INTERVIEW

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Tracks 1-24

Continued

Tracks 1-24 (continued)

Track 20 Clinical characteristics and natural history of BCC and SCC of the skin

Track 21 Mechanism of action of the hedgehog inhibitor vismodegib (GDC-0449) in BCC of the skin

Track 22 Tolerability of vismodegib in advanced cutaneous BCC

Track 23 First-line cetuximab monotherapy for unresectable SCC of the skin

Track 24 Clinical responses observed with hedgehog inhibitors in advanced cutaneous BCC

Select Excerpts from the Interview

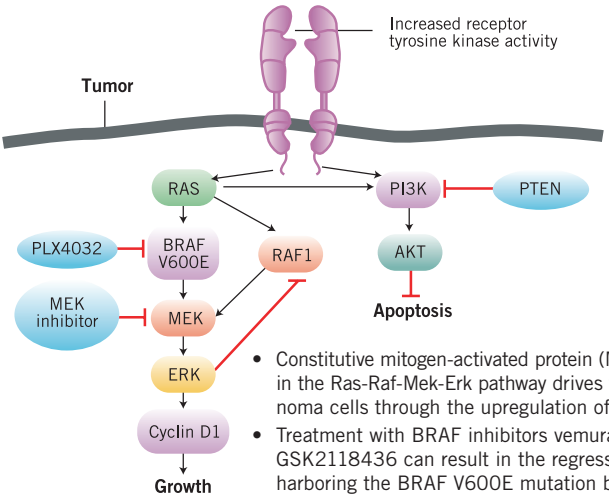
Tracks 3-6

DR LOVE: Would you provide an overview of the significance of BRAF gene mutations in melanoma and other human tumor types?

DR FLAHERTY: The discovery of the BRAF mutation in cancer, particularly in melanoma, dates back to 2002. Mutations of the BRAF gene are relatively common across all tumor types — approximately seven to eight percent of all cancers harbor a BRAF mutation. In melanoma, BRAF gene mutations are found in approximately 50 to 60 percent of patients, which tops the list in terms of the prevalence of a BRAF mutation in a particular tumor type (Davies 2002).

1.1

Intracellular Signaling Pathways in Melanoma Known to Be Important in the Response to Targeted Therapy



- Constitutive mitogen-activated protein (MAP) kinase signaling in the Ras-Raf-Mek-Erk pathway drives the growth of melanoma cells through the upregulation of cyclin D1 expression.
- Treatment with BRAF inhibitors vemurafenib (PLX4032) and GSK2118436 can result in the regression of melanomas harboring the BRAF V600E mutation because these drugs block the activity of the mutant BRAF.

There was focus for several years on testing the first-generation BRAF inhibitor sorafenib, an agent approved for the treatment of renal cell carcinoma and hepatocellular carcinoma, largely on the basis of its VEGF receptor antagonism. Unfortunately, sorafenib didn't prove to be a particularly effective BRAF inhibitor in melanoma (Flaherty 2010), which left the door open for investigation of prospectively developed BRAF inhibitors in this setting.

The first generation of those inhibitors — vemurafenib (PLX4032) and GSK2118436 — has now established its utility in early clinical trials (Kefford 2010). These are small molecules that inhibit tyrosine kinases, but they're fairly focused on BRAF and among the most selective of the kinase inhibitors developed to date. Both agents are comparable among patients who have metastatic melanoma harboring a BRAF mutation (1.1).

These drugs have demonstrated tumor regression in approximately 80 percent of patients receiving treatment in Phase I trials. Vemurafenib was then taken into a larger, single-agent Phase II trial, and that finding was confirmed in a larger cohort of patients (Ribas 2011).

If you focus solely on responses by RECIST, it works out to be about a more than 60 percent confirmed response rate for both agents (Ribas 2011; Kefford 2010). Duration of response is heterogeneous, but the average duration of response with the BRAF inhibitors thus far is approximately nine months for those patients who experience responses.

The compounds differ a bit in terms of toxicities. Grades 3 and 4 cutaneous toxicities are most prevalent. Rash occurs with both of these agents (1.2). It's a diffuse, macular rash that can be pruritic in some patients but differs from the acneiform or follicular rash associated with epidermal growth factor receptor inhibitors.

In the case of vemurafenib, other common Grade 3 toxicities include arthralgia and photosensitivity. Common side effects for GSK2118436 are headache and drug-related fever in a subset of patients. A unique toxicity

1.2 Tolerability and Side Effects of Novel BRAF Inhibitors in Metastatic Melanoma

Select adverse events	Vemurafenib[1] (n = 132)	GSK2118436[2] (n = 35)
	≥Grade 3	**All grades**
Arthralgia	6%	—
Rash	7%	31%
Photosensitivity reaction	3%	—
Pyrexia	—	37%
Headache	—	29%
Squamous cell carcinoma	26%	9% (Grade 3)

[1] Ribas A et al. *Proc ASCO* 2011;**Abstract 8509**; [2] Kefford R et al. *Proc ASCO* 2010;**Abstract 8503**.

that can emerge with these compounds is cutaneous squamous cell carcinoma (SCC) (1.2). These generally present early in the course of therapy as individual lesions. Approximately two months into treatment, patients will develop nonpigmented cutaneous lesions, often at a site of prior sun exposure.

These lesions have been histologically confirmed in many cases to be SCC. In all cases, they've been well differentiated or even clustering with another entity, referred to as keratoacanthoma, which is a keratinocyte proliferation with no metastatic potential. This is something that practitioners will have to be attuned to because these patients will need to be followed by a dermatologist in addition to an oncologist.

Track 11

DR LOVE: What is your treatment algorithm for patients with BRAF mutation-negative melanoma who are not eligible for or don't wish to receive high-dose interleukin?

DR FLAHERTY: That's where the landscape has been changing so rapidly. We now have one if not two therapies that have shown efficacy such that many of us are considering them as our next-generation standard of therapy in the immunotherapy category. One such agent is ipilimumab, which was presented in a plenary presentation at ASCO 2010. Those Phase III results have now been published in *The New England Journal of Medicine* (Hodi 2010).

We've known for some time that cancer cells, particularly in melanoma, are able to evade and turn off the immune cells that have an ability to recognize them. Ipilimumab is a unique immune modulating agent and quite different from so-called cytokine-based therapies like interleukin-2 or interferon. It's a monoclonal antibody that engages the CTLA-4 receptor on the surface of T cells that normally functions as a negative regulator of T cell function and thus acts in part of the process by which immune responses are turned off.

This natural brake on the activation of lymphocytes or T cells was hypothesized to be a potential therapeutic opportunity. Ipilimumab blocks the CTLA-4 receptor, not allowing it to be engaged. This essentially alleviates the brake and allows T cells to be more active. That mechanism has been confirmed now on two levels as this agent has been evaluated in Phase II trials and also recently a Phase III trial that demonstrated a survival advantage compared to vaccine therapy for patients with previously treated metastatic melanoma (Hodi 2010).

Track 18

DR LOVE: Would you comment on the role of nanoparticle albumin-bound (*nab*) paclitaxel in metastatic melanoma?

DR FLAHERTY: Phase II data suggest a promising response rate with single-agent *nab* paclitaxel that exceeds any two-drug combination evaluated to date, including carboplatin and paclitaxel (Hersh 2010; [1.3]).

1.3

Efficacy and Tolerability of *Nab* Paclitaxel in Previously Treated and Chemotherapy-Naïve Metastatic Melanoma

Efficacy	Chemotherapy-naïve cohort (n = 37)	Previously treated cohort (n = 37)
Confirmed CR or PR	21.6%	2.7%
PR + SD ≥16 wk	48.6%	37.8%
Median PFS	4.5 months	3.5 months
Median OS	9.6 months	12.1 months
One-year OS	41.0%	49.0%
Select Grade 3 or 4 adverse events		
Neutropenia	41%	14%
Sensory neuropathy	19%	5%

CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival; OS = overall survival

Hersh EM et al. *Cancer* 2010;116(1):155–63.

1.4

Phase III Study of *Nab* Paclitaxel versus Dacarbazine in Previously Untreated Metastatic Malignant Melanoma (mMM)

Protocol ID: NCT00864253 **Target accrual:** 514 (Open)

Eligibility

- Stage IV mMM
- ECOG PS 0 to 1
- No prior adjuvant cytotoxic chemotherapy (prior adjuvant therapy with interferon, GM-CSF and/or vaccines permitted)

R

Nab* paclitaxel
150 mg/m² weekly every 3 or 4 weeks

Dacarbazine*
1,000 mg/m² every 3 weeks

* Dose reductions of *nab* paclitaxel to 120 and 90 mg/m² and of dacarbazine to 800 and 600 mg/m² and the use of filgrastim for neutropenic fever allowed

www.clinicaltrials.gov, July 2011.

Nab paclitaxel hasn't been compared to carboplatin/paclitaxel directly, but a not-yet-reported study has been completed comparing *nab* paclitaxel directly to dacarbazine (1.4), the current FDA-approved standard chemotherapy in this setting. Based on the Phase II data, this has a reasonable chance of being a positive study, and if it is, *nab* paclitaxel would work its way into the melanoma armamentarium.

Track 23

DR LOVE: What about advanced squamous cell skin cancer? Any new agents?

DR FLAHERTY: The hope has been that EGFR inhibitors might be efficacious in SCC because this tumor type seems to have some dependence on epidermal growth factor receptor signaling and this may be an exploitable target. The first Phase II data with the monoclonal antibody cetuximab were presented at ASCO 2010, and a reasonably robust response rate was reported (Maubec 2010; [1.5]).

Additional patients seemed to be gaining some benefit manifested by reasonably long-lasting minor responses. We seem to have some potential to build on with this drug. ■

1.5

Phase II Trial of Cetuximab as First-Line Monotherapy for Patients with Unresectable Squamous Cell Carcinoma of the Skin

Efficacy: Tumor response at six weeks, n (%)	Intent-to-treat population (n = 36)
Response rate (CR + PR)	4 (11%)
Control rate (CR + PR + SD)	25 (69%)
Efficacy: Best response, n (%)	
Response rate (CR + PR)	10 (28%)
Control rate (CR + PR + SD)	25 (69%)

CR = complete response; PR = partial response; SD = stable disease

Maubec E et al. *Proc ASCO* 2010;**Abstract 8510**.

SELECT PUBLICATIONS

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Smalley KS, Sondak VK. **Melanoma — An unlikely poster child for personalized cancer therapy.** *N Engl J Med* 2010;363(9):876-8.