- and bortezomib-refractory MM (n = 225, 113)	0.52	0.77
Lenalidomide as last prior treatment (n = 85, 49)	0.38	0.53
Bortezomib as last prior treatment (n = 132, 66)	0.52	0.87

HR <1.0 favors POM + LoDEX
HiDEX = high-dose dexamethasone; HR = hazard ratio; PFS = progression-free survival; OS = overall survival

San Miguel JF et al. *Proc ASCO* 2013;**Abstract 8510**.

Track 6

DR LOVE: What kind of cytogenetic findings affect your treatment approach in the up-front setting? Do you change the type of induction therapy you use?

DR MUNSHI: Up front, cytogenetics change little. RVD works in either setting. Bortezomib can overcome t(4;14), and lenalidomide has similar activity. However, consolidation and maintenance therapy may be affected.

For example, for a patient with a 17p deletion who would otherwise have a poor prognosis, and to some extent for patients with t(4;14) or t(4;16), we need more intensive treatment. They would benefit from consolidation therapy and potentially a 2-drug maintenance regimen such as lenalidomide and bortezomib for a longer period. More importantly, younger patients should be considered for possible allogeneic transplant because their outcome could be quite poor. Another complicating issue is that the 17p deletion in a few cells may not mean much. Data from France indicated that when 60% of cells contain 17p, a poor prognosis is connoted and one should consider a more aggressive intervention moving forward (Avet-Loiseau 2007). ■

SELECT PUBLICATIONS

Avet-Loiseau H et al. **Genetic abnormalities and survival in multiple myeloma: The experience of the Intergroupe Francophone du Myelome.** *Blood* 2007;109(8):3489-95.

San Miguel JF et al. **MM-003: A phase III, multicenter, randomized, open-label study of pomalidomide (POM) plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).** *Proc ASCO* 2013;**Abstract 8510**.

INTERVIEW

John O Mascarenhas, MD

Dr Mascarenhas is affiliated with the Myeloproliferative Disorders Research Consortium and the Mount Sinai School of Medicine Tisch Cancer Institute in New York, New York.

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Select Excerpts from the Interview

Tracks 3, 6-7, 10, 12

DR LOVE: Would you discuss the efficacy of JAK inhibitors, especially ruxolitinib, in patients with myelofibrosis (MF) with and without JAK mutations?

DR MASCARENHAS: It was initially thought that only patients with JAK mutations would benefit from JAK inhibitors. That turned out not to be the case. All patients with MF have heightened expression of the JAK-STAT signaling pathway within their hematopoietic system. The JAK2 V617F mutation is only one factor that can lead to upregulation of this pathway. It's because of the heightened activity of this pathway that the JAK1/2 inhibitor ruxolitinib in particular has been successful in the treatment of MF, irrespective of V617F mutational status.

DR LOVE: How do you decide whether to administer ruxolitinib?

DR MASCARENHAS: The commercial availability of ruxolitinib has changed the treatment landscape. Ruxolitinib is effective in palliating symptoms and reducing splenomegaly, and some evidence indicates that prolonged therapy for 24 to 48 months may

lead to the retardation of fibrosis in the marrow. That's an interesting finding with compelling implications. Despite the fact that the COMFORT-I and II trials were for intermediate- and high-risk MF (Verstovsek 2012; Cervantes 2012), I believe that patients with symptomatic low-risk MF can benefit from ruxolitinib. For patients with platelet counts lower than 50 x 10^9/L or those with transfusion-dependent anemia, ruxolitinib is not an option.

DR LOVE: Do you base your treatment decision-making about ruxolitinib mainly on disease symptomatology?

DR MASCARENHAS: I consider the bigger picture. It is not known whether a patient with low-risk MF who has a large spleen but otherwise feels well will benefit in the long term from ruxolitinib. I don't administer ruxolitinib to such patients, but I'm not necessarily opposed to it.

DR LOVE: What are your treatment considerations for patients with intermediate- or high-risk MF?

DR MASCARENHAS: Patients with intermediate- or high-risk MF do not necessarily need to have symptoms to be eligible for ruxolitinib. Although longer-term follow-up and more studies are needed, the evidence thus far from the COMFORT-I and II studies of a modest but statistically significant improvement in overall survival suggests that symptoms alone should not be the trigger for ruxolitinib therapy for these patients.

DR LOVE: How do you dose ruxolitinib in patients with thrombocytopenia?

DR MASCARENHAS: It's well established from the COMFORT-I and II studies that patients with platelet counts greater than 100 x 10^9/L can receive ruxolitinib. Based on data presented from Study 258, it is also possible to treat patients with platelet counts of 50 to 100 x 10^9/L (Talpaz 2012; [3.1]). My recommendation is to start low and titrate upward. I wouldn't recommend ruxolitinib at a platelet count lower than 50 x 10^9/L.

With a platelet count of 50 to 100 x 10^9/L, I start at 5 mg BID and slowly increase that on a monthly basis. At times, I titrate up so that the patient receives 5 mg in the morning and 10 mg in the evening. I adopt a stepwise and careful approach. With platelet counts of 100 to 150 x 10^9/L, I tend to use 10 mg BID. I follow these patients weekly for the first 1 to 2 months to avoid abrupt cessation of the agent.

3.1

Efficacy of Titrated Low-Dose Ruxolitinib (Rux) in Patients with Low Platelet Counts (Study 258) versus Efficacy at Full Dose (COMFORT-I Study)

	Study 258	COMFORT-I study	
Efficacy parameter	Titrated low-dose rux (n = 22)	Rux (n = 155)	Placebo (n = 154)
≥50% reduction in total symptom score	36.4%	45.9%	5.3%
≥35% reduction in spleen volume	33.3%	41.9%	0.7%

For patients with baseline platelet counts of 50 to 100 × 10^9/L, starting rux at a dose of 5 mg BID and titrating to 10 mg BID or greater resulted in spleen volume reductions and improvements in symptoms and quality of life that were consistent with those seen in the COMFORT-I study.

Talpaz M et al. *Proc ASH* 2012;**Abstract 176**.

DR LOVE: What about the issue of cytopenias and ruxolitinib, particularly anemia? Does the presence or absence of anemia influence your starting dose?

DR MASCARENHAS: It is important for patients who are transfusion independent at baseline and their family members to understand that, although ruxolitinib effectively addresses symptoms and reduces spleen size, it can cause anemia. This is usually predictable and occurs within 3 months. One needs to weigh the quality-of-life aspect of blood transfusions versus symptom improvement. For most patients, the odds are in favor of remaining on the drug, especially after they start ruxolitinib and are feeling better.

DR LOVE: Would you discuss the withdrawal symptoms that can be associated with sudden discontinuation of ruxolitinib and how you approach stopping therapy?

DR MASCARENHAS: This has been an area of controversy. In the COMFORT-I and II studies, symptoms returned to baseline within 7 to 10 days of stopping. This was predictable. A single-institution study reported that patients who stopped treatment abruptly developed withdrawal syndrome, which in one case was a sepsis-like state (Tefferi 2011; [3.2]). In my experience, symptoms rebound. My practice is to try to taper treatment when I can. If I have to stop abruptly, I almost always use a prednisone taper to blunt the return of symptoms. ■

3.2

Serious Adverse Events During Ruxolitinib Therapy Discontinuation in Patients with Myelofibrosis (MF)

- This report discussed the occurrence of sometimes severe withdrawal symptoms during ruxolitinib discontinuation and described the details of these events in 5 severely affected cases among 47 Mayo Clinic patients with MF in whom ruxolitinib therapy had been discontinued.
- This "ruxolitinib withdrawal syndrome" was characterized by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias and occasional hemodynamic decompensation, including a septic shock-like syndrome.
- It is speculated that the underlying mechanism for "ruxolitinib withdrawal syndrome" involves rapid changes in inflammatory cytokine activity, but such challenges do not necessarily undermine the benefit of ruxolitinib in a select patient group with advanced MF, including those with severe constitutional symptoms, profound cachexia and symptomatic splenomegaly.

"Our experience calls for full disclosure of the ruxolitinib withdrawal syndrome to patients with MF before initiating ruxolitinib therapy, and treatment discontinuation must be done under close physician supervision and preferably in a tapering schedule."

Tefferi A et al. *Mayo Clin Proc* 2011;86(12):1188-91.

SELECT PUBLICATIONS

Cervantes F et al. **Long-term safety, efficacy, and survival findings from COMFORT-II, a Phase 3 study comparing ruxolitinib with best available therapy (BAT) for the treatment of myelofibrosis (MF).** *Proc ASH* 2012;**Abstract 801**.

Mascarenhas J, Hoffman R. **A comprehensive review and analysis of the effect of ruxolitinib therapy on the survival of patients with myelofibrosis.** *Blood* 2013;121(24):4832-7.

Talpaz M et al. **Efficacy, hematologic effects, and dose of ruxolitinib in myelofibrosis patients with low starting platelet counts (50-100 x 10^9/L): A comparison to patients with normal or high starting platelet counts.** *Proc ASH* 2012;**Abstract 176**.

Tefferi A, Pardanani A. **Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis.** *Mayo Clin Proc* 2011;86(12):1188-91.

Verstovsek S et al. **Long-term outcome of ruxolitinib treatment in patients with myelofibrosis: Durable reductions in spleen volume, improvements in quality of life, and overall survival advantage in COMFORT-I.** *Proc ASH* 2012;**Abstract 800**.

INTERVIEW

B Douglas Smith, MD

Dr Smith is Associate Professor of Oncology in the Division of Hematologic Malignancies at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

Tracks 1-15

Track 1 Recent advances in the treatment of acute myeloid leukemia (AML)

Track 2 Activity and tolerability of the polo-like kinase (Plk) inhibitor volasertib (BI 6727) with low-dose cytarabine in relapsed/refractory AML

Track 3 Expanded indications for allogeneic stem cell transplant in AML

Track 4 Mechanism of action and integration of the newly FDA-approved agent omacetaxine into clinical practice for patients with chronic myeloid leukemia (CML) and its potential use in AML

Track 5 Alternative treatment algorithms for older patients with AML

Track 6 Current clinical management of myelodysplastic syndrome

Track 7 Effectiveness of first-generation (imatinib) and second-generation (nilotinib and dasatinib) tyrosine kinase inhibitors (TKIs) in CML

Track 8 Monitoring responses in patients with CML receiving imatinib

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Track 10 Mechanism of action of ponatinib

Track 11 Use of omacetaxine for patients with chronic- and accelerated-phase CML

Track 12 **Case discussion:** A 28-year-old patient with CML who attained a complete molecular remission on imatinib wishes to become pregnant

Track 13 **Case discussion:** A 62-year-old patient who initially received dasatinib but is switched to alternate TKI therapy after experiencing bilateral pleural effusions

Track 14 Treatment and outcome with acute promyelocytic leukemia (APL)

Track 15 Results from the Phase III APL0406 trial of all-trans retinoic acid (ATRA) and arsenic trioxide versus ATRA and idarubicin for newly diagnosed, nonhigh-risk APL

Select Excerpts from the Interview

Tracks 2, 5

DR LOVE: Would you talk about recent developments in salvage approaches for acute myeloid leukemia (AML), including the role of new agents?

DR SMITH: Two "holy grails" persist in AML therapy. One is the treatment of AML in older patients, and the second is treatment of relapsed AML or salvage-based treatment. A few years back there was a large push toward using epigenetic-modifying agents like 5-azacitidine or decitabine as primary therapy for older patients, whose acute leukemia was likely to have arisen from myelodysplastic syndromes (MDS), for which these drugs were originally approved. The idea was that you might induce bone marrow stability

and possibly even complete remission in a proportion of patients despite the fact that those patients had AML and not simply MDS.

Some patients clearly benefit from azacitidine and decitabine in this setting. The problem is that these are not typically long-term therapies for most patients, so an effort has been made to combine other agents with azacitidine and decitabine to try to make them more effective.

One such study combined lenalidomide, an agent already approved for treatment of MDS, with 5-azacitidine as induction therapy for high-risk MDS or for AML in older patients. That combination appears to be effective (Pollyea 2013). If we can get more patients into remission and keep them there longer, that would be an exciting combination, provided it's reasonably well tolerated. And all the preliminary data suggest that it is reasonably well tolerated.

DR LOVE: Would you also discuss the study presented at ASH 2012 of volasertib in combination with low-dose cytarabine for patients with untreated AML ineligible for intensive treatment?

DR SMITH: Volasertib is an inhibitor of polo-like kinase, an enzyme that regulates cell division. Blocking this enzyme is thought to enhance cell death in the tumor. The results of the Phase II study comparing volasertib in combination with low-dose cytarabine to cytarabine alone reported that the addition of volasertib to cytarabine resulted in higher response rates but more toxicity (Maertens 2012; [4.1]). This highlights one of the challenges of developing new drugs for AML.

4.1

Randomized Phase II Study of Volasertib (V) (BI 6727) in Combination with Low-Dose Cytarabine (LDAC) versus LDAC Monotherapy for Patients with Previously Untreated Acute Myeloid Leukemia Ineligible for Intensive Treatment

	V + LDAC (n = 42)	LDAC (n = 45)	HR	*p*-value
Objective response rate	31%	13%	NR	0.0523
Median event-free survival	170 days	69 days	0.56	0.0237

"More pts who received V + LDAC experienced ≥grade 3 AEs than those who received LDAC (95.2% vs 68.9%), particularly blood and lymphatic system disorders (81.0% vs 44.4%), gastrointestinal disorders (21.4% vs 6.7%), and infections and infestations (45.2% vs 22.2%)."

HR = hazard ratio; NR = not reported

Maertens J et al. *Proc ASH* 2012;**Abstract 411**.

Tracks 4, 11

DR LOVE: What are your thoughts about the use of omacetaxine for the treatment of chronic myeloid leukemia (CML) or AML?

DR SMITH: Omacetaxine acts by blocking the translation of proteins like BCR-ABL, which is important in the development of CML. It has an important inhibitory effect in cells that are dependent on abnormal tyrosine kinase activity. One of the fascinating aspects of this agent is its ability to inhibit leukemia stem cells, which are responsible for initiation and maintenance of the disease.

Omacetaxine has been approved for the treatment of multiple tyrosine kinase inhibitor (TKI)-resistant CML but may also have potential in AML to minimize the risk of relapse or improve responses in high-risk groups. For patients with CML or AML who have minimal residual disease resistant to primary therapy, it may be possible to eradicate the disease with the addition of omacetaxine. This is particularly appealing in CML because you can get patients to a stage at which the disease is undetectable by polymerase chain reaction (PCR) with TKI therapy and potentially cure them with omacetaxine.

I have used omacetaxine to treat multiple TKI-resistant CML. It is administered twice daily for 2 weeks for induction, followed by maintenance or consolidation therapy. We have seen success with this agent, and it has enabled patients to reach a stage at which they can be evaluated for a transplant.

Track 15

DR LOVE: Would you talk about the Phase III study of all-trans retinoic acid (ATRA) with arsenic trioxide compared to ATRA with chemotherapy for patients with low- to intermediate-risk acute promyelocytic leukemia (APL)?

DR SMITH: This was an interesting study comparing induction and consolidation using a nonchemotherapy regimen with ATRA and arsenic trioxide to an ATRA/idarubicin-based therapy referred to as AIDA for patients with nonhigh-risk APL (Lo-Coco 2013; [4.2]). An analysis of the primary endpoint, event-free survival at 2 years, demonstrated that the nonchemotherapy arm was not inferior to the traditional chemotherapy arm. Also, fewer deaths and less toxicity occurred in the nonchemotherapy group. It may be that with longer follow-up even more of a benefit is observed on the nonchemotherapy arm. Many academic centers and cooperative groups are now interested in incorporating a nonchemotherapy treatment arm for patients with low-risk APL. ■

4.2

Phase III Study of ATRA with Arsenic Trioxide (ATO) versus ATRA with Idarubicin (AIDA) for Patients with Low- to Intermediate-Risk Acute Promyelocytic Leukemia

	ATRA/ATO (n = 77)	AIDA (n = 79)	*p*-value
Two-year event-free survival	97%	86%	<0.001*
Two-year overall survival	99%	91%	0.02

* For noninferiority; $p = 0.02$ for superiority of ATRA/ATO

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

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

SELECT PUBLICATIONS

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

Larson RA et al. **Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up.** *Leukemia* 2012;26(10):2197-203.

Pollyea DA et al. **Sequential azacitidine plus lenalidomide combination for elderly patients with untreated acute myeloid leukemia.** *Haematologica* 2013;98(4):591-6.

INTERVIEW

Nathan H Fowler, MD

Dr Fowler is Co-Director of Clinical and Translational Research in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-14

Track 1 Mechanism of action of lenalidomide and synergy with rituximab in lymphoma

Track 2 Mechanism of action of the type II anti-CD20 monoclonal antibody obinutuzumab

Track 3 Development of the R^2 regimen of lenalidomide/rituximab in indolent lymphoma or MCL

Track 4 RELEVANCE: A Phase III trial of R^2 versus rituximab-based chemotherapy → rituximab maintenance for previously untreated FL

Track 5 Results from the StiL NHL 1-2003 and BRIGHT studies of BR in previously untreated indolent or mantle-cell lymphomas

Track 6 Activity of R^2 in indolent lymphomas and CLL

Track 7 Clinical experience with lenalidomide for B-cell lymphomas

Track 8 Activity of the BTK inhibitor ibrutinib and the PI3K delta inhibitor idelalisib in B-cell NHL

Track 9 Rasburicase for tumor lysis syndrome and tumor flare in aggressive lymphomas and CLL

Track 10 **Case discussion:** A 52-year-old patient with composite FL (80% Grade I/II, 20% Grade IIIb) achieves a complete remission with R-CHOP

Track 11 **Case discussion:** An 81-year-old patient with asymptomatic Grade I/II FL initially undergoes observation

Track 12 **Case discussion:** A 62-year-old patient who received BR 5 years ago for Stage III FL presents with recurrent disease in the neck and groin

Track 13 Criteria for assessing risk in patients with MCL

Track 14 Use of endoscopy to assess response in the colon in patients with MCL

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you discuss the background for the study of the lenalidomide/rituximab (R^2) regimen for indolent lymphomas?

DR FOWLER: Initially we launched a pilot study of the R^2 regimen based on results from studies in mantle-cell lymphoma (MCL) cell lines and mouse models showing that it produced better results than either agent alone. This pilot study was for 30 patients with treatment-naïve indolent lymphomas.

Early on we observed a strong signal in FL. In fact, when we first presented the data about 3 years ago, the complete response rate for FL was 100%. So the study was expanded to enroll about 110 patients, especially those with FL (Fowler 2012; [5.1]), and in this population the complete response rate for patients with FL was 87%.

5.1

Efficacy and Safety Results of the Phase II Trial of Lenalidomide and Rituximab for Patients with Untreated Indolent Lymphomas

Efficacy	FL (n = 46)	SLL (n = 30)	MZL (n = 27)	All patients (n = 103)
Overall response rate	98%	80%	89%	90%
CR/CRu	87%	27%	67%	64%
PR	11%	53%	22%	26%
Stable disease	2%	13%	11%	8%
Progressive disease	0%	7%	0%	2%
Two-year PFS*	89%	NR	NR	83%
Safety	**All patients**			
Neutropenia	40%			
Thrombocytopenia	6%			

FL = follicular lymphoma; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; CR = complete response; CRu = unconfirmed CR; PR = partial response; PFS = progression-free survival; NR = not reported

* Median follow-up of 22 months

Fowler N et al. *Proc ASH* 2012;**Abstract 901**.

That was the basis for the ongoing Phase III RELEVANCE trial for patients with previously untreated FL (NCT01650701). Patients are randomly assigned to receive R[2] or rituximab/chemotherapy, including R-CHOP, R-CVP or rituximab/bendamustine (BR), followed by rituximab maintenance therapy. We hope that biologic treatment with an immune-modulated antibody will produce better results than any of the 3 common choices of standard chemotherapy.

Track 5

DR LOVE: In general practice, what is the most commonly used first-line rituximab-based chemotherapy regimen outside of a trial setting?

DR FOWLER: The results of the randomized STiL trial for patients with newly diagnosed low-grade NHL or MCL demonstrated a dramatically longer progression-free survival and less myelosuppression with BR than with R-CHOP (Rummel 2013; [5.2]). We've seen a rapid paradigm shift in the way newly diagnosed FL is treated. Based on my experience with patients referred from community oncologists and in the practices of my colleagues, I believe BR has replaced R-CHOP as the new standard for indolent disease.

It is important to clarify whether the disease has undergone transformation or if it has any Grade III components, in which case I treat with R-CHOP. I believe that for higher-grade lymphomas BR is equivalent to R-CHOP, although we don't have enough data to support this.

DR LOVE: What is your view on the preliminary results of the BRIGHT trial of BR presented at ASH 2012 (Flinn 2012; [5.2])?

DR FOWLER: We don't have the progression-free survival data from the BRIGHT study yet. From the preliminary results, BR appears to be similar in efficacy to

5.2

Phase III Study Results with Bendamustine/Rituximab (BR) versus Standard First-Line Chemotherapy for Indolent and Mantle-Cell Lymphomas

	BRIGHT[1]		StiL NHL 1-2003[2]	
Efficacy	**BR** (n = 213)	**R-CHOP/R-CVP** (n = 206)	**BR** (n = 261)	**R-CHOP** (n = 253)
Overall response rate	94%	84%	93%	91%
Complete response rate (all)	31%	25%	40%	30%
	HR, 1.26; $p = 0.0225$*		$p = 0.021$	
Complete response rate (mantle-cell lymphoma)	51%	24%	Not reported (NR)	
	HR, 1.95; $p = 0.0180$†			
Median progression-free survival (all)	NR		69.5 mo	31.2 mo
			HR, 0.58; $p < 0.0001$	
Select adverse events	**BR** (n = 224)	**R-CHOP/R-CVP** (n = 223)	**BR** (n = 261)	**R-CHOP** (n = 253)
Nausea (any grade)	63%	48%	NR	NR
Fatigue (any grade)	51%	50%	NR	NR
Alopecia (any grade)	NR	NR	0%	100%
Neutropenia (Grade 3 or 4)	44%	70%	29%	69%
Lymphopenia (Grade 3 or 4)	62%	30%	74%	43%
Leukopenia (Grade 3 or 4)	38%	54%	37%	72%

* Test for noninferiority; † Test for superiority

HR = hazard ratio

[1] Flinn IW et al. *Proc ICML* 2013;**Abstract 084**; [2] Rummel MJ et al. *Lancet* 2013;381(9873):1203-10.

R-CHOP in terms of overall response rate and complete response rate in low-grade lymphomas, although in the STiL trial complete response rates were better with BR. The slight difference in the use of R-CVP or R-CHOP in the design of the BRIGHT trial may explain the slightly lower rate of complete responses observed. The preliminary BRIGHT results suggest that BR is noninferior to R-CHOP or R-CVP.

In my practice BR is generally better tolerated than R-CHOP — no question about it. Most of my patients receiving BR are young parents who are able to work full time. Unlike R-CHOP, not much toxicity occurs with BR. ■

SELECT PUBLICATIONS

Flinn IW et al. **An open-label, randomized study of bendamustine and rituximab (BR) compared with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in first-line treatment of patients with advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL): The Bright study.** *Proc ASH* 2012;**Abstract 902**.

Fowler N et al. **Lenalidomide and rituximab for untreated indolent lymphoma: Final results of a phase II study.** *Proc ASH* 2012;**Abstract 901**.

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.

Rummel MJ et al. **Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas — Final results of the randomized Phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2010;**Abstract 856**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a Phase II trial of R² for patients with treatment-naïve indolent lymphomas, the complete response rate was _____ for patients with FL.**
   a. Higher than 85%
   b. 0%
   c. 50%

2. **In a Phase I/II trial, carfilzomib in combination with lenalidomide and low-dose dexamethasone as front-line therapy for patients with newly diagnosed multiple myeloma generated high response rates but was associated with which of the following side effects?**
   a. Hyperglycemia
   b. Fatigue
   c. Muscle cramping
   d. Thrombocytopenia
   e. All of the above

3. **Results from the Phase III CLL11 trial, which is evaluating obinutuzumab with chlorambucil or rituximab with chlorambucil for patients with previously untreated CLL, reported superior overall response rate and progression-free survival in both anti-CD20 antibody-containing arms versus chlorambucil alone.**
   a. True
   b. False

4. **A Phase II study of volasertib in combination with low-dose cytarabine versus low-dose cytarabine alone for patients with previously untreated AML demonstrated greater efficacy and more toxicity with the addition of volasertib.**
   a. True
   b. False

5. **The Phase III RELEVANCE trial is evaluating _____ versus rituximab in combination with standard chemotherapy followed by rituximab maintenance therapy for patients with previously untreated FL.**
   a. R²
   b. BR
   c. Both a and b

6. **Results from the Phase III BRIGHT trial demonstrated that _____ was noninferior to R-CHOP or R-CVP for patients with previously untreated indolent NHL or MCL.**
   a. BR
   b. Lenalidomide
   c. R²

7. **The Phase III MM-003 trial for patients with relapsed or refractory MM reported a statistically significant improvement in _____ with pomalidomide and low-dose dexamethasone compared to high-dose dexamethasone alone in the intent-to-treat population.**
   a. Median progression-free survival
   b. Median overall survival
   c. Both a and b

8. **Which of the following statements is true according to the Mayo Clinic report on 5 patients with MF who experienced serious adverse events during ruxolitinib therapy discontinuation?**
   a. Ruxolitinib withdrawal syndrome was characterized by acute relapse of disease symptoms, accelerated splenomegaly and worsening of cytopenias
   b. Ruxolitinib withdrawal syndrome was characterized by occasional hemodynamic decompensation, including a septic shock-like syndrome
   c. Ruxolitinib therapy discontinuation must be performed under close physician supervision and preferably in a tapering manner
   d. All of the above

9. **A study by Talpaz and colleagues demonstrated that for patients with baseline platelet counts of 50 to 100 x 10^9/L, starting ruxolitinib at 5 mg BID and titrating to 10 mg BID or higher resulted in _____.**
   a. Spleen volume reductions
   b. Improvements in symptoms and quality of life
   c. No improvement in spleen volume
   d. Both a and b

10. **A Phase III study of ATRA with arsenic trioxide versus ATRA with idarubicin (AIDA) for patients with low- to intermediate-risk APL demonstrated that _____.**
    a. The ATRA/arsenic trioxide regimen was not inferior to the AIDA regimen in the analysis of 2-year event-free survival
    b. Overall survival was higher on the ATRA/arsenic trioxide arm than on the AIDA arm
    c. Both a and b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2013

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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
Novel agents under investigation for the treatment of AML (omacetaxine, volasertib [BI 6727]) and NHL/CLL (ibrutinib, idelalisib)	4 3 2 1	4 3 2 1
Clinical trial results with and ongoing studies of the R^2 regimen of lenalidomide/rituximab for indolent lymphomas	4 3 2 1	4 3 2 1
Long-term efficacy and safety data — StiL and BRIGHT trials — with BR for the treatment of newly diagnosed indolent lymphomas	4 3 2 1	4 3 2 1
Ongoing trials evaluating brentuximab vedotin-based therapies in HL	4 3 2 1	4 3 2 1
Serious adverse events during ruxolitinib treatment discontinuation in patients with MF	4 3 2 1	4 3 2 1

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.....

.....

.....

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

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- Incorporate new therapeutic strategies into the best-practice management of Hodgkin 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 and maintenance treatment strategies for patients with multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Recall potentially practice-changing clinical research on the care of patients with newly diagnosed and relapsed/refractory acute myeloid leukemias. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors and protein translation inhibitors as therapeutic options for patients with chronic myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Appropriately incorporate ruxolitinib into the treatment of JAK2 mutation-positive or mutation-negative myelofibrosis, with consideration of dosing based on platelet counts. . . . 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 investigation for indolent and aggressive B-cell non-Hodgkin lymphomas. . . . . 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:

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Nikhil C Munshi, MD	4 3 2 1	4 3 2 1
John O Mascarenhas, MD	4 3 2 1	4 3 2 1
B Douglas Smith, MD	4 3 2 1	4 3 2 1
Nathan H Fowler, 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:

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