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Dermatologic Oncology™ UPDATE

Melanoma, Basal Cell and Squamous Cell Carcinoma

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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LAUNCH ISSUE

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Dermatologic Oncology Update
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OVERVIEW OF ACTIVITY

Taken together, melanoma and nonmelanoma skin cancer — basal cell and cutaneous squamous cell cancer (BCC and SCC) — likely represent the most prevalent form of human cancer. Fortunately, the vast majority of skin cancers present as minimally invasive BCC and SCC and, as such, are 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, malignant melanoma is the most aggressive form of skin cancer with a predilection toward distant metastases, even when identified in the clinically early stages of disease. Thus melanoma and nonmelanoma skin cancer are distinct entities, each posing unique challenges to the oncology community. Featuring information on the latest research developments along with expert perspectives, this CME activity is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Integrate practice-changing clinical trial results into the evidence-based treatment algorithm for front-line and subsequent management of advanced melanoma (MSC) and nonmelanoma skin cancer (NMSC).
- Recognize immune-related adverse events (irAEs) associated with anti-CTLA-4 antibody therapy, and offer supportive management strategies to minimize and/or manage these side effects.
- Communicate a mechanistic understanding of the relationship between development of clinically apparent irAEs and melanoma response to ipilimumab.
- Compare and contrast the patterns of tumor response resulting from melanoma treatment with cytotoxic versus immunotherapeutic agents.
- Summarize the scientific rationale for the current investigation of B-raf inhibitors in melanoma.
- Explain the fundamental role of hedgehog signaling in BCC pathogenesis and treatment.
- Recall the design of ongoing clinical trials in advanced MSC and NMSC, and consent or refer eligible patients for study participation.

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INTERVIEW

Keith T Flaherty, MD

Dr Flaherty is Associate Professor at Harvard Medical School and Director of Developmental Therapeutics at Massachusetts General Hospital Cancer Center in Boston, Massachusetts.

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Track 3 Identification of B-raf mutations in cancer and the development of targeted systemic treatments

Track 4 Efficacy of first-generation B-raf inhibitors — vemurafenib (PLX4032) and GSK2118436 — in B-raf-mutant metastatic melanoma

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Continued

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Select Excerpts from the Interview

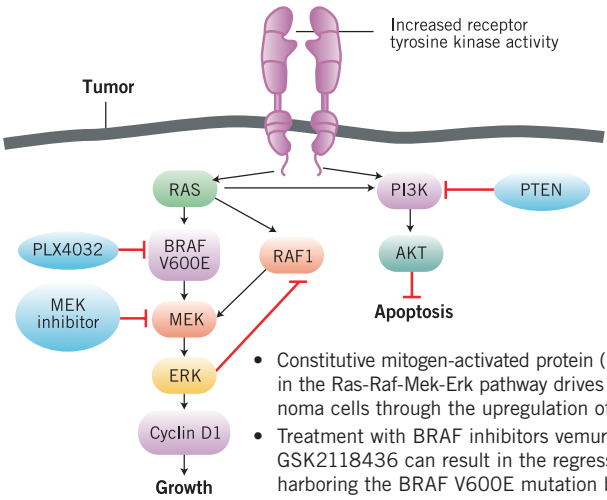
Tracks 3-6

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/m^2 weekly every 3 or 4 weeks

Dacarbazine*
1,000 mg/m^2 every 3 weeks

* Dose reductions of *nab* paclitaxel to 120 and 90 mg/m^2 and of dacarbazine to 800 and 600 mg/m^2 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

Davies H et al. **Mutations of the BRAF gene in human cancer.** *Nature* 2002;417(6892):949-54.

Flaherty KT et al. **Final results of E2603: A double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma.** *Proc ASCO* 2010;**Abstract 8511**.

Hersh EM et al. **A phase 2 clinical trial of *nab*-paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma.** *Cancer* 2010;116(1):155-63.

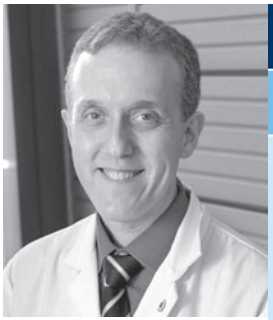
Hodi FS et al. **Improved survival with ipilimumab in patients with metastatic melanoma.** *N Engl J Med* 2010;262(8):711-23.

Kefford R et al. **Phase I/II study of GSK2118436, a selective inhibitor of oncogenic mutant BRAF kinase, in patients with metastatic melanoma and other solid tumors.** *Proc ASCO* 2010;**Abstract 8503**.

Maubec E et al. **Cetuximab as first-line monotherapy in patients with skin unresectable squamous cell carcinoma: Final results of a phase II multicenter study.** *Proc ASCO* 2010;**Abstract 8510**.

Ribas A et al. **BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with *BRAF* V600E mutation-positive metastatic melanoma.** *Proc ASCO* 2011;**Abstract 8509**.

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



INTERVIEW

Jedd D Wolchok, MD, PhD

Dr Wolchok is Director of Immunotherapy Clinical Trials, Associate Attending Physician in the Melanoma-Sarcoma Service and Associate Director of the Ludwig Center for Cancer Immunotherapy at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: What is your take on the emerging data with BRAF inhibitors in melanoma?

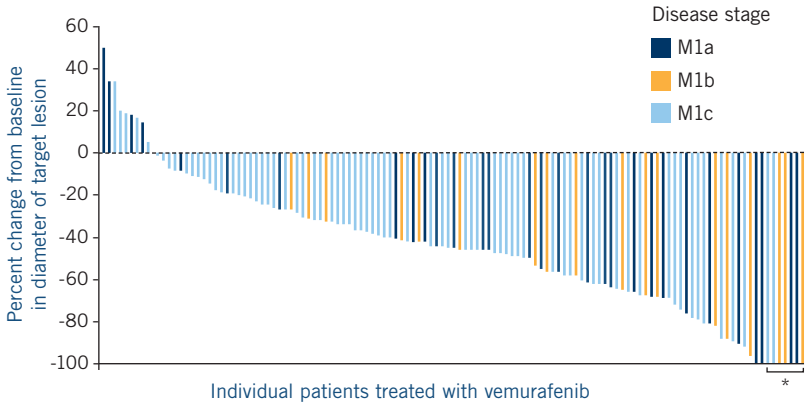
DR WOLCHOK: Once BRAF was identified as important based on the Cancer Genome Project, then various groups started to look for inhibitors of BRAF, the most well studied of those now being vemurafenib. Phase II data have

shown that a patient with a BRAF mutation has a 60 to 70 percent likelihood of experiencing a major response with this agent (Ribas 2011; [2.1]).

Results were also recently announced from the Phase III randomized trial evaluating vemurafenib versus dacarbazine. The authors reported improvements in both progression-free survival and overall survival with the BRAF inhibitor compared to dacarbazine (page 19).

2.1

Antitumor Response in Patients Receiving Treatment on a Phase II Trial of the Oral BRAF Inhibitor Vemurafenib (PLX4032)



*7 confirmed CRs

With permission from Ribas A et al. *Proc ASCO* 2011;**Abstract 8509**.

Track 6

DR LOVE: Would you describe ipilimumab's mechanism of action?

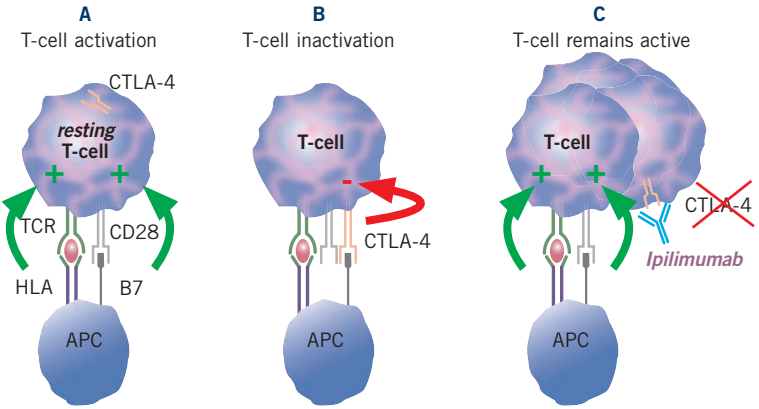
DR WOLCHOK: CTLA-4, a molecule found on the surface of T cells, prevents the overactivation of T cells. Laboratory studies have shown that mice lacking CTLA-4 cannot survive more than three weeks because a lack of CTLA-4 results in T cell-mediated organ destruction. Temporarily blocking CTLA-4 using an antibody such as ipilimumab allows the immune system to work harder than it would otherwise (Wolchok 2011; [2.2]). However, because this is not a permanent blockade — antibodies only have about a two-week half-life — the severe consequences associated with a complete loss of CTLA-4, such as in the mouse studies, are not a serious concern.

Specific side effects are associated with this class of drugs. Two CTLA-4-blocking antibodies, ipilimumab and tremelimumab, have been evaluated in clinical trials and have similar clinical activity and side effects (Hodi 2010; Kirkwood 2010). Ipilimumab has recently received FDA approval for the treatment of metastatic melanoma. Not surprisingly, the side effects are associ-

ated with excessive activation of the immune system. The most common areas affected are the skin and the gastrointestinal tract. With proper vigilant management, these side effects are reversible (Hodi 2010; [2.3]).

2.2

Ipilimumab, a CTLA-4-Blocking Monoclonal Antibody, Augments T-Cell Activation



(A) The antigen-presenting cell (APC) presents a peptide or protein on its cell surface to bind the T-cell receptor (TCR). For T-cell activation, B7 must also bind to CD28, leading to the upregulation of CTLA-4.

(B) CTLA-4 has a higher affinity for B7 than CD28, causing the inhibition of T-cell activation.

(C) Ipilimumab, a fully human monoclonal antibody, blocks CTLA-4 leading to T-cell potentiation.

With permission from Wolchok J et al. *Proc ASCO* 2011;**Abstract LBA5**.

2.3

Incidence and Management of Adverse Events During a Phase III Study of Ipilimumab with or without Vaccine Therapy Compared to Vaccine Therapy Alone in Metastatic Melanoma

"The frequency of grade 3 or 4 immune-related adverse events was 10 to 15% in the ipilimumab groups and 3.0% in the gp100-alone group...the majority of adverse events being immune-related and consistent with the proposed mechanism of action of ipilimumab. As shown in phase 2 studies, prompt medical attention and early administration of corticosteroids are critical to the management of immune-related adverse events. Management guidelines (algorithms) for immune-related adverse events involve close patient follow-up and the administration of high-dose systemic corticosteroids — which were used as necessary in our study — for grade 3 or 4 events."

Hodi FS et al. *N Engl J Med* 2010;262(8):711-23.

Track 7

DR LOVE: Can you comment on the use of corticosteroids for immune-mediated toxicity associated with the use of ipilimumab?

DR WOLCHOK: We're not sure how steroids specifically work to improve the side effect. We know steroids are lympholytic — they kill lymphocytes — and are anti-inflammatory. The real mystery is why steroids interfere with the side effects but heretofore do not interfere with the antitumor effect. The pathway underlying the antitumor activity must differ from the pathway associated with side effects and the observed steroid sensitivity.

DR LOVE: Are the antitumor effects of ipilimumab compromised in a patient who receives concomitant corticosteroids?

DR WOLCHOK: We don't know the exact answer at this time, but I believe timing is important. Administering steroids up front along with anti-CTLA-4 antibodies may be harmful. However, in the treatment of side effects, steroids are used six to 10 weeks later, and that could be why we haven't seen any interference with antitumor effects.

Tracks 8-9

DR LOVE: Would you review some of the unique aspects of evaluating response after immunotherapy for melanoma and what data are available with these agents?

DR WOLCHOK: Response to immunotherapy must be considered differently from response to chemotherapy — we're treating the patient, not the tumor, with immunotherapy. Traditional response criteria evaluate response to chemotherapy, which damages DNA, resulting in tumor shrinkage four to six weeks later.

Tumors may grow before they get smaller with immunotherapy. For this reason, evaluating response at a predetermined empiric time point will prevent the recognition of response in 10 to 25 percent of patients, who will respond later. The traditional paradigm by which new lesions automatically represent disease progression must be reconsidered — with immunotherapy, some tumors may become smaller as a new tumor appears. The new tumor may dissipate later because the immune system takes longer to recognize it.

Based on these facts, we have proposed a new set of response criteria called the Immune-Related Response Criteria. These response criteria do not involve complicated science. Only two distinctions from standard WHO or RECIST criteria are used. The first distinction requires confirmation of disease progression in the same manner in which we usually confirm response. For example, if a patient's tumor has worsened at week 12 according to the imaging results but the patient's condition is not clinically deteriorating and performance status is maintained, the scans should be repeated in four to six weeks. Between 10 and 25 percent of patients will improve in that period. The second distinction states that total tumor burden — that is, new and index lesions — must be considered when response is judged. By contrast, using standard response criteria, treatment is considered a failure if a new tumor appears despite the regression of index lesions.

According to Phase II data with ipilimumab, 24.2 percent of patients are alive two years after diagnosis (Wolchok 2010), which is respectable for a disease with a nine- to 11-month median survival. Phase III data have been published, and according to the standard response criteria, the response rate to ipilimumab was between five and 17 percent. If you include long-term stable disease, the response rate is closer to 25 percent. A slightly longer than three-month improvement in overall survival was reported for patients receiving ipilimumab compared to control. Approximately twice as many patients who received ipilimumab were alive at the landmark time points of one and two years as those who received the vaccine alone (Hodi 2010).

Tracks 10, 12

DR LOVE: Are there any trials evaluating combination immunotherapy in melanoma?

DR WOLCHOK: A molecule called PD-1 is the "emergency brake" on T cells — it mediates programmed T cell death. Not unexpectedly, melanoma cells express the ligand on their surface that causes T cell death. This is the ultimate weapon that a tumor cell can use to defend itself against an attacking T cell, as it has the ligand that triggers apoptosis of an attacking T cell. The antibody that blocks this interaction in trials of melanoma is called MDX-1106. Some encouraging data have been reported in melanoma, renal cell cancer and lung cancer documenting the importance of this PD-1 pathway in the immunobiology of these tumors (Sznol 2010).

At this time, a trial is evaluating the combined use of ipilimumab with MDX-1106 to determine whether the combination will produce a more potent type of tumor immunity. Preclinical models support this rationale. In the ongoing Phase I dose escalation trial, we are carefully evaluating potential synergistic side effects and proceeding cautiously. ■

SELECT PUBLICATIONS

Hodi FS et al. **Improved survival with ipilimumab in patients with metastatic melanoma.** *N Engl J Med* 2010;262(8):711-23.

Kirkwood JM et al. **Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma.** *Clin Cancer Res* 2010;16(3):1042-8.

Ribas A et al. **BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma.** *Proc ASCO* 2011;**Abstract 8509**.

Sznol M et al. **Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies.** *Proc ASCO* 2010;**Abstract 2506**.

Wolchok J et al. **Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma.** *Proc ASCO* 2011;**Abstract LBA5**.

Wolchok JD et al. **Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study.** *Lancet Oncol* 2010;11(2):155-64.

INTERVIEW

Aleksandar Sekulic, MD, PhD

Dr Sekulic is Assistant Professor of Dermatology at Mayo Clinic in Scottsdale, Arizona.

Tracks 1-16

Select Excerpts from the Interview

Track 6

DR LOVE: What treatment options are currently available for patients with basal cell carcinoma (BCC) of the skin that requires systemic therapy?

DR SEKULIC: At this point, treatment options include the use of targeted inhibitors of the so-called hedgehog signaling pathway. This has been an

exciting area of progress in research during the past decade, as it illustrates the true "bench-to-bedside" transition — a pathway was identified that is involved in virtually all cases of BCC, and the agent was developed to specifically target a member of that pathway called smoothened homolog (SMO).

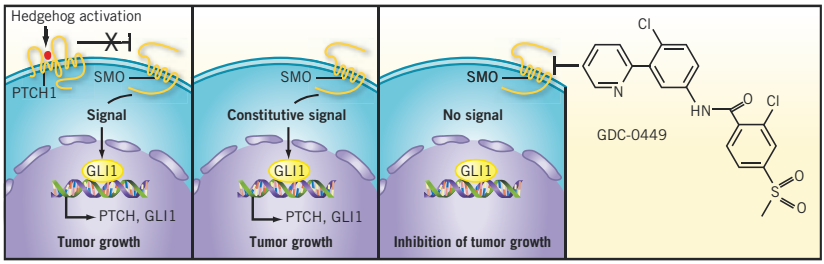
DR LOVE: Would you discuss what the hedgehog pathway is and what kind of agents are available to inhibit it?

DR SEKULIC: The hedgehog signaling pathway relies on SMO, an active protein, which is normally repressed by a protein called patched homolog. When patched is not inhibiting SMO, SMO induces the proliferation of cells. In basal cell nevus syndrome, or Gorlin-Goltz syndrome, patients have mutations or loss of the patched gene, thus losing the repression of SMO and resulting in continual activity and the proliferation of cells. The pathways are important in development, and they also seem to play an important role in so-called stem cell compartments of some tissues, such as epithelial tissues, hair follicles and so on.

Cyclopamine is an inhibitor of SMO, which is an active member of the hedgehog signaling pathway. The identification of hedgehog pathway activity in BCC led to efforts to attempt to use cyclopamine for treatment. Synthetic analogs of cyclopamine are now being developed, the most advanced of which is GDC-0449, which is now known as vismodegib (Von Hoff 2009; [3.1]).

3.1

Mechanism of Action of Vismodegib (GDC-0449), a Small-Molecule Inhibitor of Smoothened Homolog (SMO)



Track 7

DR LOVE: What kind of side effects and complications have been observed with vismodegib?

DR SEKULIC: Vismodegib is a small-molecule synthetic derivative of cyclopamine that is administered orally once a day. The side effects observed in the Phase I trial and published in *The New England Journal of Medicine* include hair loss, taste alterations, muscle cramping and weight loss, which may or may not be secondary to the taste alterations (Von Hoff 2009; [3.2]).

The Phase I trial was initially set up to accommodate patients with various advanced types of cancer, and drastic responses were observed in patients with BCC, leading to an expansion cohort of 33 patients. Eighteen of the 33 patients experienced objective responses, 11 maintained stable disease and four experienced progressive disease.

Out of the 18 responders, two complete responses were observed (Von Hoff 2009; [3.2]). The duration of response is still not clear, however. In some of the patients the responses continued for a couple of years, but this question must be answered in the long term.

3.2

Phase I Efficacy and Safety of Vismodegib (GDC-0449) in Advanced Cutaneous Basal Cell Carcinoma (N = 33)

Treatment outcomes	n	Percent
Objective response	18	55%
Complete response	2	6%
Partial response	16	48%
Stable disease	11	33%
Progressive disease	4	12%

Adverse events (AE) summary: No dose-limiting toxic effects or Grade 5 events were observed during the study period. A single Grade 4 AE (asymptomatic hyponatremia) occurred. Eight Grade 3 AEs deemed to be possibly related to vismodegib were reported in six patients, including four with fatigue, two with hyponatremia, one with muscle spasm and one with atrial fibrillation.

Von Hoff DD et al. *N Engl J Med* 2009;361(12):1164–72.

Track 9

DR LOVE: What other trials of vismodegib are ongoing?

DR SEKULIC: A Phase II trial has accrued, and the goal of the trial is to evaluate overall response rates in patients with locally advanced or metastatic BCC, similar to the population that was studied in the Phase I study of vismodegib. Another trial is evaluating operable BCC with treatment for three months in one cohort compared to a cohort of patients who receive treatment for three months and are then observed for six months. At the end of the three-month treatment in cohort one and at the end of the observation period after treatment in the second cohort, the original tumor is removed. The questions being asked are, is there a clearance of the tumor, and what is the durability of response after the drug is stopped? ■

SELECT PUBLICATIONS

Kasiske BL et al. **Cancer after kidney transplantation in the United States.** *Am J Transplant* 2004;4(6):905–13.

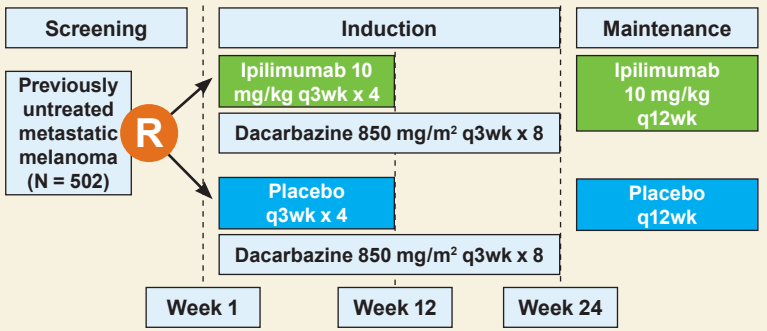
Von Hoff DD et al. **Inhibition of the hedgehog pathway in advanced basal-cell carcinoma.** *N Engl J Med* 2009;361(12):1164–72.

Phase 3 Randomized Study of Ipilimumab (IPI) plus Dacarbazine (DTIC) vs DTIC Alone as First-Line Treatment in Patients with Unresectable Stage III or IV Melanoma

Wolchok J et al.

Proc ASCO 2011;Abstract LBA5.

Study 024: A Phase III Placebo-Controlled Trial of First-Line DTIC ± IPI (10 mg/kg)



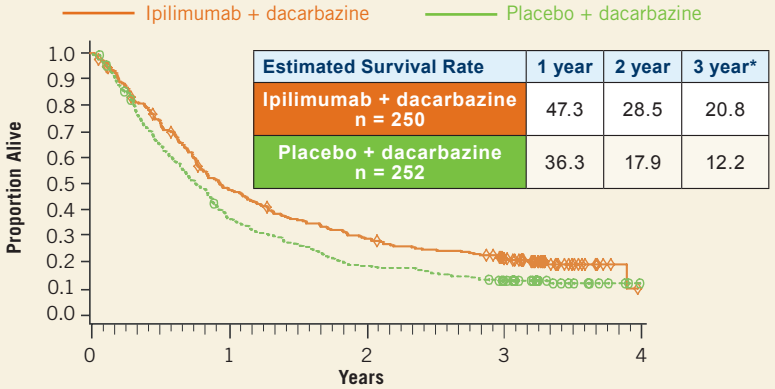
Wolchok J et al. *Proc ASCO* 2011;Abstract LBA5.

Study 024: Response and Survival

Clinical parameter	DTIC + placebo (n = 252)	IPI + DTIC (n = 250)	Hazard ratio	*p*-value
Median overall survival	9.1 mo	11.2 mo	0.72	0.0009
Disease control rate	30.2%	33.2%	—	—
Best overall response Complete response Partial response Stable disease	10.3% 0.8% 9.5% 19.8%	15.2% 1.6% 13.6% 18.0%	—	—
Duration of response	**8.1 mo**	**19.3 mo**	**—**	**—**

Wolchok J et al. *Proc ASCO* 2011;Abstract LBA5.

Study 024: Overall Survival



Estimated Survival Rate	1 year	2 year	3 year*
Ipilimumab + dacarbazine n = 250	47.3	28.5	20.8
Placebo + dacarbazine n = 252	36.3	17.9	12.2

* 3-year survival was a post-hoc analysis

With permission from Wolchok J et al. *Proc ASCO* 2011;Abstract LBA5.

Study 024: Safety Summary

- **Types of adverse events associated with IPI consistent with previous studies**
  - **— Mainly affect skin, GI tract, liver, endocrine system**
- **Mechanism (immune)-based:**
  - **— Managed with established guidelines**
  - **— Generally responsive to dose interruptions/discontinuation, corticosteroids and/or other immunosuppressants**
- **Rates of high-grade events with IPI + DTIC were different from those observed in Phase II**
  - **— Elevated AST (21.9%) and ALT (18.2%) — higher (Phase II data not available)**
  - **— Diarrhea (4.0% vs 25.7%) and colitis (2.0% vs 2.9%)**
  - **— No GI perforations**

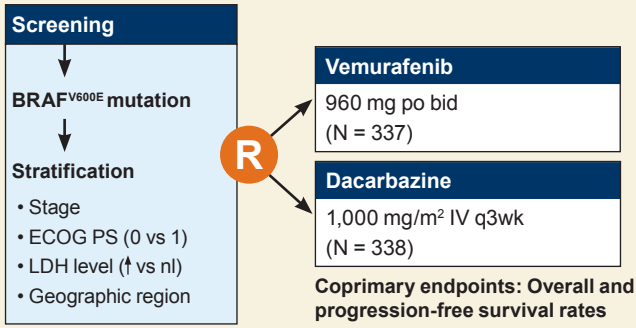
Wolchok J et al. *Proc ASCO* 2011;Abstract LBA5.

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Chapman PB et al.

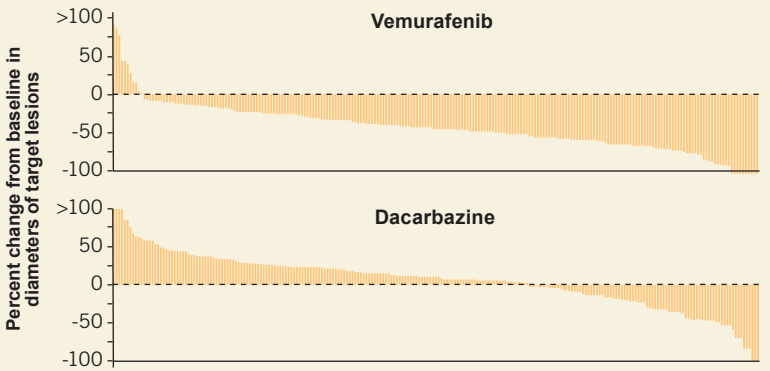
N Engl J Med 2011;364(26):2507-16.

BRIM3: A Phase III Trial of BRAF Inhibitor Vemurafenib versus DTIC in BRAF^{V600E}-Mutated Melanoma



Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

Maximal Tumor Shrinkage by Individual Patient



With permission from Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

BRIM3: Efficacy Results

Clinical parameter	DTIC	Vemurafenib	HR	*p*-value
ORR (n = 220, 219) CR PR	5.0% 0% 5.0%	48.0% 0.9% 47.5%	—	<0.001
Estimated six-month OS rate (n = 336, 336)	64%	84%	0.37	<0.001
Median PFS (n = 274, 275)	1.6 mo	5.3 mo	0.26	<0.001

HR = hazard ratio; ORR = overall response rate; CR = complete response; PR = partial response; OS = overall survival; PFS = progression-free survival

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

BRIM3: Select Adverse Events

Adverse event, %	DTIC (n = 282)		Vemurafenib (n = 336)	
	Grade 2	Grade 3	Grade 2	Grade 3
Arthralgia	<1%	<1%	18%	3%
Rash	0%	0%	10%	8%
Cutaneous squamous cell carcinoma	—	<1%	—	12%
Keratoacanthoma	0%	0%	2%	6%

- ≥Grade 4 adverse events in vemurafenib arm: Neutropenia (<1%)

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The prevalence of BRAF mutations is lower in patients with malignant melanoma relative to rates reported in other cancer types.**
   a. True
   b. False

2. **Treatment with vemurafenib can result in the regression of melanoma harboring _____.**
   a. Activating mutations in the KIT gene
   b. BRAF V600E mutation
   c. Neither of the above
   d. Both of the above

3. **A Phase II study of *nab* paclitaxel for patients with previously treated or chemotherapy-naïve metastatic melanoma reported a confirmed complete response/partial response rate of approximately _____ in patients with previously untreated disease.**
   a. Two percent
   b. 22 percent
   c. 44 percent

4. **Vismodegib, or GDC-0449, is a synthetic analog of cyclopamine designed to inhibit the smoothened homolog in patients with BCC.**
   a. True
   b. False

5. **Ipilimumab, with or without a gp100 peptide vaccine, improved overall survival compared to gp100 alone for patients with previously treated metastatic melanoma.**
   a. True
   b. False

6. **Grade 3 or 4 diarrhea induced by anti-CTLA-4 treatments should be treated with _____.**
   a. Fluid and electrolyte replacement only
   b. Motility agents
   c. High-dose systemic corticosteroids
   d. None of the above

7. **In a Phase I study of vismodegib for patients with advanced cutaneous BCC, the adverse events observed included _____.**
   a. Hair loss
   b. Taste alterations
   c. Muscle cramping
   d. a and b only
   e. All of the above

8. **A Phase III randomized study of ipilimumab with dacarbazine versus dacarbazine alone as first-line therapy for patients with unresectable Stage III or IV melanoma reported a statistically significant improvement in _____ with the addition of ipilimumab.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Dermatologic Oncology Update — Issue 1, 2011

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 ONE — 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
BRIM3: A Phase III study comparing vemurafenib to dacarbazine in Stage IIIC or IV V600E BRAF-mutated melanoma	4 3 2 1	4 3 2 1
Survival and response of ipilimumab with glycoprotein 100 (gp100) peptide vaccine versus gp100 alone in a Phase III trial of previously treated metastatic melanoma	4 3 2 1	4 3 2 1
Response data with *nab* paclitaxel monotherapy and ongoing trial comparison to dacarbazine in metastatic melanoma	4 3 2 1	4 3 2 1
Inhibition of the hedgehog pathway with vismodegib (GDC-0449) in advanced, cutaneous BCC	4 3 2 1	4 3 2 1
First-line cetuximab monotherapy in unresectable SCC of the skin	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No If no, please explain: .....

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

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No If no, please explain: .....

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:

- Integrate practice-changing clinical trial results into the evidence-based treatment algorithm for front-line and subsequent management of advanced melanoma (MSC) and nonmelanoma skin cancer (NMSC). ..... 4 3 2 1 N/M N/A
- Recognize immune-related adverse events (irAEs) associated with anti-CTLA-4 antibody therapy, and offer supportive management strategies to minimize and/or manage these side effects. ..... 4 3 2 1 N/M N/A
- Communicate a mechanistic understanding of the relationship between development of clinically apparent irAEs and melanoma response to ipilimumab ... 4 3 2 1 N/M N/A
- Compare and contrast the patterns of tumor response resulting from melanoma treatment with cytotoxic versus immunotherapeutic agents ..... 4 3 2 1 N/M N/A
- Summarize the scientific rationale for the current investigation of B-raf inhibitors in melanoma. ..... 4 3 2 1 N/M N/A
- Explain the fundamental role of hedgehog signaling in BCC pathogenesis and treatment ..... 4 3 2 1 N/M N/A
- Recall the design of ongoing clinical trials in advanced MSC and NMSC, and consent or refer eligible patients for study participation. ..... 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Keith T Flaherty, MD	4 3 2 1	4 3 2 1
Jedd D Wolchok, MD, PhD	4 3 2 1	4 3 2 1
Aleksandar Sekulic, 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:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

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Dermatologic Oncology™ UPDATE

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Dermatologic Oncology™ UPDATE

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