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Hematologic Oncology™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Owen A O'Connor, MD, PhD
Gareth John Morgan, PhD, FRCPath
Richard M Stone, MD
Joseph M Connors, MD

EDITOR

Neil Love, MD

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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

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with multiple myeloma.
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors as therapeutic options for patients with chronic myeloid leukemia.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas.
- Recall potentially practice-changing clinical research on the care of patients with newly diagnosed acute promyelocytic leukemia.
- Appropriately incorporate ruxolitinib into the treatment of JAK2 mutation-positive or mutation-negative myelofibrosis.
- Incorporate new therapeutic strategies into the best-practice management of Hodgkin lymphoma.

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EDITOR

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INTERVIEW

Owen A O'Connor, MD, PhD

Dr O'Connor is Professor of Medicine and Developmental Therapeutics and Director for the Center of Lymphoid Malignancies at Columbia University Medical Center College of Physicians and Surgeons at NewYork-Presbyterian Hospital in New York, New York.

Tracks 1-10

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss the treatment options for patients with relapsed/refractory CD30-negative peripheral T-cell lymphoma (TCL)?

DR O'CONNOR: In my practice, we tend to use the FDA-approved single agents, pralatrexate and romidepsin, for patients with relapsed or refractory peripheral TCL. Evaluation of the data reveals that romidepsin and pralatrexate are able to achieve substantial remissions in many patients.

In the PROPEL trial evaluating pralatrexate for relapsed or refractory peripheral TCL, patients had received a median of 3 prior lines of therapy (O'Connor 2011). For patients who received pralatrexate after their first relapse, the response rate was higher than the response rate for the entire study population. Because these diseases generally perform poorly with combination therapy, I tend to consider these new agents earlier.

DR LOVE: How do you choose between romidepsin and pralatrexate?

DR O'CONNOR: In my experience, pralatrexate works faster than romidepsin. I would administer pralatrexate first if I had a sense that a patient had a lot of disease-related symptoms and required disease control, assuming the patient was not malnourished. For those with small-volume disease with a good performance status, we administer romidepsin because it requires more time to provide benefit.

DR LOVE: What has been your clinical experience with the toxicity of pralatrexate and romidepsin?

DR O'CONNOR: With pralatrexate, the big issue is mucositis. The incidence of Grade 3/4 mucositis in the PROPEL study was 22%. If a patient develops even low-grade mucositis, we treat it early with leucovorin between the intervening doses of pralatrexate, which seems to have a big effect on lowering its incidence. Also, we may start pralatrexate at a lower dose and gradually escalate. Another side effect of pralatrexate is thrombocytopenia. Romidepsin is well tolerated with durable responses, but like most HDAC inhibitors it has side effects including fatigue, anorexia and thrombocytopenia. If I have a patient who is a little older who I don't believe would be able to tolerate the potential mucositis with pralatrexate, I will consider administering romidepsin first in that scenario.

Track 6

DR LOVE: What is the rationale for trials evaluating the integration of up-front pralatrexate and romidepsin in TCL?

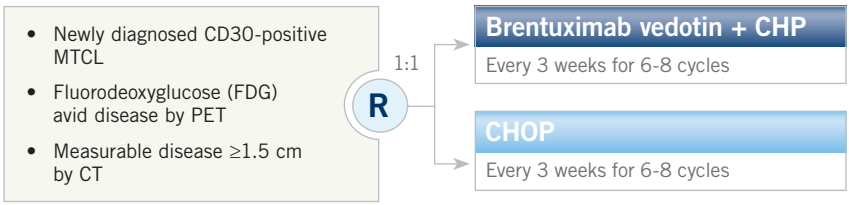
DR O'CONNOR: Our independent review board recently approved a Phase I/II study that will investigate the combination of pralatrexate with romidepsin in the up-front setting. The rationale is based on our laboratory data with preclinical murine models of TCL. This will be the first trial to evaluate combining these active T-cell-specific agents to try to build new platforms that could challenge CHOP as an up-front regimen.

DR LOVE: Continuing with the concept of trials of up-front treatment, would you discuss the ongoing Phase III ECHELON-2 trial for patients with newly diagnosed mature TCL (MTCL)?

1.1

ECHELON-2: An Ongoing Phase III Trial of Brentuximab Vedotin/CHP versus CHOP Chemotherapy in the Front-Line Treatment of CD30-Positive Mature T-Cell Lymphoma (MTCL)

Target Accrual: n = 300



Primary endpoint: Progression-free survival by independent review

CHP = cyclophosphamide/doxorubicin/prednisone

O'Connor OA et al. *Proc ASCO* 2013;**Abstract TPS8611**.

DR O'CONNOR: The ECHELON-2 trial is an important registration-directed study of brentuximab vedotin/CHP versus CHOP in MTCL (O'Connor 2013; [1.1]). Because it is only for MTCL, it will account for approximately one third of patients with TCL. If the activity of brentuximab vedotin/CHP is anywhere close to what we've observed in anaplastic large cell lymphoma and the early signals that we see in TCL and diffuse large B-cell lymphoma, this may represent one of the first big advances to a CHP backbone by adding a new agent that could advance the up-front induction care for these patients.

Other randomized Phase III trials in peripheral TCL are evaluating pralatrexate or romidepsin with CHOP (1.2). This makes 3 international studies in the up-front setting for patients with TCL.

1.2

Select Ongoing Phase III Clinical Trials of Romidepsin and Pralatrexate for Patients with Peripheral T-Cell Lymphoma

Trial ID	N	Treatment arms
NCT01796002 (Ro-CHOP)	420	• Romidepsin + CHOP • CHOP
NCT01420679	549	• CHOP-based CT → pralatrexate • CHOP-based CT → observation

CT = chemotherapy

www.clinicaltrials.gov, October 2013.

Tracks 7-8

DR LOVE: Would you discuss the results of the Phase II BELIEF trial?

DR O'CONNOR: The BELIEF trial evaluated a new HDAC inhibitor, belinostat, in relapsed or refractory PTCL and reported a response rate of approximately 26% (O'Connor 2013; [1.3]). The duration of response and much of the BELIEF trial results are similar to what we've observed with the other HDAC inhibitors. It's difficult to compare it to vorinostat because we have little to no experience with vorinostat in PTCL.

Of note, the BELIEF trial reaffirmed that HDAC inhibitors have a unique class effect in TCL, with activity of 25% to 30%. One of the interesting observations of the BELIEF trial was the activity in patients with low platelet counts. More important, belinostat was well tolerated irrespective of the baseline platelet count.

DR LOVE: What are your thoughts on the results of the subset analysis of the BELIEF trial in patients with angioimmunoblastic T-cell lymphoma (AITL)?

DR O'CONNOR: An interesting observation from the BELIEF study was the response rate in AITL (Horwitz 2013; [1.3]). This was higher than previously reported in the PROPEL study with pralatrexate. With belinostat, the response rate in AITL was markedly higher than what was reported in the overall patient population. That was taken as a signal that some interesting biology may be targeted by belinostat in patients with the AITL subtype that is not targeted by the other HDAC inhibitors. This is a provocative finding, but we need more data.

1.3

Efficacy and Safety Results from the Phase II BELIEF Trial of Single-Agent Belinostat, a Novel Pan-HDAC Inhibitor, for Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

Outcome	All patients* (n = 120)	AITL† (n = 22)	Baseline platelet counts*	
			≥100,000/uL	<100,000/uL
ORR	25.8%	46%	28%	15.0%
Median DoR	13.6 months	NR	13.6 months	4.1 months
Median PFS	1.6 months	4.2 months	1.8 months	1.3 months
Median OS	7.9 months	NR	9.2 months	4.3 months
Median TTR	5.6 weeks	NR	5.6 weeks	6.4 weeks
Grade ≥3 AEs	(n = 129)	(n = 22)	(n = 105)	(n = 24)
Thrombocytopenia	15%	23%	6%	54%
Neutropenia	13%	9%	10%	25%
Leukopenia	13%	9%	9%	29%
Anemia	12%	27%	8%	29%
Dyspnea	6%	NR	NR	NR
Pneumonia	6%	NR	NR	NR

AITL = angioimmunoblastic T-cell lymphoma; ORR = overall response rate; DoR = duration of response; NR = not reported; PFS = progression-free survival; OS = overall survival; TTR = time to response; AEs = adverse events

* O'Connor OA et al. *Proc ASCO* 2013;**Abstract 8507**; † Horwitz S et al. *Proc ICML* 2013;**Abstract 153**.

Track 10

DR LOVE: In light of the recent FDA approval of lenalidomide for relapsed or progressive mantle-cell lymphoma (MCL), how do you sequence lenalidomide and bortezomib?

DR O'CONNOR: I've seen bortezomib work remarkably well in patients with chemotherapy-resistant MCL. When combined with alkylating agents such as cyclophosphamide or bendamustine, it converts chemotherapy-resistant or refractory disease to chemotherapy-sensitive disease. So bortezomib can help overcome acquired and intrinsic drug resistance by its integration even into previously used chemotherapy regimens.

My bias has been that we'll probably try up-front lenalidomide for most patients provided they have no urgent need for rapid cytoreduction. MCL has been managed with lenalidomide-based regimens for several years. I've seen elderly patients ineligible for combination chemotherapy receive lenalidomide-based therapy and achieve sustained complete responses. ■

SELECT PUBLICATIONS

Horwitz S et al. **Belinostat in angioimmunoblastic T-cell lymphoma: Results from the pivotal BELIEF trial.** *Proc ICML* 2013;**Abstract 153**.

O'Connor OA et al. **Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study.** *J Clin Oncol* 2011;29(9):1182-9.

INTERVIEW

Gareth John Morgan, PhD, FRCPath

Dr Morgan is Professor of Haematology and Consultant Haematologist at the Institute of Cancer Research and Royal Marsden Hospital in Sutton, Surrey, United Kingdom.

Tracks 1-14

Select Excerpts from the Interview

Tracks 3, 5, 13

DR LOVE: What is your approach to up-front therapy for younger transplant-eligible patients with multiple myeloma?

DR MORGAN: Triplet combinations with an alkylating agent, steroids and an IMiD or a proteasome inhibitor are the current standard. One can choose a combination that will work best for a particular patient. I am in favor of administering triplet rather than doublet therapy to maximize the response. I believe that as more tolerable proteasome inhibitors are developed, the next generation of studies will evaluate quadruplet therapies with an IMiD, a proteasome inhibitor, an alkylating agent and a steroid for these patients.

DR LOVE: How do you care for older patients who are not candidates for a transplant?

DR MORGAN: In older patients, high-dose combination chemotherapy can be toxic. So we must be careful with this population and consider treatment options depending on whether they are frail or more robust.

We administer the cyclophosphamide, lenalidomide and dexamethasone regimen we've developed. I believe that this treatment will be widely adopted because it's well tolerated and elicits good responses. For the frail patient, I believe lenalidomide with low-dose dexamethasone is a good approach.

Track 4

DR LOVE: What is your approach to post-transplant maintenance?

DR MORGAN: I am impressed by post-transplant maintenance data with IMiDs and proteasome inhibitors. Three studies with lenalidomide maintenance have shown impressive results (Attal 2012; McCarthy 2012; Palumbo 2012) with a 1.5- to 2-year improvement in progression-free survival and an overall survival benefit in the CALGB-100104 study. I believe that lenalidomide maintenance is becoming the standard therapy for the future.

The HOVON-65 study compared a thalidomide-based approach to a bortezomib-based approach as maintenance for patients with newly diagnosed multiple myeloma. The bortezomib-based regimen was superior to the thalidomide approach (Sonneveld 2012; [2.1]). This suggests a signal for ongoing bortezomib therapy long term.

2.1

Results of the HOVON-65/GMMG-HD4 Trial: Bortezomib Induction and Maintenance Therapy for Patients with Newly Diagnosed Multiple Myeloma

Progression-free survival (PFS)	PAD → bortezomib	VAD → thalidomide	Hazard ratio	*p*-value
Median PFS (ITT population)	35 mo	28 mo	0.75	0.002
Patients with increased creatinine (>2 mg/dL)	30 mo	13 mo	0.45	0.004
Patients with del(17p13)	22 mo	12 mo	0.47	0.01

PAD = bortezomib/doxorubicin/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; ITT = intention to treat

Sonneveld P et al. *J Clin Oncol* 2012;30(24):2946-55.

Tracks 6-10

DR LOVE: Any comments on carfilzomib? How do you use it currently in your practice?

DR MORGAN: Carfilzomib is an epoxyketone-based proteasome inhibitor, whereas bortezomib is a boronic acid-based inhibitor. Carfilzomib irreversibly inhibits the proteasome, resulting in sustained activity, whereas bortezomib is a reversible inhibitor.

Phase I studies reported that carfilzomib elicited good response rates, was well tolerated and lacked neurotoxicity. The Phase II trial that led to the approval of this agent for patients with relapsed/refractory multiple myeloma demonstrated good responses

2.2

PX-171-003-A1: Results of a Phase II Study of Single-Agent Carfilzomib for Patients with Relapsed/Refractory Multiple Myeloma

Responses	All patients (n = 257)	Patients with unfavorable cytogenetics (n = 71)
Overall response rate	23.7%	29.6%
Complete response	0.4%	0%
Very good partial response	5.1%	4.2%
Partial response	18.3%	25.4%
Clinical benefit rate	37.0%	33.8%
Median progression-free survival	3.7 months	3.6 months
Median duration of response	7.8 months	6.9 months
Select adverse events (n = 266)	**All grades**	**Grade 3 or 4**
Anemia	46%	24%
Thrombocytopenia	39%	29%
Lymphopenia	23%	20%
Fatigue	49%	7.5%
Dyspnea	34%	3.4%
Peripheral neuropathy	12.4%	1.1%

Siegel DS et al. *Blood* 2012;120(14):2817-25.

(Siegel 2012; [2.2]) with carfilzomib, and currently it is being used for that subset of patients. I believe, however, that the triplet of carfilzomib, dexamethasone and lenalidomide or cyclophosphamide would be more effective. Hence, that is what I administer for patients with relapsed/refractory disease.

I have only used carfilzomib up front in clinical trials. The combination of carfilzomib, lenalidomide and dexamethasone could be effective, but we're awaiting the results of the randomized clinical trials. Currently, I believe it would be premature to use carfilzomib in the up-front setting.

DR LOVE: What has been reported in terms of tolerability of carfilzomib?

DR MORGAN: Although carfilzomib is a more potent proteasome inhibitor, it doesn't cause significant neuropathy (2.2). A cardiac signal has been reported and, though we should watch for that, it is not significant enough to restrict the use of the drug in the up-front or relapsed setting. Overall I believe carfilzomib is safer and has better activity than bortezomib.

I have not observed dyspnea in patients to whom I've administered carfilzomib. We should watch for dyspnea and be careful to not overhydrate patients. If a patient develops dyspnea, one must consider the possibility of fluid overload.

DR LOVE: Would you discuss what is known about the recently approved agent pomalidomide in multiple myeloma?

DR MORGAN: When lenalidomide and pomalidomide were first being developed, pomalidomide was the more active compound in vivo but lenalidomide was taken forward first. But now we have this more active agent that is effective when lenalido-

mide fails. Good data exist with pomalidomide in the relapsed/refractory setting, and its use carries a progression-free and overall survival benefit.

The entry criteria for that study were tight, and I believe in the real world they will be relaxed a little. But pomalidomide is still to be used for patients for whom a proteasome inhibitor has failed, lenalidomide has failed and no other obvious choice is available. And I believe it will find a good home there and it will be active (San Miguel 2013; [2.3]).

DR LOVE: Would you discuss the sequencing of carfilzomib and pomalidomide and which one you prefer to use to start therapy?

DR MORGAN: We do not yet have data from clinical trials to address this question. For a patient whose disease relapses quickly after an IMiD-containing regimen, I would suggest switching to an agent with a different mode of action and vice versa.

With carfilzomib, the number and timing of infusions make it difficult for older people or those who travel. So for patients who live far away from the hospital or are frail, I would opt for pomalidomide first. ■

2.3

MM-003: Final Efficacy Analysis of a Phase III Trial of Pomalidomide (Pom) in Combination with Low-Dose Dexamethasone (d) versus High-Dose Dexamethasone (D) for Relapsed/Refractory Multiple Myeloma

Efficacy	Pom + d (n = 302)	D (n = 153)	Hazard ratio	*p*-value
Median PFS	4.0 mo	1.9 mo	0.48	<0.0001
Median OS	12.7 mo	8.1 mo	0.74	0.0285
Overall response rate	31%	10%	—	<0.0001
Select adverse events (Grade 3 or 4)	**Pom + d** (n = 300)		**D** (n = 150)	
Neutropenia	48%		16%	
Anemia	33%		37%	
Thrombocytopenia	22%		26%	
Pneumonia	13%		8%	
Bone pain	7%		5%	
Fatigue	5%		6%	

PFS = progression-free survival; OS = overall survival

San Miguel J et al. *Lancet Oncol* 2013;14(11):1055-66.

SELECT PUBLICATIONS

Attal M et al. **Lenalidomide maintenance after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366(19):1782-91.

McCarthy PL et al. **Lenalidomide after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366(19):1770-81.

Palumbo A et al. **Continuous lenalidomide treatment for newly diagnosed multiple myeloma.** *N Engl J Med* 2012;366(19):1759-69.

San Miguel J et al. **Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial.** *Lancet Oncol* 2013;14(11):1055-66.

INTERVIEW

Richard M Stone, MD

Dr Stone is Director of the Adult Leukemia Program at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

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Track 1 Differential management of acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL)

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Select Excerpts from the Interview

Track 4

DR LOVE: What are your thoughts on 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 STONE: First, to clarify low- versus high-risk APL because I've been asked about this by community oncologists, all you have to remember is the white blood cell count at diagnosis. A white blood cell count higher than 10,000 equates to high-risk disease, and a count lower than 10,000 indicates either intermediate- or low-risk APL.

I believe the standard treatment has changed for patients with APL with white blood cell counts lower than 10,000 because of a seminal work published recently in *The New England Journal of Medicine* by Francisco Lo-Coco and colleagues. These authors used ATRA and arsenic trioxide without chemotherapy. The results of this trial were impressive and demonstrated an advantage with the chemotherapy-free approach (Lo-Coco 2013; [3.1]).

For patients with higher-risk disease, I'll use the CALGB-9710 regimen, which is "3 plus 7" and retinoic acid for induction therapy and then arsenic trioxide consolidation followed by more anthracycline or ATRA for late consolidation. You could also add gemtuzumab ozogamicin for patients with high-risk APL.

3.1

Phase III Study of All-trans Retinoic Acid (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.

Tracks 8, 10-11

DR LOVE: What is your algorithm for managing myelofibrosis (MF), and where does ruxolitinib fit in?

DR STONE: A JAK2 inhibitor should be considered for patients with symptomatic splenomegaly or constitutional symptoms. For patients with anemia only, it's not clear if a JAK2 inhibitor is effective. More than 50% of patients with symptomatic splenomegaly or constitutional symptoms will experience improvement with ruxolitinib. I am concerned about worsening the anemia with treatment, but if you lower the dose, patients tend to fare well. I also watch out for cytopenias, which are usually transient. If you must stop treatment, the "rebound phenomenon" can occur.

DR LOVE: What is the mechanism of the rebound phenomenon?

DR STONE: If a patient experiences a response to ruxolitinib and then stops taking it, a cytokine storm occurs. It's difficult to understand, but my notion is that ruxolitinib reduces the circulating levels of cytokines, in turn limiting receptor binding. If treatment is stopped, the system is prepared to respond in an aggressive manner.

DR LOVE: Do general oncologists understand that patients without JAK mutations benefit from JAK inhibition?

DR STONE: Even the scientists don't understand the pathophysiologic role of JAK2 in MF. Why do some patients with JAK2 mutations develop MF and some develop polycythemia vera or essential thrombocythemia? I feel for the oncologists who treat a rare disease like MF.

DR LOVE: What do we know about cross resistance among JAK inhibitors?

DR STONE: Not much. Some of the newer trials allow patients to enroll if they have already received ruxolitinib, so we should be watching at the next ASH meeting for the data. My guess is that because each one seems to inhibit a different spectrum of the JAK2 family, we may see some noncross resistance.

The future of MF will include combination therapy. One of the prime agents to combine with a JAK2 inhibitor is an HDAC inhibitor (NCT01693601). Data indicate that HDAC inhibitors have activity in MF (DeAngelo 2013). This will be an important combination, as will combining IMiDs with JAK2 inhibitors.

Track 13

DR LOVE: Where are we with the 5 tyrosine kinase inhibitors (TKIs) now approved for the treatment of CML?

DR STONE: Dasatinib (Hochhaus 2012) and nilotinib (Saglio 2010), when compared head to head to imatinib, seemed to be better, but that was using the endpoint of cytogenetic or molecular response. Is that a good surrogate for long-term outcome? We're not certain. The bosutinib versus imatinib trial wasn't positive, although that was probably a design issue (Cortes 2012).

Should we routinely use nilotinib or dasatinib up front? The nilotinib trial reported a reduction in transformation to accelerated phase or blast crisis, so you could argue for that. In patients with a greater risk of pleural effusion, don't use dasatinib. If the patient prefers to be able to eat immediately before and after, don't use nilotinib. In older patients, imatinib is fine. In a few years, though, if imatinib goes off patent and the cost decreases, you could make a strong case for it. The responses are great, and you can use nilotinib or dasatinib to rescue patients whose disease progresses on imatinib.

Bosutinib is probably the best-tolerated agent, aside from some initial diarrhea. Ponatinib is approved for patients with disease progression after prior TKI therapy. It is generally considered a third-line agent, and it is the only one that works for T315I mutations. It is the most potent TKI, but it's difficult to take.

Editor's note: Subsequent to this interview, the FDA suspended the marketing of ponatinib and its evaluation in clinical trials based on a recent observation of an increased risk of life-threatening blood clots and severe narrowing of blood vessels (**www.fda.gov/Drugs/DrugSafety/ucm373040.htm**). ■

SELECT PUBLICATIONS

Cortes JE et al. **Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: Results from the BELA trial.** *J Clin Oncol* 2012;30(28):3486-92.

DeAngelo DJ et al. **Phase II trial of panobinostat, an oral pan-deacetylase inhibitor in patients with primary myelofibrosis, post-essential thrombocythaemia, and post-polycythaemia vera myelofibrosis.** *Br J Haematol* 2013;162(3):326-35.

Hochhaus A et al. **Dasatinib versus imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): DASISION 3-year follow-up.** *Proc ASCO* 2012;**Abstract 6504**.

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

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

INTERVIEW

Joseph M Connors, MD

Dr Connors is Clinical Director at BC Cancer Agency Centre for Lymphoid Cancer and Clinical Professor at the University of British Columbia in Vancouver, British Columbia, Canada.

Tracks 1-14

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: What are your thoughts on the data evaluating bendamustine/rituximab (BR) for previously untreated indolent or MCL, particularly the results from the StiL NHL 1-2003 trial that were recently published and the more recent BRIGHT study?

DR CONNORS: Bendamustine has had a peculiar development path, originally being developed and used behind the "Iron Curtain" and then gradually moving into the Western world. The first study you mentioned was a comparison of R-CHOP to BR, and somewhat to everyone's surprise the BR combination outperformed R-CHOP.

4.1 **Phase III Study Results with Bendamustine/Rituximab (BR) versus Standard First-Line Therapy for Indolent Non-Hodgkin Lymphoma and Mantle-Cell Lymphomas**

	BRIGHT[1]		StiL NHL 1-2003[2]	
Efficacy	**BR** (n = 213)	**R-CHOP or 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%
	CR ratio = 1.26; $p = 0.0225$*		$p = 0.021$	
Complete response rate (mantle-cell lymphoma)	51%	24%	Not reported (NR)	
	CR ratio = 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 or R-CVP** (n = 215)	**BR** (n = 261)	**R-CHOP** (n = 253)
Nausea (any grade)	63%	48%	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

CVP = cyclophosphamide/vincristine/prednisone; CR = complete response; HR = hazard ratio

[1] Flinn IW et al. *Proc ICML* 2013;**Abstract 084**; Flinn IW et al. *Proc ASH* 2012;**Abstract 902**.
[2] Rummel MJ et al. *Lancet* 2013;381(9873):1203-10.

Progression-free survival was substantially improved, as was tolerability, without the cardiotoxicity or the same level of myelosuppression (Rummel 2013; [4.1]).

Thus, the side-effect profile of bendamustine is more attractive. This has led to wide adoption of the BR combination for patients with indolent B-cell lymphomas. That being said, the StiL study concentrated more on efficacy, and I'm not sure we were able to discern the full spectrum of toxicity.

The BRIGHT study has now contributed some useful information about the spectrum of toxicity. It reminds us that although bendamustine is a potent agent, it does cause myelosuppression and somewhat more nausea than expected (Flinn 2013; [4.1]). In our experience here in British Columbia, we've observed more rashes with bendamustine, so the patients are definitely still experiencing chemotherapy-type symptoms. But these symptoms are all manageable, and bendamustine is attractive to older patients, who seem to be able to tolerate it fairly well in full doses.

DR LOVE: Do you generally use rituximab maintenance any time you're administering rituximab/chemotherapy for follicular lymphoma, or are there situations in which you don't take such an approach?

DR CONNORS: That practice has become our standard for patients with indolent lymphomas. Although studies that addressed its potential usefulness were focused on follicular lymphoma (FL), it doesn't seem too much of an extrapolation to include the other indolent B-cell lymphomas.

Debate continues about which maintenance schedule to use, with no clear superiority in any one of them. So you'll see variations in the dosing between 375 mg/m^2 and 500 mg/m^2, and you'll see variation in the interval between 2 months and 3 months. I suppose we're being a bit parsimonious here, but with no evidence in favor of one or the other, we use the every 3-months schedule and the 375-mg/m^2 dosing.

Track 5

DR LOVE: A strategy that's currently being investigated in the large Phase III RELEVANCE trial is the so-called R-squared (R^2) regimen of lenalidomide and rituximab versus standard therapy — BR, R-CHOP or R-CVP (rituximab with cyclophosphamide/vincristine/prednisone) — followed by rituximab maintenance for patients with previously untreated FL. What are your thoughts on this study (NCT01650701)?

DR CONNORS: We're in the final stages of gaining approval to join that trial through the NCIC Clinical Trials Group.

Exciting preliminary data with this combination lead us to believe that it might perform as well as any other regimen we have to offer, including BR. These data point to a high level of efficacy and favorable tolerability with the R^2 regimen (Fowler 2012; Martin 2013; [4.2]).

The management of FL is suddenly accelerating. I believe we should look toward a day in the not-too-distant future when we won't be talking at all about regimens like CHOP or CVP. And we may well also move beyond combinations like BR.

4.2

ALLIANCE/CALGB-50803: A Phase II Trial of Lenalidomide/Rituximab for Previously Untreated Follicular Lymphoma

Response	Overall (n = 57)	Response by FLIPI score		
		FLIPI 0-1 (n = 17)	FLIPI 2 (n = 36)	FLIPI 3 (n = 2)
ORR	93%	94%	92%	100%
CR	72%	77%	70%	100%
PR	21%	18%	22%	NR
SD	4%	0%	6%	NR

FLIPI = Follicular Lymphoma International Prognostic Index; ORR = overall response rate; CR = complete response; PR = partial response; NR = not reported; SD = stable disease

Martin P et al. *Proc ICML* 2013;**Abstract 063**.

Track 7

DR LOVE: What is your take on the new data reported at ASCO 2013 on the efficacy of the anti-CD20 antibody obinutuzumab (GA101) in previously untreated chronic lymphocytic leukemia (CLL)?

DR CONNORS: It was a little complicated to figure out what was and was not comparable. The trial was structured with a standard arm of chlorambucil and then 2 separate

experimental arms — chlorambucil with obinutuzumab and chlorambucil with rituximab. So the comparisons that were reported at ASCO and examined for statistical validity were obinutuzumab and chlorambucil to chlorambucil alone and then separately rituximab and chlorambucil to chlorambucil alone.

The authors purposely avoided comparing the 2 experimental arms, so we were left to imagine the comparison. I am a little wary of that because differences exist in the distribution of prognostic factors and other aspects of the patient groups on each of these arms. The study must mature further before we can make those comparisons.

That said, it did emerge that on a backbone of chlorambucil you can improve outcomes with either of the 2 anti-CD20 interventions (Goede 2013; [4.3]). Some theoretical and preclinical reasoning supports the possible superiority of obinutuzumab, but enough similarity is evident between the 2 antibodies that I want to see more hard data and firm evidence before I'm willing to believe that obinutuzumab is a more effective agent.

I don't believe we will see obinutuzumab on the market and commercially available until it demonstrates at least equivalence if not superiority to another anti-CD20 molecule.

Editor's note: Subsequent to this interview additional important findings from this study were reported in a press release (4.3), and on November 1, 2013, the FDA granted approval of obinutuzumab in combination with chlorambucil for previously untreated CLL. ■

4.3

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

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

Goede V et al. **Obinutuzumab (GA101) + chlorambucil (Clb) or rituximab (R) + Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase 3 trial.** *Proc ASCO* 2013;**Abstract 7004**.

Martin P et al. **Alliance/CALGB 50803: A phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Proc ICML* 2013;**Abstract 063**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Based on the results of the pivotal PROPEL study, _____ is a ≥Grade 3 adverse event frequently associated with pralatrexate therapy among patients with relapsed or refractory peripheral T-cell lymphoma.**
   a. Mucositis
   b. Thrombocytopenia
   c. Headache
   d. Both a and b
   e. All of the above

2. **The ongoing Phase III ECHELON-2 trial is evaluating the efficacy and safety of front-line _____ versus CHOP chemotherapy for patients with CD30-positive mature T-cell lymphoma.**
   a. Brentuximab vedotin
   b. Brentuximab vedotin + CHP
   c. Brentuximab vedotin + CHOP
   d. Romidepsin + CHOP

3. **Which of the following statements is true with regard to the results of the Phase II BELIEF trial of single-agent belinostat for patients with relapsed or refractory peripheral T-cell lymphoma?**
   a. Myelosuppression was a frequent Grade 3 or higher side effect of belinostat
   b. Belinostat demonstrated activity in patients with baseline platelet counts of 100,000/uL or higher but not in those with less than 100,000/uL
   c. The activity of belinostat was approximately doubled in patients with angioimmunoblastic T-cell lymphoma compared to the overall patient population.
   d. Both a and c
   e. All of the above

4. **The Phase III MM-003 trial for patients with multiple myeloma 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

5. **In the Phase II PX-171-003-A1 trial of single-agent carfilzomib for patients with relapsed/refractory multiple myeloma, commonly observed adverse events included _____.**
   a. Myelosuppression
   b. Fatigue
   c. Dyspnea
   d. All of the above

6. **Follow-up data from the DASISION trial evaluating dasatinib versus imatinib in newly diagnosed CML in chronic phase indicated significant improvements in cytogenetic response for patients receiving dasatinib.**
   a. True
   b. False

7. **In the treatment of myelofibrosis, JAK2 inhibition with ruxolitinib has shown to be beneficial for _____.**
   a. Patients with JAK2 mutations
   b. Patients without JAK2 mutations
   c. Both a and b
   d. None of the above

8. **Results from the Phase III BRIGHT trial demonstrated that _____ was noninferior to R-CHOP or R-CVP for patients with previously untreated indolent non-Hodgkin lymphoma or MCL.**
   a. BR
   b. Lenalidomide
   c. R^2

9. **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. R^2
   b. BR
   c. Both a and b

10. **Initial results from the Phase III CLL11 trial, which is evaluating obinutuzumab/chlorambucil or rituximab/chlorambucil for patients with previously untreated CLL, indicated a superior overall response rate and superior progression-free survival in both anti-CD20 antibody-containing arms compared to chlorambucil alone.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 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
Initial results from the Phase III CLL11 trial of obinutuzumab (GA101) with chlorambucil (Clb) or rituximab with Clb versus Clb alone in previously untreated CLL	4 3 2 1	4 3 2 1
ECHELON-2: A Phase III trial of brentuximab vedotin in combination with CHP versus CHOP as front-line therapy for CD30-positive TCL	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 and MCL	4 3 2 1	4 3 2 1
Newly approved therapeutic options for patients with relapsed or refractory CML	4 3 2 1	4 3 2 1
High response rates with belinostat for patients with the angioimmunoblastic TCL subtype of PTCL on the BELIEF trial	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

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☐ This activity validated my current practice
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☐ Other (please explain): .....

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

.....

.....

.....

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

- 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 as therapeutic options for patients with chronic myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens under evaluation for indolent and aggressive B-cell and T-cell non-Hodgkin lymphomas. . . . . 4 3 2 1 N/M N/A
- Recall potentially practice-changing clinical research on the care of patients with newly diagnosed acute promyelocytic leukemia. . . . . 4 3 2 1 N/M N/A
- Appropriately incorporate ruxolitinib into the treatment of JAK2 mutation-positive or mutation-negative myelofibrosis. . . . . 4 3 2 1 N/M N/A
- Incorporate new therapeutic strategies into the best-practice management of Hodgkin lymphoma. . . . . 4 3 2 1 N/M N/A

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.....

Would you recommend this activity to a colleague?

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.....

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Faculty	Knowledge of subject matter	Effectiveness as an educator
Owen A O'Connor, MD, PhD	4 3 2 1	4 3 2 1
Gareth John Morgan, PhD, FRCPath	4 3 2 1	4 3 2 1
Richard M Stone, MD	4 3 2 1	4 3 2 1
Joseph M Connors, 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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