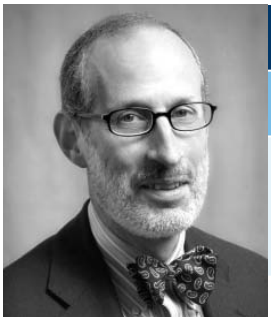

INTERVIEW

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**.