INTERVIEW

Michael A Postow, MD

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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.