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Dermatologic Oncology™ UPDATE

Systemic Management of Malignant Melanoma and Basal Cell Carcinoma

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Jeffrey Weber, MD, PhD
Michael A Postow, MD
Evan J Lipson, MD
Antoni Ribas, MD, PhD

EDITOR

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2 Audio CDs
Monograph

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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 cancer presents as minimally invasive BCC and SCC and, as such, is 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. Thus melanoma and nonmelanoma skin cancer are distinct entities, each posing unique challenges to the oncology community. Featuring up-to-date 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

- Recognize immune-related adverse events associated with ipilimumab alone or in combination with nivolumab, and offer supportive management strategies to minimize and/or manage these side effects.
- Use biomarkers, clinical characteristics and mutational analyses to select individualized front-line and subsequent treatment approaches for patients with advanced melanoma.
- Recall existing and emerging research information demonstrating the effect of combining BRAF and MEK inhibitors for patients with BRAF mutation-positive metastatic melanoma, and use this information to guide treatment planning for these patients.
- Counsel patients regarding the risk of BRAF inhibitor-associated secondary nonmelanoma skin cancers and other adverse events, and implement appropriate surveillance and management strategies.
- Appraise the rationale for and clinical trial data with investigational anti-PD-1/PD-L1 antibodies for advanced desmoplastic melanoma.
- Identify patients with locally advanced or metastatic BCC for whom vismodegib may be an appropriate treatment consideration.

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EDITOR

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Research To Practice
Miami, Florida

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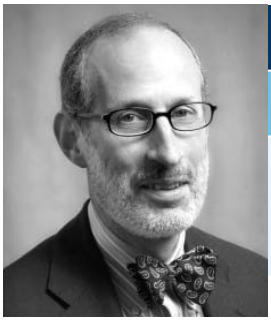


INTERVIEW

Jeffrey Weber, MD, PhD

Dr Weber is Deputy Director at the Laura and Isaac Perlmutter Cancer Center and Professor of Medicine at NYU Langone Medical Center in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-4, 7

DR LOVE: Would you discuss the results of the Phase III CheckMate 067 trial of nivolumab or ipilimumab alone or in combination for patients with untreated advanced melanoma that were presented at ASCO 2015 and published recently in *The New England Journal of Medicine*?

DR WEBER: In this Phase III trial, 945 patients were randomly assigned to the combination of nivolumab and ipilimumab or either agent alone. The response rate was

approximately 58% on the combination arm versus 43.7% with nivolumab and 19% on the ipilimumab arm. The overall response rate was clearly superior with nivolumab/ipilimumab.

Progression-free survival, one of the primary endpoints, was 11.5 months with the combination versus 2.9 months with ipilimumab and 6.9 months with nivolumab. A significant improvement was evident with the nivolumab/ipilimumab combination versus ipilimumab alone, with a hazard ratio of 0.42 and an impressive *p*-value. The combination was also superior to nivolumab alone, although the study wasn't powered to determine that difference.

Interestingly, in the subgroup of patients with PD-L1-positive tumors the progression-free survival curves for the nivolumab and nivolumab/ipilimumab arms overlapped. Clear superiority was noted with both the combination and nivolumab alone versus ipilimumab (Larkin 2015; Wolchok 2015; [1.1]). These results suggest that for patients who have immunogenic tumors, up-front therapy with nivolumab alone may be effective.

DR LOVE: What is your choice of first-line therapy for patients with BRAF wild-type melanoma?

DR WEBER: My preference for up-front treatment is immunotherapy for patients who have indolent, low-burden disease. I would offer these patients either nivolumab or pembrolizumab. For patients who have high LDH, aggressive disease and a significant disease burden my choice would be the combination of ipilimumab and nivolumab whenever possible. With the nivolumab/ipilimumab combination, those patients who respond typically experience a deep response.

1.1

CheckMate 067: Results of a Phase III Trial of Nivolumab (Nivo) or Ipilimumab (Ipi) Alone or in Combination for Patients with Untreated, Advanced Melanoma

Efficacy	Nivo (n = 316)	Nivo + ipi (n = 314)	Ipi (n = 315)
Overall			
Median PFS	6.9 mo	11.5 mo	2.9 mo
ORR	43.7%	57.6%	19.0%
PFS: Nivo/ipi vs ipi, HR 0.42, $p < 0.001$; nivo/ipi vs nivo, HR 0.74, p = NR; nivo vs ipi, HR 0.57, $p < 0.001$			
Efficacy by PD-L1 status			
Median PFS			
PD-L1-positive (n = 80, 68, 75)	14.0 mo	14.0 mo	3.9 mo
PD-L1-negative (n = 208, 210, 202)	5.3 mo	11.2 mo	2.8 mo
ORR			
PD-L1-positive (n = 80, 68, 75)	57.5%	72.1%	21.3%
PD-L1-negative (n = 208, 210, 202)	41.3%	54.8%	17.8%
Efficacy by BRAF mutation status			
Median PFS			
Mutant	5.6 mo	11.7 mo	4.0 mo
Wild type	7.9 mo	11.2 mo	2.8 mo

PFS = progression-free survival; ORR = overall response rate; HR = hazard ratio; NR = not reported

Larkin J et al. *N Engl J Med* 2015;373(1):23-34; Wolchok JD et al. *Proc ASCO* 2015;**Abstract LBA1**.

Editor's note: Subsequent to this interview, on September 30, 2015, the FDA granted accelerated approval to nivolumab in combination with ipilimumab for patients with previously untreated BRAF V600 wild-type, unresectable or metastatic melanoma.

DR LOVE: How do you treat metastatic BRAF-mutant melanoma in the first-line setting?

DR WEBER: I would administer immunotherapy as first-line therapy for patients who have low-burden, indolent, asymptomatic disease. The median survival with up-front immunotherapy is longer than with BRAF/MEK combination therapy, which can be reserved for relapse. The response rate and survival with BRAF/MEK treatment after disease progression on immunotherapy are excellent and just as good as up-front therapy. However, if immunotherapy is administered after failure of BRAF/MEK therapy, responses are not as good as in the BRAF/MEK inhibitor-naïve population.

A study presented at ASCO 2015 investigating dabrafenib with or without trametinib for patients with BRAF mutation-positive metastatic melanoma showed a tail or plateau on the overall survival curve at 30% to 40% after 4 years of follow-up (Daud 2015a). Long-term survival with BRAF inhibition or immunotherapy is possible. However, the median survival in the subpopulation of patients with previously untreated disease in the Phase I KEYNOTE-001 trial of pembrolizumab was approximately 31 months — the longest in any well-conducted randomized trial in melanoma (Daud 2015b).

When the Phase III CheckMate 067 data mature, you may well see a longer median. Patients with melanoma can fare well on immunotherapy. No up-front treatment with BRAF inhibition can yield better results. Median survival with a BRAF/MEK inhibitor combination is approximately 25 months (Daud 2015a; [1.2]).

For patients with BRAF mutations who need dramatic regression of disease, a BRAF/MEK inhibitor combination is the treatment of choice. I would offer this to a patient who has aggressive, high-LDH disease and a significant tumor burden.

1.2

Efficacy and Safety of Dabrafenib/Trametinib versus Dabrafenib Alone for Previously Untreated BRAF Mutation-Positive Advanced Melanoma

Efficacy	Dabrafenib + trametinib (n = 211)	Dabrafenib (n = 212)	Hazard ratio	*p*-value
Overall response rate	69%	53%	—	0.0014
Median progression-free survival	11.0 mo	8.8 mo	0.67	0.0004
Median overall survival	25.1 mo	18.7 mo	0.71	0.0107

	Dabrafenib + trametinib (n = 209)		Dabrafenib (n = 211)	
Select adverse events	**Any grade**	**Grade 3**	**Any grade**	**Grade 3**
Any	87%	32%	90%	30%
Pyrexia	52%	7%	25%	2%
Fatigue	27%	2%	28%	<1%
Rash	24%	0%	20%	<1%

Long GV et al. *Lancet* 2015;386(9992):444-51.

DR LOVE: What do we know about the efficacy and toxicity associated with the combination of BRAF and MEK inhibitors, specifically dabrafenib/trametinib and vemurafenib/cobimetinib?

DR WEBER: Both dabrafenib/trametinib and vemurafenib/cobimetinib are good combinations in terms of efficacy. I believe what will distinguish them is their toxicity profiles. With dabrafenib/trametinib, toxicities such as papillomas and rash are common, but the skin toxicities with BRAF inhibitors are diminished by the addition of a MEK inhibitor. Some chronic dermatologic toxicity, such as rash and itching, can still be observed. Rarely, fatigue, diarrhea, nausea and keratoacanthomas can occur. However, after 16 weeks on the combination, patients generally fare well.

With the vemurafenib/cobimetinib combination, a different spectrum of toxicity is observed. A lower incidence of fever and fatigue but more hepatic toxicity and an overall higher incidence of Grade 2 or higher toxicities have been reported.

Physicians are familiar with the dabrafenib/trametinib combination, but the cobimetinib/vemurafenib combination is also effective and will probably be approved (see editor's note, page 9).

Tracks 10-14

DR LOVE: Moving to basal cell carcinoma (BCC), would you discuss the latest data with the hedgehog pathway inhibitor vismodegib and its implications for clinical practice?

DR WEBER: A 12-month update on the ERIVANCE study of the efficacy of vismodegib in advanced BCC demonstrated response rates of approximately 33% for patients in the metastatic setting and 48% for those with locally advanced disease. The median duration of exposure to the drug is more than 12 months (Sekulic 2015). So treatment with vismodegib in this setting is effective.

However, few patients will die of this disease. Most patients with BCC in this country undergo surgery. I have seen patients who have had disfiguring surgery. For these patients, preoperative therapy with a hedgehog pathway inhibitor would be a major advance. I believe the best use for vismodegib will be in the neoadjuvant setting, to shrink tumors and facilitate easier surgery.

DR LOVE: What are the side effects associated with vismodegib?

DR WEBER: Patients experience muscle aches, pains, fevers and malaise. Many patients will develop dysgeusia and experience a metallic taste. Sometimes liver function abnormalities and nausea/diarrhea are observed, but they are usually not of a high grade. Patients can be offered treatment holidays to mitigate these side effects.

DR LOVE: The STEVIE study presented at ASCO 2015 reported that treatment breaks for patients with advanced BCC who were receiving vismodegib did not seem to compromise efficacy. Would you comment on the results of that study?

DR WEBER: We generally give patients receiving vismodegib treatment breaks for up to a month. The dysgeusia, fatigue, malaise, muscle aches and arthralgias improve. Patients feel much better and, surprisingly, if a patient has experienced a response, it does not affect the efficacy (Dummer 2015; [1.3]).

DR LOVE: Would you comment on other hedgehog pathway inhibitors, such as sonidegib?

DR WEBER: Most of the other hedgehog inhibitors will be "me-too" drugs with similar efficacy. I believe the major differences will be in the side-effect profiles. A lower incidence of muscle spasms and dysgeusia and a higher incidence of hepatic toxicity have been reported with sonidegib (1.4). ■

1.3

Effect of Treatment Breaks on Vismodegib-Associated Patient Outcomes in Advanced Basal Cell Carcinoma: Exploratory Analysis of the STEVIE Study

	Number of treatment breaks			
Efficacy	**0** (n = 358)	**1** (n = 72)	**2** (n = 39)	**≥3** (n = 13)
ORR	61%	65%	95%	85%
Median PFS	19.8 mo	19.0 mo	NE	NE
Median DoT	n = 368	n = 76	n = 41	n = 14
Including breaks	223.5 d	229 d	399 d	454 d
Adverse events	n = 368	n = 76	n = 41	n = 14
Dysgeusia	51%	58%	63%	93%
Muscle spasms	59%	70%	81%	93%
Alopecia	59%	63%	78%	79%
Grade ≥3 TEAEs	39%	45%	66%	79%

ORR = objective response rate; PFS = progression-free survival; NE = not estimable; DoT = duration of treatment; TEAEs = treatment-emergent adverse events

Dummer R et al. *Proc ASCO* 2015;**Abstract 9024**.

1.4

Efficacy and Safety of Sonidegib and Vismodegib for Advanced Basal Cell Carcinoma

Efficacy	**Sonidegib (200 mg)**[1]	**Vismodegib (150 mg)**[2]
Overall response rate		
Locally advanced (n = 66, 63)	47%	48%
Metastatic (n = 13, 33)	15%	33%
Select adverse events	**Sonidegib (200 mg)** (n = 79)	**Vismodegib (150 mg)**[3] (n = 99)
Dysgeusia	38%	51%
Muscle spasms	49%	68%
Alopecia	43%	63%
Increased blood creatinine kinase	29%	Not reported

[1] Migden M et al. *Lancet Oncol* 2015;16(6):716-28. [2] Sekulic A et al. *J Am Acad Dermatol* 2015;72(6):1021-6. [3] Sekulic A et al. *N Engl J Med* 2012;366(23):2171-9.

SELECT PUBLICATIONS

Daud A et al. **Updated overall survival (OS) results for BRF113220, a phase I-II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with BRAF V600 metastatic melanoma (MM).** *Proc ASCO* 2015a;**Abstract 9036**.

Daud A et al. **Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001.** *Proc ASCO* 2015b;**Abstract 9005**.

INTERVIEW

Michael A Postow, MD

Dr Postow is Assistant Attending Physician in the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you talk about the data that led to the approval of the dabrafenib/trametinib combination and how these results compare to those with similar combinations, specifically vemurafenib and cobimetinib?

DR POSTOW: The combination of dabrafenib and trametinib was initially approved by the FDA on the basis of improved response rate and progression-free survival in a large Phase I/II study (Flaherty 2012).

The final overall survival analysis from the Phase III COMBI-d study evaluating dabrafenib and trametinib versus dabrafenib alone has now also been presented and subsequently published. The combination demonstrated an overall survival benefit in comparison to dabrafenib alone (Long 2015). Additionally, a separate randomized

Phase III study reported improved overall survival with dabrafenib/trametinib versus vemurafenib monotherapy (Robert 2015), so we now have 2 large data sets demonstrating improved overall survival with dabrafenib/trametinib compared to single-agent BRAF inhibition.

Vemurafenib is now being combined with cobimetinib, and this BRAF and MEK inhibitor combination has also been shown to improve progression-free survival in comparison to vemurafenib monotherapy (Larkin 2015a; [2.1]). So it will be of interest to find out how effective vemurafenib and cobimetinib can be in combination and how side effects may differ between this combination and dabrafenib/trametinib.

Dabrafenib/trametinib causes more febrile reactions, which appears to be the most problematic issue with that combination. Vemurafenib/cobimetinib seems to cause fewer fevers and chills, which might be an advantage.

DR LOVE: If the combination of vemurafenib and cobimetinib were approved, would you consider switching, particularly if a patient had persistent problems with fever?

DR POSTOW: I would absolutely switch to vemurafenib/cobimetinib for any patients who couldn't tolerate dabrafenib/trametinib. I would probably still lean toward starting patients with dabrafenib/trametinib to find out whether it was tolerable, only because that combination has a clear overall survival benefit. Our hope is that vemurafenib/cobimetinib can demonstrate improved overall survival with longer follow-up.

Editor's note: Subsequent to this interview, on the basis of the extension of progression-free survival in the Phase III coBRIM study, on November 10, 2015 the FDA granted approval to cobimetinib in combination with vemurafenib for the treatment of BRAF-positive unresectable or metastatic melanoma.

2.1

coBRIM: A Phase III Study of Cobimetinib (Cobi) and Vemurafenib (Vemu) for Advanced BRAF-Mutated Melanoma

Efficacy[1]	**Cobi + vemu** (n = 238)	**Placebo + vemu** (n = 240)	Hazard ratio	
Median PFS	12.25 mo	7.20 mo	0.58	
ORR	69.5%	50.0%	—	
	Cobi + vemu (n = 254)		**Placebo + vemu** (n = 239)	
Select AEs[2]	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Diarrhea	50%	6%	28%	0%
Nausea	39%	1%	23%	1%
Rash	33%	6%	30%	5%
Photosensitivity reaction	26%	2%	15%	0%
Pyrexia	24%	2%	22%	0%
Cutaneous SCC	<1%	2%	0%	11%

PFS = progression-free survival; ORR = objective response rate; AEs = adverse events; SCC = squamous cell carcinoma

[1] Larkin JMG et al. *Proc ASCO* 2015a;**Abstract 9006**; [2] Larkin J et al. *N Engl J Med* 2014;371(20):1867-76.

Track 10

DR LOVE: Would you discuss the toxicities observed with nivolumab/ipilimumab combination therapy (Larkin 2015b; [2.2])?

DR POSTOW: The side effects are qualitatively similar to what's been observed with either ipilimumab or nivolumab alone, but with the combination, these toxicities are more frequent. The rate of Grade 3 or 4 side effects with the combination is certainly higher than with nivolumab alone.

Most adverse events except for those that are endocrine related are manageable with immunosuppression. So even if side effects occur, most people get through them. Typically, the toxicities seen include rash, diarrhea, colitis and liver inflammation. The combination is also associated with neurologic side effects such as aseptic meningitis or encephalitis. Those issues should be considered in patients with altered mental status, headache or neck stiffness. ■

2.2

CheckMate 067: Treatment-Related Adverse Events (TRAEs) of Nivolumab (Nivo) or Ipilimumab (Ipi) Alone or in Combination for Untreated Advanced Melanoma

	Nivo + ipi (n = 313)		Nivo (n = 313)		Ipi (n = 311)	
Select TRAEs	All	G3/4	All	G3/4	All	G3/4
Skin related	59.1%	5.8%	41.9%	1.6%	54.0%	2.9%
Pruritus	33.2%	1.9%	18.8%	0%	35.4%	0.3%
Rash	28.4%	2.9%	21.7%	0.3%	20.9%	1.6%
Maculopapular rash	11.8%	1.9%	4.2%	0.3%	11.9%	0.3%
GI related	46.3%	14.7%	19.5%	2.2%	36.7%	11.6%
Diarrhea	44.1%	9.3%	19.2%	2.2%	33.1%	6.1%
Colitis	11.8%	7.7%	1.3%	0.6%	11.6%	8.7%
Hepatic related	30.0%	18.8%	6.4%	2.6%	7.1%	1.6%
Increased ALT	17.6%	8.3%	3.8%	1.3%	3.9%	1.6%
Increased AST	15.3%	6.1%	3.8%	1.0%	3.5%	0.6%
Endocrine related	30.0%	4.8%	14.4%	0.6%	10.9%	2.3%
Hypothyroidism	15.0%	0.3%	8.6%	0%	4.2%	0%

G3/4 = Grade 3 or 4 TRAEs

Larkin J et al. *N Engl J Med* 2015b;373(1):23-34; Wolchok J et al. *Proc ASCO* 2015;**Abstract LBA1**.

SELECT PUBLICATIONS

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

Larkin J et al. **Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.** *N Engl J Med* 2015b;373(1):23-34.

Long GV et al. **Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial.** *Lancet* 2015;386(9992):444-51.

Robert C et al. **Improved overall survival in melanoma with combined dabrafenib and trametinib.** *N Engl J Med* 2015;372(1):30-9.

INTERVIEW

Evan J Lipson, MD

Dr Lipson is Assistant Professor of Medical Oncology in the Melanoma and Cancer Immunology Programs at the Johns Hopkins University School of Medicine's Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland.

Tracks 1-15

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your work investigating PD-L1 expression in Merkel cell carcinoma (MCC) and the potential use of immune checkpoint blockade for MCC?

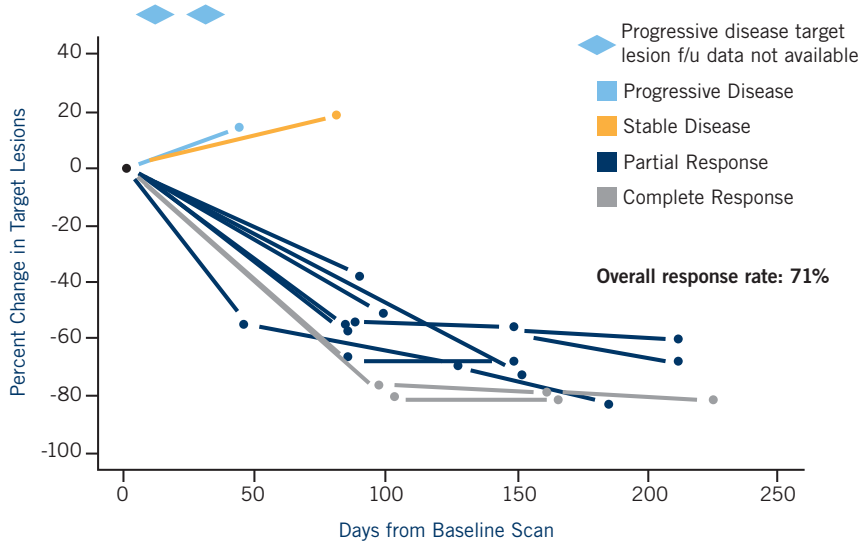
DR LIPSON: MCC is a rare but deadly skin cancer that is often associated with the Merkel cell polyomavirus and sun exposure. Despite appropriate first-line treatment, the cancer often recurs either locally or in another location. Because of the association with the virus and the belief that the immune milieu is active, we undertook a study to assess the association between the presence of the virus in the tumor and expression of

PD-L1. The study demonstrated that patients whose tumors expressed PD-L1 experienced a longer overall survival than those with PD-L1-negative tumors (Lipson 2013).

This suggests that enhancing the immune response with a checkpoint inhibitor could boost the ability of the immune system to destroy the tumor. Currently anti-PD-1/anti-PD-L1 antibodies are being explored for patients with unresectable or metastatic MCC, and we have observed some good responses (Nghiem 2015; [3.1]).

3.1

Phase II Trial of the Activity of Pembrolizumab as First Systemic Therapy for Advanced Merkel Cell Carcinoma



With permission from Nghiem P et al. *Proc ECC* 2015;**Abstract 22LBA**.

Tracks 3-4

DR LOVE: Your group recently reported on the safety of ipilimumab in patients with advanced melanoma and preexisting hepatitis B or C. Would you discuss those results?

DR LIPSON: Studies of immune checkpoint blockade have generally excluded patients with any immunologic comorbidity. One of the potential side effects of administering checkpoint inhibitors is autoimmune hepatitis. We published a case series last year evaluating the effect of using ipilimumab in patients with preexisting hepatitis B or C.

Our results showed that in these patients, viral hepatitis was stable. Patients tolerated the agent well, and the rates of liver function test abnormalities were similar to those of a normal population (Ravi 2014). It was a small study, but it does suggest that in patients with underlying viral hepatitis, ipilimumab can be safely used with close monitoring.

DR LOVE: Would you also discuss your work evaluating the administration of ipilimumab in patients who had undergone kidney or liver transplantation?

DR LIPSON: We studied the safety and efficacy of ipilimumab in 2 patients with metastatic melanoma who had previously undergone kidney transplantation and found that neither of the patients' renal allografts was affected by this therapy (Lipson 2014a). Both of the patients demonstrated an antitumor response to ipilimumab.

The other report was of a patient with a liver transplant who received ipilimumab therapy and who also did not experience rejection of the allograft (Morales 2015). These reports suggest that these patients who are immunosuppressed can still experience responses to checkpoint inhibitors. I would emphasize that these are small trials, however. We cannot conclude that checkpoint blockade is safe across the board in patients with kidney and liver transplants. It is important to have a conversation with your patient about the potential risks.

Track 5

DR LOVE: Another interesting area of research that you have been involved with is the use of circulating tumor DNA (ctDNA) to monitor tumor burden in patients with melanoma who are receiving treatment with checkpoint inhibitors. Would you discuss that work?

DR LIPSON: This study addresses a common issue in patients receiving checkpoint blockade therapy. In a small but meaningful percent of patients, tumors may seem to enlarge or appear anew before regressing. So the question was, how can you accurately predict a response to a checkpoint inhibitor early in the course of therapy?

The study evaluated patients with melanoma receiving checkpoint blockade agents who had mutations that were detectable in the peripheral blood. The levels of ctDNA were analyzed during therapy. In general, levels of ctDNA correlated with what the radiologic scans were demonstrating. Patients who were experiencing both radiologic and clinical disease progression had rising levels of ctDNA.

Interestingly, a patient who had undergone a biopsy of a soft-tissue lesion experienced a huge spike in the level of ctDNA, which stayed elevated for several weeks. So a perturbation in the tumor environment through a needle biopsy released a large bolus of tumor into circulation. Another woman who was receiving ipilimumab for locally advanced unresectable melanoma with neck lymphadenopathy showed disease progression by clinical evaluation. However, her ctDNA dropped to an undetectable level midway through her therapy, which was an early indicator that she was going to respond. She did eventually experience a complete response (Lipson 2014b). ■

SELECT PUBLICATIONS

Lipson EJ et al. **Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma.** *J Clin Oncol* 2014a;32(19):e69-71.

Lipson EJ et al. **Circulating tumor DNA analysis as a real-time method for monitoring tumor burden in melanoma patients undergoing treatment with immune checkpoint blockade.** *J Immunother Cancer* 2014b;2(1):42.

Lipson EJ et al. **PD-L1 expression in the Merkel cell carcinoma microenvironment: Association with inflammation, Merkel cell polyomavirus and overall survival.** *Cancer Immunol Res* 2013;1(1):54-63.

Morales RE et al. **Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation.** *J Immunother Cancer* 2015;3:22.

Ravi S et al. **Ipilimumab administration for advanced melanoma in patients with pre-existing hepatitis B or C infection: A multicenter, retrospective case series.** *J Immunother Cancer* 2014;2(1):33.

INTERVIEW

Antoni Ribas, MD, PhD

Dr Ribas is Professor of Medicine, Surgery and Molecular and Medical Pharmacology and Director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center at the University of California Los Angeles David Geffen School of Medicine in Los Angeles, California.

Tracks 1-12

Track 1 CheckMate 067: Efficacy and safety results of a Phase III trial of nivolumab, ipilimumab or the combination for patients with untreated advanced melanoma

Track 2 Mechanistic underpinnings for the increased progression-free survival rates with the nivolumab/ipilimumab combination among patients with a negative PD-L1 tumor status on the CheckMate 067 trial

Track 3 Depth and duration of response with nivolumab/ipilimumab versus nivolumab or ipilimumab monotherapy

Track 4 Sequence and selection of first-line therapy for patients with metastatic melanoma — Role of immunotherapy versus BRAF inhibition

Track 5 Response to anti-PD-1/PD-L1 therapy in patients with metastatic desmoplastic melanoma

Track 6 Considerations for the use of BRAF and/or MEK inhibitor-based first-line therapy for BRAF mutation-positive metastatic melanoma

Track 7 Activity of BRAF or MEK inhibition or the combination versus immunotherapy as treatment for patients with BRAF mutation-positive melanoma and CNS metastases

Track 8 Atypical patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial

Track 9 Response rates of anti-PD-1 antibodies versus ipilimumab as first-line therapy for metastatic melanoma

Track 10 Activity and ongoing investigations of anti-PD-L1-based strategies in metastatic melanoma

Track 11 Counseling patients about the side-effect profiles of anti-PD-1/CTLA-4 combination therapy

Track 12 Use of immune checkpoint blockade in patients with prior autoimmune disorders

Select Excerpts from the Interview

Tracks 4, 6

DR LOVE: What is your usual approach to patients with newly diagnosed metastatic melanoma outside a clinical trial?

DR RIBAS: I now consider immunotherapy as the first line of therapy in the majority of patients with metastatic melanoma. I am comfortable discussing this option with patients even before the results of BRAF testing are available. BRAF/MEK inhibitors are effective therapies but yield a much shorter duration of response compared to immunotherapy. The duration of response to immunotherapies can be measured in years.

DR LOVE: When would you consider using a single-agent anti-PD-1 antibody versus the combination with ipilimumab?

DR RIBAS: The majority of immune responses to cancer are mediated by T cells that recognize something that's altered in the tumor. In melanoma, damage from UV radiation induces a high mutational load. These tumors are more likely to induce an immune response that then is inhibited by PD-1.

So if I have a 65-year-old patient with melanoma that started in a sun-exposed area such as the scalp and became metastatic, I would offer this patient single-agent anti-PD-1 therapy. This tumor is likely to have a high mutational load that would promote T-cell infiltration. I believe that we would see a higher response rate to single-agent anti-PD-1 antibodies. This is not based on clinical trial data but on my clinical experience.

In randomized trials, the anti-PD-1 antibodies pembrolizumab and nivolumab have shown greater efficacy than ipilimumab. So if I decide to use a checkpoint inhibitor, I would consider either pembrolizumab or nivolumab, which elicit similar response rates. The only practical difference is that pembrolizumab is administered every 3 weeks and nivolumab is administered every 2 weeks.

The combination of nivolumab and ipilimumab has recently demonstrated promising results (Larkin 2015; [1.1, page 4]). A biopsy of the tumor would be useful as a guide to help determine who would benefit from single-agent therapy versus a combination approach. Currently assays focus on evaluating PD-L1 expression alone. I foresee in the future we will be able to assess if T-cells are colocalizing with PD-L1. If T-cell infiltration and interaction of T-cells occur with the tumor, single-agent anti-PD-1- or PD-L1-blocking antibodies would be effective. However, if T-cells are absent, combination therapy that facilitates T-cell infiltration may be more appropriate.

DR LOVE: What are the clinical situations in which you would start with BRAF/MEK inhibitor therapy?

DR RIBAS: BRAF/MEK inhibitors in combination are outstanding therapies that elicit approximately a 70% objective response rate and a median overall survival of more than 2 years (Long 2015). So they have shifted the survival curve of patients with metastatic melanoma and changed the natural course of the disease. The median duration of response to combination therapy is 13 months. Some patients experience long-lasting responses, but the majority of patients who respond will experience relapse.

Patients who present with more aggressive disease may be less likely to respond to immunotherapy because their tumors have overwhelmed the immune system and the immune system is no longer capable of recognizing them. Although these patients tend to experience spectacular responses to BRAF/MEK inhibitor combination therapy, these responses are short-lived. Bulky tumors rarely show evidence of T-cell infiltration, and patients with these BRAF-mutant tumors would benefit from BRAF/MEK inhibitor combination therapy.

Patients with more indolent BRAF-mutant melanoma may derive benefit from BRAF/MEK inhibitors for years. I have a couple of patients who were on the Phase I trial of the BRAF inhibitor vemurafenib who have survived for more than 5 years. However, patients with indolent disease are more likely to respond to immunotherapy with fewer side effects, and the majority of these patients usually experience a durable response.

Track 5

DR LOVE: Would you describe the role of anti-PD-1/PD-L1 therapy for patients with metastatic desmoplastic melanoma?

DR RIBAS: Desmoplastic melanoma is a subset of the disease that comprises approximately 1% of melanomas. It tends to appear in the chronically sun-exposed areas of the head and neck and is usually a local disease with infrequent metastases. These patients require surgery that can be disfiguring.

Typically, desmoplastic melanomas are not responsive to most treatments. However, these tumors respond well to PD-1 blockade (Eroglu 2015; [4.1]). It is likely that this is because desmoplastic melanomas are tumors that have a higher mutational load caused by chronic sun exposure. One of the diagnostic features is a T-cell response in the tumor. Those T cells were turned off by PD-L1, and this inhibition must be released to elicit an immune response.

4.1

Response to Anti-PD-1/PD-L1 Therapy in Patients with Metastatic Desmoplastic Melanoma

Efficacy	N = 24
Overall response rate	71%
Complete response	42%
Partial response	29%
Median progression-free survival (PFS)	Not reached
6-month PFS rate	77%
Median overall survival (OS)	Not reached
1-year OS rate	80%

Ongoing responses: 14 of 17 patients (82%); 2 patients with partial responses had no evidence of disease after resection of progressing metastases

Eroglu Z et al. *Proc ASCO* 2015;**Abstract 9011**.

Track 8

DR LOVE: You were part of a group that presented data at ASCO on atypical patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial. Would you discuss those results?

DR RIBAS: The presentation at ASCO was based on a large series of patients with metastatic melanoma who received pembrolizumab. Responses were assessed using immune-related response criteria (irRC) in addition to conventional response criteria. If a patient had an initial readout of disease progression, that patient was allowed to stay on study at the discretion of the investigator. Progression had to be confirmed by irRC. If an initial readout of disease progression was observed on a scan but the patient eventually experienced a response, we defined that as pseudoprogression. The frequency of pseudoprogression was approximately 5% (Wolchok 2015; [4.2]).

A similar incidence of pseudoprogression has been observed with CTLA-4 and PD-1 blockade. To determine what is actually occurring in the tumor, a biopsy is required.

It could be that the tumor continues to progress but responds eventually or that the tumor is actually responding but an influx of immune cells induces inflammation and makes the tumor appear larger. The majority of biopsies we have performed on patients with pseudoprogression show tumor growth with an immune response that increases with time. The immune infiltrate eventually predominates and destroys the cancer. I've also seen biopsies of an inflammatory reaction, and the amount of tumor is small. The inflammatory reaction makes the tumor appear larger. That tends to happen more frequently in my experience in lymph nodes rather than in visceral metastases.

DR LOVE: How do you distinguish pseudoprogression from real tumor progression clinically?

DR RIBAS: Clinical judgment should be used in determining the best course of action. If the scans show objective disease progression and the patient is feeling worse with more overall symptoms, I would not conclude this is pseudoprogression and would not wait for an eventual response. If a scan shows that a lesion is bigger but the patient feels better, I may decide to continue therapy because these patients can sometimes experience response. The best approach would be to biopsy the tumor. If the tumor is growing larger and no immune infiltrate is present, I would not consider it to be pseudoprogression but rather true disease progression. ■

4.2

Early and Late Pseudoprogression in Patients with Metastatic Melanoma Treated with Pembrolizumab on the Phase III KEYNOTE-001 Trial

Timing of pseudoprogression	Definition	Rate of pseudoprogression
Early	≥25% increase in tumor burden at week 12 not confirmed as progressive disease (PD) on the 2 subsequent assessments	4.6%
Late	≥25% increase in tumor burden at any assessment after week 12 not confirmed as PD at the next assessment	4.3%

Wolchok J et al. *Proc ASCO* 2015;**Abstract 3000**.

SELECT PUBLICATIONS

Eroglu Z et al. **Response to anti-PD1/PDL1 therapy in patients with metastatic desmoplastic melanoma.** *Proc ASCO* 2015;**Abstract 9011**.

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

Han D et al. **Clinicopathologic predictors of survival in patients with desmoplastic melanoma.** *PLoS One* 2015;10(3):e0119716.

Larkin J et al. **Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.** *N Engl J Med* 2015;373(1):23-34.

Long GV et al. **Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial.** *Lancet* 2015;386(9992):444-51.

Mahoney KM et al. **The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma.** *Clin Ther* 2015;37(4):764-82.

Wolchok J et al. **Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001.** *Proc ASCO* 2015;**Abstract 3000**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III CheckMate 067 trial of nivolumab or ipilimumab alone or in combination for patients with untreated advanced melanoma demonstrated a benefit with the combination in terms of progression-free survival in comparison to ipilimumab in _____.**
   a. The overall population
   b. Patients with PD-L1-positive tumors
   c. Both a and b
   d. Neither a nor b

2. **Exploratory analysis of the STEVIE study of the effect of vismodegib treatment breaks on outcomes for patients with advanced BCC demonstrated that treatment holidays adversely affected _____.**
   a. Overall response rate
   b. Progression-free survival
   c. Both a and b
   d. Neither a nor b

3. **The mechanism of action of sonidegib is _____.**
   a. Immune checkpoint inhibition
   b. BRAF inhibition
   c. Hedgehog pathway inhibition

4. **Recent preliminary, small reports from Lipson and colleagues suggest that ipilimumab generates responses and is safe for patients with advanced melanoma who have undergone _____.**
   a. Liver transplantation
   b. Kidney transplantation
   c. Both a and b

5. **In the Phase III CheckMate 067 trial for patients with treatment-naïve advanced melanoma, adverse events associated with the combination of nivolumab and ipilimumab included _____.**
   a. Rash
   b. Colitis
   c. Diarrhea
   d. Increased transaminitis
   e. Hypothyroidism
   f. All of the above

6. **A study by Lipson and colleagues evaluating the effect of ipilimumab in patients with preexisting hepatitis B or C demonstrated that _____.**
   a. The viral hepatitis was stable after ipilimumab therapy
   b. Ipilimumab was well tolerated
   c. The rate of liver function test abnormalities was significantly higher than in a normal population
   d. Both a and b
   e. All of the above

7. **Interim results of a Phase II trial of pembrolizumab as first systemic therapy for patients with advanced MCC demonstrated that this anti-PD-1 agent produces no response in MCC.**
   a. True
   b. False

8. **The incidence of skin toxicities associated with a BRAF inhibitor is increased with the addition of a MEK inhibitor in the treatment of melanoma.**
   a. True
   b. False

9. **Which of the following statements is true regarding desmoplastic melanoma?**
   a. It tends to appear in chronically sun-exposed areas of the body, most commonly on the head and neck
   b. It is a rare form of cancerous melanoma
   c. It responds well to PD-1 blockade
   d. Both a and c
   e. All of the above

10. **The results from a study by Wolchok and colleagues investigating patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial suggest that atypical patterns of response occur in some patients and that the use of conventional response criteria alone may underestimate clinical benefit from immunotherapy.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Dermatologic Oncology Update — Issue 1, 2015

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

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

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

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

	BEFORE	AFTER
Patient selection for immunotherapy versus BRAF/MEK inhibition as first-line treatment for BRAF mutation-positive melanoma	4 3 2 1	4 3 2 1
CheckMate 067: Results of a Phase III trial of nivolumab, ipilimumab or the combination for patients with untreated advanced melanoma	4 3 2 1	4 3 2 1
Atypical patterns of response in patients with metastatic melanoma treated with pembrolizumab on the KEYNOTE-001 trial	4 3 2 1	4 3 2 1
Incidence of dysgeusia and muscle cramps associated with the Hedgehog inhibitors vismodegib and sonidegib	4 3 2 1	4 3 2 1
Activity of pembrolizumab as first systemic therapy for advanced MCC	4 3 2 1	4 3 2 1
Progression-free survival advantage with the addition of cobimetinib to vemurafenib for advanced BRAF mutation-positive melanoma	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).....

Approximately how many new patients with the following do you see per year?

Melanoma:..... Basal cell carcinoma:..... Merkel cell carcinoma:.....

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

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If no, please explain:.....

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

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☐ 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

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

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

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

- Recognize immune-related adverse events associated with ipilimumab alone or in combination with nivolumab, and offer supportive management strategies to minimize and/or manage these side effects.....4 3 2 1 N/M N/A
- Use biomarkers, clinical characteristics and mutational analyses to select individualized front-line and subsequent treatment approaches for patients with advanced melanoma.....4 3 2 1 N/M N/A
- Recall existing and emerging research information demonstrating the effect of combining BRAF and MEK inhibitors for patients with BRAF mutation-positive metastatic melanoma, and use this information to guide treatment planning for these patients.....4 3 2 1 N/M N/A
- Counsel patients regarding the risk of BRAF inhibitor-associated secondary nonmelanoma skin cancers and other adverse events, and implement appropriate surveillance and management strategies.....4 3 2 1 N/M N/A

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

- Appraise the rationale for and clinical trial data with investigational anti-PD-1/PD-L1 antibodies for advanced desmoplastic melanoma. . . . . 4 3 2 1 N/M N/A
- Identify patients with locally advanced or metastatic BCC for whom vismodegib may be an appropriate treatment consideration. . . . . 4 3 2 1 N/M N/A

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. . . . . .

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PART 2 — Please tell us about the faculty and editor for this educational activity

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Faculty	Knowledge of subject matter	Effectiveness as an educator
Jeffrey Weber, MD, PhD	4 3 2 1	4 3 2 1
Michael A Postow, MD	4 3 2 1	4 3 2 1
Evan J Lipson, MD	4 3 2 1	4 3 2 1
Antoni Ribas, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

. . . . . .

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. . . . . .

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