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Hematologic Oncology™ UPDATE

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

FACULTY INTERVIEWS

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Hagop M Kantarjian, MD
Ian W Flinn, MD, PhD
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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.
- 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 evaluation for indolent and aggressive B-cell non-Hodgkin lymphomas.

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EDITOR

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INTERVIEW

Sagar Lonial, MD

Dr Lonial is Professor, Vice Chair of Clinical Affairs and Director of Translational Research for the B-Cell Malignancy Program in the Department of Hematology and Medical Oncology at Emory University School of Medicine's Winship Cancer Institute in Atlanta, Georgia.

Tracks 1-15

Select Excerpts from the Interview

Track 7

DR LOVE: What is your treatment approach for older patients with newly diagnosed multiple myeloma (MM) who are not eligible for transplant?

DR LONIAL: This is an interesting area, and updated data were presented at ASH 2012 on a Phase III trial in this setting comparing bortezomib/melphalan/prednisone and thalidomide followed by bortezomib/thalidomide maintenance (VMPT-VT) to VMP with no maintenance. This trial previously reported a progression-free survival advantage with the 4-drug combination followed by maintenance (Palumbo 2010), but the updated data reported a survival advantage too (Palumbo 2012; [1.1]). This is interesting because I would attribute most of that survival benefit not to the 4-agent induction therapy but to the VT maintenance.

These results demonstrate that maintenance therapy plays an important role in older patients because these patients tend to be frail. They tend not to tolerate disease relapse well in the sense that their reserve may not be as great as that of a younger patient. So you want to maximize the duration of first response because you may not have the opportunity to re-treat when they experience relapse.

1.1

Overall Survival Benefit with Bortezomib/Melphalan/Prednisone/ Thalidomide → Maintenance Bortezomib/Thalidomide (VMPT-VT) versus VMP in Newly Diagnosed Multiple Myeloma

Outcome	VMPT-VT (n = 254)	VMP (n = 257)	Hazard ratio	*p*-value
Median PFS	35.3 mo	24.8 mo	0.58	<0.0001
Five-year PFS	29%	13%		
Median TTNT	46.6 mo	27.8 mo	0.52	<0.0001
Five-year TTNT	41%	19%		
Median OS	Not reached	60.6 mo	0.70	0.01
Five-year OS	61%	51%		

PFS = progression-free survival; TTNT = time to next treatment; OS = overall survival

Palumbo A et al. *Proc ASH* 2012;**Abstract 200**.

Track 8

DR LOVE: As we move forward with better tolerated therapies and schedules, such as carfilzomib and subcutaneous and weekly bortezomib, would you discuss where we're heading with regard to identifying the next generation of such therapies?

DR LONIAL: We took a step forward with carfilzomib, which can be administered for a longer period without interruptions because of a reduced risk of neuropathy. We now have another investigational agent in the form of the oral proteasome inhibitor ixazomib (MLN9708), which seems to have pharmacokinetics a bit different from those of bortezomib. The fact that it's an oral agent seems to reduce the risk of neuropathy significantly.

When ixazomib is combined with lenalidomide and dexamethasone, the response rates are impressive (Kumar 2012; [1.2]). I believe that oral proteasome inhibitors are exciting in that they minimize side effects and improve patient convenience.

Track 9

DR LOVE: Would you talk about the available data and your own clinical experience with carfilzomib in MM?

DR LONIAL: Carfilzomib was approved based on a Phase II multicenter trial for patients with heavily pretreated disease, most of whom were either resistant or intolerant to bortezomib and lenalidomide (Siegel 2012). The response rate was about 23%, and for the patients with truly double-refractory disease it was around 15% to 18%. We learned from this trial that when patients experienced a response, they could continue to receive carfilzomib for long periods and did not experience issues with neuropathy as is observed with bortezomib.

1.2

Results from a Phase I/II Study of Weekly Ixazomib (MLN9708) in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma

Efficacy	Phase I* (n = 15)	RP2D† (n = 52)	Total (n = 64)
Overall response rate	100%	90%	92%
Complete response	33%	23%	23%
TRAEs	**Phase I (n = 15)**	**RP2D (n = 53)**	**Total (n = 65)**
Any TRAE	100%	96%	97%
Any TRAE Grade ≥3	60%	51%	52%
Dose reduction due to AEs	53%	40%	43%
	Grade 1	**Grade 2**	**Grade 3**
Peripheral neuropathy	20%	9%	3%

RP2D = recommended Phase II dose; TRAE = treatment-related adverse event; AE = adverse event
* Dose cohorts: 1.68 mg/m^2, 2.23 mg/m^2, 2.97 mg/m^2, 3.95 mg/m^2
† 2.23 mg/m^2 converted to 4.0-mg fixed dose based on population pharmacokinetic analysis

Kumar SK et al. *Proc ASH* 2012;**Abstract 332**.

Another Phase II trial of single-agent carfilzomib for patients with bortezomib-naïve relapsed and/or refractory MM reported response rates comparable if not superior to those with bortezomib in a somewhat earlier relapse setting (Vij 2012). These results also support the fact that delivering carfilzomib for a longer duration allows for longer progression-free survival. Other recent data with carfilzomib for patients with newly diagnosed MM demonstrate that by maintaining the full dose and schedule or even increasing the dose to 36 mg/m^2 from 27 mg/m^2, which is the FDA label dose, you can improve depth of response and tolerability does not appear to suffer much.

DR LOVE: What information do we have about the use of up-front carfilzomib, lenalidomide and low-dose dexamethasone (CRd), for which data were recently presented at ASCO and subsequently published in *Blood* (Jakubowiak 2012)?

DR LONIAL: These data included high response rates and stringent complete response rates in excess of 60%. A smaller study from the NCI evaluating the CRd regimen for patients with newly diagnosed MM that was presented at ASH 2012 recapitulated these results by reporting high response rates, a particularly high complete response rate and exceedingly favorable tolerability (Korde 2012; [1.3]).

Track 11

DR LOVE: Given that the FDA recently granted accelerated approval to pomalidomide for patients with MM who have received at least 2 prior therapies, including lenalidomide and bortezomib, how have you integrated this agent into your practice?

DR LONIAL: Pomalidomide is a third-generation IMiD following thalidomide and lenalidomide, and in many ways it is the most potent because its dosing is much lower than its predecessors. About 1 in 3 patients with lenalidomide-refractory disease will experience a response to pomalidomide (Lacy 2011), so it is clearly an active agent. At

ASH 2012, a late-breaking abstract by Dr Dimopoulos reported on a European study of pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone alone for relapsed/refractory MM. The study reported high response rates and a large survival advantage with the combination (Dimopoulos 2012). Again, this speaks to the power of pomalidomide to overcome drug resistance.

For now, this is not an agent I would use in the up-front setting. I will administer pomalidomide in the relapsed setting, especially in patients with lenalidomide-resistant MM. Of course, we will see a push to move this agent earlier in the treatment algorithm. What I believe is unique about pomalidomide compared to lenalidomide or thalidomide is that it appears to have activity in high-risk MM, specifically deletion 17p and other high-risk categories, so this may be an interesting agent in the up-front setting for patients with high-risk disease. ■

1.3

Phase II Study of Carfilzomib with Lenalidomide and Low-Dose Dexamethasone (CRd) for Newly Diagnosed Multiple Myeloma

Efficacy	CRd (n = 28)
Stringent complete response	65%
Very good partial response	20%
Partial response	10%
Select Grade 3 and 4 toxicities	
Liver function tests elevation	20%
Fatigue	15%
Rash/pruritus	15%
Heart failure	10%
Lymphopenia	60%

Korde N et al. *Proc ASH* 2012;**Abstract 732**.

SELECT PUBLICATIONS

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

Lacy MQ et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease.** *Blood* 2011;118(11):2970-5.

Lonial S, Kaufman JL. **The era of combination therapy in myeloma.** *J Clin Oncol* 2012;30(20):2434-6.

Palumbo A et al. **Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial.** *J Clin Oncol* 2010;28(34):5101-9.

Richardson PG et al. **Bortezomib or high-dose dexamethasone for relapsed multiple myeloma.** *N Engl J Med* 2005;352(24):2487-98.

Siegel DS et al. **A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma.** *Blood* 2012;120(14):2817-25.

Vij R et al. **An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma.** *Blood* 2012;119(24):5661-70.

INTERVIEW

Hagop M Kantarjian, MD

Dr Kantarjian is Chairman and Professor in the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

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Track 1 Integration of newly approved therapeutic options into the treatment for chronic myeloid leukemia (CML)

Track 2 Monitoring patients with CML who have achieved a complete cytogenetic remission

Track 3 Activity and tolerability of ponatinib and bosutinib in patients with CML experiencing disease progression on front-line tyrosine kinase inhibitor (TKI) therapy

Track 4 Monitoring and treatment of TKI-associated side effects and complications

Track 5 Importance of patient compliance and close monitoring with TKI therapy

Track 6 Defining the goals of TKI treatment in CML

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Track 8 Administration route, clinical activity and tolerability of omacetaxine

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Track 18 Diagnosis and treatment for acute promyelocytic leukemia

Track 19 Therapeutic options for patients with acute myeloid leukemia and inversion of chromosome 16

Track 20 Clinical activity of the novel agents inotuzumab ozogamicin and blinatumomab in acute lymphoblastic leukemia (ALL)

Track 21 Responses to first- and second-generation TKIs in Philadelphia chromosome-positive ALL

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Select Excerpts from the Interview

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DR LOVE: How have you incorporated recently approved agents for chronic myeloid leukemia (CML) into your practice (Jain 2013; [2.1])?

2.1

Overview of Approved Agents in Chronic Myeloid Leukemia

Agent	Therapeutic targets	Recommended dose	Main side effects	Cautions
Imatinib	ABL, KIT, PDGFR, DDR1, NQO2	400 mg daily orally	Myelotoxicity, edema, rash, nausea, skin pigmentation, elevated liver enzymes, diarrhea, myalgia, headache	Pregnancy, severe CHF and prepubertal age group
Dasatinib	SRC family, PDGFR, KIT, EPHA2	100 mg daily with dose adjustments	Myelotoxicity, thrombocytopenia, pleural effusions, QT prolongation, low phosphate, diarrhea	Severe CHF, antiplatelet drugs and CYP3A4 inhibitors
Nilotinib	ABL, KIT, PDGFR, DDR1, NQO2, VEGF	300 mg twice a day (first line), 400 mg twice a day (second line)	Elevated liver/pancreatic enzymes and glucose, prolonged QTc, skin rash, myelotoxicity, diarrhea, myalgia, nausea	Long QT syndrome, hypokalemia and low magnesium, pancreatitis; administer on empty stomach
Bosutinib	ABL, SRC family	500 mg daily	Diarrhea, elevated liver enzymes, myelotoxicity, edema, nausea, rash	Hepatotoxicity, pregnancy, lactation, prolonged QTc
Ponatinib	Pan-BCR-ABL kinase and SRC kinase	45 mg daily	Pancreatitis, hepatotoxicity, hypertension, rash, myelotoxicity, thrombocytopenia, edema	Hepatotoxicity, advanced age, pancreatitis, thromboembolism, pregnancy, lactation, prolonged QTc
Omacetaxine	Protein translation inhibitor	1.25 mg/m^2 subcutaneous twice a day (14 days as induction, 7 days as maintenance)	Myelotoxicity, thrombocytopenia, fatigue, injection site reactions, infections, diarrhea	Advanced age, myelosuppression, hyperglycemia, infections

CHF = congestive heart failure

Jain P et al. *Curr Treat Options Oncol* 2013;14(2):127-43.

DR KANTARJIAN: Three new agents were approved for the treatment of CML in 2012 — ponatinib, bosutinib and omacetaxine. Ponatinib and bosutinib are BCR-ABL tyrosine kinase inhibitors (TKIs). Currently, imatinib, nilotinib and dasatinib can be used as front-line therapy. Ponatinib is effective for patients with T315I mutations. Dasatinib and nilotinib and the 3 newly approved drugs can be used as salvage therapy.

Outside a protocol setting I would administer nilotinib, which is highly effective and safe, as front-line therapy. Dasatinib is also an option, but pleural effusions and myelosuppression are concerns. In comparison to imatinib, the second-generation TKIs are more effective, are less toxic, cost the same and hence are preferable.

DR LOVE: What are your thoughts on the activity and tolerability of the other newly approved agent, omacetaxine?

DR KANTARJIAN: Omacetaxine is a semisynthetic formulation of homoharringtonine. It modulates RNA structure and enhances apoptosis in leukemia cells. It is active in patients with CML refractory to several lines of therapy, with major and complete cytogenetic responses achieved in 15% to 30% of patients (Cortes 2012; [2.2]). It can be administered as a subcutaneous injection twice daily for 2 weeks for induction and

2.2

Phase II Study of Omacetaxine After Tyrosine Kinase Inhibitor Failure in Patients with Chronic-Phase Chronic Myeloid Leukemia with the T315I Mutation

Endpoint	N = 62
Hematologic response	
Complete response	77%
Cytogenetic response	
Major response	23%
Complete response	16%

Cortes J et al. *Blood* 2012;120(13):2573-80.

anywhere from 1 to 7 days as maintenance/consolidation therapy. Omacetaxine has not been proven to elicit durable responses once therapy is stopped.

We do not observe any significant toxicities with this agent except myelosuppression. The duration of therapy can be adjusted from 1 to 7 days, depending on the degree of myelosuppression with each course. I've administered omacetaxine to patients for up to 4 years, achieved disease control and did not observe any long-term side effects. Although it is effective as salvage therapy, it is not as effective as the TKIs. However, I believe it will be useful in combination with TKIs in the future.

DR LOVE: So how is this combination of omacetaxine with a TKI being explored currently in clinical trials?

DR KANTARJIAN: We are exploring it in a study for patients with CML who have achieved complete cytogenetic response to a TKI but with molecular evidence of disease. For these patients, omacetaxine will be added to the TKI. The endpoints will be complete molecular response (CMR) at 12 months and the durability of CMR. We are trying to determine whether the sequence of therapy can produce both functional and molecular cures in CML.

We have 3 pilot trials investigating the combination of a TKI with omacetaxine, pegylated interferon or either azacitidine or decitabine. We will enroll 20 patients in each trial and determine which of these 3 combinations can produce the highest rate of CMR and expand that combination.

Tracks 11-14, 16

DR LOVE: Would you discuss the role of ruxolitinib in the management of myelofibrosis (MF)?

DR KANTARJIAN: Ruxolitinib is the first FDA-approved agent for the management of MF. It is effective regardless of the presence of the JAK2 mutation. The COMFORT-I and COMFORT-II trials reported that patients experience an improvement in their constitutional symptoms within a week after starting ruxolitinib. The spleen shrinks, and quality of life improves (Verstovsek 2012; Harrison 2012).

Updated data from these trials showed a survival benefit with ruxolitinib even though crossover after disease progression on the control arm was allowed. The survival benefit is impressive and points to the notion that early treatment with ruxolitinib may prolong the lives of patients with MF. If a patient whose disease has responded to ruxolitinib

with significant shrinkage of the spleen experiences an increase in spleen size, one should not stop therapy unless all the benefit related to ruxolitinib is lost.

DR LOVE: Would you discuss your recent paper in the journal *Blood* about the therapeutic effects of ruxolitinib in patients with MF without splenomegaly (Benjamini 2012)?

DR KANTARJIAN: We reported that patients will experience an improvement in symptoms with ruxolitinib even if they do not have clinically significant splenomegaly. Patients who experience a significant worsening of their quality of life related to the splenomegaly and constitutional symptoms can derive benefit from ruxolitinib. Patients who have undergone a splenectomy and have constitutional symptoms will also benefit from the JAK2 inhibitor.

DR LOVE: How would you approach initial dosing of ruxolitinib in patients with low platelet counts?

DR KANTARJIAN: For a patient with normal hemoglobin levels and platelet counts, ruxolitinib can be started at 15 mg BID and dose adjusted if cytopenias occur. If a patient has baseline anemia or platelet counts between 50 and 100 x 10^9/L, one can start ruxolitinib at a lower dose of 5 mg BID (Talpaz 2012; [2.3]). However, you have to escalate to a dose of 10 mg or more BID to get the maximum benefit.

Currently, we don't have many data to determine how to care for patients with platelet counts of less than 50 x 10^9/L. I would start these patients at 5 mg BID and dose adjust to reach at least 10 mg BID. Platelet counts should be monitored closely.

2.3

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

	Study 258	COMFORT-I	
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 COMFORT-I.

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

Track 22

DR LOVE: What are your thoughts on the novel B-cell receptor inhibitors ibrutinib and idelalisib in the management of relapsed/refractory chronic lymphocytic leukemia (CLL)?

DR KANTARJIAN: The Bruton TKI ibrutinib and the PI3 kinase delta inhibitor idelalisib can be administered orally as single agents or in combination with monoclonal antibodies, such as rituximab or ofatumumab. They produce a high response rate in patients with relapsed/refractory CLL (Byrd 2012; [2.4]; Coutre 2012; [2.5]).

The responses are durable and these agents are well tolerated. These are big breakthroughs and could lead to a paradigm shift in the treatment of CLL. These targeted agents are currently available only in a clinical trial, and we need to do our best to get patients on such trials because those who experience a complete response may go on to transplant and potential cure. ■

2.4

Phase Ib/II Study of Single-Agent Ibrutinib for Relapsed/ Refractory Chronic Lymphocytic Leukemia

Efficacy	Ibrutinib (n = 61)
Overall response rate	67%
Complete response	3%
Partial response	64%

The majority of adverse events were Grade ≤2 in severity — most commonly diarrhea, fatigue, upper respiratory tract infections, rash, nausea and arthralgias. No evidence of cumulative toxicity or long-term safety concerns was seen with a median follow-up of 16 months.

Byrd JC et al. *Proc ASH* 2012;**Abstract 189**.

2.5

Phase I Study of Idelalisib with Rituximab (R) and/or Bendamustine (B) in Relapsed/Refractory Chronic Lymphocytic Leukemia

Efficacy	Idelalisib + R (n = 19)	Idelalisib + B (n = 18)	Idelalisib + BR (n = 15)
Overall response rate	79%	78%	87%
Lymph node response	90%	78%	87%

Grade ≥3 adverse events included febrile neutropenia (15%), pneumonia (12%), transaminase elevation (10%), diarrhea (6%) and dyspnea (4%). Idelalisib was generally well tolerated in combination therapy for a period of 2.5 years.

Coutre SE et al. *Proc ASH* 2012;**Abstract 189**.

SELECT PUBLICATIONS

Benjamini O et al. **Therapeutic effects of ruxolitinib in patients with myelofibrosis without clinically significant splenomegaly.** *Blood* 2012;120(13):2768-9.

Cortes J et al. **Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation.** *Blood* 2012;120(13):2573-80.

Coutre SE et al. **Combinations of the selective phosphatidylinositol 3-kinase-delta (PI3Kdelta) inhibitor GS-1101 (CAL-101) with rituximab and/or bendamustine are tolerable and highly active in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): Results from a Phase I study.** *Proc ASH* 2012;**Abstract 191**.

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

Jain P et al. **Chronic myeloid leukemia: Overview of new agents and comparative analysis.** *Curr Treat Options Oncol* 2013;14(2):127-43.

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

INTERVIEW

Ian W Flinn, MD, PhD

Dr Flinn is Director of Blood Cancer Research at Tennessee Oncology's Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-9

Track 1 Results from BRIGHT: A Phase III trial of bendamustine/rituximab (BR) versus standard first-line chemotherapy in previously untreated, advanced indolent non-Hodgkin lymphoma (NHL) or mantle-cell lymphoma (MCL)

Track 2 Clinical experience with BR

Track 3 Stem cell collection after BR

Track 4 Approach to second-line therapy for disease progressing on BR

Track 5 Clinical implications of the RESORT trial — rituximab maintenance versus rituximab re-treatment upon disease progression for low tumor burden indolent NHL

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Select Excerpts from the Interview

Tracks 1, 4, 6-8

DR LOVE: Will you discuss the results you presented at ASH 2012 on the BRIGHT trial of bendamustine/rituximab (BR) versus standard first-line chemotherapy in previously untreated indolent lymphoma or mantle-cell lymphoma (MCL)? Would you also comment on how these results compare to those from the StiL NHL 1-2003 trial, which also evaluated the BR regimen in this setting?

DR FLINN: The Phase III BRIGHT study evaluated BR versus standard chemotherapy, either R-CHOP or R-CVP (rituximab/cyclophosphamide/vincristine/prednisone), in patients with previously untreated low-grade lymphoma or MCL. The StiL trial had previously reported that patients who received BR experienced superior response rates and progression-free survival compared to those who received standard chemotherapy, and that study was an important backdrop to initiation of this trial.

The StiL trial was not done for the purpose of FDA approval, so it wasn't performed to a level of scrutiny that was needed to obtain bendamustine approval as a front-line agent for patients with lymphoma. But the BRIGHT study was designed with that purpose — to prove that BR was not inferior to R-CHOP or R-CVP — and

3.1

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%	23%	40%	30%
	HR, 1.34; $p = 0.0084$*		$p = 0.021$	
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 = 221)	**R-CHOP/R-CVP** (n = 215)	**BR** (n = 261)	**R-CHOP** (n = 253)
Nausea (any grade)	63%	47%	NR	NR
Fatigue (any grade)	51%	50%	NR	NR
Alopecia (any grade)	4%	34%	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

[1] Flinn IW et al. *Proc ASH* 2012a;**Abstract 902**; [2] Rummel MJ et al. *Lancet* 2013;381(9873):1203-10.

it did prove that. We reported that BR was at least equivalent, and perhaps in some subgroups, such as patients with MCL, it may be superior in terms of response rate. We are awaiting longer follow-up to determine the progression-free survival (3.1).

Some differences were observed in the toxicity profiles. We reported less alopecia with BR, as you might expect, and less neuropathy was also observed, so BR was a better-tolerated regimen from that standpoint. Based on previous experience, I anticipated less nausea with bendamustine, but that turned out not to be the case. It seemed just as much nausea and vomiting occurred in patients receiving BR as for those on the control arm. It wasn't horrible on either arm, but I expected BR to be better. Also on the BR arm a small increase in opportunistic infections such as shingles or oral herpes infections was observed.

In my practice I believe BR is well tolerated, and I now administer BR as front-line therapy for patients with MCL or follicular lymphoma (FL). Probably more than half of patients are now receiving front-line treatment with this approach, if I understand the data correctly. More and more community oncologists are comfortable with this regimen and prefer it to the harsher R-CHOP regimen.

DR LOVE: I believe that a number of people would have been happy to see equal efficacy with less toxicity, but the StiL trial reported superiority for the BR arm. Any explanation as to why the BRIGHT study did not find the same? Could it have been an events issue or something to do with the trial design?

DR FLINN: I don't know of a major design issue in this trial that would explain the differences. The StiL trial allowed patients with Grade III FL and the BRIGHT trial

did not. BRIGHT is also early on in terms of its analysis, so it will be interesting to see whether a difference in progression-free survival is observed.

DR LOVE: How do you think through second-line therapy when a patient experiences disease progression on first-line BR?

DR FLINN: My approach would depend on the duration of remission — someone with a long first remission could go back to receiving BR. You could also switch to R-CHOP. I don't use a lot of fludarabine any more in patients with low-grade lymphoma, but that's a possibility. Of course, you could administer radioimmunotherapy. I'm excited about some of the newer agents, such as antibody-drug conjugates and the B-cell receptor inhibitors ibrutinib and idelalisib. We hope these drugs will make it into our armamentarium within the next year or so.

DR LOVE: What are some of the other data sets you presented at ASH 2012 in indolent lymphomas or MCL?

DR FLINN: The combination of BR and bortezomib seems to have activity in the refractory setting and, as is always the case, we want to move more effective therapies up front. We modified the regimen a bit to make it friendlier to community practice. We reported better response rates than those reported in the BRIGHT trial, but then again this was only a Phase II study with a much more selected patient population (Flinn 2012b). It's hard to know whether it was really a home run in terms of increasing response rates. I'm uncertain as to whether we will pursue this combination as a comparator in a larger trial.

We also presented data from our Phase I/II LYM 58 trial, which is a study of bortezomib/lenalidomide and rituximab for patients with newly diagnosed or relapsed/refractory MCL (Flinn 2012c). The regimen was well tolerated. We reported an unusual incidence of rashes — worse than you would see in patients with myeloma — and the reasons for that aren't clear to me.

Initially, the trial was open only to patients with relapsed disease, and 3 of the first 4 patients experienced a complete response. So we've now opened it up in the front-line setting.

DR LOVE: What are your thoughts on the so-called R-squared regimen — lenalidomide and rituximab — in indolent lymphomas?

DR FLINN: I like the R-squared approach a lot. The Phase II data from Nathan Fowler at MD Anderson were impressive, especially in patients with FL (Fowler 2012). I would never have predicted such high response rates. Hopefully, those results will translate into other diseases, such as MCL. We are now participating in the Phase III RELEVANCE trial, which is open in the United States and compares R-squared to standard chemotherapy — BR, R-CHOP or R-CVP — followed by rituximab maintenance for patients with previously untreated FL (NCT01650701). ■

SELECT PUBLICATIONS

Flinn IW et al. **Bendamustine, bortezomib, and rituximab in patients with previously untreated low grade lymphoma: A Phase II trial of the Sarah Cannon Research Institute.** *Proc ASH* 2012b;**Abstract 1624**.

Flinn IW et al. **Rituximab, lenalidomide, and bortezomib in the first-line or second-line treatment of patients with mantle cell lymphoma: A Phase I/II trial.** *Proc ASH* 2012c;**Abstract 2748**.

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

INTERVIEW

Andrew D Zelenetz, MD, PhD

Dr Zelenetz is Vice Chair of Medical Informatics in the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-13

Track 1 Evolution of treatment modalities in early-stage Hodgkin lymphoma (HL)

Track 2 Interim PET scanning in ABVD-treated advanced-stage HL

Track 3 ABVD versus AVD in combination with brentuximab vedotin in advanced-stage HL: Pilot study results, safety and future directions

Track 4 Tolerability, rates of neuropathy and clinical experiences with brentuximab vedotin

Track 5 Methodological concerns with the StiL trial design: BR versus R-CHOP as first-line treatment for indolent lymphomas and MCL

Track 6 Reconciling the StiL NHL 1-2003 and BRIGHT study results

Track 7 Results from a Phase II study of bendamustine in relapsed/refractory HL

Track 8 Efficacy and side effects of pralatrexate and romidepsin in T-cell lymphomas

Track 9 Activity of brentuximab vedotin in CD30-positive lymphomas

Track 10 Comparison of referring and final pathology for T-cell lymphomas

Track 11 CNS prophylaxis for diffuse large B-cell lymphoma (DLBCL) in the rituximab era

Track 12 Risk of CNS involvement in patients with primary breast DLBCL

Track 13 Incidence of misdiagnoses of hematologic cancers

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you discuss the recent clinical trial data with brentuximab vedotin in advanced-stage Hodgkin lymphoma (HL)?

DR ZELENETZ: Brentuximab vedotin was initially combined with ABVD in a clinical trial, and unexpected pulmonary toxicity resulted. In fact, some deaths occurred because of the pulmonary toxicity, so the study was modified to AVD with brentuximab vedotin. The data were recently updated at ASH by Dr Ansell and were an extension of what Dr Younes reported previously (Younes 2011) — that AVD with brentuximab vedotin is highly efficacious in the treatment of HL (Ansell 2012; [4.1]).

We still need a randomized study, and an upcoming international Phase III randomized trial will compare ABVD to AVD with brentuximab vedotin in patients with advanced-stage disease (4.2). However, they are setting the bar rather high. We know that approximately 80% of patients will be cured with ABVD, so for this to succeed we have to go from 80% to about 90% for a positive trial, and by diluting the patient population with a number of patients who will fare quite well, I'm concerned that the

4.1 **Discontinuation of Bleomycin in a Study of Front-Line Chemotherapy with Brentuximab Vedotin (B-Vedotin) for Newly Diagnosed Advanced-Stage Hodgkin Lymphoma**

	ABVD + b-vedotin	AVD + b-vedotin
Complete response (n = 22, 25)	95%	96%
Grade ≥3 pulmonary toxicity (n = 25, 26)	24%	0%

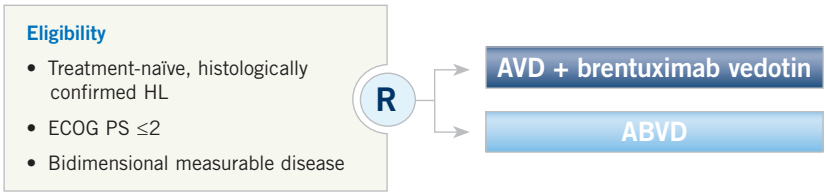
Toxicity resembling that of bleomycin led to its discontinuation in 11 patients. Eight of those 11 patients discontinued bleomycin and were able to complete treatment with AVD and b-vedotin.

A = doxorubicin; B = bleomycin; V = vinblastine; D = dacarbazine

Ansell SM et al. *Proc ASH* 2012;**Abstract 798**.

4.2 **Ongoing Phase III Front-Line Study of ABVD versus AVD with Brentuximab Vedotin in Patients with Advanced Hodgkin Lymphoma (HL)**

Protocol ID: NCT01712490 **Target Accrual:** 1,040



A = doxorubicin; B = bleomycin; V = vinblastine; D = dacarbazine

www.clinicaltrials.gov. Accessed April 30, 2013.

study could fail even if the agent provides a significant benefit to the small group of patients at poor risk.

DR LOVE: How do you incorporate brentuximab vedotin in your practice for HL outside of a protocol setting?

DR ZELENETZ: We are administering quite a bit of brentuximab vedotin according to its label indication, and that is in patients whose disease has progressed after high-dose therapy and autologous stem cell transplant. We are not currently using it up front, either on a clinical trial or off, because the Phase III trial has not yet opened at our center.

DR LOVE: What have you observed in terms of side effects and tolerability?

DR ZELENETZ: We've seen a fair amount of neuropathy. It is most significant in patients who have received a lot of prior vinca alkaloids and in patients with a history of neuropathy. However, it tends to be self limited and goes away with time. Only a few patients experience persistent long-term neuropathy.

We've also observed patients with rash, but again, it's usually self limited. Brentuximab vedotin has been well tolerated overall, and that's why it lends itself to combination with AVD in HL. In non-Hodgkin lymphoma, we are thinking of combining it with CHOP.

DR LOVE: Any other trial concepts that involve using brentuximab vedotin up front? How often do you see older patients with HL? Do you have patients for whom you want to avoid chemotherapy and thus use brentuximab vedotin earlier and maybe for longer than you might for a younger patient?

DR ZELENETZ: We have a trial with up-front brentuximab vedotin followed by AVD and brentuximab vedotin again. It is a novel approach, and the first patient we enrolled achieved a near-complete response when the chemotherapy was started.

Track 7

DR LOVE: What are your thoughts on the use of bendamustine in HL?

DR ZELENETZ: Alison Moskowitz conducted a study of bendamustine in relapsed/refractory HL that reported prompt responses followed by prompt disease progression (Moskowitz 2013; [4.3]). So unfortunately, despite a high response rate, responses are not durable with single-agent bendamustine in HL.

It's feasible to use bendamustine as a successful bridge to transplant in some patients, and it's possible that combining bendamustine with other agents would be the way to go in this patient population. Combining bendamustine with brentuximab vedotin could provide less toxicity than 16 doses of brentuximab vedotin alone, with more durability than bendamustine alone. ■

4.3

Results from a Phase II Study of Bendamustine in Relapsed/Refractory Hodgkin Lymphoma

	Bendamustine (n = 36)
Overall response rate	53%
Complete response	33%
Partial response rate	19%
Median duration of response	5 mo

Conclusion: "This study confirms the efficacy of bendamustine in heavily pretreated patients with HL.... Although the response rate was high, the number of patients proceeding to alloSCT after this treatment was disappointing.

The principal reason why more patients did not proceed to alloSCT was lack of durable response with bendamustine....Therefore, bendamustine may better serve as an initial debulking agent that could be followed by a non–cross-resistant agent to maintain the response. Furthermore, combining bendamustine with other agents may improve both the rate and duration of response, enabling more patients to proceed to consolidation."

Moskowitz AJ et al. *J Clin Oncol* 2013;31(4):456-60.

SELECT PUBLICATIONS

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

Love N et al. **Medical oncologists' clinical experiences and comfort levels with 20 recently approved agents.** *Proc ASCO* 2013;**Abstract e17570**.

Moskowitz AJ et al. **Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma.** *J Clin Oncol* 2013;31(4):456-60.

Younes A et al. **Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma.** *Proc ASH* 2011;**Abstract 955**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A Phase III trial reported by Palumbo and colleagues evaluating bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide (VMPT-VT) versus VMP in newly diagnosed MM reported that VMPT-VT significantly prolonged overall survival compared to VMP.**
   a. True
   b. False

2. **A Phase I/II study of _____, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone demonstrated an overall response rate of approximately 90% among patients with previously untreated MM.**
   a. Bortezomib
   b. Carfilzomib
   c. Ixazomib (MLN9708)

3. **The Phase III MM-003 trial for patients with MM that is refractory to both lenalidomide and bortezomib demonstrated a significant improvement in _____ with pomalidomide and low-dose dexamethasone versus high-dose dexamethasone alone.**
   a. Median progression-free survival
   b. Median overall survival
   c. Both a and b

4. **A recent study reported on the comparable efficacy of ruxolitinib at a lower dose of 5 mg BID, escalated to a dose of 10 mg or more BID, versus full-dose ruxolitinib for patients with MF who have platelet counts between 50 and 100 x 10^9/L.**
   a. True
   b. False

5. **Results from a Phase II study by Moskowitz and colleagues demonstrated response rates that were both rapid and durable when patients with relapsed or refractory HL received bendamustine.**
   a. True
   b. False

6. **Omacetaxine is a semisynthetic formulation of homoharringtonine that _____.**
   a. Acts by modulating RNA structure and enhancing apoptosis in leukemia cells
   b. Is a TKI
   c. Is associated with significant myelosuppression
   d. Both a and c
   e. All of the above

7. **The Phase III BRIGHT study demonstrated that _____ was noninferior to R-CHOP/R-CVP in patients with previously untreated, indolent non-Hodgkin lymphoma or MCL.**
   a. Lenalidomide
   b. BR
   c. Ibrutinib

8. **The Phase III RELEVANCE trial is evaluating _____ versus rituximab in combination with standard chemotherapy followed by rituximab maintenance in patients with previously untreated FL.**
   a. Bendamustine/bortezomib/rituximab
   b. R^2 (rituximab/lenalidomide)
   c. Both a and b

9. **In a study for patients with newly diagnosed advanced-stage HL, a(n) _____ incidence of pulmonary toxicity was associated with the combination of brentuximab vedotin and ABVD compared to brentuximab vedotin and AVD.**
   a. Increased
   b. Decreased
   c. Comparable

10. **An ongoing Phase III trial (NCT01712490) is evaluating ABVD versus AVD with _____ as front-line therapy for patients with advanced HL.**
    a. Brentuximab vedotin
    b. Bendamustine
    c. Neither a nor b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 1, 2013

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Impact of JAK2 mutation status on response and survival outcomes with the JAK2 inhibitor ruxolitinib in MF	4 3 2 1	4 3 2 1
Novel agents under investigation for the treatment of MM (ixazomib, elotuzumab, daratumumab) and CLL (ibrutinib, idelalisib)	4 3 2 1	4 3 2 1
Long-term efficacy and safety data — StiL NHL 1-2003 and BRIGHT trials — with BR for the treatment of newly diagnosed indolent lymphomas	4 3 2 1	4 3 2 1
Survival advantage with pomalidomide in combination with low-dose dexamethasone in relapsed/refractory MM	4 3 2 1	4 3 2 1
Efficacy and tolerability of carfilzomib/lenalidomide and low-dose dexamethasone for newly diagnosed MM	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

.....

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

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

.....

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

.....

.....

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

☐ Yes ☐ No

If no, please explain: .....

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

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

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

- 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
- 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 evaluation 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:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

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

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

PART 2 — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Sagar Lonial, MD	4 3 2 1	4 3 2 1
Hagop M Kantarjian, MD	4 3 2 1	4 3 2 1
Ian W Flinn, MD, PhD	4 3 2 1	4 3 2 1
Andrew D Zelenetz, MD, PhD	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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