

New Approaches to Managing AKs and Cutaneous Cancers

— S E M I N A R H I G H L I G H T S —



Actinic Keratosis and Squamous Cell Carcinoma: Advances in Nonsurgical Treatment

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Melanoma: A Brief Update on Clinical Implications of New Data

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TARGET AUDIENCE

The target audience for this educational supplement is dermatologists and other health care professionals involved in the treatment of patients with actinic keratosis (AK), nonmelanoma skin cancer (NMSC), and malignant melanoma.

ACCREDITATION

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EDUCATIONAL NEEDS

The prevalence of both NMSC and cutaneous malignant melanoma continues to increase. Prompt diagnosis and treatment of both NMSC—that is, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)—and malignant melanoma are crucial to preservation of tissue, prevention of disfigurement and loss of function, prevention of metastatic disease, and long-term survival. Although BCC, an NMSC, rarely metastasizes, it can invade the deeper cutaneous tissues and, eventually, bone, causing considerable soft tissue and bone damage and requiring significant surgical excision; when lesions occur on the face, both the disease and its surgical treatment can be catastrophically disfiguring. AK is a skin condition that, without treatment, may progress to Bowen's disease (SCC in situ) or invasive SCC in an estimated 10% of cases; unfortunately, it is not possible at this time to determine which AK lesions are likely to progress, so treatment of AK is recommended. Clinicians must be continually updated on advances in understanding the pathophysiology of these diseases, as well as the results of research on new uses for existing agents and the promising, emerging and potential therapies that are being investigated.

LEARNING OBJECTIVES

By reading and studying this supplement, participants in this activity should be prepared to:

- Summarize the updated information presented regarding the agents that are currently available for treating AK (ie, diclofenac, 5-fluorouracil, imiquimod, and photodynamic therapy)
- Describe and better recognize in clinical practice outlier lesions (also known as “ugly ducklings”) as potential markers of malignant melanoma
- Explain the advances in understanding the pathophysiology of NMSC and malignant melanoma
- Discuss the new and emerging modalities that hold promise for effective treatment of AK, Bowen's disease, invasive SCC, and malignant melanoma.

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Actinic Keratosis and Squamous Cell Carcinoma: Advances in Nonsurgical Treatment

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Recent research has yielded new information on the pathophysiology of actinic keratosis (AK) and squamous cell carcinoma (SCC). This information has led, in turn, to new avenues of research, new investigational treatment, and new medical therapies for these diseases (Table). Evidence from studies of these nonsurgical approaches is discussed in this article.

Experience With Interferon in SCC

Interferon has been studied for the treatment of in situ SCC (or Bowen's disease) and invasive SCC. The earliest publication was an open-label study by Edwards and colleagues,¹ who treated 34 patients (27 patients with SCC and 7 patients with Bowen's disease) with intralesional interferon- α 2b, 1.5 million IU, three times a week for 3 weeks. After a total of nine injections, at the end of 21 weeks, the areas were excised and histologically examined for cure. Overall, the histologic cure rate was 97%; in the group with invasive SCC—ie, eliminating the patients with Bowen's disease—the cure rate was 96%. Figure 1 shows a patient with invasive SCC who had no evidence of malignancy after this treatment.

Imiquimod in AKs and SCC: Rationale and Mechanism of Action

Imiquimod has been well studied and is approved by the US Food and Drug Administration (FDA) for the treatment of AK. It has also been studied investigational for the treatment of SCC.

Imiquimod works by multiple mechanisms to activate both the innate and the adaptive immune systems in the area of the topically applied agent. Among other mechanisms, imiquimod activates toll-like receptor 7,² which releases nuclear factor κ B from the cytoplasm to enter the nucleus, acting on a variety of chromosomes that are then transcribed into messenger RNA. The resulting release of cytokines and chemokines causes

TABLE. CURRENTLY AVAILABLE MEDICAL THERAPIES FOR ACTINIC KERATOSIS

Currently available:

- Interferon
- Imiquimod 5%
- Imiquimod 3.75%
- 5-Fluorouracil
- Diclofenac
- Photodynamic therapy
(aminolevulinic acid; methyl aminolevulinate)

activation of natural killer cells and antigen-presenting cells. Ultimately, the enhanced T-helper type 1 cytokine and chemotactic activity translate to both antiviral and antitumor activity, most of which is mediated by the elaboration of interferon- α .

More recently, the possibility of another pathway has been described in SCC—involving Foxp3+ regulatory T cells. These T cells infiltrate and surround SCCs and induce local immunosuppression and, ultimately, immune tolerance to tumors. They do so by elaborating the immunosuppressive cytokines interleukin-10 (IL-10) and transforming growth factor- β (TGF- β). Clark and colleagues³ have demonstrated that in vivo application of imiquimod to cutaneous SCC

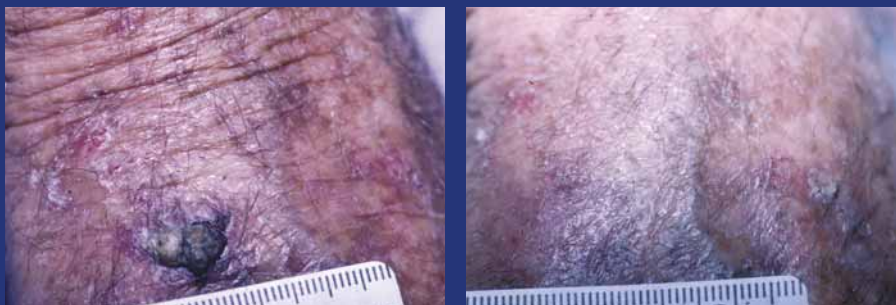
can inhibit the secretion of IL-10 and TGF- β , thus reversing the immunosuppression caused by the Foxp3+ regulatory T cells.

Additionally, it has been shown that the blood vessels in SCC do not express E-selectin, which signals T cells to congregate. In the absence of E-selectin—as is the case with SCC—the T cells do not congregate and provide immune surveillance and removal of SCC cells. Huang and coworkers⁴ demonstrated that in vivo use of imiquimod on SCC induces E-selectin in the blood vessels, and also results in recruitment of cutaneous lymphocyte antigen-positive and CD8+ T cells around the SCC tumor, allowing infiltration and destruction of the SCC.

Imiquimod: New Regimens and Strengths

The safety and efficacy of imiquimod in the treatment of AKs have been demonstrated in multiple studies for more than a decade. This agent was first approved in a 5% concentration in 1997 for the treatment of anogenital warts and, in 2004, was also approved for the treatment of AKs. The approved regimen for AKs was application to areas of 25 cm² or less on the face or balding scalp, twice weekly for 16 weeks.

FIGURE 1. SQUAMOUS CELL CARCINOMA LESION OF THE HAND



This patient (baseline photo, left) was treated with intralesional interferon- α 2b, 1.5 million IU, three times a week for 3 weeks. At 21 days, after a total of nine treatments, a histologic cure was documented, and, as shown (right), no clinical evidence of malignancy remained.

Source: Edwards et al.¹ Used with permission from Edwards L, Berman B, Rapini RP, et al. Treatment of cutaneous squamous cell carcinomas by intralesional interferon alfa-2b therapy. *Arch Dermatol*. 1992;128:1486-1489. Copyright © 1992 American Medical Association. All rights reserved.

Subsequent studies showed that other regimens could further refine the benefits of this agent, and research goals included strategies for expanding the treatment area beyond the previous 25-cm² limit; shortening the treatment regimens to less than 16 weeks; simplifying the dosing regimen; and decreasing the concentration of the drug to enhance tolerability of daily dosing. Based on the results of a number of clinical studies, including those by Stockfleth et al,⁵ Jorizzo and colleagues,⁶ and Alomar and coworkers,⁷ a three-times-weekly, 4-4-4 protocol (4 weeks of treatment, a 4-week no-treatment interval, then an additional 4 weeks of imiquimod 5% applications) was approved in Europe. More recently, a dose-response study was done to explore the possibility of using imiquimod 5% daily, but this frequency was not well tolerated.⁸

To examine the safety and efficacy of treating AKs using imiquimod at lower concentrations, with increased dosing frequency, with a shorter total duration of treatment, and on larger treatment areas, two pairs of identical studies of imiquimod 2.5% and 3.75% were performed. The regimens were cyclic: either 2 weeks of daily applications followed by 2 weeks' rest, then another 2 weeks of daily use (the 2-2-2 protocol); or 3 weeks of daily application followed by 3 weeks' rest, then another 3 weeks of daily use (the 3-3-3 protocol). Patients were randomly assigned to one of three 2-2-2 protocols (imiquimod 2.5%, or 3.75%, or placebo) or one of three 3-3-3 protocols (also imiquimod 2.5%, or 3.75%, or placebo). Patients were evaluated 8 weeks following completion of treatment. The results of the 3-3-3 protocols were reported in an article by Hanke and colleagues.⁹ The results of the 2-2-2 protocols led to the recent approval of imiquimod 3.75% and were reported in an article by Swanson et al¹⁰; the findings are summarized here.

A total of 479 patients with 5 to 20 AK lesions were randomized (in a 1:1:1 ratio) to receive imiquimod 2.5%, imiquimod 3.75%, or placebo. Patients were instructed to apply the study creams to the entire face or balding scalp once daily for 2 weeks, followed by a 2-week interval of no treatment, then another 2 weeks of daily applications of the cream. At the 8-week posttreatment assessment, complete clearance was seen in 30.6% of patients in the imiquimod 2.5% group and 35.6% of patients in the imiquimod 3.75% group, compared with 6.3% in the placebo group. Partial clearance (ie, $\geq 75\%$ reduction in lesions) was seen in 48.1% of patients in the imiquimod 2.5% group and 59.4% of those in the

imiquimod 3.75% group, compared with 22.6% in the placebo group. The differences in all treatment groups compared to placebo were statistically significant ($P < 0.001$). **Figure 2** illustrates the treatment course and responses in a patient with AKs of the scalp treated with imiquimod 3.75%.

A total of 15 adverse events were reported in 12 patients (2 in the placebo group, 5 of those using imiquimod 2.5%, and 5 using imiquimod 3.75%). In only one of these cases (a patient with severe diarrhea) did an investigator consider the adverse event probably related to the study cream. Six patients (3 in the placebo group, 1 in the imiquimod 2.5% group, and 2 in the imiquimod 3.75% group) had adverse events that caused them to discontinue participation in the study.

The authors added that further studies should be done to evaluate these new formulations of imiquimod for sustained clearance of AK lesions as well as for treating AKs on areas of the body other than the face and scalp.

Several nonsurgical modalities are available or currently being studied that are effective and safe for the treatment of AKs and SCC.

New Findings With Other AK Treatments: A Brief Overview

5-Fluorouracil (5-FU)

A previously known mechanism of action of 5-FU is inhibition of the enzyme thymidylate synthase, which is involved in DNA synthesis. 5-FU also inhibits DNA replication and causes a cell cycle arrest and, ultimately, induces apoptosis. More recently, it has been found that 5-FU also inhibits the activity of the exosome, an exoribonuclease complex that ensures quality control of RNA produced in each cell. Inhibition of the exosome adversely affects the quality of RNA, causing cell death.¹¹

Diclofenac 3% Gel

The rationale for the use of a topical nonsteroidal anti-inflammatory drug, such as diclofenac, for treating AKs is blockage of cyclooxygenase 2 (COX-2) expression. COX-2

expression and calcium-dependent phospholipase A₂ increase on exposure to ultraviolet light, which in turn increases prostaglandin E₂, resulting in increased hyperplasia and angiogenesis and, therefore, potential progression of AKs and SCCs. In addition, inhibition of COX-2 expression blocks Bcl2, a natural antiapoptotic that inhibits cell death in AK lesions.¹²⁻¹⁴

Photodynamic Therapy (PDT)

Aminolevulinic acid (ALA) is taken up, presumably, by rapidly dividing malignant cells, then is converted to protoporphyrin IX, which absorbs intense light, elaborating singlet oxygen. Singlet oxygen is very high-energy but very short-lived, so it interferes with and destroys the plasma and mitochondrial membranes of rapidly dividing cells. (Because it is short-lived, it does not persist long enough to damage neighboring cells.)¹⁵

The protocol for using PDT, as originally approved by the FDA, involved application of a 20% solution of ALA to individual lesions, followed by exposure of the treated area to blue light. Although PDT was approved specifically as a targeted therapy, it is common practice among dermatologists to apply ALA to an entire area, using it as field therapy (similar to the use of imiquimod, 5-FU, and diclofenac). Touma and colleagues¹⁶ studied the use of PDT for shorter incubation times and over a broad area of facial skin for AKs and diffuse photodamage. These investigators demonstrated that shorter incubation did not adversely affect PDT efficacy.

More recently, another compound for PDT, methyl aminolevulinate (MAL), has been studied. ALA methyl ester is activated by red instead of blue light and requires curettage of individual AKs and occlusion prior to therapy. In a head-to-head study in patients with Bowen's disease,¹⁷ MAL was compared to cryotherapy and 5-FU. The ALA compound seemed to be more effective—approximately 80% clearance with MAL methyl versus 67% with cryotherapy and 69% with 5-FU.

Investigational Agent, Ingenol Mebutate

Ingenol mebutate is a novel topical agent currently being studied for the treatment of AKs. This drug was developed from the sap of *Euphorbia peplus*, the common milkweed plant, which is a traditional topical treatment for skin conditions, including AKs. The results of several clinical studies were presented recently at the annual meeting of the American Academy of Dermatology, demonstrating promising efficacy and safety of this agent.¹⁸⁻²⁰

Conclusion

Several nonsurgical modalities are available or currently being studied that are effective and safe for the treatment of AKs and SCC. Ongoing research has provided or clarified mechanisms of action for these agents, and studies have examined the use of protocols that differ from those used at the time of the agents' FDA approval. The results of recent studies of new formulations of imiquimod demonstrated the safety and efficacy of using lower concentrations of this immune response modifier in a regimen that allows daily application for a shorter duration. Imiquimod 3.75% has been approved for daily use in two 2-week cycles for the entire face or balding head. Further understanding of the underlying pathophysiology of AKs and SCCs will likely result in the development of other new compounds that target these lesions at the cellular level. ■

FIGURE 2. SCALP AKs TREATED WITH IMIQUIMOD 3.75% IN A 2-2-2 REGIMEN



This series of photographs shows a patient with AKs on the scalp at baseline, or week 0 (A); at week 2, the end of the first 2 weeks of daily applications of the medication (B); at week 4, following 2 weeks with no treatment (C); at week 6, the end of the second 2-week daily cycle (D); and at week 14, or 8 weeks following the last treatment application (E). The final photo shows complete clearance of the lesions.

Source: Courtesy of Brian Berman, MD, PhD.

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Melanoma: A Brief Update on Clinical Implications of New Data

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According to the most recent Surveillance Epidemiology and End Results statistics from the National Cancer Institute,¹ the incidence of cutaneous melanoma currently is increasing at a rate of about 3% per year. Melanoma, the fifth most common cancer in men and the sixth most common in women, is one of the few cancers for which the incidence and mortality rates in the United States are still increasing. As of 2009, the lifetime risk for melanoma in men was 1 in 39. For women, the lifetime risk was 1 in 58; it remains the most common cancer in women between 25 and 29 years of age and is still the most common cause of cancer-related deaths in women between 30 and 35 years of age.

Improved Understanding of Pathophysiology and Risk

Exposure to ultraviolet (UV) radiation has long been implicated as a cause of melanoma. In recent years, studies have further defined the relationship between UV exposure of the skin and the development of cutaneous melanoma. For example, Pleasance and colleagues² sequenced and catalogued the somatic mutations from an individual melanoma cancer. These researchers showed that the dominant mutational signature reflected UV-induced DNA damage, lending further support to the association between UV radiation and melanoma.

Using five melanoma oncogenes as examples (*NRAS*, *BRAF*, *MITF*, *NEDD9*, and *KIT*), Berger and Garraway³ reviewed the strategies that have been developed for discovering and analyzing such oncogenes. Further research in this arena likely will yield new methods of diagnosis as well as improved, targeted treatments in the coming years.

Family history remains a strong risk factor. In addition, both clinically atypical moles and the total number of nevi have long been recognized as independent risk factors for melanoma.

Recently, a complex pattern in a nevus as visualized with a dermatoscope also has been recognized as a predictor of risk for melanoma.⁴ This pattern is defined as a nevus that reveals both a reticular network and globules.

Both clinically atypical moles and the total number of nevi have long been recognized as independent risk factors for melanoma.

Current Screening Recommendations

Individuals at increased risk for melanoma should be examined regularly by a clinician and should be advised to perform routine skin self-examinations for suspicious lesions.

The value of universal screening remains controversial. No studies have proved conclusively that screening the general population for melanoma would be beneficial. Of interest, however, is a study from the Lawrence Livermore National Laboratory,⁵ where investigators instituted an educational and screening program for all employees. The program resulted in a progressively decreased incidence of thicker melanomas and a reduction of melanoma-related mortality to zero.

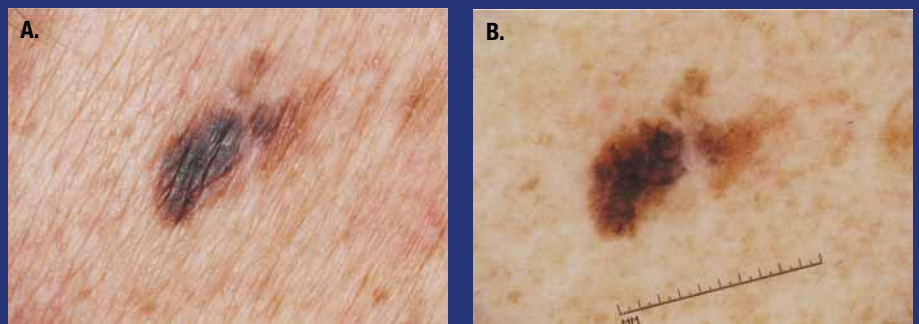
Although this was not a randomized, controlled study, the results do underscore the value of public education, self-examination, periodic skin examination by a clinician, and recognition by the general public of signs that may indicate melanoma that should prompt examination by a clinician.

Improving Diagnosis With Dermoscopy

Most clinicians are aware of the signs for identifying possible melanomas—*asymmetry*, *border irregularity*, *color variegation*, *diameter greater than 6 mm*—but, recently, “*evolving*” or *changing pattern* has been added, so the alphabetical mnemonic now is *ABCDE* (**Figure 1**). In addition, both clinicians and patients should be aware of the recent recognition of the “*ugly duckling*” sign that may indicate the presence of types of melanoma (such as nodular melanoma) that may not manifest the classic *ABCDE* signs.⁶

The ugly duckling lesion, also known as an “*outlier*” lesion (**Figure 2**), is one that looks or feels different than other lesions (its “*siblings*”) in the same area or one that changes over time in a way that is different from the way the others change.

FIGURE 1. MELANOMA LESION



This lesion (A) shows the classic clinical features of cutaneous malignant melanoma: asymmetry, border irregularity, color variegation, and diameter greater than 6 mm (or ABCD features). A clinician following a patient with such a lesion may also note that the lesion has been evolving (the “E” in the new ABCDE mnemonic of clinical signs of melanoma). On dermoscopy (B), an irregular blotchy area and regression structures are evident, which are highly suggestive of melanoma.

Source: Courtesy of Ashfaq A. Marghoob, MD.

The use of a dermatoscope adds to the sensitivity and specificity of that examination because it increases the clinician's ability to diagnose melanoma and to exclude benign lesions from the differential.⁷ Even those who are not specialists in dermatology can easily acquire the necessary observational skills, and a hand-held, highly portable dermatoscope can be purchased for a few hundred dollars or less. The International Dermoscopy Society is a good source of information on the use of this instrument and can be accessed online at <http://dermoscopy-ids.org>. An online tutorial and interactive dermoscopy atlas is available online, free of charge (<http://www.dermoscopy.org>).

Nondermatologists also should be encouraged to practice "opportunistic skin examination." Any clinical encounter with a patient is an opportunity to simply observe the exposed areas of the skin during physical examination—for example, a quick scan of the back and chest during lung auscultation in a patient complaining of a cough.

Update in Staging

The staging system used for melanoma has remained essentially the same over the past decade, except for one important change: the mitotic index recently has been added to the staging system. A melanoma with mitosis greater than zero increases the staging from 1A to 1B.⁸ In addition, many surgeons now feel that a patient with even a thin melanoma (ie, <1 mm), but a mitotic index greater than zero, is a candidate for sentinel lymph node biopsy.⁸

Emerging Treatment Options

Two general approaches appear to be promising as future treatment strategies: T-cell manipulation and targeting the mitogen-activated protein (MAP) kinase pathway.

The therapy that shows the most promise in T-cell manipulation is anticytotoxic

T-lymphocyte antigen-4 (anti-CTLA-4) treatment. It is thought that one mechanism by which melanoma cells may escape destruction by the immune system is via attachment to the B7 protein on CTLA-4, which inhibits activation of T cells. Anti-CTLA-4 treatment blocks the B7 receptor, preventing T cells from being inactivated.⁹

The other approach that has generated great interest is targeting mutations in the MAP kinase pathway. Recent attention has focused on *BRAF*-inhibiting therapy,¹⁰ as well as strategies to block the growth of melanomas that express *C-KIT* mutations.¹¹

Conclusion

Prevention and early detection and treatment remain the keys to long-term survival in patients with melanoma. This requires an increased awareness on the part of both the general public and physicians (including those who are not dermatology specialists) to recognize manifestations of melanoma such as the ABCDE and "ugly duckling" signs.

Although screening of the general public cannot be recommended currently, all clinicians—regardless of their specialty—should routinely perform opportunistic screening for cutaneous melanoma, without additional time or effort devoted to the patient encounter unless a suspicious lesion is noticed. Furthermore, clinicians in all specialties should consider having a dermatoscope readily available so that questionable pigmented lesions can be quickly characterized. ■

FIGURE 2. OUTLIER LESION: "THE UGLY DUCKLING"



The "ugly duckling" sign recently has been recognized as an important clue to the possible presence of melanoma. In this patient, the ugly duckling, or outlier lesion, looks markedly different from the other lesions ("sibling lesions") in the same area.

Source: Courtesy of Ashfaq A. Marghoob, MD.

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CME Post-Test Answer Sheet and Evaluation Form

Release Date of Activity: August 2010 • Expiration Date of Activity for AMA PRA Credit: September 2012 • Estimated Time to Complete This Activity: 1.0 hour

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Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate.

1. Activation of toll-like receptor 7 is a mechanism of action for:
 - A. Aminolevulinic acid
 - B. Diclofenac
 - C. Imiquimod
 - D. Ingenol mebutate
2. The study reported by Swanson et al demonstrated the efficacy and safety of imiquimod 3.75% in patients with _____ of the head and scalp.
 - A. Actinic keratosis
 - B. Basal cell carcinoma
 - C. Malignant melanoma
 - D. Squamous cell carcinoma
3. 5-Fluorouracil induces _____ by two known mechanisms: inhibition of the enzyme thymidylate synthase, which is involved in DNA synthesis, and inhibition of the activity of an exoribonuclease complex that ensures quality control of RNA produced in each cell.
 - A. Activation of T cells
 - B. Apoptosis
 - C. Inhibition of the BRAF oncogene
 - D. Manipulation of the mitogen-activated protein (MAP) kinase pathway
4. Recently, a fifth letter has been added to the mnemonic of long-recognized signs for identifying possible melanomas (asymmetry, border irregularity, color variegation, diameter >6 mm)—the letter E, for _____.
 - A. Encrusted
 - B. Enduring
 - C. Erratic
 - D. Evolving
5. An "ugly duckling" lesion should raise the index of suspicion for _____.
 - A. Basal cell carcinoma
 - B. Bowen's disease
 - C. Invasive squamous cell carcinoma
 - D. Melanoma
6. It is thought that one mechanism by which melanoma cells may escape destruction by the immune system is via attachment to the B7 protein on cytotoxic T-lymphocyte antigen-4, which inhibits activation of _____.
 - A. B cells
 - B. C-KIT mutation expression
 - C. T cells
 - D. The MAP kinase pathway

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

Please Print

Name: _____

Specialty: _____

Degree: MD DO PharmD RPh NP RN BS PA

Other _____

Affiliation: _____

Address: _____

City: _____ State: _____ Zip: _____

Telephone: _____ Fax: _____

E-mail: _____

Signature: _____

(All information is confidential.)

CME CREDIT VERIFICATION: I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 1.0 CME credit(s) will be issued for this activity.

PRETEST ASSESSMENT: Please rate your current knowledge of NMSC and AKs on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

POST-TEST ASSESSMENT: Please rate your current knowledge of NMSC and AKs on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

1. Summarize the updated information presented regarding the agents that are currently available for treating AK (ie, diclofenac, 5-fluorouracil, imiquimod, and photodynamic therapy). 1 2 3 4 5

2. Describe and better recognize in clinical practice outlier lesions (also known as "ugly ducklings") as potential markers of malignant melanoma. 1 2 3 4 5
3. Explain the advances in understanding the pathophysiology of NMSC and malignant melanoma. 1 2 3 4 5
4. Discuss the new and emerging modalities that hold promise for effective treatment of AK, Bowen's disease, invasive SCC, and malignant melanoma. 1 2 3 4 5

How do you rate the overall quality of the activity? 1 2 3 4 5

How do you rate the educational content of the activity? 1 2 3 4 5

After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? Yes No

If yes, what change(s) will you make? _____

If no, why not? _____

Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? Yes No

If no, please comment: _____

Suggested topics for future activities: _____

Suggested authors for future activities: _____

Would you be willing to participate in postactivity follow-up surveys? Yes No

Would you be willing to participate in a phone, e-mail, or in-person discussion exploring ways to improve our CME activities? Yes No

The University of Louisville thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients' care.