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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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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

- Develop an understanding of the biologic rationale for and early efficacy and toxicity data with the use of chimeric antigen receptor (CAR)-directed T-cell therapy and, where appropriate, facilitate patient access to ongoing trials of this investigational approach.
- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction, consolidation and maintenance treatment approaches for patients with multiple myeloma.
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors and the protein translation inhibitor omacetaxine as therapeutic options for patients with chronic myeloid leukemia.
- Effectively integrate the evidence-based use of novel induction and maintenance therapeutic strategies into the individualized care of patients with indolent B-cell lymphomas.
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients.

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FACULTY — **Dr Rajkumar** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Porter** — Contracted Research: Novartis Pharmaceuticals Corporation; Other Remunerated Activities: Genentech BioOncology (faculty and spouse). **Dr Evens** — Advisory Committee and Contracted Research: Celgene Corporation, Millennium: The Takeda Oncology Company, Seattle Genetics. **Dr Cortes** — Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

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INTERVIEW

David L Porter, MD

Dr Porter is the Jodi Fisher Horowitz Professor of Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center at the University of Pennsylvania Health System in Philadelphia, Pennsylvania.

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Tracks 1-6

DR LOVE: Would you talk about the principles of chimeric antigen receptor (CAR) T-cell therapy?

DR PORTER: The advent of lentiviral vectors has allowed us to efficiently deliver genetic material into T cells. Another major advance in CAR T-cell therapy is the ability to expand T cells ex vivo to numbers that are clinically meaningful. The development of anti-CD3/CD28-coated magnetic beads, to engage the T-cell receptor with appropriate costimulation, allowed the activation and expansion of T cells in culture.

The inclusion of new signaling molecules in the CAR causes robust proliferation and improves the antitumor activity of the T cells. These signaling molecules provide a survival signal to the T cells so they can persist for a long time. One of the most interesting recent findings is that genetically modified T cells can be infused into a patient and can expand by 1,000-fold or more, with long-term persistence.

It has been known for a long time that you could redirect the target of an autologous T cell. Preclinical studies showed that the genetically modified redirected T cells could kill cancer cells expressing the appropriate target.

Experiments in mice revealed that these modified T cells could undergo robust proliferation. Various iterations of the CAR were tested, and we were able to optimize the signaling and cosignaling domains. Inclusion of the 4-1BB costimulatory domain was shown to make the CAR more potent. This technology was also shown to be safe. The next step was to test it in clinical trials.

DR LOVE: Would you discuss the available clinical trial data with CAR T-cell therapy for patients with chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL)?

DR PORTER: Our group at the University of Pennsylvania has treated more than 70 cases of CLL and ALL. The CAR we have engineered targets CD19, a molecule expressed on the surface of most B-cell cancers. T cells are collected by leukapheresis and transduced with a lentivirus encoding the CAR construct. The genetically modified cells are expanded and activated in the laboratory. Patients are infused with the CAR-modified T cells in an outpatient setting.

The first 3 patients with CLL to whom we administered CAR T-cell therapy had incredibly rapid antitumor responses. All of the patients had heavily pretreated, extensive disease (Porter 2011). Although we expected this technology would work, we were surprised by the potency of the therapy.

At ASH 2013 we reported the updated results of a pilot trial of 14 patients with relapsed/refractory CLL. The overall response rate was 57%, with half of those being complete responses and half partial responses (Porter 2013a; [1.1]). Even the partial responses were remarkable and clinically meaningful. A number of patients had complete clearance of CLL from their blood and bone marrow. Patients with bulky adenopathy slowly improve over time.

The CLL trials are ongoing and early in development. However, 2 patients we had initially seen are in remission after about 3.5 years. They still have genetically modified T cells detectable in their blood and bone marrow. The follow-up on the other patients in remission ranges from about 3 to 18 months.

We have also treated relapsed/refractory ALL in adults and children who have a dismal prognosis. All 5 of the evaluable adult patients achieved a complete remission. We have a collaboration with Steve Grupp from Children's Hospital, who has administered CAR-modified T cells to pediatric patients with relapsed/refractory disease.

Many of the patients on the study had experienced relapse after allo-SCT. The complete remission rate was 82% with the CAR T-cell therapy (Grupp 2013; [1.2]). This has no precedent in relapsed/refractory ALL. Several of these patients have experienced relapse, but the ongoing complete remission rate is more than 50%, which is remarkable.

DR LOVE: What kinds of complications have you seen with CAR T-cell therapy?

DR PORTER: Delayed cytokine release syndrome (CRS) is observed in all responding patients between 4 and 20 days after infusion of CAR-modified T cells. This syndrome starts with febrile episodes, which can last a few days with fevers that are quite high. Patients have to be carefully evaluated to ensure there is no infection. Nausea, anorexia and in some cases severe myalgia and arthralgia can also occur (Porter 2013a). As it progresses with time, patients may develop hypotension and hypoxia, which may require intensive care.

1.1

Efficacy and Safety of CAR-Modified T Cells Directed Against CD19 in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

Efficacy	n = 14	Response in blood, marrow, nodes
Overall response rate	8 (57%)	NED
Complete response*	4 (28.5%)	PR (n = 2)
Partial response (PR)	4 (28.5%)	Blood, marrow NED, nodes PR (n = 2)

Select adverse events

- Cytokine release syndrome (CRS) in all responding patients
  - Characterized by high fever, myalgia, nausea, hypotension, hypoxia
  - Rapidly reversed with steroids (n = 1) or tocilizumab (n = 4)
- Tumor lysis syndrome coincident with T-cell expansion
- Hepatotoxicity (reversible, Grade 3/4 in 4 responding patients)
- Renal toxicity (Grade 3/4 in 4 patients)

Conclusions: CTL019 cells can undergo robust in vivo expansion and can persist for at least 3 years. CTL019 therapy is associated with a significant CRS that responds rapidly to anticytokine treatment. CTL019 cells can induce potent and sustained responses for patients with advanced, relapsed and refractory CLL regardless of p53 mutation status.

NED = no evidence of disease
* Minimal residual disease-negative

Porter DL et al. *Proc ASH* 2013a;**Abstract 4162**.

1.2

CAR T Cells Targeting CD19 (CTL019) Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence in Children and Adults with Relapsed, Refractory Acute Lymphoblastic Leukemia (ALL)

Response	n = 17
Complete response (CR)	82%
Ongoing bone marrow CR	64.7%

- CT019 cells undergo robust in vivo expansion and can persist for 15 months or longer in patients with relapsed ALL.
- These cells can induce potent and durable responses in patients with relapsed/refractory ALL.

Grupp SA et al. *Proc ASH* 2013;**Abstract 67**.

CRS is associated with high levels of IL-6 and can be rapidly reversed with the IL-6 receptor antagonist tocilizumab (1.1, 1.3). The toxicities associated with CAR T-cell therapy can be severe but in all cases have been reversible. We have not had any deaths related to the therapy.

Tumor lysis syndrome is observed in many cases and occurs concurrently with CRS. Both syndromes occur at the time of peak expansion of the genetically modified T cells. I believe they're both related to rapid T-cell proliferation. Complications from the tumor lysis syndrome can be prevented by administering a xanthine oxidase inhibitor such as allopurinol. Rasburicase is effective in treating the hyperuricemia associated with tumor lysis syndrome.

1.3

Managing Cytokine Release Syndrome (CRS) Associated with Novel T-Cell-Engaging Therapies

"CRS correlates with both toxicity and efficacy in patients receiving novel T cell-engaging therapies like CAR-modified T cells. Elevations in effector cytokines and cytokines associated with hemophagocytic lymphohistiocytosis or macrophage activation syndrome, such as interleukin (IL)-10 and IL-6, may be markedly elevated. Corticosteroids may control some of these toxicities. However, their potential to block T-cell activation and abrogate clinical benefit is a concern. One approach developed targets IL-6, a prominent cytokine in CRS, using the IL-6R antagonist tocilizumab."

Maude SL et al. *Cancer J* 2014;20(2):119-22.

DR LOVE: Is there a reason this therapy is not effective in some patients?

DR PORTER: We don't understand why this therapy works for some patients and not for others. We are currently trying to identify which patients may benefit. A randomized Phase II, dose-optimization study of CAR-modified T cells in patients with relapsed/refractory CLL is currently ongoing. A preliminary analysis of the results reported at ASH 2013 suggests that there is no dose-response or dose-toxicity effect (Porter 2013b; [1.4]).

We have ongoing studies investigating different factors of the patients' immune systems. The T-cell function of patients whose disease does and does not respond are being compared. As of now we have not been able to identify any factors that would predict which patients would experience response. ■

1.4

Correlation between CTL019 Dose and Response or Toxicity in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Response (n)	High dose (5×10^8) cells	Low dose (5×10^7) cells
Major response (CR + PR)	4	3
No response	5	6
Toxicity (n)	**High dose (5×10^8) cells**	**Low dose (5×10^7) cells**
CRS	5	6
No CRS	4	3

CR = complete response; PR = partial response; CRS = cytokine release syndrome

Porter DL et al. *Proc ASH* 2013b;**Abstract 873**.

SELECT PUBLICATIONS

Grupp S et al. **T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory ALL.** *Proc ASH* 2013;**Abstract 67**.

Maude SL et al. **Managing cytokine release syndrome associated with novel T cell-engaging therapies.** *Cancer J* 2014;20(2):119-22.

Porter DL et al. **Chimeric antigen receptor modified T cells directed against CD19 (CTL019 cells) have long-term persistence and induce durable responses in relapsed, refractory CLL.** *Proc ASH* 2013a;**Abstract 4162**.

Porter DL et al. **Chimeric antigen receptor therapy for B-cell malignancies.** *J Cancer* 2011;2:331-2.

INTERVIEW

S Vincent Rajkumar, MD

Dr Rajkumar is Professor of Medicine in the Division of Hematology and Chair of the Myeloma Amyloidosis Dysproteinemia Group at the Mayo Clinic in Rochester, Minnesota.

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Track 1 Redefining treatment parameters in smoldering multiple myeloma (MM)

Track 2 Survival advantage with lenalidomide in combination with low-dose dexamethasone compared to observation for patients with high-risk smoldering MM

Track 3 ECOG-E3A06: A Phase III trial of lenalidomide versus observation for asymptomatic high-risk smoldering MM

Track 4 Initial results of the Phase III FIRST trial of lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM

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Track 8 **Case discussion:** A 66-year-old patient with standard-risk MM with t(11;14) translocation achieves a complete response with RVD followed by autologous stem cell transplant

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Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What were the important points of your recently published article on redefining smoldering multiple myeloma (SMM) (Dispenzieri 2013)?

DR RAJKUMAR: Some features are associated with a high risk of disease progression. The earlier therapy is initiated, the easier it is to prevent the occurrence of bone disease, acute renal failure or vertebral compression fracture. At least 3 markers indicate that therapy should be initiated for MM regardless of whether a patient has end-organ damage. These are bone marrow with greater than 60% involvement, serum free light chain (FLC) ratio of 100 or greater and MRI scan of 1 or more focal lesion.

DR LOVE: Would you discuss the interventions available for high-risk SMM?

DR RAJKUMAR: In a Spanish trial of lenalidomide and dexamethasone (len/dex) versus observation for patients with high-risk SMM, early treatment prolonged time to disease

progression and increased overall survival (OS) (Mateos 2013; [2.1]). Although this study has some caveats in the sense that the definitions used for high-risk SMM are not widely accepted, it gives us confidence that early therapy is not harmful but has the potential to save lives.

I would encourage patient participation in the ongoing US ECOG-E3A06 trial of lenalidomide versus observation. The trial is evaluating patients with high-risk SMM with 10% or greater plasma cells in the bone marrow. Patients should have measurable monoclonal protein levels and an abnormal FLC ratio. With these criteria, the risk of disease progression is about 20% per year, meaning that 50% of patients will experience disease progression within 2 years.

This cohort of patients closely resembles the Spanish trial population. However, without the US trial, we will not be able to use single-agent lenalidomide for the treatment of MM outside the United States because regulatory bodies will not accept lenalidomide/dexamethasone as proof that lenalidomide works. Also, some differences exist between the 2 trials, including age differences and questions about the eligibility criteria in the Spanish trial. Therefore, a confirmatory trial is needed to ascertain whether lenalidomide is indeed useful in high-risk SMM.

2.1

Phase III Study of Induction Therapy with Lenalidomide (Len) in Combination with Dexamethasone Followed by Maintenance Len for Patients with High-Risk Smoldering Multiple Myeloma (SMM)

Survival	Treatment (n = 57)	Observation (n = 62)	Hazard ratio	*p*-value
Median time to progression	Not reached	21 months	0.18	<0.001
Three-year overall survival (OS) rate since enrollment	94%	80%	0.31	0.03
Five-year OS rate since SMM diagnosis	94%	78%	0.28	0.02
Responses	**Induction (n = 57)**	**Maintenance (n = 50)**	**Hazard ratio**	***p*-value**
Overall response rate	79%	90%	Not reported	
	Treatment (n = 62)		Observation (n = 63)	
Adverse events (induction)	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
Neutropenia	18%	5%	0%	0%
Anemia	24%	2%	5%	0%
Infections*	41%	6%	22%	0%
Asthenia	18%	6%	10%	0%
Diarrhea	21%	2%	4%	0%

* Grade 5 infection developed in 1 patient in the treatment group.

Mateos MV et al. *N Engl J Med* 2013;369(5):438-47.

Track 4

DR LOVE: Would you discuss the initial results of the Phase III FIRST trial for transplant-ineligible patients with newly diagnosed MM?

DR RAJKUMAR: This is a large study of 1,623 patients who received melphalan/prednisone/thalidomide (MPT) or lenalidomide/low-dose dexamethasone (Rd) (Facon 2013; [2.2]). It has 2 Rd arms — treatment for 18 months or continuously until disease progression. The study demonstrated an OS improvement with Rd. It's the first time a nonmelphalan-based regimen yielded better results in elderly patients with MM. Rd represents a new standard treatment in this setting.

In the United States, melphalan has not been widely used for elderly patients in the past 5 to 10 years. Outside the United States, where melphalan-based regimens are the standard, the FIRST trial changes that. Rd is a good option because it's oral. For patients with trisomies, it's a particularly good option. Elderly patients with high-risk cytogenetic features would be more likely to be candidates for a bortezomib-based regimen such as bortezomib/cyclophosphamide/dexamethasone (CyBorD).

DR LOVE: What are your thoughts on the differences observed between the 2 Rd arms?

DR RAJKUMAR: Unlike other MM treatments, Rd is chronically suppressive. The 18-month schedule yielded a TTP of 21.9 months, suggesting that once therapy is discontinued, the disease recurs. If this regimen is chosen, it needs to be administered on a chronically suppressive schedule until disease progression.

2.2

Initial Results from the Phase III FIRST Trial of Lenalidomide in Combination with Low-Dose Dexamethasone (Rd) versus MPT in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Outcome	Rd18 (n = 541)	Continuous Rd (n = 535)	MPT (n = 547)
Median PFS*	20.7 months	25.5 months	21.2 months
p-value	0.00001		—
	—	0.00006	
Four-year OS rate*	55.7%	59.4%	51.4%
p-value	0.307		—
	—	0.0168	
ORR	73.4%	75.1%	62.3%
Grade 3/4 adverse events	(n = 540)	(n = 532)	(n = 541)
Neutropenia	26.5%	27.8%	44.9%
Infections	21.9%	28.9%	17.2%
Anemia	15.7%	18.2%	18.9%
Pneumonia	8.3%	8.1%	5.7%
Thrombocytopenia	8.0%	8.3%	11.1%

PFS = progression-free survival; OS = overall survival; ORR = overall response rate
* No significant difference between Rd18 and MPT ($p > 0.05$)

Facon T et al. *Proc ASH* 2013;**Abstract 2**.

Tracks 6, 12

DR LOVE: How do you use the currently approved proteasome inhibitors in MM, and in what situations do you envision using novel agents in this class?

DR RAJKUMAR: With regard to carfilzomib, I believe it's a well-tolerated agent. Many of the initial renal problems with administration of this agent have been solved with dosing and fluid administration. Concern exists about cardiac or pulmonary side effects, which I pay attention to, but we need to better understand the frequency and exact mechanism of these issues.

Another point I want to make with regard to carfilzomib is the neuropathy rate. It does seem to be lower, but one caveat is that many of the carfilzomib trials excluded patients with preexisting neuropathy. So you have to be fair to bortezomib, in the sense that gauging the true rate of this neuropathy risk will require more studies in which carfilzomib is administered ahead of bortezomib. A Phase III Intergroup trial comparing bortezomib/lenalidomide/dexamethasone to carfilzomib/lenalidomide/dexamethasone is available across the United States. This kind of trial is necessary before we conclude that one regimen is better than the other.

These proteasome inhibitors are also useful as maintenance therapy. Each has a different side-effect profile and mode of administration (2.3). Based on the differences, these agents are suitable for different patients. Also, some noncross resistance occurs. For instance, carfilzomib works in patients for whom bortezomib has failed and vice versa.

Ixazomib is of particular interest because it's a once-weekly pill. This makes it a good drug for compliance, especially for elderly patients, and a more attractive maintenance approach. It's well tolerated at the right doses. ■

2.3 Key Features of the Proteasome Inhibitors Bortezomib, Carfilzomib and Ixazomib

Feature	Bortezomib	Carfilzomib	Ixazomib (MLN9708)
Generation	First in class	Second generation	Second generation
Inhibition type	Reversible inhibitor	Irreversible inhibitor	Reversible inhibitor
Half-life	110 minutes	<30 minutes	18 minutes
Mode of administration	Intravenous, subcutaneous	Intravenous	Oral
Most common associated side effects	Peripheral neuropathy, diarrhea	Fatigue, hematologic toxicity	Thrombocytopenia, fatigue, rash
Clinical stage	Approved for MM	Approved for R/R MM	Phase III trials in ND and R/R MM

MM = multiple myeloma; R/R = relapsed or refractory; ND = newly diagnosed

Moreau P et al. *Blood* 2012;120(5):947-59; Dick LR, Fleming PE. *Drug Discov Today* 2010;15(5-6):243-9.

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Dispenzieri A et al. **Smoldering multiple myeloma requiring treatment: Time for a new definition?** *Blood* 2013;122(26):4172-81.

Facon T et al. **Initial Phase 3 results of the FIRST (frontline investigation of lenalidomide + dexamethasone versus standard thalidomide) trial (MM-020/IFM 0701) in newly diagnosed multiple myeloma patients ineligible for stem cell transplantation.** *Proc ASH* 2013;**Abstract 2**.

Kunoczlpva L et al. **Proteasome inhibitors — Molecular basis and current perspectives in multiple myeloma.** *J Cell Mol Med* 2014;[Epub ahead of print].

Mateos MV et al. **Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma.** *N Engl J Med* 2013;369(5):438-47.

Usmani SZ. **How long can we let the myeloma smolder?** *Expert Rev Hematol* 2014;7(1):17-9.

INTERVIEW

Andrew M Evens, DO, MSc

Dr Evens is Professor of Medicine and Chief of the Division of Hematology/Oncology at Tufts Medical Center and Director of the Lymphoma Program and Interim Director at Tufts Cancer Center in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: Would you discuss your ongoing Phase II ECOG-E2408 trial of bendamustine/rituximab (BR) with or without bortezomib followed by rituximab with or without lenalidomide for high-risk follicular lymphoma (FL)?

DR EVENS: This is a 3-arm study with BR as the backbone for induction for 6 cycles followed by 2 years of rituximab maintenance (NCT01216683). Bortezomib is integrated as part of induction into 1 arm. Lenalidomide will be added to a third arm at 20 mg for a year as consolidation. The goal is to achieve high remission rates and long survival without a lot of side effects. Blood, bone marrow and tissue samples will be collected for correlative studies. Host genetics will be analyzed. We are trying to identify predictive markers to determine which patients will benefit from a specific therapy.

DR LOVE: Would you also discuss the Phase III LYM-3001 study of bortezomib/rituximab versus rituximab alone for relapsed/refractory FL?

DR EVENS: LYM-3001 was the largest randomized study ever conducted in FL, with more than 500 patients with relapsed FL randomly assigned to bortezomib/rituximab or rituximab alone. The results indicated an increase in progression-free survival of 1.8 months with bortezomib/rituximab versus rituximab (Coiffier 2011). That improvement, though statistically significant, was not clinically meaningful.

A retrospective follow-up study analyzed specific biomarkers to determine which patient subgroups might benefit from bortezomib/rituximab or rituximab alone. Patients who had a specific single-nucleotide polymorphism related to the proteasome level along with low expression of CD68, a marker associated with the number of tumor-infiltrating macrophages, had a significantly better PFS with the addition of bortezomib to rituximab, and a trend for an association with OS was observed (Coiffier 2013). We need such analysis in prospective studies to identify better predictive markers, and we'll evaluate these and other biomarkers in ECOG-E2408.

Track 7

DR LOVE: What is your take on the study presented at ASH 2013 comparing consolidation therapy with a single dose of ^{90}Y-ibritumomab tiuxetan to rituximab maintenance for patients with newly diagnosed FL?

DR EVENS: This randomized Phase II trial evaluated 2 years of rituximab maintenance or a single dose of ^{90}Y-ibritumomab tiuxetan consolidation in patients with newly diagnosed FL responding to R-CHOP. I thought any differences would be insignificant, so it was interesting that PFS analysis favored the rituximab arm (Lopez-Guillermo 2013; [3.1]). These data are not mature and will need further follow-up.

3.1

Phase II Study Comparing Consolidation Therapy with a Single Dose of ^{90}Y-Ibritumomab Tiuxetan to Rituximab Maintenance for Patients with Newly Diagnosed Follicular Lymphoma Responding to R-CHOP

Efficacy	Rituximab maintenance (n = 62)	^{90}Y-ibritumomab tiuxetan (n = 64)
Three-year progression-free survival	77%	63%
	Hazard ratio = 0.517, p = 0.044	

- No significant differences in overall survival or time to next treatment were observed between arms. The safety profile was reasonable with no unexpected toxicities in either arm.

Lopez-Guillermo A et al. *Proc ASH* 2013;**Abstract 369**.

I'm not sure these results will be practice changing. I believe the standard is still 2 years of rituximab maintenance. However, I might consider administering ^{90}Y-ibritumomab tiuxetan consolidation in certain situations — for example, for a patient who is planning to be out of town for a significant period.

Tracks 12-13, 15

DR LOVE: Would you discuss the Phase II study of single-agent brentuximab vedotin as front-line therapy for Hodgkin lymphoma (HL) in patients older than age 60 (Yasenchak 2013)?

DR EVENS: This is an interesting study. HL is a more virulent disease in older patients. This Phase II study reported a respectable response rate with single-agent brentuximab vedotin without chemotherapy. The critical question is whether the response will be durable. Will relapses occur because of the lack of an alkylating or chemotherapeutic agent? We will need to see those data. Even so, this would be an attractive treatment strategy for older patients who cannot tolerate chemotherapy.

DR LOVE: Your group presented a poster at ASH 2013 on pancreatitis as a serious adverse event in patients who are receiving brentuximab vedotin (Gandhi 2013). Would you discuss that data set?

DR EVENS: This study was initiated after an elderly woman, who was on an ongoing study of brentuximab vedotin for previously untreated HL, developed pancreatitis 9 days after the second dose of brentuximab vedotin and died a week later. She had no risk factors. An autopsy showed that she had no evidence of disease and both the tumor and pancreas were necrotic. High-resolution immunohistochemistry showed CD30 on her exocrine pancreatic cells. This is one of the few normal tissues that expresses CD30. We reached out to lymphoma specialists at other centers and were able to put together a total of 9 cases. Pancreatitis is a rare adverse event, but I believe it is real. It is on the label so practitioners are aware that pancreatitis should be considered in the differential diagnosis for a patient who presents with abdominal pain.

DR LOVE: What are your thoughts on the ongoing Phase II study of brentuximab vedotin for patients with relapsed/refractory CD30-positive NHL (Bartlett 2013)?

DR EVENS: This was one of the most important presentations at ASH 2013. The study demonstrated a good response rate with single-agent brentuximab vedotin for patients with relapsed/refractory diffuse large B-cell lymphoma, which is difficult to treat.

Response to brentuximab vedotin was irrespective of the intensity of CD30 levels, a theme that is also emerging in other studies. This could result in part from off-target effects. In addition, currently available staining techniques may not be highly sensitive and CD30 expression is probably higher than we can detect. We would not want to exclude patients from therapy because our technology cannot detect a certain marker. Hence, ongoing studies are evaluating the efficacy of brentuximab vedotin in B-cell lymphomas regardless of CD30 expression (eg, NCT01925612).

Track 17

DR LOVE: Would you comment on the results of the Phase III CLL11 trial comparing obinutuzumab/chlorambucil to rituximab/chlorambucil for patients with CLL and coexisting conditions?

DR EVENS: The study demonstrated an impressive benefit for obinutuzumab/chlorambucil compared to rituximab/chlorambucil in terms of PFS (Goede 2014; [3.2]). I believe the superiority of obinutuzumab compared to rituximab may be because of the way it binds to CD20, resulting in less complement-related cell death, increased direct cell killing and greater antibody-dependent cellular cytotoxicity. Obinutuzumab was recently approved for untreated CLL in combination with chlorambucil. I believe in the future it will be used in the front-line setting in combination with chemotherapy. ■

3.2

Final Stage II Results of the Phase III CLL11 Trial of Obinutuzumab/Chlorambucil (O-Clb) versus Rituximab/Chlorambucil (R-Clb) for Patients with Chronic Lymphocytic Leukemia and Comorbidities

Efficacy	O-Clb	R-Clb
Overall response rate (ORR) (n = 333, 329)	78.4%	65.1%
Complete response	20.7%	7.0%
Partial response	57.7%	58.1%
Median progression-free survival (PFS) (n = 333, 330)	26.7 mo	15.2 mo
Death rates (n = 333, 330)	8%	12%
Select Grade ≥3 adverse events	O-Clb (n = 241)	R-Clb (n = 225)
Infusion-related reaction	21%	4%
Neutropenia	35%	27%
Anemia	5%	4%
Thrombocytopenia	11%	4%
Infection	11%	13%

ORR: O-Clb versus R-Clb, $p < 0.001$; PFS: O-Clb versus R-Clb: hazard ratio (HR) = 0.39, $p < 0.001$

Death rates: O-Clb versus R-Clb: HR = 0.66, $p = 0.08$

Goede V et al. *New Engl J Med* 2014;370(12):1101-10.

SELECT PUBLICATIONS

Bartlett NL et al. **A Phase 2 study of brentuximab vedotin in patients with relapsed or refractory CD30-positive non-Hodgkin lymphomas: Interim results in patients with DLBCL and other B-cell lymphomas.** *Proc ASH* 2013;**Abstract 848**.

Coiffier B et al. **Prespecified candidate biomarkers identify follicular lymphoma patients who achieved longer progression-free survival with bortezomib-rituximab versus rituximab.** *Clin Cancer Res* 2013;19(9):2551-61.

Coiffier B et al. **Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive, follicular lymphoma: A randomised phase 3 trial.** *Lancet Oncol* 2011;12(8):773-84.

Gandhi M et al. **Pancreatitis in patients treated with brentuximab vedotin: A previously unrecognized serious adverse event.** *Proc ASH* 2013;**Abstract 4380**.

Goede V et al. **Head-to-head comparison of obinutuzumab (GA101) plus chlorambucil (Clb) versus rituximab plus Clb in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final stage 2 results of the CLL11 trial.** *Proc ASH* 2013;**Abstract 6**.

Yasenchak C et al. **A Phase 2 study of single-agent brentuximab vedotin for front-line therapy of Hodgkin lymphoma in patients age 60 years and above: Interim results.** *Proc ASH* 2013;**Abstract 4389**.

INTERVIEW

Jorge E Cortes, MD

Dr Cortes is DB Lane Cancer Research Distinguished Professor for Leukemia Research and Deputy Chairman and Section Chief of AML and CML in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-11

Track 1	Selection of an up-front tyrosine kinase inhibitor (TKI) in chronic myeloid leukemia (CML)
Track 2	Management of CML in patients who have not achieved a complete molecular response to TKI therapy
Track 3	Monitoring responses in patients with CML receiving TKI therapy
Track 4	Indications for changing TKI therapy and/or dose adjustments
Track 5	Incidence of renal dysfunction among patients with CML treated with TKIs
Track 6	Importance of patient compliance and close monitoring with TKI therapy
Track 7	Results of the STIM1 and STIM2 studies of imatinib cessation for patients with CML in chronic phase in deep molecular response
Track 8	Discontinuation of TKI therapy for patients with CML who wish to become pregnant
Track 9	Omacetaxine mepesuccinate: Ongoing evaluations of fixed dosages and combination with TKI therapy for CML
Track 10	Clinical experience with the second-generation TKI bosutinib for CML
Track 11	Recent FDA-revised indications and future directions for ponatinib in CML

Select Excerpts from the Interview

Tracks 1, 5-6

DR LOVE: Would you discuss what we know about the various approved tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML)?

DR CORTES: The long-term follow-up data of the ENESTnd trial of nilotinib (Saglio 2013) and the DASISION trial of dasatinib (Cortes 2013a) were presented at ASH 2013. The results are reassuring because they continue to be positive, with durable long-term responses and the incidence of deeper molecular responses continuing to be greater for patients who receive dasatinib or nilotinib compared to imatinib.

Longer follow-up data with imatinib also indicate that patients fare well (Kantarjian 2012). Although many no longer experience a response to imatinib, approximately 60% of those who started imatinib therapy about 10 to 15 years ago are still faring well.

Also, data show that higher doses of imatinib are effective in CML. Although this increases toxicity, in the long term the results are better. These results are important because generic imatinib will soon become available. However, for optimal results, I would treat CML with a second-generation TKI.

DR LOVE: Could you describe the study by your group presented at ASH 2013 evaluating the incidence of acute and chronic renal failure among patients with CML treated with TKIs?

DR CORTES: Any of the TKIs bring the potential for renal dysfunction. Long-term imatinib therapy may result in a decline in glomerular filtration rates (Yilmaz 2013; [4.1]). This seems to be more prominent with imatinib than with dasatinib or nilotinib. It is an event that we need to monitor carefully and one that needs to be addressed promptly. It will occur more frequently in elderly patients and those with risk factors such as diabetes and hypertension.

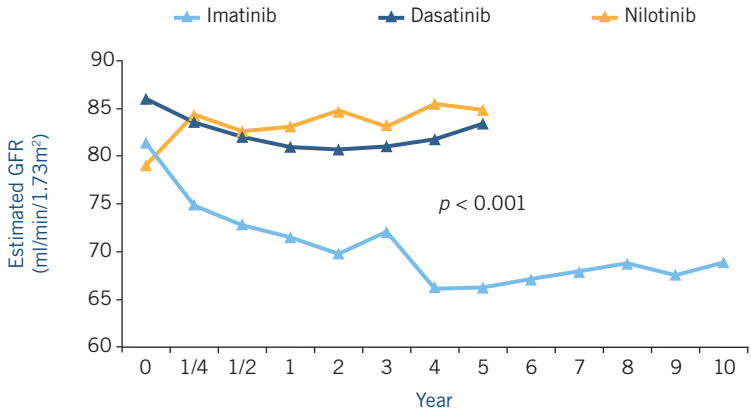
DR LOVE: Can you comment on patient compliance when undergoing TKI therapy?

DR CORTES: Some studies have addressed the time needed for TKI interruption for a patient to experience relapse. Patient adherence during the first 3 months was studied to assess how this affects the probability of achieving the best molecular response at 3 months (Apperley 2013). Patients who experienced any treatment interruption, even as short as 1 day, have a reduced probability of achieving a good response at 3 months. If it's more than 14 days, the chance of achieving the deeper molecular response is much lower.

Careful monitoring every 3 to 6 months allows you to discuss with the patient the importance of the long-term treatment goals. Also, it provides the opportunity to keep emphasizing what the results mean and what the potential implications of missing a dose could be. I discuss it every 3 to 6 months with all my patients.

4.1

Changes in Glomerular Filtration Rates (GFR) in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors (TKIs)



Conclusion: Long-term treatment with imatinib may cause a significant decline in estimated GFR. Interestingly, treatment with nilotinib may cause a slight improvement in GFR. It is important that patients are monitored for renal function during therapy with TKIs, with particular attention to those with risk factors for renal dysfunction.

With permission from Yilmaz et al. *Proc ASH* 2013;**Abstract 1488**.

Tracks 10-11

DR LOVE: What is your clinical experience with the second-generation TKI bosutinib?

DR CORTES: I use it frequently. Bosutinib works well after imatinib failure, achieving a similar response rate to dasatinib or nilotinib. It has activity in the third-line setting, with about 30% to 40% of patients achieving a major cytogenetic response. It's fairly safe and causes low cardiac toxicity. It is associated with gastrointestinal toxicity — diarrhea, in particular — which tends to be transient and manageable.

DR LOVE: What is the current status of ponatinib in CML, and how do you envision it being used in the future?

DR CORTES: Ponatinib is an outstanding agent from an efficacy viewpoint. Patients for whom 2 or more TKIs have failed or those with the T315I mutation achieve high response rates on ponatinib. None of the other TKIs is as potent.

The marketing and sales of ponatinib were temporarily suspended recently because of the risk of serious thrombosis and stenosis. However, ponatinib is back on the market but with more warnings to make physicians aware of these risks and so that patients are properly selected and carefully monitored to reduce these risks. Studies of front-line ponatinib were going on when its marketing was temporarily suspended. The results from a single-arm front-line study at our institution were outstanding (Cortes 2013b). I believe it can be used in many other settings. We need more studies, particularly exploring ways to reduce its toxicity.

Track 9

DR LOVE: Would you discuss the role of omacetaxine as a single agent or in combination therapy with a TKI for CML?

DR CORTES: Omacetaxine is a valuable agent, but its schedule of administration is unfriendly because it's administered subcutaneously twice a day. It has to be administered in the doctor's office. Future studies will investigate fixed doses and once-daily schedules. The combination of omacetaxine with a TKI will be attractive in blast-phase CML because the TKI alone is not good enough. We are about to start a study in which patients with minimal residual disease on a TKI will receive a small dose of omacetaxine in addition to the TKI. Although omacetaxine appears to be effective at eradicating leukemic stem cells in vitro, the TKIs are unable to do so. ■

SELECT PUBLICATIONS

Apperley JF et al. **Dose interruption/reduction of tyrosine kinase inhibitors in the first 3 months of treatment of CML is associated with inferior early molecular responses and predicts for an increased likelihood of discontinuation of the 1st line agent.** *Proc ASH* 2013;**Abstract 93**.

Cortes JE et al. **Four-year (yr) follow-up of patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: Efficacy based on early response.** *Proc ASH* 2013a;**Abstract 653**.

Cortes JE et al. **Ponatinib as initial therapy for patients with chronic myeloid leukemia in chronic phase (CML-CP).** *Proc ASH* 2013b;**Abstract 1483**.

Kantarjian H et al. **Very long-term follow-up results of imatinib mesylate therapy in chronic phase chronic myeloid leukemia after failure of interferon alpha therapy.** *Cancer* 2012;118(12):3116-22.

Saglio G et al. **ENESTnd update: Nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) and the impact of early molecular response (EMR) and Sokal risk at diagnosis on long-term outcomes.** *Proc ASH* 2013;**Abstract 92**.

Yilmaz M et al. **Estimated glomerular filtration rate changes in patients (pts) with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKI).** *Proc ASH* 2013;**Abstract 1488**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following is true regarding the CRS related to CAR T-cell therapy?**
   a. It manifests as fever, nausea, myalgia and hypotension
   b. It is associated with high levels of IL-6
   c. It is irreversible
   d. Both a and b

2. **Updated results of a pilot trial by Porter and colleagues of chimeric antigen receptor T-cell therapy for patients with relapsed/refractory CLL reported an overall response rate of _____.**
   a. 12%
   b. 57%
   c. 82%

3. **Tocilizumab, an IL-6 receptor antagonist, is effective at reversing the cytokine release syndrome associated with chimeric antigen receptor-modified T-cell therapy.**
   a. True
   b. False

4. **The results of a Phase III study of induction therapy with lenalidomide and dexamethasone followed by maintenance lenalidomide for patients with high-risk SMM demonstrated a statistically significant improvement in _____ versus observation only.**
   a. Time to disease progression
   b. Three-year OS rate
   c. Five-year OS rate
   d. All of the above

5. **The ongoing Phase III ECOG-E3A06 trial is evaluating _____ versus observation alone for patients with asymptomatic high-risk SMM.**
   a. Lenalidomide
   b. Lenalidomide in combination with low-dose dexamethasone
   c. Lenalidomide in combination with high-dose dexamethasone

6. **A Phase II study of single-agent brentuximab vedotin for the treatment of relapsed or refractory CD30-positive non-Hodgkin lymphomas demonstrated promising antitumor activity in patients with DLBCL with a broad range of CD30 expression levels.**
   a. True
   b. False

7. **Results from a Phase II trial comparing consolidation therapy with a single dose of ^{90}Y-ibritumomab tiuxetan to rituximab maintenance for patients with newly diagnosed FL who have experienced a response to R-CHOP demonstrated statistically significant differences in _____ favoring rituximab maintenance.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b

8. **The final Stage II results of the Phase III CLL11 trial for patients with CLL and coexisting medical conditions demonstrated that obinutuzumab/chlorambucil was superior to rituximab/chlorambucil in terms of _____.**
   a. Progression-free survival
   b. Overall response rate
   c. Both a and b

9. **Based on the results of a study by Yilmaz and colleagues, long-term treatment with _____ may result in a significant decline in the glomerular filtration rate in patients with CML.**
   a. Dasatinib
   b. Imatinib
   c. Nilotinib

10. **_____ is an FDA-approved potent TKI for the treatment of chronic myeloid leukemia that was temporarily suspended because of a risk of serious thrombosis and stenosis.**
    a. Ponatinib
    b. Bosutinib
    c. Dasatinib
    d. Omacetaxine mepesuccinate
    e. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 1, 2014

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
Responses to CAR-directed therapy and management of treatment-associated cytokine release syndrome in relapsed/refractory ALL and CLL	4 3 2 1	4 3 2 1
Survival advantage with and ongoing trials of lenalidomide versus observation for high-risk smoldering MM	4 3 2 1	4 3 2 1
Clinical trial results and ongoing studies of R^2 for FL and MCL	4 3 2 1	4 3 2 1
Rare incidence of brentuximab vedotin-associated pancreatitis	4 3 2 1	4 3 2 1
Importance of monitoring renal function among patients with CML receiving long-term TKI therapy and/or those with risk factors for renal dysfunction	4 3 2 1	4 3 2 1
Response and survival outcomes for patients with untreated CLL and comorbidities on the Phase III CLL11 trial evaluating obinutuzumab/chlorambucil or rituximab/chlorambucil versus chlorambucil alone	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:

- Develop an understanding of the biologic rationale for and early efficacy and toxicity data with the use of chimeric antigen receptor (CAR)-directed T-cell therapy and, where appropriate, facilitate patient access to ongoing trials of this investigational approach. . . . . 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, consolidation and maintenance treatment approaches 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 the protein translation inhibitor omacetaxine as therapeutic options for patients with chronic myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Effectively integrate the evidence-based use of novel induction and maintenance therapeutic strategies into the individualized care of patients with indolent B-cell lymphomas. . . . 4 3 2 1 N/M N/A
- Review emerging clinical trial data on the efficacy and safety of brentuximab vedotin for patients with CD30-positive lymphomas, and use this information to prioritize protocol and nonresearch options for these patients. . . . . 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
David L Porter, MD	4 3 2 1	4 3 2 1
S Vincent Rajkumar, MD	4 3 2 1	4 3 2 1
Andrew M Evens, DO, MSc	4 3 2 1	4 3 2 1
Jorge E Cortes, 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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