INTERVIEW

Keith T Flaherty, MD

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Tracks 1-15

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

Efficacy	Vemurafenib		Dacarbazine	
Median progression-free survival (n = 275, 274)*	5.3 mo		1.6 mo	
Six-month overall survival (n = 336, 336)	84%		64%	
	Vemurafenib (n = 336)		Dacarbazine (n = 282)	
Select adverse events	Grade 2	Grade 3	Grade 2	Grade 3
Cutaneous squamous cell carcinoma	NR	12%	0%	<1%
Keratoacanthoma	2%	6%	0%	0%
Photosensitivity skin reactions†	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

Efficacy	**Dabrafenib** (n = 187)		**Dacarbazine** (n = 63)	
Median progression-free survival*	5.1 mo		2.7 mo	
Overall response rate	50%		6%	
Select adverse events	Grade 2	Grade 3 or 4	Grade 2	Grade 3 or 4
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

1.3

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. ■

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

Efficacy	*Nab*-P* (n = 264)	Dacarbazine† (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
Select Grade ≥3 adverse events	(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^2 days 1, 8, 15 q4wk; † Dacarbazine, 1,000 mg/m^2 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.