HOU | 2015 VOL 8 | ISSUE 3

Hematologic Oncology™ UPDATE

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

FACULTY INTERVIEWS

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David P Steensma, MD
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EDITOR

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OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given individual requires careful consideration of patient-specific characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments and the perspectives of experts, 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

- Reevaluate your current treatment approach for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data.
- Customize the selection of systemic therapy for patients with newly diagnosed and progressive mantle-cell lymphoma, recognizing the recent addition of bortezomib, lenalidomide and ibrutinib as FDA-endorsed options.
- Develop a rational plan to incorporate B-cell receptor signaling inhibitors and novel CD20 monoclonal antibodies into the treatment of chronic lymphocytic leukemia and other B-cell neoplasms.
- Incorporate newly approved agents and strategies in the treatment of newly diagnosed and relapsed or refractory multiple myeloma.
- Develop an understanding of the biologic rationale for and early efficacy data with the use of immunotherapeutic approaches for patients with various hematologic cancers.
- Recognize the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment.

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Release date: January 2016; Expiration date: January 2017

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EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Amgen Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, ImmunoGen Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

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INTERVIEW

Steven Coutre, MD

Dr Coutre is Professor of Medicine (Hematology) at Stanford University School of Medicine in Stanford, California.

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DR LOVE: Would you discuss the results of the Phase III CLL10 trial of fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR) for patients with untreated advanced chronic lymphocytic leukemia (CLL) (Eichhorst 2014)?

DR COUTRE: FCR has become the major regimen used for initial treatment of CLL in fit patients, but BR is becoming increasingly popular and has a reputation for being a kinder and gentler regimen. The CLL10 trial of FCR versus BR included patients older and younger than age 65. The primary endpoint was progression-free survival (PFS), and FCR was superior. More patients achieved a complete response with FCR, and that translated to a PFS of 55.2 months versus 41.7 months with BR.

The tradeoff was tolerability. FCR led to a higher incidence of neutropenia, thrombocytopenia and infections. By age group, the tolerability issues were observed primarily

in patients older than age 65. However, there is no cutoff age in place for the use of FCR. The most important aspect is the treatment goal. One has to consider each patient individually, and one size does not fit all.

DR LOVE: How have the results of the German Phase III CLL11 trial of chlorambucil with or without the anti-CD20 monoclonal antibodies obinutuzumab or rituximab for patients with untreated CLL and comorbidities influenced your practice?

DR COUTRE: The relevant part of the CLL11 trial was the comparison of obinutuzumab/chlorambucil to rituximab/chlorambucil (Goede 2014). In terms of the primary endpoint of PFS, the obinutuzumab/chlorambucil combination was superior at 26.7 months versus 15.2 months for rituximab/chlorambucil. No difference is apparent yet in overall survival (OS). If you're considering rituximab, you might opt for obinutuzumab instead because patients achieve better and more durable responses. In my practice, I would choose obinutuzumab for an older, symptomatic patient for whom I want to achieve disease control if I didn't feel that the patient would tolerate BR.

In the trial, obinutuzumab was used in combination with chlorambucil. However, I do not believe that chlorambucil adds any benefit to obinutuzumab, and therefore I always administer obinutuzumab as a single agent rather than in combination with chlorambucil even for older patients.

Tracks 5, 7-10

DR LOVE: What is your clinical experience with ibrutinib, and how do you integrate it into the treatment algorithm for patients with CLL with and without adverse cytogenetics?

DR COUTRE: Ibrutinib has tremendous activity. Essentially all patients respond to ibrutinib therapy when it is initially administered, including those who often do not respond to the standard agents, such as patients with the 17p deletion or those with fludarabine-refractory disease. It is great to know that you can tell your patients that you are going to recommend a once-a-day pill and they're going to experience a response.

With ibrutinib, the lymph nodes shrink dramatically in a matter of days and at the same time, you see lymphocytosis. Fortunately, that doesn't cause any clinical problems, but you need to make your patients aware of this issue. Ibrutinib is generally quite well tolerated. It causes easy bruising and a bit of diarrhea, which eventually goes away. I have patients who've been on ibrutinib continuously for up to 5 years. It is not associated with cumulative side effects. As a result, ibrutinib is FDA approved for patients with CLL who have received 1 prior therapy. It is also indicated up front for patients with 17p deletion.

DR LOVE: Would you administer ibrutinib up front for patients without 17p deletion?

DR COUTRE: Absolutely. We've recently reported data from the randomized Phase III RESONATE-2 trial addressing that issue in patients with treatment-naïve disease. Patients aged 65 or older with untreated CLL or small lymphocytic lymphoma (SLL) without 17p deletion received chlorambucil or ibrutinib, and single-agent ibrutinib was superior (Tedeschi 2015; [1.1]).

The RESONATE-2 trial also revealed that ibrutinib can cause atrial fibrillation. However, it was generally brief in duration, occurring only for a matter of days. We

1.1

RESONATE-2: Efficacy and Safety Results from a Phase III Trial of Ibrutinib (Ibr) versus Chlorambucil (Clb) for Patients Age 65 or Older with Untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma without 17p Deletion

Efficacy (by IRC)	Ibr	Clb	HR	*p*-value
Median PFS*	NR	18.9 mo	0.16	<0.0001
Median OS	NR	NR	0.16	0.0010
24-month OS	97.8%	85.3%	—	—
Median EFS	NR	12 mo	0.17	<0.0001
ORR	86.0%	35.3%	—	—
CR/CRi	4.4%	1.5%	—	—
≥50% reduction in LNB	91.2%	36.8%	—	<0.0001
Select AEs (all grades)	**Ibr**		**Clb**	
Leading to discontinuation	9%		23%	
Atrial fibrillation	6%		1%	
Major hemorrhage	4%		2%	

IRC = independent review committee; HR = hazard ratio; PFS = progression-free survival; NR = not reached; OS = overall survival; EFS = event-free survival; ORR = overall response rate; CR = complete response; CRi = incomplete CR; LNB = lymph node burden; AEs = adverse events

* Consistent across subgroups, including ≥70 years, del(11q) and unmutated IGHV

- Rates of sustained hematologic improvements were significantly higher with Ibr versus Clb, including for patients with baseline anemia (84% versus 45%; $p < 0.0001$) or thrombocytopenia (77% versus 43%; $p = 0.0054$).
- Median duration of treatment was 17.4 mo with Ibr versus 7.1 mo with Clb.
- Hypertension was more frequent with Ibr but limited to Grade ≤3.

Tedeschi A et al. *Proc ASH* 2015;**Abstract 495**.

need to understand it better, but for right now, I would say it shouldn't preclude you from choosing ibrutinib for patients with even chronic atrial fibrillation if you feel it's the best agent to treat their CLL.

DR LOVE: How do idelalisib and ibrutinib "match up" in relapsed CLL, and how do you approach sequencing these agents?

DR COUTRE: Idelalisib is an effective agent. In our early trials of single-agent idelalisib, I couldn't tell you if its efficacy was any different from that of ibrutinib. The pattern of response is exactly the same, with rapid shrinkage of lymph nodes and lymphocytosis that resolves with time. However, the safety issues are different. Idelalisib does not cause bleeding issues or atrial fibrillation, but many patients may experience asymptomatic transaminitis. When this happens, idelalisib should be discontinued. The transaminitis usually resolves within a couple of weeks, after which idelalisib can be reinitiated. Most often, even without dose reduction, it never reoccurs.

As patients stay on the drug longer, we have also observed a diarrheal illness. The median time to its onset is about 9 months, although it can present up to 2 or 3 years after initiation of treatment. It appears as profuse, watery diarrhea, with all the characteristics of colitis. We've learned to treat it with steroids.

Outside of a trial setting, I'll choose either idelalisib or ibrutinib for patients with previously treated disease. Although I will not administer BR to a patient who received

first-line FCR, I will consider idelalisib or ibrutinib as second-line therapy. I tend to use ibrutinib to avoid idelalisib-associated colitis. We have limited experience with idelalisib after progression on ibrutinib or vice versa, but patients can respond.

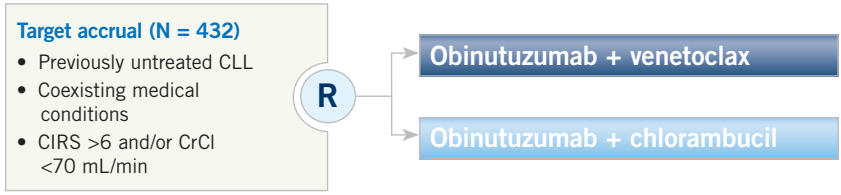
DR LOVE: What are your thoughts on the investigation of the novel second-generation Bcl-2 inhibitor venetoclax in CLL?

DR COUTRE: In a Phase I dose-escalation trial, venetoclax produced extremely high response rates, including among patients with heavily pretreated disease (Seymour 2013). However, it is associated with tumor lysis syndrome, but we have learned that a reduced initial dose followed by slow dose escalation decreases the likelihood of this toxicity. Several trials of venetoclax in CLL are ongoing, including the Phase III CLL14 trial evaluating obinutuzumab in combination with venetoclax or chlorambucil for patients with previously untreated CLL and coexisting comorbidities (1.2). ■

1.2

CLL14: A Phase III Trial of Obinutuzumab in Combination with Venetoclax or Chlorambucil for Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Coexisting Comorbidities

Protocol ID: NCT02242942



CIRS = cumulative illness rating scale; CrCl = creatinine clearance

- Prior to the randomized study, CLL14 includes a nonrandomized safety run-in phase to assess the tolerability of obinutuzumab and venetoclax
- **Primary endpoint:** Progression-free survival

Fischer K et al. *Proc ASH* 2015;**Abstract 496**; **www.clinicaltrials.gov**. Accessed December 2015.

SELECT PUBLICATIONS

Eichhorst B et al. **Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 study).** *Proc ASH* 2014;**Abstract 19**.

Fischer K et al. **Results of the safety run-in phase of CLL14 (BO25323): A prospective, open-label, multicenter randomized phase III trial to compare the efficacy and safety of obinutuzumab and venetoclax (GDC-0199/ABT-199) with obinutuzumab and chlorambucil in patients with previously untreated CLL and coexisting medical conditions.** *Proc ASH* 2015;**Abstract 496**.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.

Seymour JF et al. **Bcl-2 inhibitor ABT-199 (GDC-0199) monotherapy shows anti-tumor activity including complete remissions in high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).** *Proc ASH* 2013;**Abstract 872**.

Tedeschi A et al. **Results from the international, randomized phase 3 study of ibrutinib versus chlorambucil in patients 65 years and older with treatment-naïve CLL/SLL (RESONATE-2).** *Proc ASH* 2015;**Abstract 495**.

INTERVIEW

David P Steensma, MD

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

Tracks 1-9

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss some of the most promising new agents and strategies under investigation for patients with acute myeloid leukemia (AML)?

DR STEENSMA: One area of interest involves investigation of agents targeting FLT3 mutations, which are driver mutations commonly associated with AML. The 2 general classes of FLT3 mutations are internal tandem duplication (ITD) mutations and tyrosine kinase domain (TKD) mutations. Both constitutively activate the FLT3 receptor, but ITD mutations tend to be associated with more proliferative disease and a poorer prognosis, and they're more common than TKD mutations. Some kinase inhibitors will inhibit both ITD and TKD, and some will inhibit only ITD.

FLT3 inhibitors have typically shown relatively limited efficacy as single agents. They're often used in the salvage setting after the disease has relapsed. Sorafenib has FLT3-ITD inhibitory activity and has been used in relapsed/refractory FLT3-positive AML, resulting in remission in some patients. Data presented during the plenary session at ASH 2014 from a study in which sorafenib was added to "7 plus 3" chemotherapy indicated that patients receiving that combination fared better in terms of relapse-free survival. A trend toward improved OS regardless of FLT3 status was also apparent (Rollig 2014).

One novel FLT3 inhibitor that is active as a single agent in AML is gilteritinib (ASP2215). Single-agent gilteritinib has demonstrated a high complete response rate (Levis 2015; [2.1]). When you inhibit the FLT3 receptor, the cells upregulate the ligand to try to circumvent the inhibition, and that's been a challenge that some other FLT3 inhibitors have faced in the past that's delayed their development.

Another interesting agent in this drug class that is being evaluated in combination with 7 plus 3 is midostaurin. Exciting data from the Phase III CALGB-10603 (RATIFY) trial were presented at ASH 2015 (Stone 2015; [2.2]). These FLT3 inhibitors primarily differ with respect to the narrowness of their kinase inhibitory profiles.

2.1

Results of a Phase I/II Dose-Escalation Study of the Potent FLT3/AXL Inhibitor Gilteritinib (ASP2215) for Patients with Relapsed/Refractory Acute Myeloid Leukemia

	Clinical response by mutation status		
	FLT3 mutation-positive		FLT3 wild type
	20-450 mg (n = 127)	**≥80 mg** (n = 106)	**20-450 mg** (n = 57)
ORR (CRc + PR)	52%	57.5%	8.8%
CRc (CR + CRp + CRi)	40.9%	47.2%	5.3%
CR	6.3%	6.6%	0%
CRp	3.9%	4.7%	1.8%
CRi	30.7%	35.8%	3.5%
PR	11.0%	10.4%	3.5%

ORR = overall response rate; CR = complete remission; CRc = composite CR; PR = partial remission; CRp = CR with incomplete platelet recovery; CRi = CR with incomplete hematologic recovery

- Treatment-related adverse events included diarrhea (13.4%), fatigue (12.4%), anemia (7.2%), peripheral edema (7.2%), nausea (6.7%) and dysgeusia (5.2%).
- Serious adverse events included febrile neutropenia (27.3%), sepsis (11.9%), pneumonia (8.8%), hypotension (5.7%) and respiratory failure (5.7%).

Levis MJ et al. *Proc ASCO* 2015;**Abstract 7003**.

Tracks 8-9

CASE DISCUSSION: A 65-year-old woman with hydroxyurea-resistant polycythemia vera receives ruxolitinib

DR STEENSMA: Most patients with polycythemia vera fare well with only phlebotomy and aspirin or, if they are considered to be at higher risk, meaning they are older than age 60 or have experienced a prior thrombosis, then phlebotomy in combination with aspirin and hydroxyurea. Some patients don't fare so well, however, and this 65-year-old woman was one of them. She had received hydroxyurea after presenting with polycythemia vera, and one symptom that the hydroxyurea was unable to control was severe bone pain, especially in her ribs and spine. She also developed constitutional symptoms, such as night sweats, that weren't as severe.

We discussed other options, including pegylated interferon or ruxolitinib, to control her pain. She opted to try ruxolitinib, which was recently approved by the FDA for patients who are intolerant to or have inadequate response to hydroxyurea. Her bone pain did not completely go away but got much better, and ruxolitinib also improved

2.2

Phase III CALGB-10603 (RATIFY) Trial of Midostaurin in Combination with Daunorubicin/Cytarabine Induction and High-Dose Cytarabine Consolidation and as Maintenance Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutations

Efficacy	Midostaurin (n = 360)	Placebo (n = 357)	Hazard ratio	*p*-value
Median OS	74.7 mo	26.0 mo	0.77	0.007
Median OS, SCT censored*	NR	NR	0.77	0.047
Median EFS	8.0 mo	3.0 mo	0.80	0.0044
Median EFS, SCT censored*	8.2 mo	3.0 mo	0.84	0.025

OS = overall survival; SCT = stem cell transplant; NR = not reached; EFS = event-free survival

* Censored for transplant analyses

No statistically significant differences were observed in the overall rate of Grade ≥3 hematologic or nonhematologic adverse events between midostaurin and placebo.

Stone RM et al. *Proc ASH* 2015;**Abstract 6**.

her associated symptoms. So I believe a small niche exists in polycythemia vera for JAK inhibitors, but by no means should they be the first-line therapy because hydroxyurea is inexpensive and we have many years of experience with it.

DR LOVE: What is your clinical experience with patients in whom ruxolitinib needs to be discontinued?

DR STEENSMA: One of the most common questions I hear from community oncologists is whether ruxolitinib can be discontinued for patients who are not faring well. I was involved in the early trials of ruxolitinib, and when patients were hospitalized for an infection, for example, and ruxolitinib was stopped suddenly, their condition became much worse. They experienced something of a "cytokine storm," and a couple of patients had to be intubated or even died.

An infection or major operation will trigger cytokine release, so a patient who is acutely ill with an infection is not someone for whom you want to suddenly stop a JAK inhibitor, because JAK inhibitors block cytokine signaling. Ruxolitinib is a highly potent inhibitor of cytokines involved in infection and inflammation. That's probably why patients feel much better and why their symptoms improve after starting therapy with ruxolitinib.

If you suddenly stop the JAK inhibitor, you reverse the benefit received from treatment and patients can become seriously ill. So JAK inhibitors should not be stopped abruptly in those situations. But it is acceptable to stop ruxolitinib "cold turkey" in certain cases — for example, for patients who are chronically ill and have been receiving ruxolitinib for 3 to 4 months without any benefit. ■

SELECT PUBLICATIONS

Levis MJ et al. **Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML).** *Proc ASCO* 2015;**Abstract 7003**.

Rollig C et al. **Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: Results from 267 patients treated in the randomized placebo-controlled SAL-SORAML trial.** *Proc ASH* 2014;**Abstract 6**.

INTERVIEW

Philippe Moreau, MD

Dr Moreau is Professor of Hematology and Head of the Hematology Department at University Hospital Hotel-Dieu in Nantes, France.

Tracks 1-15

Track 1 **Case discussion:** An 82-year-old man with newly diagnosed Stage III, IgG kappa multiple myeloma (MM) receives lenalidomide/dexamethasone

Track 2 Results of the Phase III FIRST trial of lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM

Track 3 Continuous versus fixed duration of Rd treatment

Track 4 Dosing of lenalidomide in elderly patients with MM

Track 5 Effect of adverse cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed MM treated with continuous Rd

Track 6 Results of a Phase I/II trial of the newly FDA-approved oral proteasome inhibitor ixazomib in combination with Rd for previously untreated MM

Track 7 Results of the Phase III TOURMALINE-MM1 trial: Improvement in progression-free survival with the addition of ixazomib to Rd for patients with relapsed/refractory MM

Track 8 Perspective on the development and potential role of the oral proteasome inhibitor oprozomib

Track 9 **Case discussion:** A 62-year-old woman whose disease relapses 2 years after autologous stem cell transplant (ASCT) is enrolled on the ASPIRE study and achieves a complete remission with carfilzomib/Rd (CRd)

Track 10 Therapeutic options for induction and maintenance therapy in patients with MM

Track 11 Activity and tolerability of CRd

Track 12 Incidence and management of carfilzomib-associated dyspnea

Track 13 Perspective on the integration of CRd and panobinostat/bortezomib/dexamethasone into the treatment landscape for relapsed/refractory MM

Track 14 Results of ELOQUENT-2: A Phase III trial of lenalidomide/dexamethasone with or without the newly FDA-approved monoclonal antibody elotuzumab for relapsed/refractory MM

Track 15 Activity of the newly FDA-approved anti-CD38 antibody daratumumab for heavily pretreated or double-refractory MM

Select Excerpts from the Interview

Tracks 2-3, 5

DR LOVE: You were one of the investigators on the Phase III FIRST trial of lenalidomide and dexamethasone for transplant-ineligible patients with multiple myeloma (MM). Would you discuss the results of this study (Benboubker 2014)?

DR MOREAU: This trial was primarily for patients age 65 or older. It was a 3-arm study comparing melphalan/prednisone/thalidomide (MPT) for 12 cycles to lenalidomide/

low-dose dexamethasone (Rd) for 18 cycles or continuously until disease progression. A total of 1,623 patients were enrolled and randomly assigned in a 1:1:1 ratio. The primary endpoint was PFS. The study clearly demonstrated that continuous Rd was superior with a median PFS of 25.5 months versus 20.7 months with Rd for 18 cycles and 21.2 months with MPT. Continuous Rd was also associated with a clear OS benefit.

I believe that Rd should be used continuously until disease progression if patients are able to tolerate the combination. Reviewing the data carefully, approximately 35% of patients older than 75 years on the continuous Rd arm had to discontinue treatment because of adverse events such as gastrointestinal (GI) toxicity, fatigue, neutropenia or infections. The message is that continuous Rd should be tried if possible and discontinued when necessary.

DR LOVE: Would you provide some insight into the results of the subanalysis of the "FIRST" trial investigating the effects of cytogenetics on treatment outcomes that were recently presented at the ASH 2015 meeting (Avet-Loiseau 2015; [3.1])?

DR MOREAU: In the relapsed setting, it is known that Rd is less effective for patients with poor cytogenetics. This can also be true in the up-front setting. If a patient presents with disease harboring the t(4;14) translocation, a 3-drug combination such as RVd-lite is probably a good regimen to consider, with the use of once-weekly bortezomib to limit toxicity.

3.1

Effect of Cytogenetics on Treatment Outcomes for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM) Treated with Lenalidomide/Low-Dose Dexamethasone (Rd) in the Phase III FIRST Trial

Median PFS	High risk (n = 142)	Nonhigh risk (n = 620)	All patients (n = 762)
Rd continuous	8.4 mo	31.1 mo	25.3 mo
Rd18	17.5 mo	21.2 mo	20.4 mo
MPT	14.6 mo	24.9 mo	23.3 mo
Three-year OS	n = 142	n = 620	n = 762
Rd continuous	40.7%	77.1%	70.7%
Rd18	39.6%	71.0%	64.9%
MPT	46.8%	64.8%	61.5%
ORR	n = 142	n = 620	n = 762
Rd continuous	76.7%	81.0%	80.2%
Rd18	67.3%	79.9%	77.4%
MPT	68.1%	70.9%	70.4%

PFS = progression-free survival; Rd18 = Rd for 18 cycles; MPT = melphalan/prednisone/thalidomide; OS = overall survival; ORR = overall response rate

Conclusions: These data support the use of continuous Rd as a standard treatment option for patients with NDMM who are ineligible for transplant, especially those without high-risk cytogenetics. Additional PFS and OS benefits may be achieved in patients with high-risk cytogenetics when continuous Rd is used as a backbone for combination therapy with a novel agent.

Avet-Loiseau H et al. *Proc ASH* 2015;**Abstract 730**.

Tracks 7-8

DR LOVE: What are some of the key ongoing trials evaluating oral proteasome inhibitors for patients with MM?

DR MOREAU: Two Phase III TOURMALINE trials of ixazomib in combination with lenalidomide/dexamethasone in MM are ongoing. One is for patients with relapsed/refractory MM (TOURMALINE-MM1). The other is for patients with newly diagnosed MM (NCT01850524). The latter is dedicated to patients who are not eligible for stem cell transplant.

At the ASH 2015 meeting, I will present the results of the pivotal Phase III TOURMALINE-MM1 trial (Moreau 2015; [3.2]). The study will show an improvement in PFS with ixazomib. Based on the results of this study, I believe ixazomib in combination with lenalidomide/dexamethasone will soon be FDA approved as treatment for patients with MM who have received 1 prior therapy. Because this was an international study, the triplet regimen should also be approved in Europe soon.

Oprozomib is another oral proteasome inhibitor. It's currently under investigation in Phase II trials. Ixazomib was quickly developed based on the simplicity of the dosing schedule. Although ixazomib is associated with no important toxicity, oprozomib is. Oprozomib causes significant GI toxicity, so its formulation is currently under investigation. As yet, the optimal dose of oprozomib is unknown, and a lot of work must be done for its clinical development.

Editor's note: Subsequent to this interview, on November 20, 2015 the FDA granted approval to ixazomib in combination with lenalidomide/dexamethasone as treatment for patients with MM who have received 1 prior therapy.

3.2

TOURMALINE-MM1: Efficacy and Safety Results of a Phase III Trial of Lenalidomide (R) and Dexamethasone (d) with or without Ixazomib (I) for Patients with Relapsed or Refractory Multiple Myeloma

Efficacy	**IRd** (n = 360)	**Rd** (n = 362)	Hazard ratio	*p*-value
Median progression-free survival	20.6 mo	14.7 mo	0.742	0.012
Response	**IRd**	**Rd**	Odds ratio	*p*-value
Overall response rate	78.3%	71.5%	1.44	0.035
Median duration of response	20.5 mo	15.0 mo	Not reported	Not reported
Select Grade ≥3 adverse events	**IRd**		**Rd**	
Neutropenia	19%		16%	
Thrombocytopenia	13%		5%	
Pneumonia	6%		8%	
Diarrhea	6%		2%	
Rash	4%		1%	
Renal failure	2%		3%	

Moreau P et al. *Proc ASH* 2015;**Abstract 727**.

Tracks 14-15

DR LOVE: Can you provide an overview of the monoclonal antibodies daratumumab and elotuzumab in the management of MM and where you think these agents are headed?

DR MOREAU: These monoclonal antibodies are one of the most important steps forward in the treatment of MM. In my opinion, the most fascinating agent in this class is daratumumab, an anti-CD38 monoclonal antibody. Daratumumab is not toxic, and it has single-agent activity in patients who have received 3 or more lines of prior therapy or have double-refractory MM (Lonial 2015a).

The median duration of response was approximately 8 months. I believe that the future use of daratumumab will likely be in combination with agents such as lenalidomide/dexamethasone or bortezomib/dexamethasone.

We are awaiting the results of the Phase III POLLUX trial of lenalidomide/dexamethasone with or without daratumumab in relapsed or refractory MM (NCT02076009). The trial quickly enrolled about 600 patients. The primary endpoint of the study is PFS. The secondary endpoints include OS, and we are hoping for an improvement in OS with daratumumab. I believe daratumumab will be the first monoclonal antibody to be FDA approved for MM and that it will be the most widely used one in the future.

Elotuzumab targets SLAMF7 but has no single-agent activity. In combination with lenalidomide, synergistic activity is evident. The results of the Phase III ELOQUENT-2 trial for patients with relapsed/refractory MM clearly demonstrated that lenalidomide/dexamethasone in combination with elotuzumab was superior to lenalidomide/dexamethasone alone in terms of PFS (Lonial 2015b). The results of the Phase III ELOQUENT-1 trial of lenalidomide/dexamethasone with or without elotuzumab for patients with newly diagnosed MM should also be presented soon (NCT01335399).

Editor's note: Subsequent to this interview, on November 16, 2015 the FDA granted accelerated approval to daratumumab for patients with MM who received at least 3 prior treatments, and on November 30, 2015 the FDA approved elotuzumab for use in combination with lenalidomide and dexamethasone for patients with MM following the failure of 1 to 3 prior therapies. ■

SELECT PUBLICATIONS

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906-17.

Lonial S et al. **Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius).** *Proc ASCO* 2015a;**Abstract LBA8512**.

Lonial S et al. **Elotuzumab therapy for relapsed or refractory multiple myeloma.** *N Engl J Med* 2015b;373(7):621-31.

Moreau P et al. **Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRd), significantly extends progression-free survival (PFS) for patients (pts) with relapsed and/or refractory multiple myeloma (RRMM): The phase 3 Tourmaline-MM1 study (NCT01564537).** *Proc ASH* 2015;**Abstract 727**.

INTERVIEW

Peter Martin, MD

Dr Martin is Assistant Professor of Medicine in the Division of Hematology/Oncology at Weill Cornell Medical College in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Track 4

DR LOVE: Would you discuss the Phase II study presented by your group at ASH 2014 evaluating the R^2 regimen of lenalidomide and rituximab for patients with untreated mantle-cell lymphoma (MCL) (Ruan 2014; [4.1])?

DR MARTIN: We've known for a long time that lenalidomide has significant activity in MCL. So we wanted to determine if a subset of patients with MCL could benefit from less aggressive therapy with R^2.

In this study patients with newly diagnosed MCL received R^2 as induction for 1 year, followed by R^2 maintenance until disease progression. Overall the regimen was reason-

ably well tolerated. Many patients required a dose reduction of lenalidomide. In some cases, we stopped the rituximab alone if patients developed infections.

To our surprise, the regimen was also remarkably effective. At 2 years, the PFS rate was about 85%. This is significant considering that the average PFS with R-CHOP is in the range of 18 months to 2 years (Ruan 2014; [4.1]).

One could argue that that the R^2 regimen is continuous therapy, as opposed to R-CHOP, which is intermittent over 18 weeks. Nonetheless, I believe that for patients with MCL who require treatment and have higher MIPI scores, these results are promising. In the future, I believe we'll see more trials that use continuous therapies with creative regimens in the up-front setting.

4.1

Phase II Trial of Lenalidomide with Rituximab (R^2) as Initial Treatment for Mantle-Cell Lymphoma

Efficacy	(n = 38)
ORR	84.2%
CR	52.6%
Median PFS	Not reached
2-year PFS	83.9%
Select adverse events	**Grade 3 or 4** (n = 38)
Neutropenia	47%
Thrombocytopenia	13%
Anemia	8%
Rash	26%
Tumor flare	11%

ORR = overall response rate; CR = complete response; PFS = progression-free survival

Ruan J et al. *Proc ASH* 2014;**Abstract 625**.

Tracks 5-6

DR LOVE: How do you approach the issue of maintenance rituximab for patients with MCL?

DR MARTIN: Our preference is to enroll patients with MCL who require treatment in the ECOG-E1411 trial. This is a US intergroup study in which patients with untreated MCL receive induction with BR with or without bortezomib. In the maintenance phase patients receive rituximab with or without lenalidomide for 2 years (NCT01415752).

Off study, we generally administer BR, but occasionally, for young patients with aggressive disease, we recommend a cytarabine-containing induction regimen followed by autologous stem cell transplant (ASCT). We do not routinely administer rituximab maintenance in the post-stem cell transplant setting.

Many oncologists do not consider rituximab maintenance after chemotherapy induction to be standard. We know that it's beneficial after R-CHOP. The European Mantle Cell Lymphoma Network study in older patients with MCL showed compelling data

with an OS benefit in patients who received ongoing rituximab maintenance after that regimen (Kluin-Nelemans 2012). We don't have data on the efficacy of rituximab maintenance after BR, but we prefer to give patients the benefit of the doubt and often offer them rituximab maintenance.

DR LOVE: Can you talk about the results of the Phase III LYMA study evaluating the efficacy of rituximab maintenance in young patients with previously untreated MCL after R-DHAP followed by ASCT?

DR MARTIN: In the LYMA trial, young patients with newly diagnosed MCL received 4 cycles of R-DHAP induction therapy followed by ASCT and then were randomly assigned to rituximab maintenance versus watch and wait for 3 years. If patients did not achieve at least a partial response after R-DHAP, they could receive R-CHOP. However, most patients fared well with R-DHAP.

A clear benefit in PFS was observed, but no OS benefit has been achieved so far (Le Gouill 2014; [4.2]). The lack of evidence of an OS benefit is the main reason that I do not recommend rituximab maintenance after ASCT. I would like to see the data published and evaluated in a peer review setting. The other reason I don't offer it is that we don't do ASCT for many patients at our center.

4.2

First Interim Analysis of the Phase III LYMA Trial of Rituximab Maintenance versus Watch and Wait After R-DHAP and Autologous Stem Cell Transplant in Young Patients with Untreated Mantle-Cell Lymphoma

Efficacy	Rituximab (n = 119)	Watch and wait (n = 119)	*p*-value
Two-year EFS	93.2%	81.5%	0.015*
Two-year OS	93.4%	93.9%	NS

EFS = event-free survival; OS = overall survival; NS = not significant

* Hazard ratio = 2.1

Progression-free survival was statistically significant between the study arms ($p = 0.015$).

Le Gouill S et al. *Proc ASH* 2014;**Abstract 146**.

Tracks 12-14

DR LOVE: Would you discuss the study that led to the approval of idelalisib for follicular lymphoma (FL) and how that agent fits into your practice?

DR MARTIN: Idelalisib was approved by the FDA based on a Phase II trial in which patients with FL that was refractory to both rituximab and an alkylating agent received single-agent idelalisib. In this treatment-resistant group of patients, the median PFS was 11 months and the response rate was 57% (Gopal 2014). So patients without other good options responded well to idelalisib.

Interestingly, that study included a variety of histologies, but the FDA approved idelalisib only for patients with FL who had received at least 2 prior therapies. We generally recommend idelalisib for patients with disease that is refractory to rituximab and an alkylating agent. When patients do not have a lot of other treatment options, idelalisib is an attractive agent.

It is also a good option for older patients and those who have to travel long distances and prefer to have an oral agent. At our academic center at Cornell, we have multiple clinical trials open for these patients. We offer single-agent idelalisib for patients who don't want to participate in these studies.

DR LOVE: What do you recommend for patients with FL who experience relapse after up-front BR?

DR MARTIN: Most patients with FL in the United States receive BR as front-line therapy, although some patients still undergo treatment with R-CHOP. We have good data for bendamustine-based therapies in the second-line setting as well. We don't have data on the efficacy of R-CHOP for patients whose disease progresses on bendamustine-based therapy.

FL is a heterogeneous disease. Some patients experience progression quickly and are likely to have chemotherapy-resistant disease. These patients are at high risk and require immediate treatment. One approach is to administer more intensive chemotherapy. If they've received an anthracycline, ICE and DHAP would be options. Otherwise, R-CHOP followed by ASCT for patients who are eligible for transplant would be reasonable. Another alternative would be to try an approach without chemotherapy. Idelalisib would be a good option, particularly for older patients who are not candidates for an anthracycline-based regimen or ASCT.

Patients who experience disease progression late after BR or R-CHOP may not need treatment for a long period of time. My preference is to observe these patients. I believe it's important to remember that we're not treating FL to cure it but rather to improve longevity and, most importantly, improve quality of life. If patients do need treatment, the same options as in the front-line setting can be considered, namely, single-agent rituximab, immunochemotherapy, idelalisib, lenalidomide or a clinical trial.

DR LOVE: What is your view on the efficacy of the R^2 regimen for newly diagnosed FL?

DR MARTIN: R^2 is clearly active in FL. CALGB-50401 was a Phase II clinical trial in which patients with recurrent FL were randomly assigned to the R^2 regimen or lenalidomide alone. The R^2 arm was superior to lenalidomide (Leonard 2015). The CALGB-50803 study by our group also showed that this regimen was active as up-front therapy for patients with FL (Martin 2014).

I believe that based on the synergy between lenalidomide and rituximab they should be used in combination. However, lenalidomide is not yet approved by the FDA for the treatment of FL, and that has an effect on insurance coverage. ■

SELECT PUBLICATIONS

Gopal AK et al. **PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma.** *N Engl J Med* 2014;370(11):1008-18.

Kluin-Nelemans HC et al. **Treatment of older patients with mantle-cell lymphoma.** *N Engl J Med* 2012;367(6):520-31.

Leonard JP et al. **Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance).** *J Clin Oncol* 2015;133(31):3635-40.

Martin P et al. **CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Proc ASCO* 2014;**Abstract 8521**.

Ruan J et al. **Sustained remission with the combination biologic doublet of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma: A multi-center phase II study report.** *Proc ASH* 2014;**Abstract 625**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The results of the Phase III RESONATE-2 trial of ibrutinib versus chlorambucil for patients age 65 years or older with untreated CLL/SLL without 17p deletion demonstrated that single-agent ibrutinib is superior to chlorambucil in terms of _____.**
   a. PFS
   b. OS
   c. Event-free survival
   d. Overall response rate
   e. All of the above

2. **The ongoing Phase III CLL14 trial is evaluating obinutuzumab in combination with _____ or chlorambucil for patients with previously untreated CLL and coexisting comorbidities.**
   a. Venetoclax (ABT-199)
   b. Rituximab
   c. Bendamustine
   d. Ibrutinib

3. **Adverse events associated with idelalisib include _____.**
   a. Atrial fibrillation
   b. Hemorrhage
   c. Transaminitis
   d. Both a and b
   e. All of the above
   f. None of the above

4. **The Phase III CALGB-10603 (RATIFY) trial evaluating midostaurin in combination with daunorubicin/cytarabine induction therapy and cytarabine consolidation and as maintenance for patients with newly diagnosed AML with FLT3 mutations demonstrated a statistically significant improvement in _____ on the midostaurin arm.**
   a. OS
   b. Grade ≥3 hematologic adverse events
   c. Both a and b
   d. Neither a nor b

5. **The results of the Phase III TOURMALINE-MM1 trial of lenalidomide and dexamethasone with or without ixazomib for patients with relapsed or refractory MM failed to demonstrate a statistically significant improvement in PFS with the addition of ixazomib.**
   a. True
   b. False

6. **_____ is an anti-CD38 monoclonal antibody with single-agent activity that recently received FDA approval as treatment for patients with MM who have received at least 3 prior lines of therapy.**
   a. Elotuzumab
   b. Daratumumab
   c. Ixazomib

7. **The results of the Phase III FIRST trial of lenalidomide and low-dose dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with MM demonstrated that _____ is the superior regimen in terms of PFS and OS.**
   a. Rd continuously administered until disease progression
   b. Rd administered for 18 cycles
   c. MPT administered for 12 cycles

8. **The first interim analysis of the Phase III LYMA trial of rituximab maintenance therapy versus watch and wait after R-DHAP and ASCT for young patients with untreated MCL demonstrated a statistically significant improvement in _____ with rituximab maintenance.**
   a. Event-free survival rate at 2 years
   b. OS rate at 2 years
   c. PFS
   d. Both a and c
   e. All of the above

9. **Side effects observed with the lenalidomide/rituximab combination in the treatment of MCL include _____.**
   a. Neutropenia
   b. Rash
   c. Thrombocytopenia
   d. All of the above

10. **Idelalisib has been approved by the FDA for the treatment of FL that is _____.**
    a. Refractory to 1 prior line of therapy
    b. Refractory to 2 prior lines of therapy
    c. Previously untreated

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 2015

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

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

	BEFORE	AFTER
Activity and incidence of tumor lysis syndrome with the novel second-generation Bcl-2 inhibitor venetoclax (ABT-199) in CLL	4 3 2 1	4 3 2 1
Effect of cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed MM treated with continuous Rd on the Phase III FIRST trial	4 3 2 1	4 3 2 1
Novel agents under investigation for FLT3-ITD-mutated AML (ie, gilteritinib, midostaurin)	4 3 2 1	4 3 2 1
Activity and tolerability of the recently FDA-approved anti-CD38 antibody daratumumab for heavily pretreated or double-refractory MM	4 3 2 1	4 3 2 1
Sustained remission with the lenalidomide/rituximab (R^2) regimen as initial therapy for MCL	4 3 2 1	4 3 2 1
Use of single-agent obinutuzumab for previously untreated CLL	4 3 2 1	4 3 2 1

Practice Setting:

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☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

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

☐ Yes ☐ No
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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:

- Reevaluate your current treatment approach for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data. . . . . 4 3 2 1 N/M N/A
- Customize the selection of systemic therapy for patients with newly diagnosed and progressive mantle-cell lymphoma, recognizing the recent addition of bortezomib, lenalidomide and ibrutinib as FDA-endorsed options. . . . . 4 3 2 1 N/M N/A
- Develop a rational plan to incorporate B-cell receptor signaling inhibitors and novel CD20 monoclonal antibodies into the treatment of chronic lymphocytic leukemia and other B-cell neoplasms. . . . . 4 3 2 1 N/M N/A
- Incorporate newly approved agents and strategies in the treatment of newly diagnosed and relapsed or refractory multiple myeloma. . . . . 4 3 2 1 N/M N/A

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

- Develop an understanding of the biologic rationale for and early efficacy data with the use of immunotherapeutic approaches for patients with various hematologic cancers. . . . . 4 3 2 1 N/M N/A
- Recognize the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment. . . . . 4 3 2 1 N/M N/A

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David P Steensma, MD	4 3 2 1	4 3 2 1
Philippe Moreau, MD	4 3 2 1	4 3 2 1
Peter Martin, 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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This activity is supported by educational grants from Astellas Pharma Global Development Inc, Celgene Corporation, Genentech BioOncology, Incyte Corporation, Janssen Biotech Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Seattle Genetics, Takeda Oncology and Teva Oncology.

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Release date: January 2016
Expiration date: January 2017
Estimated time to complete: 3 hours