

# Dermatologic Oncology™

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U P D A T E

Systemic Management of Malignant Melanoma,  
Basal Cell and Squamous Cell Carcinoma

Bridging the Gap between Research and Patient Care

**FACULTY INTERVIEWS**

Keith T Flaherty, MD  
Rene Gonzalez, MD  
Anna C Pavlick, MS, DO  
Jeffrey A Sosman, MD

**EDITOR**

Neil Love, MD

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2 Audio CDs  
Monograph



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## *Dermatologic Oncology Update*

### A Continuing Medical Education Audio Series

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#### OVERVIEW OF ACTIVITY

Taken together, melanoma and nonmelanoma skin cancer — basal cell carcinoma (BCC) and cutaneous squamous cell cancer (SCC) — likely represent the most prevalent form of human cancer. Fortunately, the vast majority of skin cancers present as minimally invasive BCC and SCC and, as such, are highly curable with local treatment alone. However, in rare instances these characteristically indolent lesions progress and necessitate systemic intervention with the support of limited randomized clinical evidence. In contrast, cancerous melanoma is the most aggressive form of skin cancer with a predilection toward distant metastases, even when identified in the early stages of the disease. Thus melanoma and nonmelanoma skin cancer are distinct entities, each posing unique challenges to the oncology community. Featuring information on the latest research developments along with expert perspectives, this CME activity is designed to assist medical oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

#### LEARNING OBJECTIVES

- Develop a treatment algorithm for BRAF V600 mutation-positive and wild-type advanced melanoma.
- Counsel patients regarding the risk of BRAF inhibitor-associated secondary nonmelanoma skin cancers and other cutaneous and noncutaneous adverse events, and implement appropriate surveillance and management strategies.
- Recognize immune-related adverse events associated with anti-CTLA-4 antibody therapy with ipilimumab, and offer supportive management strategies to minimize and/or manage these side effects.
- Evaluate the potential clinical and research implications of recent Phase III trial results evaluating the combination of MEK and BRAF inhibitors in the treatment of melanoma.
- Appraise the rationale for and clinical data with investigational anti-PD-1 immunotherapy for advanced solid tumors.
- Rationally incorporate established and novel cytotoxic agents into the treatment algorithm for advanced melanoma.
- Identify patients with locally advanced or metastatic BCC for whom hedgehog inhibitor therapy may be an appropriate treatment option.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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FACULTY INTERVIEWS



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Director, Henri and Belinda Termeer Center for Targeted Therapies  
Massachusetts General Hospital Cancer Center  
Associate Professor, Harvard Medical School  
Director of Developmental Therapeutics  
Boston, Massachusetts



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Director, Melanoma Research Clinics  
University of Colorado Comprehensive Cancer Center  
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Associate Professor of Medicine and Dermatology  
Director, NYU Melanoma Program  
Director, NYU Clinical Trials Office  
Assistant Director for Clinical Research and Education  
New York University Langone Medical Center  
New York, New York



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Professor of Medicine  
Ingram Professor of Cancer Research  
ACS Mary Hendrickson-Johnson Melanoma Professor  
Melanoma Program Director  
Cell Proliferation and Signal Transduction Program Co-Leader  
Vanderbilt University Medical Center  
Division of Hematology/Oncology  
Nashville, Tennessee

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## EDITOR



**Neil Love, MD**  
Research To Practice  
Miami, Florida

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## INTERVIEW

### Keith T Flaherty, MD

Dr Flaherty is Director of the Henri and Belinda Termeer Center for Targeted Therapies at the Massachusetts General Hospital Cancer Center and Associate Professor at Harvard Medical School in Boston, Massachusetts.

#### Tracks 1-15

- Track 1** Rationale for dual targeting of BRAF and MEK signaling in melanoma
- Track 2** Impact of BRAF and MEK inhibitors on the MAP kinase pathway
- Track 3** Efficacy and toxicity profiles of the FDA-approved BRAF inhibitors vemurafenib and dabrafenib
- Track 4** Potential role for the newly FDA-approved MEK inhibitor trametinib in advanced melanoma
- Track 5** Re-treatment versus switching of BRAF inhibitor therapy in patients with BRAF-mutant melanoma and disease progression
- Track 6** Updated safety and efficacy results from a Phase I/II study of dabrafenib in combination with trametinib for BRAF inhibitor-naïve metastatic melanoma
- Track 7** Increased incidence of pyrexia with dabrafenib/trametinib
- Track 8** Rising costs of cancer care
- Track 9** Sequencing high-dose interleukin-2 (IL-2) and ipilimumab in BRAF-positive and BRAF-negative melanoma
- Track 10** Incidence and management of ipilimumab-associated adverse events
- Track 11** Safety and activity of anti-PD-1 antibodies in melanoma
- Track 12** CA033: Results of a Phase III trial of *nab* paclitaxel versus dacarbazine for patients with previously untreated metastatic melanoma
- Track 13** Activity of paclitaxel and *nab* paclitaxel in metastatic melanoma
- Track 14** Treatment options for patients with resected Stage IV melanoma and NED
- Track 15** Re-treatment with ipilimumab in patients who achieved a partial response before disease progression

#### Select Excerpts from the Interview

##### Track 3

► **DR LOVE:** How would you compare the efficacy and side effects of the BRAF inhibitors dabrafenib — which was recently approved by the FDA — and vemurafenib?

► **DR FLAHERTY:** No studies have compared dabrafenib and vemurafenib head to head, so we have to rely on cross-trial comparisons. Large trials with dabrafenib and vemurafenib demonstrate similar efficacy in terms of response rate, progression-free survival and overall survival (Chapman 2011; [1.1]; Hauschild 2012; [1.2]).

The overall incidence and likelihood of toxicity are comparable, but some toxicities differ. With vemurafenib photosensitivity can be a problem, especially for those patients who live in southern climates. Pyrexia is frequently observed with dabrafenib but not with vemurafenib. So the choice between these agents would depend on which toxicity is of concern for a particular patient.

Rash is a common skin problem, and the risk of cutaneous squamous cell carcinoma exists with both agents. Arthralgia is slightly more common with vemurafenib than dabrafenib. Fatigue is another side effect associated with both drugs. Both agents can cause liver function test abnormalities, but this is a little more likely with dabrafenib than with vemurafenib. Studies report that clinical benefit can be observed with both drugs even when dose reductions or interruptions were used to manage side effects.

1.1

**Phase III BRIM-3 Trial Comparing Vemurafenib to Dacarbazine in Previously Untreated Metastatic Melanoma with BRAF V600E Mutations**

<b>Efficacy</b>	<b>Vemurafenib</b>		<b>Dacarbazine</b>	
Median progression-free survival (n = 275, 274)*	5.3 mo		1.6 mo	
Six-month overall survival (n = 336, 336)	84%		64%	
	<b>Vemurafenib (n = 336)</b>		<b>Dacarbazine (n = 282)</b>	
<b>Select adverse events</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 2</b>	<b>Grade 3</b>
Cutaneous squamous cell carcinoma	NR	12%	0%	<1%
Keratoacanthoma	2%	6%	0%	0%
Photosensitivity skin reactions <sup>†</sup>	12%		Not reported	
Arthralgia	18%	3%	<1%	<1%
Rash	10%	8%	0%	0%
Fatigue	11%	2%	12%	2%
Nausea	7%	1%	11%	2%
Alopecia	8%	0%	0%	0%
Pruritus	6%	1%	0%	0%
Hyperkeratosis	5%	1%	0%	0%
Diarrhea	5%	<1%	1%	<1%

\* HR = 0.26, p < 0.001; † Grade 3 reactions were characterized by blistering, often preventable with sunblock

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

 **Track 4**

► **DR LOVE:** The MEK inhibitor trametinib was also recently approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. How does this agent fit into your treatment algorithm?

► **DR FLAHERTY:** Studies demonstrate that the response rate and progression-free survival with trametinib are not as high as with the BRAF inhibitors, with all the caveats of cross-trial comparisons (Flaherty 2012a). Overall survival was similar, but I put more weight on the early outcome measures and would favor a BRAF inhibitor rather than a MEK inhibitor.

If one has serious concerns about developing squamous cell carcinoma, then a MEK inhibitor may be more appropriate because it does not induce MAP kinase pathway signaling and cause the proliferation of squamous cell carcinomas. Acneiform rash and diarrhea are the major side effects of concern with trametinib. Beyond that, most of the side effects that can arise are not substantial or treatment limiting. But as I said, I'd base

my decision primarily on the efficacy results, and I'll likely prefer a BRAF inhibitor just about every time.

1.2

**Phase III BREAK-3 Trial Comparing Dabrafenib to Dacarbazine for Patients with BRAF-Mutated Metastatic Melanoma**

<b>Efficacy</b>	<b>Dabrafenib (n = 187)</b>		<b>Dacarbazine (n = 63)</b>	
Median progression-free survival*	5.1 mo		2.7 mo	
Overall response rate	50%		6%	
<b>Select adverse events</b>	<b>Grade 2</b>	<b>Grade 3 or 4</b>	<b>Grade 2</b>	<b>Grade 3 or 4</b>
Squamous cell carcinoma/keratoacanthoma	2%	4%	0%	0%
Palmar-plantar hyperkeratosis	6%	2%	0%	0%
Nausea	1%	0%	14%	0%
Pyrexia	8%	3%	0%	0%
Fatigue	5%	1%	5%	0%
Arthralgia	5%	<1%	0%	0%
Neutropenia	0%	<1%	3%	12%
Thrombocytopenia	0%	<1%	0%	5%
Leukopenia	0%	0%	3%	2%

\* HR = 0.3, *p* < 0.0001

Hauschild A et al. *Lancet* 2012;380(9839):358-65.

 **Tracks 1, 6-7**

▶ **DR LOVE:** Would you discuss the rationale for dual targeting with BRAF and MEK inhibitors in melanoma?

▶ **DR FLAHERTY:** The BRAF pathway, sometimes referred to as the MAP kinase pathway, is reactivated in the vast majority of patients upon disease progression on a selective BRAF inhibitor through a variety of mechanisms that don't involve the drug target. MEK inhibitors also target the MAP kinase pathway and block the bypass pathways that arise in tumors upon progression on BRAF inhibitors.

▶ **DR LOVE:** What do we know about combining a BRAF inhibitor and a MEK inhibitor?

▶ **DR FLAHERTY:** We recently published the results from a large Phase I/II trial in which patients were randomly assigned to receive dabrafenib monotherapy or the combination of dabrafenib and trametinib. The 2-drug approach clearly delayed the time to tumor progression or development of resistance (Flaherty 2012b; [1.3]).

Most of the side effects observed with a BRAF inhibitor or a MEK inhibitor alone are reduced in severity with the combination. Single-agent trametinib trials reported an 8% incidence of Grade 3 diarrhea, whereas with the combination, diarrhea is mild to moderate at worst.

Rash is a common side effect with both agents when used alone. A patchy rash occurs with dabrafenib, and trametinib causes an acneiform rash. If rash is observed at all with the combination, it is patchy in nature and typically Grade 1 in severity. The incidence of

### Phase I/II Trial of Combined BRAF and MEK Inhibition in Metastatic Melanoma with BRAF V600 Mutations

Efficacy	Dabrafenib (n = 54)	Combination 150/2* (n = 54)	p-value
Median progression-free survival	5.8 mo	9.4 mo	<0.001
Complete or partial response	54%	76%	0.03
Select adverse events (all grades)	n = 53	n = 54	p-value
Cutaneous squamous cell carcinoma	19%	7%	0.09
Pyrexia	26%	71%	NR
Rash	36%	27%	NR
Diarrhea	28%	36%	NR

\* Dabrafenib 150 mg BID, trametinib 2 mg PO; NR = not reported

Flaherty KT et al. *N Engl J Med* 2012b;367(18):1694–703.

squamous cell carcinoma is also lower when dabrafenib and trametinib are administered together. However, the combination results in a higher incidence of pyrexia, which is mainly caused by dabrafenib. Patients can feel quite sick with fever, chills and rigors.

The role of trametinib as a single agent is not clear. Evidence suggests that sequential therapy with a BRAF inhibitor followed by a MEK inhibitor is not effective. Hence, I believe the combination is reasonable. We're awaiting the results of ongoing Phase III trials with BRAF and MEK inhibitors (NCT01584648 and NCT01689519).

#### Track 9

► **DR LOVE:** What is the current role of high-dose interleukin-2 (IL-2) in the era of ipilimumab?

► **DR FLAHERTY:** IL-2 can be considered for patients who are young, highly motivated, asymptomatic and in excellent overall health with low-volume disease and normal LDH levels. IL-2 should be administered prior to ipilimumab because administering ipilimumab first could be problematic.

Ipilimumab has a 10% objective response rate, and in aggregate, 20% to 25% of patients derive significant benefit from ipilimumab. Administering ipilimumab after IL-2 doesn't change that. Once patients receive IL-2, response can be judged quickly, and those whose disease is stable or progresses on IL-2 can receive ipilimumab. If we can "add these 2 therapies" in terms of their benefit that would be our goal, especially for patients with BRAF mutation-negative melanoma.

#### Tracks 12-13

► **DR LOVE:** Would you discuss the Phase III data comparing *nab* paclitaxel to dacarbazine in patients with chemotherapy-naïve metastatic malignant melanoma and comment on the role of *nab* paclitaxel in practice?

► **DR FLAHERTY:** This trial compared *nab* paclitaxel to dacarbazine for patients who were in relatively good condition, as measured by LDH levels. The study met its primary endpoint, with approximately a doubling of the progression-free survival with *nab*

paclitaxel compared to dacarbazine (Hersh 2012; [1.4]). Response rates were slightly higher with *nab* paclitaxel.

For patients with BRAF mutation-negative disease and a high disease burden or for those whose disease has progressed on ipilimumab, we don't have a targeted therapy approach and chemotherapy would be a consideration. Based on the available data and the NCCN guidelines, many clinicians favor carboplatin/paclitaxel. With data from this Phase III trial indicating *nab* paclitaxel has better efficacy than dacarbazine, *nab* paclitaxel would be a reasonable choice.

In practice I've administered *nab* paclitaxel approximately 10 times in the past year as most patients who have exhausted all options are enrolled on clinical trials. Carboplatin/paclitaxel was adopted as standard chemotherapy in my practice a few years ago for patients with symptomatic disease. However, I can envision adopting *nab* paclitaxel as a standard for older patients and for those who are not in excellent health, in which case doublet chemotherapy is not a compelling option from the toxicity perspective. ■

## 1.4

### CA033 Phase III Trial of *Nab* Paclitaxel (*Nab-P*) versus Dacarbazine in Patients with Previously Untreated Metastatic Malignant Melanoma

Efficacy	<i>Nab-P</i> * (n = 264)	Dacarbazine <sup>†</sup> (n = 265)	p-value
Median progression-free survival	4.8 mo	2.5 mo	0.044
Interim overall survival	12.8 mo	10.7 mo	0.094
Objective response rate	15%	11%	0.239
Disease control rate	39%	27%	0.004
<b>Select Grade ≥3 adverse events</b>	(n = 257)	(n = 257)	
Peripheral neuropathy	25%	0%	
Fatigue	8%	2%	
Alopecia	5%	0%	
Neutropenia	20%	10%	
Leukopenia	12%	7%	
Lymphocytopenia	8%	11%	
Thrombocytopenia	0%	6%	
Anemia	2%	5%	

\* *Nab-P*, 150 mg/m<sup>2</sup> days 1, 8, 15 q4wk; <sup>†</sup> Dacarbazine, 1,000 mg/m<sup>2</sup> q3wk

Hersh E et al. *Pigment Cell Melanoma Res* 2012;25(6):863.

## SELECT PUBLICATIONS

Chapman PB et al. **Improved survival with vemurafenib in melanoma with BRAF V600E mutation.** *N Engl J Med* 2011;364(26):2507-16.

Flaherty KT et al. **Improved survival with MEK inhibition in BRAF-mutated melanoma.** *N Engl J Med* 2012a;367(2):107-14.

Flaherty KT et al. **Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.** *N Engl J Med* 2012b;367(18):1694-703.

Hauschild A et al. **Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial.** *Lancet* 2012;380(9839):358-65.

Hersh E et al. **Phase 3, randomized, open-label, multicenter trial of *nab*-paclitaxel (*nab-P*) vs dacarbazine (DTIC) in previously untreated patients with metastatic malignant melanoma (MMM).** *Pigment Cell Melanoma Res* 2012;25(6):863.



## INTERVIEW

### Rene Gonzalez, MD

Dr Gonzalez is Professor of Medicine and Director of the Melanoma Research Clinic at the University of Colorado Comprehensive Cancer Center in Aurora, Colorado.

#### Tracks 1-11

- Track 1** **Case discussion:** An 88-year-old patient with BRAF V600K mutation-positive recurrent melanoma
- Track 2** Vemurafenib and the development of secondary squamous cell skin cancers
- Track 3** Response and tolerability of combination BRAF and MEK inhibition in BRAF V600E/K mutation-positive metastatic melanoma
- Track 4** Use of next-generation sequencing in melanoma
- Track 5** Mechanism of action of the investigational immunotherapy talimogene laherparepvec for unresected Stage IIIB, IIIC or IV melanoma
- Track 6** Photosensitivity reaction with BRAF/MEK combination therapy
- Track 7** **Case discussion:** A 34-year-old patient with BRAF V600E mutation-positive metastatic melanoma and favorable response to ipilimumab approximately 5 years ago reinitiates ipilimumab therapy for asymptomatic disease progression
- Track 8** Sequencing of ipilimumab and high-dose IL-2
- Track 9** Ipilimumab-associated toxicities in metastatic melanoma
- Track 10** **Case discussion:** A 42-year-old patient with BRAF wild-type metastatic melanoma experiences a complete response to high-dose IL-2
- Track 11** Correlation of NRAS mutations with clinical response to immunotherapy in advanced melanoma

## Select Excerpts from the Interview

### Tracks 1-3, 6

#### Case discussion

An 88-year-old patient with BRAF V600K mutation-positive recurrent melanoma

► **DR GONZALEZ:** This gentleman with recurrent scalp melanoma after surgery eventually developed in-transit metastases in the cervical lymph nodes and was referred to our center. He had limited treatment options. His tumor was initially determined to be BRAF wild-type with a cobas® test. However, I would recommend that oncologists perform alternative confirmatory tests to determine whether a patient's tumor harbors a BRAF mutation.

We did so in this case and ascertained that the tumor did in fact harbor a BRAF V600K mutation. Once we determined that he had BRAF mutation-positive disease, the probability of getting the tumor under control was high.

He was initially enrolled on a trial of vemurafenib for atypical mutations that we're conducting specifically for patients with non-V600E mutations to confirm that the response rate is similar to that seen in patients with V600E mutations. He achieved a partial response, but his disease eventually progressed on vemurafenib, at which point we transferred him to a trial of combination therapy with vemurafenib and GDC-0973, a MEK inhibitor (NCT01271803), on which he achieved a complete response. He is currently faring well.

► **DR LOVE:** What side effects did he experience on vemurafenib alone?

► **DR GONZALEZ:** He had a long history of sun exposure, and he developed multiple squamous cell carcinomas. We excised multiple lesions at his weekly hospital visits. That's a well-established side effect of vemurafenib, occurring in 20% to 25% of patients. This is believed to be due to paradoxical activation of the MAPK pathway in the cutaneous lesions (Su 2012).

Interestingly, the addition of GDC-0973 to vemurafenib resolved the skin toxicities because of the MEK blockade, and he has not had subsequent squamous cell cancer. This is one of the reasons I prefer therapy with the combination of BRAF and MEK inhibitors.

However, the ultraviolet A (UVA) light-induced photosensitivity caused by the BRAF inhibitor is not necessarily diminished by the addition of a MEK inhibitor. It can be extremely severe. Patients need to protect themselves from the sun because blistering burns can develop. These UVA sunburns can penetrate through car windows, and sunscreens are not particularly effective. Patients need to cover up properly.

This patient hasn't experienced any significant toxicity with combination vemurafenib/GDC-0973 except for a bit of fatigue. He continues to experience photosensitivity with the combination therapy.

## Track 5

► **DR LOVE:** Would you discuss the mechanism of action of the investigational oncolytic immunotherapeutic agent talimogene laherparepvec in melanoma?

► **DR GONZALEZ:** It's an interesting agent. We were involved in the early-phase studies of talimogene laherparepvec. It's a herpes simplex virus type 1 engineered to express GM-CSF and activate an antitumor immune response. The patient must have an injectable tumor, but it doesn't need to be limited to in-transit metastases. Theoretically, you can inject it into a lymph node, but the tumor must be injectable.

Of note, local and systemic responses have been seen with this agent. The Phase III OPTiM trial is ongoing and the results will be reported soon (Andtbacka 2013). (Editor's note: Subsequent to this interview the initial results of this study were presented [2.1].)

## Tracks 10-11

### Case discussion

A 42-year-old patient with BRAF wild-type metastatic melanoma experiences a complete response to high-dose IL-2

## OPTiM: A Phase III Trial of Talimogene Laherparepvec (T-VEC) versus Subcutaneous GM-CSF for Unresectable Stage IIIB/C and IV Melanoma

Efficacy	T-VEC (n = 295)	GM-CSF (n = 141)	Unadjusted odds ratio	p-value
Durable response rate	16.3%	2.1%	8.9	<0.0001
Time to treatment failure	8.2 mo	2.9 mo	0.42	<0.0001
<b>Select adverse events (all grades)</b>	<b>T-VEC (n = 292)</b>		<b>GM-CSF (n = 127)</b>	
Fatigue	50.3%		36.2%	
Chills	48.6%		8.7%	
Pyrexia	42.8%		8.7%	
Influenza-like illness	30.5%		15.0%	
Injection site pain	27.7%		6.3%	
Vomiting	21.2%		9.4%	
Cellulitis (Grade 3 or 4)	2.1%		<1%	

Andrbacka RH et al. *Proc ASCO* 2013; **Abstract LBA9008**.

- ▶ **DR GONZALEZ:** Given his diagnosis, the patient's treatment options were limited to immune therapy, of which the 2 current choices are high-dose IL-2 or ipilimumab. This patient received high-dose IL-2. He achieved a complete response and is now out a number of years and faring well.
- ▶ **DR LOVE:** A number of attempts have been made to predict who fares well with high-dose IL-2 and other therapies, but it's difficult to identify a factor. One such preliminary report was on the correlation of NRAS mutations with clinical response to high-dose IL-2 in about 100 patients with advanced melanoma (Joseph 2012). What are your thoughts?
- ▶ **DR GONZALEZ:** NRAS is another mutation that we look for in patients with melanoma. Some preliminary evidence has indicated that patients with NRAS mutations may respond better to immunotherapy.

NRAS mutations are interesting because they occur in approximately 20% of patients with melanoma. About 50% of patients with melanoma harbor the BRAF mutation, and if we add another 20% with NRAS mutations, which are activating both the parallel AKT pathway and the MAP kinase pathway, we can potentially target that mutation too. Those patients might respond to MEK inhibitors specifically, and other agents are available. We have pan-RAF inhibitors — BRAF is one of the RAFs, but another one called CRAF is also activated in melanoma along with NRAS. So this gene might be blocked in the same way that the BRAF gene is. That's an interesting potential new target in melanoma. ■

### SELECT PUBLICATIONS

Joseph RW et al. **Correlation of NRAS mutations with clinical response to high-dose IL-2 in patients with advanced melanoma.** *J Immunother* 2012;35(1):66-72.

Su F et al. **RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors.** *N Engl J Med* 2012;366(3):207-15.



## INTERVIEW

### Anna C Pavlick, MS, DO

Dr Pavlick is Associate Professor of Medicine and Dermatology, Director of the NYU Melanoma Program, Director of the NYU Clinical Trials Office and Assistant Director of Clinical Research and Education at the New York University Langone Medical Center in New York, New York.

### Tracks 1-16

- Track 1** Incidence of advanced squamous cell carcinoma (SCC)
- Track 2** **Case discussion:** A 40-year-old patient with a neglected tibial wound is diagnosed with metastatic SCC
- Track 3** Epidemiology of basal cell carcinoma (BCC)
- Track 4** Approved and investigational hedgehog inhibitors in BCC
- Track 5** Vismodegib-associated ageusia and muscle cramping
- Track 6** Efficacy of vismodegib in metastatic BCC
- Track 7** Investigation of hedgehog inhibitors as neoadjuvant therapy for BCC
- Track 8** Consideration of treatment holidays with hedgehog inhibition in locally advanced BCC
- Track 9** Therapeutic options for Stage II/III melanoma
- Track 10** ECOG-E1609: A Phase III trial of ipilimumab versus high-dose interferon alpha-2b for resected high-risk Stage III/IV melanoma
- Track 11** A planned Phase III trial of adjuvant vemurafenib versus observation for patients with Stage IIIB/IIIC BRAF-mutant melanoma
- Track 12** Initial treatment choice and sequencing of agents in BRAF-mutant metastatic melanoma
- Track 13** Rationale for maintenance ipilimumab in metastatic melanoma
- Track 14** Results of a Phase III study of ipilimumab in combination with dacarbazine versus dacarbazine alone as first-line treatment for patients with unresectable Stage III or IV melanoma
- Track 15** Role of *nab* paclitaxel in metastatic melanoma
- Track 16** Use of vemurafenib in patients with melanoma and brain metastasis

## Select Excerpts from the Interview

### Tracks 3-4

► **DR LOVE:** How often do you see patients with metastatic basal cell carcinoma? Also, what is your clinical experience in terms of when these patients end up seeking treatment?

► **DR PAVLICK:** I have been in practice for more than 15 years and had not seen one of these patients until recently, when an agent was developed for metastatic basal cell carcinoma. I recently opened a clinical trial that was enrolling patients with metastatic basal cell cancer, and now I have 6 patients with basal cell carcinoma.

Most cases of metastatic basal cell carcinoma that I treat are in patients who did not see a doctor until it was too late. Public awareness and education are lacking, and a lot of patients with basal cell carcinoma are in denial. Some patients believe if they observe a

lesion and do nothing it will disappear. They often state that they had a lesion for years that worsened over time, in some cases resulting in lymph node involvement.

I had a patient who had a large basal cell carcinoma on her leg, and it continued to grow until she sought treatment. She had to have an above-the-knee amputation because the margins of the tumor could not be cleanly resected.

She fared well for a couple of years but then developed lung metastases and a large pelvic mass that was obstructing her ureter and required a nephrostomy tube. The patient also developed diffuse basal cell carcinomas all over the rest of her body.

► **DR LOVE:** What treatment did she receive?

► **DR PAVLICK:** Multiple hedgehog inhibitors are being investigated for the treatment of basal cell carcinoma. Vismodegib is FDA approved, but others are in the investigational stage. She was enrolled on a clinical trial with an investigational hedgehog inhibitor called erismodegib (LDE225). She experienced a 50% reduction in her disease volume, which has lasted for almost a year.

► **DR LOVE:** What side effects did she experience on erismodegib?

► **DR PAVLICK:** Although these hedgehog inhibitors are orally administered, they are not easy to tolerate and have side effects similar to BRAF inhibitors. The patient experienced a significant alteration in taste. She also lost her hair and had to wear a wig. She has experienced intermittent muscle cramps, which is another big complaint with these agents. However, those seem to have resolved with time.

## Tracks 5-7

► **DR LOVE:** Would you discuss the mechanism of action and efficacy of vismodegib in basal cell carcinoma?

► **DR PAVLICK:** Basal cell carcinomas harbor a genetic alteration in the hedgehog pathway. The protein Smoothened transduces an antiapoptotic signal to the nucleus, allowing these cells to proliferate. The hedgehog inhibitor vismodegib works by inhibiting Smoothened, thus preventing cells from proliferating.

A Phase II study for patients with locally advanced or metastatic disease led to the approval of vismodegib (Sekulic 2012). Response rates in both groups were similar and in the 40% to 60% range with a time to disease progression longer than 9 months (3.1).

► **DR LOVE:** What are your thoughts on the change in taste and muscle cramps that patients experience while receiving vismodegib?

► **DR PAVLICK:** The change in taste is bothersome. Patients report an inability to taste or that food tastes like metal. A few patients consider coming off treatment before the holidays so they can enjoy holiday food and then go back on treatment afterward. Once the drug is discontinued, taste sensation is restored.

The other major side effect is muscle cramps, which often wake patients at night. We've tried administering quinine, lorazepam or magnesium and checking patients' electrolyte levels, but they are difficult to manage. I had a patient who had to come off therapy because the leg muscle cramps were excruciating. The reason patients develop these side effects is not understood. Almost everyone to whom I've administered a hedgehog inhibitor has also developed significant alopecia.

► **DR LOVE:** Would you consider administering vismodegib in the neoadjuvant setting for basal cell carcinoma?

► **DR PAVLICK:** Neoadjuvant therapy with vismodegib is being investigated, especially for large basal cell carcinomas, to shrink the tumor and make surgery easier (Ally 2013; Chang 2013; [3.2]). I believe it is clearly beneficial, especially in older patients who may not be amenable to wide resections, to downsize the tumor and subsequently allow a more limited resection to be performed.

### 3.1

#### ERIVANCE BCC: Updated 18-Month Analysis of a Phase II Trial of Vismodegib in Locally Advanced or Metastatic Basal Cell Carcinoma (BCC)

Efficacy	Metastatic BCC (n = 33)	Locally advanced BCC (n = 63)
Objective response rate	48.5%	60.3%
Median progression-free survival	9.3 months	12.9 months
Median overall survival	30.9 months	NE
<b>Select adverse events (n = 104)*</b>	<b>Any grade</b>	<b>Grade 3 or 4</b>
Muscle spasms	71.2%	5.8%
Alopecia	65.4%	0%
Dysgeusia	54.8%	0%
Decrease in weight	51%	6.7%
Fatigue	42.3%	4.8%
Diarrhea	26.9%	2.9%
Ageusia/hypogeusia	11.5%/10.6%	0%/0%

NE = not estimable; \* Occurring in ≥10% of patients

Sekulic A et al. *Proc ASCO* 2013; **Abstract 9037**.

### 3.2

#### Vismodegib as Neoadjuvant Treatment Prior to Surgery for Basal Cell Carcinomas (BCCs)

Single-arm study of neoadjuvant vismodegib prior to Mohs micrographic surgery (N = 5)

- Reduction in surgical defect size: 38%
- Reduction in tumor from baseline: 46%
- No BCCs in 3 tumors, residual BCC in 1, equivocal diagnosis in 3
- No recurrence after median of 3 months of follow-up

Ally M et al. *Proc American Academy of Dermatology* 2013; **Abstract S018**.

## Track 12

► **DR LOVE:** What are some of the common misconceptions about metastatic melanoma?

► **DR PAVLICK:** One common misconception among patients is that a BRAF mutation is genetically transmitted. I clearly explain to patients that this is an intrinsic mutation within the tumor that would not be genetically transmitted to members of their family. Because melanoma is not a common cancer, one of the misconceptions that some of the

community oncologists have is that if a patient has a BRAF mutation, he or she should always receive a BRAF inhibitor up front. This should not be the “knee-jerk” response.

► **DR LOVE:** A recent paper entitled “Which drug, and when, for patients with BRAF mutant melanoma?” was published in *Lancet Oncology* (Jang 2013). The authors contend that for a patient with BRAF-mutant melanoma who has nonbulky, asymptomatic disease and a normal LDH level, immunotherapy should be considered first followed by a BRAF inhibitor upon disease progression. What are your thoughts?

► **DR PAVLICK:** I agree with the authors. The one drug class that we know of that provides patients with the possibility of a durable complete response is immunotherapy. For patients with low-volume or indolent disease who have a normal LDH level and are fit and asymptomatic, even for those with a BRAF mutation, many of us will argue that immunotherapy should be administered first. This offers the patient a possibility of a complete and durable response. If the patient has BRAF-mutant disease, a BRAF inhibitor would be the next choice and the disease should respond.

## Track 15

► **DR LOVE:** In what situations do you consider chemotherapy for metastatic melanoma, and what are your thoughts on the recent study that evaluated *nab* paclitaxel versus dacarbazine (1.4, page 7)?

► **DR PAVLICK:** If I had to choose a taxane to administer to a patient with metastatic melanoma, I would pick *nab* paclitaxel. I believe it’s easier to administer, and I find it to be well tolerated despite the possibility of neurotoxicity. On a recent trial of *nab* paclitaxel versus dacarbazine for previously untreated metastatic melanoma, *nab* paclitaxel was a bit more efficacious than dacarbazine. Even though these agents are not the main focus of research right now in melanoma, that doesn’t mean we don’t have appropriate settings in which to administer them.

One such setting is for a patient with BRAF wild-type melanoma who doesn’t experience a response to ipilimumab or anti-PD-1 on a clinical trial. If you have no other clinical trial options for such a patient, what are you going to do? It’s hard to tell a patient, “Sorry, there’s nothing left for you,” so we’d treat with chemotherapy in that setting.

I consulted with such a patient this week. This patient had received ipilimumab a year ago and experienced a partial response. We observed him, and eventually his disease began to progress.

He received 4 additional doses of ipilimumab but did not experience a response, so he now has explosive disease with significant intraluminal tumors throughout his gastrointestinal tract and requires a blood transfusion every 2 weeks. I explained to him that we’d be unable to get him on a clinical trial because of his active bleeding and that we needed to try to slow the disease down. I explained that chemotherapy could at least control his disease and, we would hope, open future treatment options and that given his rapidly progressing disease I’d like to try *nab* paclitaxel and carboplatin. ■

## SELECT PUBLICATIONS

Chang AL et al. **Surgical excision after neoadjuvant therapy with vismodegib for a locally advanced basal cell carcinoma and resistant basal carcinomas in Gorlin syndrome.** *JAMA Dermatol* 2013;149(5):639-41.

Jang S, Atkins MB. **Which drug, and when, for patients with BRAF-mutant melanoma?** *Lancet Oncol* 2013;14(2):e60-9.



## INTERVIEW

### Jeffrey A Sosman, MD

Dr Sosman is Professor of Medicine, Ingram Professor of Cancer Research, ACS Mary Hendrickson-Johnson Melanoma Professor, Melanoma Program Director and Cell Proliferation and Signal Transduction Co-Leader at Vanderbilt University Medical Center in Nashville, Tennessee.

#### Tracks 1-8

- |                |  |                |  |
|----------------|--|----------------|--|
| <b>Track 1</b> | Evaluation of immunotherapeutic agents and BRAF inhibitors approved in the metastatic setting as adjuvant therapy for melanoma | <b>Track 4</b> | Management of ipilimumab-induced toxicities in metastatic melanoma                       |
| <b>Track 2</b> | Risk of second cancers with BRAF inhibitors alone versus combined BRAF/MEK inhibition  | <b>Track 5</b> | Therapeutic algorithm for asymptomatic BRAF-mutant metastatic melanoma                   |
| <b>Track 3</b> | Immunotherapeutic options for asymptomatic BRAF wild-type metastatic melanoma  | <b>Track 6</b> | Hepatotoxicity with the combination of vemurafenib and ipilimumab in metastatic melanoma |
|                |  | <b>Track 7</b> | Clinical activity and safety of anti-PD-1 therapies in melanoma                          |
|                |  | <b>Track 8</b> | Ongoing trials of anti-PD-1 in melanoma  |

#### Select Excerpts from the Interview

##### Tracks 3-6

► **DR LOVE:** Would you discuss current options for immunotherapy in melanoma?

► **DR SOSMAN:** At our center, we administer high-dose IL-2 for healthy patients age 70 years or younger with good organ function and without aggressive disease because we know that a small but real cure rate exists. We would consider ipilimumab for patients with disease unresponsive to IL-2.

We don't administer first-line ipilimumab because of the concern about a late onset of the toxic effects of ipilimumab that could manifest while the patient is receiving IL-2. Although adverse events such as diarrhea, liver problems and rash usually occur earlier, they can occur later on. So IL-2 followed by ipilimumab makes more sense.

Another reason we treat in this manner is because we can determine whether the disease is responding to IL-2 by week 7 or 8. If the disease is progressing at week 8, we have no reason to continue IL-2.

However, it sometimes takes a while to see the full benefit of ipilimumab. Some patients with progressive disease at week 12 see a response at week 20 with tumor shrinkage and regression. With IL-2, I don't consider stable disease a success. I do not continue IL-2 nor do I initiate therapy with ipilimumab for those patients. I watch closely but will administer ipilimumab when the disease progresses.

► **DR LOVE:** How soon after treatment do you observe the toxic effects of ipilimumab?

► **DR SOSMAN:** In the metastatic setting, major toxic effects after the first dose are extremely rare but begin to occur after the second dose, with manifestations within the first 12 weeks. For most patients, rash is manageable and tolerable. In some cases it looks like a typical drug-reaction rash — maculopapular, usually papular. If the rash coalesces, we become much more concerned.

► **DR LOVE:** How do you manage the side effects of ipilimumab?

► **DR SOSMAN:** For the rash, we rarely use corticosteroids systemically, but we may administer them topically. We use antihistamines, including cimetidine, ranitidine and diphenhydramine cream. The rash begins to fade away once ipilimumab is discontinued but worsens after the next dose is initiated. Patients may experience pruritus early on before the second dose.

Some patients may develop colitis. We start monitoring patients early so that we can treat immediately if explosive diarrhea occurs. We'll admit a sick patient and intravenously administer steroids and perform a colonoscopy.

We also observe endocrine-related side effects — thyroiditis, adrenalitis, panhypopituitarism and hypophysitis. Of these, hypophysitis is the most troubling and most frequent issue. We monitor cortisol and thyroid-stimulating hormone levels and thyroid function every 3 weeks to ensure that we don't miss these issues because they can be major causes of severe fatigue.

► **DR LOVE:** How do you initially treat asymptomatic, BRAF-mutant metastatic melanoma?

► **DR SOSMAN:** Asymptomatic patients generally have low-volume disease and normal LDH and usually don't have liver metastases. So we may consider immunotherapy with first-line IL-2 followed by ipilimumab. I've seen cases in which the disease accelerates after progression on a BRAF inhibitor. Many of those patients did not receive a full round of immune therapy. A major concern is that if I start treatment with a BRAF inhibitor, the patient may not be able to receive an immunotherapeutic agent after that.

► **DR LOVE:** How do you manage brain metastases from BRAF-mutant melanoma?

► **DR SOSMAN:** In a situation in which the tumor is small, I administer vemurafenib and wait on local therapy. Although it's difficult to hold off on performing stereotactic radiosurgery for 1 or 2 small isolated lesions because it's easy to do, it's reasonable to monitor the systemic and brain disease closely and if the brain tumor begins to grow and stays isolated treat with stereotactic radiosurgery at that time.

► **DR LOVE:** What are your thoughts on combination therapy with vemurafenib and ipilimumab?

► **DR SOSMAN:** A study combining vemurafenib with ipilimumab in metastatic melanoma had to be discontinued because of hepatitis, the limiting factor (Ribas 2013a). The combination of these agents required dose reductions to an uncomfortable level.

## Track 7

► **DR LOVE:** Would you discuss the efficacy and side effects of anti-PD-1 antibodies in melanoma?

► **DR SOSMAN:** Anti-PD-1 antibodies bind to PD-1, a checkpoint molecule on T cells. PD-1 is a marker on exhausted T cells. So far, 2 large Phase I trials of the anti-PD-1 antibody have been performed in patients with melanoma.

The first studied nivolumab and demonstrated a robust response rate of about 30% (Sznol 2013; [4.1]). The duration of response is more than 1 year and is currently approaching 2 years. A few of the patients who responded have experienced relapse, and many have completed 2 years of therapy.

Lambrolizumab (MK-3475) is another promising monoclonal antibody that initially showed a high response rate with short follow-up. It has a similar response rate in patients with or without previous ipilimumab treatment (Ribas 2013b; [4.1]). So we may be able to use one agent and then switch to another and still provide an additional benefit.

Overall, targeting PD-1 causes less toxicity than ipilimumab. Patients experience less fatigue, but rash occurs. Less gastrointestinal and hepatobiliary toxicity is seen. Some cases of hypothyroidism have been reported. Although infrequent, pneumonitis is most concerning and requires vigilance. ■

#### 4.1

### Results from 2 Phase I Anti-PD-1 Trials: Clinical Efficacy and Safety of Nivolumab (MDX-1106) or Lambrolizumab (MK-3475) in Patients with Advanced Melanoma

Efficacy (all doses)	Nivolumab (n = 107) <sup>1</sup>	Lambrolizumab (n = 135) <sup>2</sup>
ORR	31%	38%
Median DoR	24 mo	Not reached
Median OS	16.8 mo	NR
Median PFS	3.7 mo	NR

Select AEs (all grades)	Nivolumab (n = 107)	Select AEs (all grades)	Lambrolizumab (n = 135)
Dermatologic	38%	Rash	20.7%
Gastrointestinal	19%	Fatigue	30.4%
Hepatic	7%	Diarrhea	20.0%
Pulmonary	4%	Pneumonitis	4.4%
Endocrinopathies	14%	Hypothyroidism	8.1%

ORR = objective response rate; DoR = duration of response; OS = overall survival; NR = not reported; PFS = progression-free survival; AEs = adverse events

<sup>1</sup>Sznol M et al. *Proc ASCO* 2013; **Abstract CRA9006**; <sup>2</sup>Ribas A et al. *Proc ASCO* 2013b; **Abstract 9009**.

## SELECT PUBLICATIONS

Ribas A et al. **Hepatotoxicity with combination of vemurafenib and ipilimumab.** *N Engl J Med* 2013a;368(14):1365-6.

Ribas A et al. **Clinical efficacy and safety of lambrolizumab (MK-3475, anti-PD-1 monoclonal antibody) in patients with advanced melanoma.** *Proc ASCO* 2013b; **Abstract 9009**.

Sznol M et al. **Survival and long-term follow-up of safety and response in patients (pts) with advanced melanoma (MEL) in a phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538).** *Proc ASCO* 2013; **Abstract CRA9006**.

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. Dabrafenib can lead to which of the following adverse events when used in the treatment of BRAF V600 mutation-positive melanoma?
  - a. Pyrexia
  - b. Cutaneous squamous cell carcinoma
  - c. Rash
  - d. All of the above
  
2. A Phase I/II trial comparing dabrafenib monotherapy to the combination of dabrafenib (150 mg BID) and trametinib (2 mg/day) for patients with melanoma and BRAF V600 mutations reported no significant difference in progression-free survival between the 2 treatments.
  - a. True
  - b. False
  
3. The CA033 Phase III trial of *nab* paclitaxel versus dacarbazine in previously untreated metastatic malignant melanoma demonstrated a significant difference in \_\_\_\_\_ with *nab* paclitaxel versus dacarbazine.
  - a. Median progression-free survival
  - b. Objective response rate
  - c. Both a and b
  
4. The addition of a MEK inhibitor to a BRAF inhibitor seems to eliminate the excess risk of squamous cell carcinomas.
  - a. True
  - b. False
  
5. Talimogene laherparepvec is \_\_\_\_\_.
  - a. An investigational oncolytic immunotherapeutic agent for advanced-stage melanoma
  - b. A herpes simplex virus type 1 containing the gene for GM-CSF
  - c. An agent that must be injected into a tumor to be active
  - d. Both a and c
  - e. All of the above
  
6. The Phase II ERIVANCE BCC trial of vismodegib in locally advanced or metastatic basal cell carcinoma reported that vismodegib was associated with tumor responses only in patients with locally advanced disease.
  - a. True
  - b. False
  
7. In the Phase II ERIVANCE BCC trial of vismodegib for patients with locally advanced or metastatic basal cell carcinoma, vismodegib was associated with which of the following side effects?
  - a. Dysgeusia
  - b. Muscle cramps
  - c. Alopecia
  - d. All of the above
  
8. According to a recent paper by Jang and colleagues, patients with BRAF-mutant melanoma with nonbulky asymptomatic disease and normal LDH levels should be considered for immunotherapy prior to therapy with a BRAF inhibitor because of the possibility of a durable complete response.
  - a. True
  - b. False
  
9. Hepatotoxicity is a limiting factor of combination therapy with vemurafenib and ipilimumab for patients with metastatic melanoma.
  - a. True
  - b. False
  
10. \_\_\_\_\_ is a monoclonal antibody targeting PD-1 that demonstrated an overall response rate of 38% for patients with advanced melanoma with or without previous ipilimumab treatment.
  - a. Nivolumab
  - b. Dabrafenib
  - c. Lambrolizumab

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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>	
Rationale for dual targeting of BRAF and MEK signaling in melanoma	4	3	2	1
Clinical activity and safety of novel anti-PD-1 therapies for metastatic melanoma	4	3	2	1
Management of vismodegib-associated ageusia and muscle cramping	4	3	2	1
Incidence, mechanism of development and management of vemurafenib-associated secondary nonmelanoma skin cancer	4	3	2	1
Results of the Phase III CA033 trial of <i>nab</i> paclitaxel versus dacarbazine in previously untreated metastatic malignant melanoma	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 a treatment algorithm for BRAF V600 mutation-positive and wild-type advanced melanoma. .... 4 3 2 1 N/M N/A
- Counsel patients regarding the risk of BRAF inhibitor-associated secondary nonmelanoma skin cancers and other cutaneous and noncutaneous adverse events, and implement appropriate surveillance and management strategies. .... 4 3 2 1 N/M N/A
- Recognize immune-related adverse events associated with anti-CTLA-4 antibody therapy with ipilimumab, and offer supportive management strategies to minimize and/or manage these side effects. .... 4 3 2 1 N/M N/A
- Evaluate the potential clinical and research implications of recent Phase III trial results evaluating the combination of MEK and BRAF inhibitors in the treatment of melanoma. .... 4 3 2 1 N/M N/A
- Appraise the rationale for and clinical data with investigational anti-PD-1 immunotherapy for advanced solid tumors. .... 4 3 2 1 N/M N/A
- Rationally incorporate established and novel cytotoxic agents into the treatment algorithm for advanced melanoma. .... 4 3 2 1 N/M N/A
- Identify patients with locally advanced or metastatic BCC for whom hedgehog inhibitor therapy may be an appropriate treatment option. .... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical trials. .... 4 3 2 1 N/M N/A

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

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

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Yes, I am willing to participate in a follow-up survey.  
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**PART 2 — Please tell us about the faculty and editor for this educational activity**

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal					
<b>Faculty</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
Keith T Flaherty, MD	4	3	2	1	4	3	2	1	
Rene Gonzalez, MD	4	3	2	1	4	3	2	1	
Anna C Pavlick, MS, DO	4	3	2	1	4	3	2	1	
Jeffrey A Sosman, MD	4	3	2	1	4	3	2	1	
<b>Editor</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
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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Neil Love, MD  
Research To Practice  
One Biscayne Tower  
2 South Biscayne Boulevard, Suite 3600  
Miami, FL 33131

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