

# Hematologic Oncology™

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U P D A T E

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

**FACULTY INTERVIEWS**

Anas Younes, MD  
B Douglas Smith, MD  
Rafael Fonseca, MD  
John P Leonard, MD

**EDITOR**

Neil Love, MD

**CONTENTS**

2 Audio CDs  
Monograph



### OVERVIEW OF ACTIVITY

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

### LEARNING OBJECTIVES

- Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and relapsed/refractory Hodgkin lymphoma.
- Reevaluate current treatment approaches 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-approved options.
- Appreciate the FDA approvals of novel targeted agents — ibrutinib, idelalisib, obinutuzumab and venetoclax — for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia, and discern how these therapies can be appropriately integrated into the clinical management of standard- and high-risk disease.
- Recognize the recent FDA approvals of daratumumab, elotuzumab, ixazomib and panobinostat, and identify where and how these agents should be integrated into the clinical management of relapsed or refractory multiple myeloma.
- Assess 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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FACULTY INTERVIEWS



- 3 **Anas Younes, MD**  
Chief, Lymphoma Service  
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- 7 **B Douglas Smith, MD**  
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Division of Hematologic Malignancies  
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins  
Baltimore, Maryland



- 10 **Rafael Fonseca, MD**  
Getz Family Professor of Cancer  
Chair, Department of Internal Medicine  
Mayo Clinic Arizona  
Scottsdale, Arizona



- 14 **John P Leonard, MD**  
Richard T Silver Distinguished Professor of Hematology  
and Medical Oncology  
Associate Dean for Clinical Research, Weill Cornell Medical College  
New York, New York

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

EDITOR



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## INTERVIEW

### Anas Younes, MD

Dr Younes is Chief of the Lymphoma Service at Memorial Sloan Kettering Cancer Center in New York, New York.

### Tracks 1-13

- Track 1** **Case discussion:** A 29-year-old woman with Hodgkin lymphoma (HL) previously treated with autologous stem cell transplant (ASCT) followed by brentuximab vedotin receives nivolumab on a clinical trial
- Track 2** Brentuximab vedotin as initial salvage treatment on first relapse in HL
- Track 3** Activity and ongoing investigations of immune checkpoint inhibitors in HL
- Track 4** Brentuximab vedotin as consolidation therapy for patients with HL at high risk of disease progression after ASCT
- Track 5** Durability of response with brentuximab vedotin
- Track 6** Correlation between PD-L1 expression and response to anti-PD-1 antibodies in HL
- Track 7** ECHELON-1: A Phase III trial evaluating doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) versus brentuximab vedotin/doxorubicin/vinblastine/dacarbazine as front-line therapy for advanced classical HL
- Track 8** **Case discussion:** A 72-year-old man with Stage IV diffuse large B-cell lymphoma (DLBCL) achieves a complete response after 6 cycles of R-CHOP
- Track 9** Prognostic significance of DLBCL cell of origin
- Track 10** Dose-adjusted TEDDI-R (temozolomide/etoposide/pegylated liposomal doxorubicin/dexamethasone/ibrutinib/rituximab) and ibrutinib in primary CNS lymphoma
- Track 11** Mechanism of action, activity and tolerability of the novel antibody-drug conjugate denintuzumab mafodotin in relapsed/refractory B-lineage non-Hodgkin lymphoma
- Track 12** **Case discussion:** A 32-year-old man with relapsed/refractory anaplastic large cell lymphoma experiences a complete response with brentuximab vedotin
- Track 13** Approach to up-front therapy and sequencing of later-line options in patients with peripheral T-cell lymphoma

## Select Excerpts from the Interview

### Tracks 3, 6

- ▶ **DR LOVE:** Would you discuss the efficacy of immune checkpoint inhibitors and ongoing investigation of these agents for patients with Hodgkin lymphoma (HL)?
- ▶ **DR YOUNES:** Immune checkpoint inhibitors for HL are generating a lot of excitement because as single agents the anti-PD-1 antibodies nivolumab and pembrolizumab elicit response rates exceeding 60% in the relapsed/refractory setting (Younes 2016; [1.1]). These are patients for whom autologous transplant and brentuximab vedotin have failed. Because these agents are highly active in the relapsed/refractory setting, they are now being investigated as first- and second-line therapy.

## Efficacy and Safety of Nivolumab for Relapsed/Refractory Classical Hodgkin Lymphoma

Efficacy	Phase I CA209-039 study <sup>1</sup> (n = 23)	Phase II CheckMate 205 study <sup>2</sup> (n = 80)
Objective response rate	87%	66%
Complete response	22%	9%
Partial response	65%	58%
Median PFS	Not reached	10 mo
Overall survival rate	83% (1.5 y)	99% (6 mo)
<b>Select adverse events (any grade)</b>	<b>n = 23</b>	<b>n = 80</b>
Fatigue	NR	25%
Skin related	22%	41%
Gastrointestinal	17%	26%
Hepatic	9%	10%
Pulmonary	4%	1%
Endocrine disorders	17%	18%
Hypersensitivity/infusion reactions	9%	21%

PFS = progression-free survival; NR = not reported

<sup>1</sup>Ansell S et al. *Proc ASH* 2015; **Abstract 583**; <sup>2</sup>Younes A et al. *Proc ASCO* 2016; **Abstract 7535**.

Ongoing trials are combining anti-PD-1 antibodies with brentuximab vedotin in the first-line (NCT02758717) and second-line (NCT02572167, NCT01896999) settings. Clinical trials have also been designed to evaluate immune checkpoint inhibitors after treatment with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) and concurrently with ABVD or AVD (doxorubicin/vinblastine/dacarbazine).

► **DR LOVE:** What do we know about the biology of HL and why patients with this disease respond so well to immune checkpoint inhibitors?

► **DR YOUNES:** We're learning from the solid tumor experience in terms of what predicts response to anti-PD-1 antibodies. The higher the expression of PD-L1 on tumor cells, the more robust the response to these agents. Also, the higher the number of T cells in the tumor microenvironment, especially those that express PD-1, the better the response to anti-PD-1 antibodies.

Both these phenomena are observed in HL. Reed-Sternberg cells overexpress PD-L1 and PD-L2 because of amplification of chromosome 9p24.1. This amplification also involves the JAK2 locus, which increases both activity of the JAK/STAT pathway and PD-L1 expression. Furthermore, the HL tumor environment harbors a large number of T cells. These T cells can be reprogrammed with checkpoint inhibitors to mediate killing of the malignant cells.

**Editor's note: Subsequent to this interview, on May 17, 2016, the FDA granted accelerated approval to nivolumab for the treatment of classical HL that has relapsed or progressed after autologous hematopoietic stem cell transplant and post-transplant brentuximab vedotin therapy.**

## Tracks 4-5, 7, 11

▶ **DR LOVE:** The Phase III ECHELON-1 trial that you chair is evaluating ABVD versus brentuximab vedotin/AVD as front-line therapy for advanced classical HL (NCT01712490). What is the current status of that trial?

▶ **DR YOUNES:** This trial has completed accrual with more than 1,000 patients enrolled. In about 2 years we should have interim data. The Phase I trial of brentuximab vedotin in combination with AVD for newly diagnosed, advanced HL demonstrated a progression-free survival (PFS) rate of 92% after a 3-year follow-up, which is remarkable (Connors 2014). If the results of the randomized ECHELON-1 trial are positive, it will be practice changing for patients with HL.

▶ **DR LOVE:** What is known about predictors of response and durability of response to brentuximab vedotin in HL?

▶ **DR YOUNES:** Unfortunately we have no prognostic model to predict who will achieve a complete response (CR) to treatment with brentuximab vedotin. Most patients experience their best response after 4 to 5 cycles of therapy, so we assess response at that time. Patients who achieve a partial remission can maintain that response with continued dosing but are unlikely to achieve a CR. However, patients who achieve a CR could potentially be cured. Because the response is durable for many of the patients who achieve a CR, we don't rush to consider a hematopoietic stem cell transplant. We simply observe these patients, keeping in mind that they may require transplant in the future.

▶ **DR LOVE:** What are the key tolerability issues with brentuximab vedotin?

▶ **DR YOUNES:** This agent is fairly well tolerated. Neuropathy is one of the most common side effects, but it is usually only Grade 2 in severity. Once patients start experiencing severe neuropathy the dose can be reduced or interrupted to prevent any increase in severity.

▶ **DR LOVE:** The Phase III AETHERA trial evaluating brentuximab vedotin as consolidation therapy for patients at high risk of relapse after autologous stem cell transplant (ASCT) produced promising results (Moskowitz 2015a). What are your thoughts about using brentuximab vedotin as post-transplant maintenance?

▶ **DR YOUNES:** The AETHERA trial stipulated specific indications for the use of brentuximab vedotin. Eligible patients were those at high risk of relapse or disease progression after ASCT. These patients had extranodal disease before ASCT, or they had primary refractory disease and did not achieve a CR after transplant. I would consider maintenance brentuximab vedotin for such patients in my practice. However, some patients want a break from therapy and prefer to hold off until their disease progresses.

▶ **DR LOVE:** At ASH 2015 a study investigating another antibody-drug conjugate, denintuzumab mafodotin, for relapsed/refractory B-lineage non-Hodgkin lymphoma (NHL) reported promising results (Moskowitz 2015b). What was observed in that study?

▶ **DR YOUNES:** Denintuzumab mafodotin (SGN-CD19A) is an anti-CD19 monoclonal antibody conjugated to monomethyl auristatin F, a microtubule-disrupting agent. This antibody-drug conjugate was found to be active and elicited a 30% to 40% response rate

for patients with relapsed/refractory NHL. An unusual toxicity of the cornea occurs in some patients, typically after the second cycle. This side effect is generally reversible.

## Track 10

► **DR LOVE:** At ASH 2015 a study was reported evaluating ibrutinib as part of a novel regimen called DA-TEDDI-R (dose-adjusted temozolomide, etoposide, doxorubicin, dexamethasone, ibrutinib and rituximab) for patients with untreated and relapsed/refractory disease (Dunleavy 2015; [1.2]). What are your thoughts about that study?

► **DR YOUNES:** Primary CNS diffuse large B-cell lymphoma (DLBCL) has a predominantly activated B-cell phenotype, and ibrutinib is active in patients with relapsed/refractory DLBCL of this phenotype. This provided a rationale for investigating ibrutinib for primary CNS lymphoma.

This important trial first evaluated whether ibrutinib could penetrate the CNS. It also assessed single-agent activity and whether ibrutinib could be combined with chemotherapy. Surprisingly, most of the patients with relapsed/refractory primary CNS lymphoma responded to single-agent ibrutinib. This is promising for patients with this disease. ■

### 1.2

#### Phase I Study of Dose-Adjusted TEDDI-R with Ibrutinib for Patients with Untreated or Relapsed/Refractory (R/R) Primary CNS Lymphoma

- N = 14 patients with untreated or R/R primary CNS lymphoma.
- Ibrutinib and its active metabolite achieved meaningful cerebrospinal fluid concentrations of  $>IC_{50}$  for 2 to 10 hours.
- Of 11 evaluable patients, 10 achieved partial response to ibrutinib alone before cycle 1.
- Of 14 patients, 9 achieved complete response by month 3:
  - 3 of 6 patients with R/R disease maintained the complete response for  $>8$  months and 1 for  $>15$  months.
  - 1 of 3 patients with previously untreated disease experienced relapse at 6 months.

Dunleavy K et al. *Proc ASH* 2015; **Abstract 472**.

## SELECT PUBLICATIONS

Ansell S et al. **Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039).** *Proc ASH* 2015; **Abstract 583**.

Connors JM et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed advanced stage Hodgkin lymphoma: Long-term outcomes.** *Proc ASH* 2014; **Abstract 292**.

Dunleavy K et al. **Phase I study of dose-adjusted-TEDDI-R with ibrutinib in untreated and relapsed/refractory primary CNS lymphoma.** *Proc ASH* 2015; **Abstract 472**.

Moskowitz CH et al. **Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2015a;385(9980):1853-62.

Moskowitz CH et al. **A phase 1 study of denintuzumab mafodotin (SGN-CD19A) in relapsed/refractory B-lineage non-Hodgkin lymphoma.** *Proc ASH* 2015b; **Abstract 182**.

Younes A et al. **CheckMate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) — A phase 2 study.** *Proc ASCO* 2016; **Abstract 7535**.





## INTERVIEW

### B Douglas Smith, MD

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

#### Tracks 1-15

- Track 1** **Case discussion:** A 46-year-old woman with FLT3-ITD mutation-positive acute myeloid leukemia (AML)
- Track 2** Sorafenib in the up-front management of AML
- Track 3** Novel investigational agents for FLT3-ITD-mutated AML, including gilteritinib (ASP2215)
- Track 4** Perspective on the use of the multikinase inhibitor midostaurin for newly diagnosed AML
- Track 5** **Case discussion:** A 68-year-old woman with newly diagnosed, high-risk myelodysplastic syndrome (MDS) treated with azacitidine
- Track 6** Activity of the immunomodulatory drugs lenalidomide and pomalidomide in patients with MDS with and without del(5q)
- Track 7** **Case discussion:** A 26-year-old woman with chronic-phase chronic myeloid leukemia (CML) attains a complete cytogenetic remission with imatinib
- Track 8** Choice of first-line tyrosine kinase inhibitor (TKI) therapy in CML and role of generic imatinib
- Track 9** Treatment patterns, overall survival, healthcare resource use and costs in elderly patients with CML
- Track 10** Discontinuation of TKI therapy for patients with CML who wish to become pregnant
- Track 11** Perspective on the discontinuation of TKI therapy for patients with CML
- Track 12** Clinical overview of myeloproliferative neoplasms (MPNs)
- Track 13** When to intervene in MPNs: Clinical indications for ruxolitinib
- Track 14** JAK2 inhibitor-associated herpes zoster
- Track 15** Novel agents and strategies under investigation in MPNs

#### Select Excerpts from the Interview

##### Tracks 3-4

- ▶ **DR LOVE:** What are some of the most promising new agents and strategies under investigation for patients with FLT3-mutated acute myeloid leukemia (AML)?
- ▶ **DR SMITH:** FLT3 is becoming a phenomenally interesting and important target in AML because, (1) we can measure it, (2) it offers prognostic implications and (3) a handful of drugs are in development to target this mutation and evaluate if we can improve outcomes.

Interestingly, one of the plenary presentations at ASH 2015 reported on an agent in this class. One of the main questions this study presented by Dr Rich Stone addressed was, what's the role of an additional agent to block FLT3 in the induction and maintenance

settings after transplant? In this trial, the addition of the FLT3 inhibitor midostaurin to induction chemotherapy and maintenance therapy for patients with newly diagnosed AML with FLT3 mutations provided a benefit (Stone 2015; [2.1]).

Everyone is quite excited about these results, and I do believe that if this drug becomes available for this indication it will be widely used and will most likely replace sorafenib. Midostaurin is not a perfect drug. It has toxicities associated with it, so we do have some work still to do to refine our FLT3 inhibitors.

Gilteritinib (ASP2215) is another agent in this class, and it has been studied in the relapsed/refractory setting, alone and in combination, in addition to in patients without an FLT3-ITD mutation. Unlike most other FLT3 inhibitors, gilteritinib has significant single-agent activity (Levis 2015; [2.2]).

We are hoping that this agent becomes available. It would be great to have it as an option for a patient with primary refractory AML whose disease progresses on induction therapy because it could bring about a remission and the patient could then undergo allogeneic transplant.

2.1

**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  $\geq 3$  hematologic or nonhematologic adverse events between midostaurin and placebo.

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

 **Track 6**

► **DR LOVE:** What is known about the efficacy and tolerability of immunomodulatory drugs (IMiDs) in patients with myelodysplastic syndromes (MDS), particularly those with non-del(5q) disease?

► **DR SMITH:** Lenalidomide has been studied in patients with non-del(5q) MDS and is fairly effective. Obviously you have to weigh when it's appropriate to use. For instance, given a patient with low-risk disease and anemia who needed transfusions about once a month or once every 3 weeks, I'd consider lenalidomide, as about 25% or 30% of patients will have improvement of their hemoglobin and become transfusion independent on lenalidomide (Santini 2014). It's a pill the patient can take at home, and it's relatively well tolerated. You have to be careful of cytopenias, but you can easily manage patients on this agent.

## 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**.

I do juxtapose data on lenalidomide with studies of demethylating drugs, which provide a higher likelihood of a patient with low-risk MDS becoming transfusion independent but are much more cumbersome. However, the demethylating drugs are evolving, and oral formulations of both decitabine and azacitidine have been developed (William 2014).

When we inhibit methylation continually, patients can lose their response to subcutaneous or IV drugs. If we then administer an oral formulation, we provide a different demethylating pattern by administering the agent continually for 2 or 3 weeks followed by a week or 2 off. That opens the door to gaining a better understanding of how these agents work and how we're going to use them moving forward. We do not yet have many large studies with these oral demethylating agents, but we're learning.

► **DR LOVE:** What about other IMiDs in MDS, particularly pomalidomide?

► **DR SMITH:** We know that pomalidomide has a lot of activity in the immunologic space, though we don't always know how these agents work. Pomalidomide hasn't been studied as formally as lenalidomide in MDS, but it does hold some promise. A number of people believe that administering pomalidomide in combination with some of the other agents we use in MDS, such as a demethylating agent or a histone deacetylase inhibitor, can provide alternative ways to target MDS and may turn out to offer some benefit for a lot of our patients. ■

### SELECT PUBLICATIONS

Santini V et al. **Efficacy and safety of lenalidomide versus placebo in RBC-transfusion dependent patients with IPSS low/intermediate-risk myelodysplastic syndromes without del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents: Results from a randomized phase 3 study (CC-5013-MDS-005).** *Proc ASH* 2014; **Abstract 409**.

William BM et al. **CC-486 (oral azacitidine) following allogeneic hematopoietic stem cell transplantation (AlloHSCT) in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML).** *Proc ASH* 2014; **Abstract 990**.



## INTERVIEW

### Rafael Fonseca, MD

Dr Fonseca is Getz Family Professor of Cancer and Chair of the Department of Internal Medicine at Mayo Clinic Arizona in Scottsdale, Arizona.

#### Tracks 1-11

- Track 1** Available research data on carfilzomib- and bortezomib-based induction therapy for patients with multiple myeloma (MM)
- Track 2** Activity and tolerability of carfilzomib/ lenalidomide/dexamethasone (CRd) for relapsed MM
- Track 3** Integration of the newly FDA-approved oral proteasome inhibitor ixazomib into clinical practice
- Track 4** Selection of a post-transplant maintenance regimen
- Track 5** Perspective on the use of panobinostat for relapsed/refractory MM
- Track 6** Incorporation of the newly FDA-approved monoclonal antibody elotuzumab into the therapeutic algorithm for MM
- Track 7** Clinical experience with the newly FDA-approved monoclonal antibody daratumumab
- Track 8** **Case discussion:** A 72-year-old man with relapsed/refractory MM is admitted to the ICU with hyperammonemia and receives daratumumab
- Track 9** Monitoring and management of smoldering MM
- Track 10** Evaluating CRAB criteria for patients with MM
- Track 11** Up-front therapy options for patients with MM

#### Select Excerpts from the Interview

##### Tracks 3-7

► **DR LOVE:** Certainly 2015 was an exciting year in myeloma with 4 new drugs approved by the FDA. The histone deacetylase inhibitor panobinostat was approved in February, and in November we saw approvals of the oral proteasome inhibitor ixazomib in addition to the 2 monoclonal antibodies elotuzumab and daratumumab.

I'd like to get your thoughts on all these recently approved agents. Let's start with panobinostat, which was approved in combination with bortezomib and dexamethasone on the basis of the PANORAMA-1 trial for the treatment of multiple myeloma (MM) after at least 2 other therapies, including bortezomib and an IMiD (San-Miguel 2014; [3.1]). How do you integrate panobinostat into your practice?

► **DR FONSECA:** Panobinostat is arguably the first true bench-to-bedside discovery in MM. Although the Phase III PANORAMA-1 trial produced positive results, toxicity issues have prevented the widespread use of panobinostat (3.1). In particular it is associated with diarrhea and thrombocytopenia. But I still find panobinostat exciting because when it is administered at a different dose or in combination with carfilzomib or

**PANORAMA-1: A Phase III Trial of Panobinostat and Bortezomib/Dexamethasone (PVd) versus Placebo and Bortezomib/Dexamethasone (PlacVd) for Relapsed or Relapsed and Refractory Multiple Myeloma**

Outcome	PVd (n = 387)	PlacVd (n = 381)	Hazard ratio	p-value
Median PFS	11.99 mo	8.31 mo	0.63	<0.0001
Overall response rate	60.7%	54.6%	—	0.09
	<b>PVd (n = 381)</b>		<b>PlacVd (n = 377)</b>	
<b>Select adverse events</b>	<b>Any</b>	<b>Grade ≥3</b>	<b>Any</b>	<b>Grade ≥3</b>
Thrombocytopenia	98%	68%	84%	31%
Lymphopenia	83%	54%	74%	40%
Diarrhea	68%	25%	42%	8%
Peripheral neuropathy	61%	18%	67%	15%
Asthenia/fatigue	57%	24%	41%	13%

PFS = progression-free survival; overall survival data are not yet mature

San-Miguel JF et al. *Lancet Oncol* 2014;15(11):1195-206.

IMiDs, early data show promising results with less toxicity (Berdeja 2015). This raises the question of whether panobinostat might be used in a better way.

It has not gained much traction in the relapsed or even up-front settings, simply because we have so many other treatment options. I hope and expect that in the near future, as clinical trials continue to generate results, panobinostat will acquire a greater role as a therapeutic option. However, I doubt that it will be the prime contender for use at first or second relapse.

► **DR LOVE:** On the basis of the results of the TOURMALINE-MM1 trial, the FDA also recently approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of MM after disease progression on at least 1 prior therapy (Moreau 2016; [3.2]). What are your thoughts on the utility of ixazomib in clinical practice?

► **DR FONSECA:** In many ways you can think of ixazomib as an oral bortezomib. It has demonstrated proteasome inhibitor activity, and therefore it increases the depth of response and has the ability to control the disease.

So whenever you're considering bortezomib you could be considering ixazomib. Currently it is approved only for relapsed/refractory MM, but it will continue to move forward. I can envision that this might become part of front-line therapy, and several clinical trials are testing its efficacy in that setting. However, every agent comes with its pros and cons, and we are still learning about the best ways to administer ixazomib and manage its toxicities, especially gastrointestinal toxicity. It will take us 1 or 2 years to become more familiar with this agent.

► **DR LOVE:** Next let's talk about the 2 recently approved monoclonal antibodies. Elotuzumab was approved in combination with lenalidomide and dexamethasone for patients with MM who have received 1 to 3 prior therapies. This approval was based on the results of the Phase III ELOQUENT-2 trial (Lonial 2015; [3.3]). How do you envision this agent being used in practice?

## 3.2

**TOURMALINE-MM1: A Phase III Trial of Oral Ixazomib, Lenalidomide and Dexamethasone (IRd) versus Placebo, Lenalidomide and Dexamethasone (PRd) for Relapsed/Refractory Multiple Myeloma**

Outcome	IRd (n = 360)	PRd (n = 362)	Hazard ratio	p-value
Median progression-free survival	20.6 mo	14.7 mo	0.74	0.01
Overall response rate	78.3%	71.5%	—	0.04
	IRd (n = 361)		PRd (n = 359)	
Select adverse events	Any	Grade ≥3	Any	Grade ≥3
Thrombocytopenia	31%	19%	16%	9%
Rash	36%	5%	23%	2%
Diarrhea	45%	6%	39%	3%
Constipation	35%	<1%	26%	<1%
Vomiting	23%	1%	12%	<1%
Peripheral neuropathy	27%	2%	22%	2%

Moreau P et al. *N Engl J Med* 2016;374(17):1621-34.

## 3.3

**ELOQUENT-2: A Phase III Trial of Elotuzumab and Lenalidomide/Dexamethasone (ERd) versus Lenalidomide/Dexamethasone (Rd) Alone for Relapsed/Refractory Multiple Myeloma**

Outcome	ERd (n = 321)	Rd (n = 325)	p-value	
Median progression-free survival	19.4 mo	14.9 mo	<0.001; hazard ratio 0.7	
Overall response rate	79%	66%	<0.001; odds ratio 1.9	
	ERd (n = 318)		Rd (n = 317)	
Select adverse events	Any	Grade ≥3	Any	Grade ≥3
Lymphocytopenia	99%	77%	98%	49%
Thrombocytopenia	84%	19%	78%	20%
Neutropenia	82%	34%	89%	44%
Fatigue	47%	8%	39%	8%
Second primary cancer	7%	N/A	4%	N/A

N/A = not applicable

Lonial S et al. *N Engl J Med* 2015;373(7):621-31.

► **DR FONSECA:** It is possible to administer elotuzumab to a patient who experiences a biochemical relapse while receiving lenalidomide maintenance therapy after up-front lenalidomide/bortezomib/dexamethasone. However, I believe better options exist in that situation.

I am excited about the idea of clinical trials using elotuzumab up front in the nontransplant setting for patients who are eligible to receive lenalidomide/dexamethasone — for example, an elderly patient with hyperdiploid-variant MM and multiple trisomies without high-risk factors. This constitutes a large portion of the myeloma population, and I believe this is the niche in which elotuzumab will be most used. Importantly,

elotuzumab is one of the safest options in terms of infusional toxicity, and in general monoclonal antibodies are well tolerated.

► **DR LOVE:** Last but not least, the Phase I/II GEN501 study and the Phase II SIRIUS trial led to FDA approval of single-agent daratumumab for MM in patients who have received at least 3 other therapies (3.4). What is your clinical experience with daratumumab?

► **DR FONSECA:** I typically use daratumumab as monotherapy, although several of my colleagues have used it in combination with pomalidomide and dexamethasone. I have administered it mostly in the setting of extensive prior therapy. We have the occasional patient with advanced disease for whom it is difficult to achieve much response. On the other hand, we've been gratified by some patients whose aggressive disease has been well controlled with daratumumab.

Daratumumab can require prolonged infusion, and we schedule our patients to start early in the morning. Infusion reactions occur in about 50% of patients, in which case we stop therapy, treat the reaction and then restart the infusion at 50% of the rate when the reaction has subsided. Most patients are able to get through the first dose. If the infusion can be continued, instead of admitting the patient we finish the day with whatever we are able to administer and then go on to day 2. In my experience the first infusion has been completed in every case. Subsequently the infusions are shorter, in the area of 4 hours. ■

### 3.4

#### Efficacy and Safety Results with Daratumumab Monotherapy (16 mg/kg) from the GEN501 Phase I/II Trial and the SIRIUS MMY2002 Phase II Trial for Patients with Heavily Pretreated Relapsed/Refractory Multiple Myeloma

Outcome	GEN501 <sup>1</sup> (n = 42)	SIRIUS <sup>2</sup> (n = 106)	Combined <sup>3</sup> (n = 148)
Overall response rate	36%	29.2%	31.1%
Median PFS	5.6 mo	3.7 mo	4.0 mo
Median OS	NR	Not reached	20.1 mo
One-year OS	77%	64.8%	NR
<b>Select adverse events (all grades)</b>	<b>n = 42</b>	<b>n = 106</b>	<b>n = 148</b>
Infusion-related reactions	71%	42%	48%
Fatigue	40%	40%	41.9%
Anemia	NR	33%	28.4%
Back pain	NR	22%	27%
Thrombocytopenia	NR	25%	21.6%
Neutropenia	12%	23%	20.9%

PFS = progression-free survival; OS = overall survival; NR = not reported

<sup>1</sup> Lokhorst HM et al. *N Engl J Med* 2015;373(13):1207-19; <sup>2</sup> Lonial S et al. *Lancet* 2016;387(10027):1551-60;

<sup>3</sup> Usmani SZ et al. *Blood* 2016;[Epub ahead of print].

### SELECT PUBLICATIONS

Berdeja JG et al. **Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma.** *Haematologica* 2015;100(5):670-6.

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



## INTERVIEW

### John P Leonard, MD

Dr Leonard is Richard T Silver Distinguished Professor of Hematology and Medical Oncology and Associate Dean for Clinical Research at Weill Cornell Medical College in New York, New York.

### Tracks 1-18

- Track 1 Case discussion:** A 42-year-old man with previously untreated chronic lymphocytic leukemia (CLL) receives obinutuzumab and venetoclax on a clinical trial
- Track 2** Viewpoint on efficacy and long-term outcomes with first-line fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR)
- Track 3** Counseling younger patients with CLL about long-term treatment options
- Track 4** Activity and tolerability of obinutuzumab/venetoclax in CLL
- Track 5** Management of obinutuzumab-associated infusion reactions
- Track 6** Incorporation of the newly FDA-approved agent venetoclax into the treatment algorithm for patients with CLL and 17p deletions
- Track 7** Activity of obinutuzumab versus rituximab in CLL
- Track 8** Activity of idelalisib in combination with rituximab for patients with CLL
- Track 9 Case discussion:** A 78-year-old woman with relapsed/refractory mantle-cell lymphoma (MCL) receives ibrutinib and palbociclib on a clinical trial
- Track 10** Approach to choosing observation versus initiating treatment for patients with indolent MCL
- Track 11** Incidence of extranodal disease in patients with MCL
- Track 12** Therapeutic options for patients with relapsed/refractory MCL
- Track 13** Lenalidomide and rituximab (R<sup>2</sup>) as initial treatment for MCL
- Track 14** ECOG-E1411: A Phase II trial of BR with or without bortezomib followed by consolidation rituximab with or without lenalidomide for elderly patients with previously untreated MCL
- Track 15** Outcomes in patients with MCL and disease progression on ibrutinib
- Track 16** Activity and tolerability of ibrutinib/palbociclib in relapsed/refractory MCL
- Track 17** Role of rituximab maintenance therapy in MCL
- Track 18** Updated results from the Phase II S1106 trial of R-hyper-CVAD versus BR followed by ASCT in MCL

### Select Excerpts from the Interview

#### Tracks 4, 6

► **DR LOVE:** Would you discuss what venetoclax is and how it works?

► **DR LEONARD:** Venetoclax is an oral second-generation Bcl-2 inhibitor. Bcl-2 plays a significant role in chronic lymphocytic leukemia (CLL) cells and their ability to stay alive. Most of the data on venetoclax are as a single agent in relapsed disease, and the response rates have been high. The main challenge has been the associated tumor lysis syndrome, but it can be worked out by using the recommended dosing schedule. In



relapsed disease this is less of a concern because those patients have fewer options, but you need to watch out for it.

In terms of up-front regimens, patients are not excited about being admitted to the hospital for treatment. I believe the future holds combination regimens, such as venetoclax/obinutuzumab, as we're starting to see in other settings (Flinn 2015).

We will likely end up with regimens that are a sort of chemotherapy debulking followed by venetoclax or some overlap between the chemotherapy and venetoclax. Then the question will be, what does venetoclax add? For now, it does have value in refractory disease.

**Editor's note: Subsequent to this interview, on April 11, 2016, venetoclax was approved for the treatment of CLL with 17p deletion in patients who have received at least 1 prior therapy.**

 **Track 8**

▶ **DR LOVE:** What are your thoughts on the data reported at ASH evaluating idelalisib in CLL in the up-front and relapsed settings?

▶ **DR LEONARD:** Idelalisib is a good drug for CLL if patients have contraindications to ibrutinib. There are also randomized data showing a benefit to combining it with bendamustine/rituximab (BR) (Zelenetz 2015; [4.1]), although later studies suggest the emergence of toxicities such as respiratory tract infections.

**4.1 Study 115: A Phase III Trial of Idelalisib (IDELA) with Bendamustine/Rituximab (BR) in Relapsed/Refractory Chronic Lymphocytic Leukemia**

Outcome	IDELA + BR (n = 207)		Placebo + BR (n = 209)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Median progression-free survival*	23.1 months		11.1 months	
Median overall survival	Not reached		Not reached	
Overall response rate	68%		45%	
≥50% reduction in lymph nodes	96%		61%	
<b>Select adverse events (n = 207, 209)</b>	<b>Any grade</b>	<b>Grade ≥3</b>	<b>Any grade</b>	<b>Grade ≥3</b>
Neutropenia	63%	60%	54%	46%
Pyrexia	42%	7%	30%	3%
Febrile neutropenia	22%	20%	7%	6%
Pneumonia	17%	11%	11%	6%
ALT elevation	15%	11%	1%	<1%

\*  $p = 2.8 \times 10^{-14}$

Zelenetz AD et al. *Proc ASH* 2015; **Abstract LBA-5.**

 **Tracks 13-14**

▶ **DR LOVE:** Where are we with the lenalidomide/rituximab (R<sup>2</sup>) regimen in terms of ongoing trials and available data in patients with mantle-cell lymphoma (MCL)?

► **DR LEONARD:** Lenalidomide is approved as a single agent for relapsed MCL, with an approximate 30% response rate (Goy 2013). Combining it with rituximab is an active approach. The question is, what about using it earlier in the course of the disease? We have reported data with up-front R<sup>2</sup> in a fairly balanced albeit small study for patients with MCL (Ruan 2015; [4.2]). Those patients are now out more than 3 years, and most of them are still in remission. Some are now in remission for 5 years.

Another interesting approach is being evaluated on the Phase II ECOG-E1411 study for elderly patients with untreated MCL (NCT01415752). On this study everyone is receiving BR and then some patients receive bortezomib in addition to the BR. All patients receive maintenance therapy, either rituximab alone or R<sup>2</sup>.

BR followed by rituximab is a good regimen for MCL. I believe the PFS will be somewhere between 4 and 5 years. If you add bortezomib and lenalidomide to the maintenance therapy, you might yield durable remissions.

## 4.2

### Results from a Phase II Trial of Lenalidomide and Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Efficacy	Intent-to-treat population (n = 38)
Overall response rate	87%
Complete response	61%
Median progression-free survival	Not reached
2-year progression-free survival	85%
<b>Select adverse events</b>	<b>Grade ≥3</b>
Neutropenia	50%
Thrombocytopenia	13%
Rash	29%
Tumor flare	11%

Median follow-up = 30 months

Ruan J et al. *N Engl J Med* 2015;373(19):1835-44.

## Track 16

► **DR LOVE:** Would you discuss the activity and tolerability of ibrutinib/palbociclib in relapsed/refractory MCL?

► **DR LEONARD:** Palbociclib is an oral cell-cycle inhibitor targeting cyclin-dependent kinase 4/6 (CDK4/6) that is already approved for patients with metastatic breast cancer. In MCL, the cell cycle is important because of the associated cyclin D1 expression. A drug that can target CDK4/6 makes sense.

In a Phase I study conducted a couple of years ago, we demonstrated that palbociclib had single-agent activity in relapsed MCL. We know that ibrutinib yields approximately a 70% response rate and about a 1-year PFS for patients with relapsed/refractory MCL (Wang 2013). The question is, can we improve the response rate and durability by adding palbociclib? An ongoing study is evaluating the combination, and we are seeing more CRs than you'd expect with ibrutinib alone. Slightly more cytopenias are observed when palbociclib is added, but they're manageable.

► **DR LOVE:** Would you discuss the background of the Phase II SWOG-S1106 trial evaluating R-hyper-CVAD versus BR, followed by ASCT, in MCL and the data reported at ASH (Chen 2015; [4.3])?

► **DR LEONARD:** The idea of this trial was to compare BR to R-hyper-CVAD followed by autotransplant as initial therapy for MCL, particularly in younger patients. One of the endpoints was mobilization of stem cells. The initial bias was that BR is an older person's regimen — not that effective — and R-hyper-CVAD is a younger person's regimen. Various studies of pretransplant R-hyper-CVAD produced good results and excellent curves, so that was the assumed winner. We were all surprised by the rates of mobilization failure with R-hyper-CVAD on this trial, which suggest that in the real world mobilization is a problem. Hyper-CVAD is known to be profoundly myelosuppressive. Cytopenias and even MDS can result.

BR produced high rates of minimal residual disease (MRD) negativity, and MRD negativity correlates with better outcomes. I believe our next generation of trials will focus on how to take the most patients to MRD negativity, including through the use of combination regimens with novel agents. ■

#### 4.3

#### SWOG-S1106: Updated Results of a Phase II Trial of Bendamustine/Rituximab (BR) versus R-Hyper-CVAD (RH) Followed by Autologous Stem Cell Transplant for Patients with Mantle-Cell Lymphoma

Efficacy	BR (n = 35)	RH (n = 17)
2-year progression-free survival (PFS)	81%	82%
2-year overall survival	87%	88%
Overall response rate	83%	94%
Complete response rate	40%	35%
<b>Minimal residual disease (MRD) assessment</b>		
Samples collected (n)	10	2
MRD-positive at baseline (n)*	9	2
Achieved MRD negativity before ASCT (n)	8	2
2-year PFS if MRD-negative after induction, n (%)	11 (100%)	Not reported

\* Additional patient MRD-negative at baseline remained negative after induction.

This study was closed prematurely based on predetermined criteria of stem cell mobilization failures on the RH arm (53 of planned 160 patients were accrued).

Chen R et al. *Proc ASH* 2015; **Abstract 518**.

#### SELECT PUBLICATIONS

Flinn IW et al. **Safety and efficacy of a combination of venetoclax (GDC-0199/ABT-199) and obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia — Results from a Phase 1b study (GP28331).** *Proc ASH* 2015; **Abstract 494**.

Goy A et al. **Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study.** *J Clin Oncol* 2013;31(29):3688-95.

Wang ML et al. **Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.** *N Engl J Med* 2013;369(6):507-16.

## QUESTIONS (PLEASE CIRCLE ANSWER):

- Denintuzumab mafodotin is an antibody-drug conjugate that \_\_\_\_\_.
  - Comprises an anti-CD19 antibody conjugated to monomethyl auristatin F
  - Elicited a 30% to 40% response rate for patients with relapsed/refractory NHL
  - Is associated with a generally reversible corneal toxicity
  - All of the above
  - Both b and c
- A Phase I study of dose-adjusted TEDDI-R with ibrutinib produced promising results for patients with primary CNS lymphoma in both previously untreated and relapsed/refractory settings.
  - True
  - False
- 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.
  - Median overall survival
  - Grade  $\geq 3$  hematologic adverse events
  - Both a and b
  - Neither a nor b
- Which of the following is the mechanism of action of gilteritinib (ASP2215)?
  - Demethylating agent
  - FLT3 inhibitor
  - IMiD
- Ixazomib is an oral proteasome inhibitor that recently received FDA approval for use in combination with lenalidomide and dexamethasone for the treatment of MM in patients who have received \_\_\_\_\_.
  - No previous therapy
  - At least 1 prior therapy
  - At least 2 prior therapies
  - At least 3 prior therapies
- The results of the Phase III PANORAMA-1 trial of panobinostat or placebo in combination with bortezomib and dexamethasone for patients with relapsed or relapsed and refractory MM demonstrated a statistically significant difference in \_\_\_\_\_ in favor of the panobinostat arm.
  - Median PFS
  - Overall response rate
  - Both a and b
- \_\_\_\_\_ is a monoclonal antibody that was recently FDA approved as a single agent for the treatment of MM in patients who have received at least 3 prior therapies.
  - Elotuzumab
  - Daratumumab
  - Both a and b
- The Phase II CheckMate 205 study evaluating the efficacy of nivolumab in relapsed/refractory classical HL demonstrated a 6-month overall survival rate of approximately \_\_\_\_\_.
  - 50%
  - 70%
  - 100%
- The Phase II SWOG-S1106 study evaluating BR versus R-hyper-CVAD followed by ASCT for patients with MCL was closed prematurely due to which of the following reasons?
  - Significantly higher overall response rate with BR than with R-hyper-CVAD
  - Predetermined criteria of stem cell mobilization failures on the R-hyper-CVAD arm
  - Both a and b
  - Neither a nor b
- The Phase II ECOG-E1411 study for elderly patients with previously untreated MCL is evaluating BR alone or in combination with bortezomib followed by consolidation therapy with rituximab alone or in combination with \_\_\_\_\_.
  - Idelalisib
  - Bortezomib
  - Lenalidomide

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

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

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

	<b>BEFORE</b>	<b>AFTER</b>
Dose-adjusted TEDDI-R (temozolomide/etoposide/pegylated liposomal doxorubicin/dexamethasone/ibrutinib/rituximab) with ibrutinib in untreated and relapsed/refractory primary CNS lymphoma	4 3 2 1	4 3 2 1
Activity of novel agents under investigation for FLT3-ITD-mutated AML (ie, midostaurin, gilteritinib [ASP2215])	4 3 2 1	4 3 2 1
Guidelines for initiating treatment for patients with smoldering myeloma	4 3 2 1	4 3 2 1
Updated results of the Phase II SWOG-S1106 trial of R-hyper-CVAD versus BR followed by ASCT in untreated MCL	4 3 2 1	4 3 2 1
Mechanism of action, activity and tolerability of the novel antibody-drug conjugate denintuzumab mafodotin in relapsed/refractory B-lineage NHL	4 3 2 1	4 3 2 1

**Practice Setting:**

- Academic center/medical school     Community cancer center/hospital     Group practice  
 Solo practice     Government (eg, VA)     Other (please specify).....

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

- Yes     No

If no, please explain: .....

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

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

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

.....  
 .....  
 .....

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

- Yes     No

If no, please explain: .....

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

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

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

- Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and relapsed/refractory Hodgkin lymphoma. . . . . 4 3 2 1 N/M N/A
- Reevaluate current treatment approaches 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-approved options. . . . . 4 3 2 1 N/M N/A
- Appreciate the FDA approvals of novel targeted agents — ibrutinib, idelalisib, obinutuzumab and venetoclax — for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia, and discern how these therapies can be appropriately integrated into the clinical management of standard- and high-risk disease. . . . . 4 3 2 1 N/M N/A

**EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)**

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

- Recognize the recent FDA approvals of daratumumab, elotuzumab, ixazomib and panobinostat, and identify where and how these agents should be integrated into the clinical management of relapsed or refractory multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Assess 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

**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:**

.....

**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			
Anas Younes, MD	4	3	2	1	4	3	2	1
B Douglas Smith, MD	4	3	2	1	4	3	2	1
Rafael Fonseca, MD	4	3	2	1	4	3	2	1
John P Leonard, 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

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