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Dermatologic Oncology™ UPDATE

Systemic Management of Malignant Melanoma and Basal Cell Carcinoma

Bridging the Gap between Research and Patient Care

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CME Certified

Dermatologic Oncology Update

A Continuing Medical Education Audio Series

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, cancerous 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 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.
- Develop a treatment algorithm for BRAF V600 mutation-positive and wild-type advanced melanoma.
- Compare and contrast the patterns of tumor response resulting from melanoma treatment with cytotoxic agents versus kinase inhibitors versus immunoregulatory agents.
- Recognize immune-related adverse events associated with anti-CTLA-4 antibody therapy, and offer supportive management strategies to minimize and/or manage these side effects.
- Investigate the evolving role of anti-PD-1 in advanced solid tumors.
- Evaluate the potential clinical and research implications of recent Phase III trial results evaluating the combination of MEK and BRAF inhibitors in the treatment of melanoma.
- Identify patients with locally advanced or metastatic BCC for whom hedgehog inhibitor therapy may be an appropriate treatment option.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Chapman** — Advisory Committee, Consulting Agreements and Paid Research: Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Roche Laboratories Inc. **Prof Schadendorf** — Advisory Committee: Amgen Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc; Consulting Agreements: Amgen Inc, GlaxoSmithKline; Speakers Bureau: Bristol-Myers Squibb Company, Roche Laboratories Inc.

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SELECT PUBLICATIONS

A phase III, randomized, double-blind, placebo-controlled study of vemurafenib (RO5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF mutant melanoma at high risk for recurrence. NCT01667419

Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high risk stage III melanoma: A randomized, double-blind phase 3 trial of the EORTC melanoma group. NCT00636168

Chapman PB et al. **Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAF^{V600E}-mutated melanoma.** *Proc ASCO* 2012;**Abstract 850**2.

Flaherty KT et al. **Improved survival with MEK inhibition in BRAF-mutated melanoma.** *N Engl J Med* 2012;367(2):107-14.

Freeman HJ. **Colitis associated with biological agents.** *World J Gastroenterol* 2012;18(16):1871-4.

Harding JJ et al. **Hypersensitivity skin reactions in melanoma patients treated with vemurafenib after ipilimumab therapy.** *Proc ASCO* 2012;**Abstract 8515**.

Hauschild A et al. **Phase III, randomized, open-label, multicenter trial (BREAK-3) comparing the BRAF kinase inhibitor dabrafenib (GSK2118436) with dacarbazine (DTIC) in patients with BRAF^{V600E}-mutated melanoma.** *Proc ASCO* 2012;**Abstract LBA8500**.

Kirkwood JM et al. **BREAK-MB: A phase II study assessing overall intracranial response rate (OIRR) to dabrafenib (GSK2118436) in patients (pts) with BRAF V600E/k mutation-positive melanoma with brain metastases (mets).** *Proc ASCO* 2012;**Abstract 8501**.

Livingstone E et al. **Current advances and perspectives in the treatment of advanced melanoma.** *J Dtsch Dermatol Ges* 2012;10(5):319-25.

Oberholzer PA et al. **RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors.** *J Clin Oncol* 2012;30(3):316-21.

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**.

Sarnaik AA et al. **Extended dose ipilimumab with a peptide vaccine: Immune correlates associated with clinical benefit in patients with resected high-risk stage IIIc/IV melanoma.** *Clin Cancer Res* 2011;17(4):896-906.

Sekulic A et al. **Efficacy and safety of vismodegib in advanced basal-cell carcinoma.** *N Engl J Med* 2012;366(23):2171-9.

Sosman JA et al. **Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib.** *N Engl J Med* 2012;366(8):707-14.

Topalian SL et al. **Anti-PD-1 (BMS-936558, MDX-1106) in patients with advanced solid tumors: Clinical activity, safety, and a potential biomarker for response.** *Proc ASCO* 2012;**Abstract CRA2509**.

Topalian SL et al. **Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.** *N Engl J Med* 2012;366(26):2443-54.

Weber JS et al. **Management of immune-related adverse events and kinetics of response with ipilimumab.** *J Clin Oncol* 2012;30(21):2691-7.

Weber JS et al. **Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naive metastatic melanoma.** *Proc ASCO* 2012;**Abstract 8510**.

Zimmer L et al. **Panniculitis with arthralgia in patients with melanoma treated with selective BRAF inhibitors and its management.** *Arch Dermatol* 2012;148(3):357-61.

Zimmer L et al. **Side effects of systemic oncological therapies in dermatology.** *J Dtsch Dermatol Ges* 2012;10(7):475-86.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. _____ is a selective BRAF inhibitor that has demonstrated similar activity to vemurafenib with a confirmed response rate of approximately 50% in the Phase III BREAK-3 trial comparing it to dacarbazine for patients with previously untreated, unresectable Stage III/IV BRAF V600E-mutated melanoma.

a. Dabrafenib
b. Ipilimumab
c. Trametinib
d. Anti-PD-1 antibody

2. The Phase III METRIC trial evaluated chemotherapy versus a selective MEK inhibitor called _____ for patients with BRAF-mutant advanced or metastatic melanoma.

a. Vemurafenib
b. Trametinib
c. Ipilimumab

3. A planned Phase III trial of adjuvant vemurafenib therapy versus placebo for patients with resected cutaneous BRAF-mutant melanoma at high risk of recurrence will include treatment with interferon alpha.

a. True
b. False

4. Common side effects associated with vemurafenib include _____.

a. Rash
b. Secondary epithelial skin cancer
c. Hyperkeratotic lesions
d. Photosensitivity reaction
e. All of the above

5. Anti-PD-1 antibody is associated with _____.

a. Colitis
b. Autoimmune pneumonitis
c. Both a and b
d. Neither a nor b

6. A recently published article by the National Cancer Institute demonstrated that patients who developed Grade 3 toxicities were more likely to respond to ipilimumab therapy than those without drug-induced toxicity.

a. True
b. False

7. _____ is a small-molecule hedgehog inhibitor used in the treatment of adult patients with metastatic basal cell carcinoma.

a. Vismodegib
b. Ipilimumab
c. Trametinib
d. Interleukin-2

8. Which of the following is a common vismodegib-related adverse event?

a. Ageusia
b. Muscle cramping
c. Both a and b
d. Neither a nor b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

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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 1 — 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
Management, incidence and mechanism for the development of secondary cancer associated with BRAF inhibitors	4 3 2 1	4 3 2 1
Rationale for dual targeting of BRAF and MEK signaling in melanoma	4 3 2 1	4 3 2 1
Clinical activity of dabrafenib therapy for patients with BRAF V600E/K mutation-positive melanoma with brain metastases	4 3 2 1	4 3 2 1
Role of emerging biomarkers for predicting outcomes with immunomodulatory agents and BRAF/MEK kinase inhibitors in the treatment of advanced melanoma	4 3 2 1	4 3 2 1
Clinical activity and safety of novel anti-PD-1 in the treatment of advanced solid tumors	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
- ☐ 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 1 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. . . . . 4 3 2 1 N/M N/A
- Develop a treatment algorithm for BRAF V600 mutation-positive and wild-type advanced melanoma. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the patterns of tumor response resulting from melanoma treatment with cytotoxic agents versus kinase inhibitors versus immunoregulatory agents. . . . . 4 3 2 1 N/M N/A
- Recognize immune-related adverse events 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
- Investigate the evolving role of anti-PD-1 in advanced solid tumors. . . . . 4 3 2 1 N/M N/A

- Evaluate the potential clinical and research implications of recent Phase III trial results evaluating the combination of MEK and BRAF inhibitors in the treatment of melanoma. . . . . 4 3 2 1 N/M N/A
- Identify patients with locally advanced or metastatic BCC for whom hedgehog inhibitor therapy may be an appropriate treatment option. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical trials. . . . . 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: . . . . . .

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 2 — 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
Paul B Chapman, MD	4 3 2 1	4 3 2 1
Prof Dirk Schadendorf, MD	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

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