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Cancer Therapy: Clinical

Clinical Cancer Research

Mitogen-Activated Protein/Extracellular Signal-Regulated Kinase Kinase Inhibition Results in Biphasic Alteration of Epidermal Homeostasis with Keratinocytic Apoptosis and Pigmentation Disorders

Karin Schad, Katrin Baumann Conzett, Marie C. Zipser, Valérie Enderlin, Jivko Kamarashev, Lars E. French, and Reinhard Dummer

Abstract

Purpose: Raf/mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK signaling pathway is constitutively activated in melanoma. AZD6244 blocks MEK1/2, inhibiting ERK phosphorylation. We focus on associated cutaneous toxicity and we attempt to understand the underlying pathophysiology and design treatment strategies.

Experimental Design: Dermatologic conditions of 22 patients with unresectable melanoma stage III/IV in a phase II trial were evaluated. Thirteen patients received AZD6244 initially, and nine patients were treated with AZD6244 following tumor progression with temozolomide. Biopsies were compared with matched controls in normal skin. Immunohistochemistry was performed. Half-side treatment of acute skin toxicity compared therapeutic options.

Results: Nineteen of 22 (86%) AZD6244-treated patients presented with cutaneous eruptions. Seventeen patients (77%) developed acute papulopustular rash. Chronic skin changes included xerosis, paronychia, and fissured fingertips, resembling cutaneous toxicity of epidermal growth factor receptor inhibition. In addition, we observed reduced pigmentation of hair and skin. Histology of acute skin lesions revealed a significant increase of apoptotic keratinocytes ($P = 0.0008$), focal neutrophilic infiltrates, destruction of the adnexal structures by neutrophils, and reduced cytokeratins. A significant proliferation shift from basal to suprabasal keratinocytes was shown in acute and chronic lesions. The number and viability of melanocytes was not affected. Corticosteroids plus antibacterial topical therapy ameliorate acute skin toxicity.

Conclusions: AZD6244-associated skin reactions partly overlap with those observed upon epidermal growth factor receptor inhibition. Additionally, pigmentation of skin and hair is affected. The interruption of the MEK signaling pathway results in an acute keratinocyte stress response with disturbed epidermal homeostasis, inflammation, and tissue damage. Chronic adaptation controls inflammatory tissue damage but leads to cutaneous malfunctions that explain chronic skin toxicity. *Clin Cancer Res; 16(3); 1058–64. ©2010 AACR.*

Mutations and amplifications of oncogenes are frequent genetic alterations in cancer that result in the constitutive activation of pathways promoting proliferation and survival (1). For example, kinases involved in the RAS-RAF-mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase (MEK) signaling pathway are thus activated in most melanomas (2, 3). Critically, this particular malignancy is increasing in incidence worldwide and the current lifetime risk is estimated to be 1:70 for European populations (4).

Advanced melanoma palliative therapy using cytostatic drugs, either alone or in combinatory settings, has yielded disappointing results (5). For patients with distant metastases, treatment with dacarbazine remains the standard chemotherapy despite a response rate of under 10% (6). Patients with advanced melanoma are therefore often treated in controlled clinical trials evaluating novel approaches (7). Frequent activation of the RAS-RAF-MEK signaling pathway (8, 9) presents a promising therapeutic target. Phosphorylation of ERK 1/2, a critical step in the pathway, is specifically inhibited by AZD6244. In the context of a randomized phase II trial

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Translational Relevance

Translational kinase inhibitors are targeted drugs that typically show off-target effects in the skin. A deepened understanding on the molecular mechanisms and rational therapeutic approaches for these skin toxicities are essential for a safe long-term treatment with acceptable quality of life.

in metastatic melanoma (10), we investigated acute and chronic skin reactions during systemic therapy with AZD6244 in patients with metastatic melanoma and compared topical therapies.

Patients and Methods

We evaluated the cutaneous toxicities of 22 patients with unresectable melanoma stage III/IV treated with AZD6244 (100 mg orally twice a day) in our department (10). A total of 13 patients received AZD6244 as a first-line therapy and 9 patients were treated with AZD6244 following tumor progression with temozolomide as outlined in the protocol. The follow-up intervals were according to the protocol on day 1, 8, 15, 29, 43, and 57 then every 4 wk until tumor progression. In case of severe skin toxicity, some patients came for additional unscheduled visits as needed. The treatment regimen was applied until tumor progression.

Cutaneous toxicity. In this trial, 19 of 22 (86%) AZD6244-treated patients presented with at least one cutaneous symptom. We classified the clinical manifestations according to the treatment duration into acute (<6 wk of treatment) changes with papulopustular rash and chronic changes (>6 wk of treatment) with xerosis cutis, paronychia, fissured finger tips, reduced pigmentation, and hair abnormalities. The grading system for severity determined by the National Cancer Institute [Common Toxicity Criteria (CTC) grading system for Adverse Events version 3.0] was applied (11).

Histology. A total of 13 skin lesions of treated patients were biopsied after consent and were compared with matched control biopsies of normal skin (age of ±5 y, sex, and location). Five biopsies taken were acute phase (<6 wk) and eight were chronic phase.

Paraffin-embedded skin samples were stained using the alkaline phosphatase–antialkaline phosphatase technique (12). General tissue morphology was visualized by H&E staining of 1.5-μm-thick sections, with slide assessment done by two dermatopathologists. Epidermal thickness was examined in H&E-stained slides of chronic skin lesions only. Measurements were done at the deepest point of the epidermis, equivalent to the distance from the skin surface to the bottom of the rete ridge, and at the shallowest point, equivalent to the distance from skin surface to the top of the dermal papilla. Three visual fields were selected randomly for each section at a magnification of ×10, and the mean value was calculated.

Immunohistochemistry. Sections of 1-μm thickness were prepared and stained with antibodies directed against p53 (Clone DO7, Cell Marque) and Ki67 (Clone MIB-1, DAKO). In addition, four samples of chronic and four samples of acute skin toxicity were stained for Bcl-2 (Clone 124, DAKO), and one sample of chronic changes was stained for microphthalmia-associated transcription factor (Clone SPM290, Zytomed Systems).

Evaluation. In the immunohistochemistry sections, antibody-stained cells were counted in three randomly chosen visual fields using a microscope with a ×40 magnification. For p53-stained sections, we counted p53-positive cells in the epidermis and compared this with the number of positive cells in matched control biopsies. In Ki67 sections, we counted the total number of Ki67-positive cells, differentiating between positive cells of the basal and suprabasal layers. The number of cells was compared with matched control biopsies of normal skin and mean value was calculated. Epidermal thickness was measured in H&E-stained slides of chronic skin lesions. Each measurement was done at the deepest point of the epidermis, which is equivalent to the distance from skin surface to the bottom of the rete ridge, and the shallowest point, which is the distance from skin surface to the top of the dermal papilla. Three visual fields were selected randomly for each histologic section in a microscope at ×10 magnification and mean values were calculated.

Statistics. All 13 biopsied skin lesions were included in the data analysis. The biopsies were matched to normal skin biopsies from our histologic database. Statistical analysis with unpaired *t* test was done using Excel 2003 (Microsoft Corp.).

Half-side treatment of acute skin toxicity in five patients. An acute papulopustular rash occurring a few days after therapy initiation was distinctive and urged treatment, corresponding to CTC grade 2. In three patients, we attempted a topical treatment using cream containing 10 mg/g of triclosan and 0.5 mg/g of steroid halomethason-monohydrat on one side of the face and trunk. In addition, an antibiotic acne therapeutic erythromycin gel (either 2% or 4%) was applied to the other side. Another two patients were treated with 10 mg/g triclosan and 0.5 mg/g halomethason-monohydrat (one side) or fusidine acid cream (other side). Each cream was applied daily and evaluation was done weekly. In case of superiority of one treatment over the other after 1 wk, only the more effective cream was used for further treatment.

Results

Acute skin toxicity: papulopustular rash

Seventeen of 22 (77%) patients developed an acute (within 6 weeks) papulopustular rash. The morphology of skin changes presented with papulopustules without comedones. The most commonly affected areas were the

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face, upper chest, and back and less frequently on the scalp, arms, and legs. Typically, a caudal progression was observed. The palms, soles, and mucosa were spared (Fig. 1).

In general, the papulopustular rash manifested between 1 and 3 weeks after treatment onset. After the first week of therapy, 7 of 14 (50%) patients presented with CTC grade 1 or 2 rash. Rashing peaked during the second and third week and diminished over the following 6 weeks. After 12 weeks of treatment, only two of eight (25%) patients showed rash with CTC grade 2. Thereafter, no patients presented rash with greater than CTC grade 1. The percentage of CTC grade 1 increased over time (Fig. 2).

Chronic skin toxicity: xerosis cutis, paronychia, fissured finger tips, reduced pigmentation, hair abnormalities

Chronic skin changes (> 6 weeks) included xerosis cutis, paronychia, and fissured finger tips, similar to that observed with epidermal growth factor receptor (EGFR) inhibition (Supplementary Fig. S5A and B; Table 1B; Fig. 3A). In addition, we observed reduced pigmentation of hair and skin correlating with the AZD6244 treatment period (Fig. 3B and C). Hair abnormalities such as nonscarring alopecia, trichomegaly of the eyebrows, facial hypertrichosis, and thinning of the hair as seen with EGFR inhibitors were not observed in our patients (Table 1A–C).

Xerosis cutis. After week 6 of the treatment phase with the MEK inhibitor, 6 of 17 (35%) active patients complained of xerosis cutis (Supplementary Fig. S5A). The skin, mainly on the extremities and trunk, was erythematous with fine scaling and papules associated with itching. Xerosis began no earlier than after 8 weeks of therapy (Supplementary Table S4A).

Paronychia. After 6 weeks of therapy, two patients (12%) treated with AZD6244 developed inflammation of the lateral nail wall. Clinically, this presented as a periungual inflammation with redness, swelling, and exudative granulation tissue (Supplementary Fig. S4B; Fig. 3A). A CTC grading for severity for this event does not exist.

Fissured finger tips. Parallel to the development of xerosis cutis, some patients showed painful symmetrical fissuring of the finger tips (n = 4, 24%) after 6 weeks of treatment (Supplementary Figs. S5B and S4C). Rhagades of the skin above the interphalangeal articulation were also seen, as reported with EGFR inhibitors (13, 14).

Hair abnormalities and pigment changes. In patients treated longer than 6 weeks, we observed reduced pigmentation of the hair and skin (similar to vitiligo) in two patients (Fig. 3B and C). Reduced pigmentation of the hair began with MEK inhibitor treatment and proceeded according to the growth rate of the hair. We observed repigmentation upon treatment discontinuation.

Histology. A total of 13 biopsies were done: 5 samples were taken in the acute phase (week 0-6) and 8 samples in the chronic phase (>6 weeks). In acute lesions, apoptotic keratinocytes with sunburn cell morphology (Supplementary Fig. S6D) and focal infiltrates mainly of neutrophils and occasional lymphocytes with destruction of adnexal structures were seen. The number of melanocytes was not reduced in acute and chronic skin lesions. There was no change in immunoreactivity of microphthalmia-associated transcription factor or Bcl-2 in the melanocytes. Epidermal thinning as mentioned in the literature (15, 16) could not be shown in our samples (Supplementary Fig. S6C; P = 0.276).

Immunohistochemistry

In all 13 AZD6244 skin samples, the number of p53-positive cells (proapoptotic keratinocytes) was significantly elevated compared with matched controls (Supplementary Fig. S6A and Table S2; P = 0.00080).

Ki67 was used as a quantitative marker for keratinocytic proliferation. In our samples, the total number of the Ki67-positive cells did not significantly differ in the AZD6244 group compared with matched controls (P = 0.14), indicating that overall proliferation rates are similar in both groups. However, Ki67-positive cells showed a significant shift from the basal to the suprabasal keratinocyte layer in AZD6244-treated patients with rash (Supplementary Fig. S6B and Table S3; P = 1.242 E-10).

Half-side treatment experiment

All of our patients treated in the half-side experiment (n = 5) with cream containing 0.5 mg/g halomethason-monohydrat

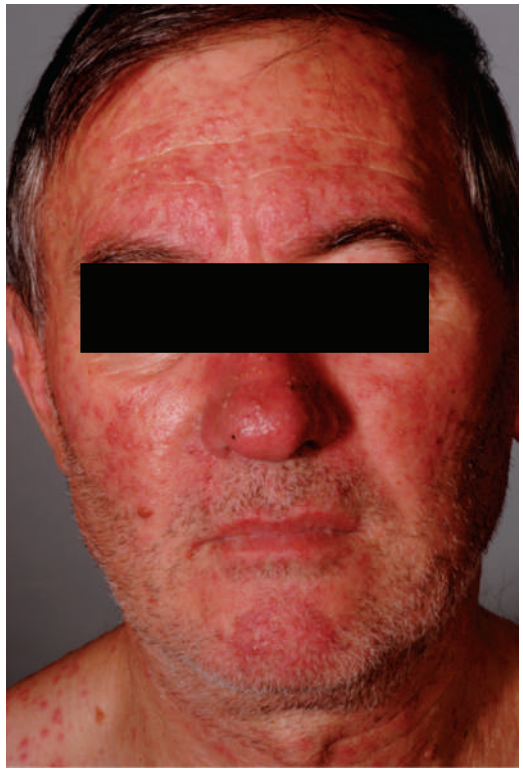

Fig. 1. Papulopustular rash of the face of a 56-y-old man, 2 wks after treatment start with the MEK inhibitor.

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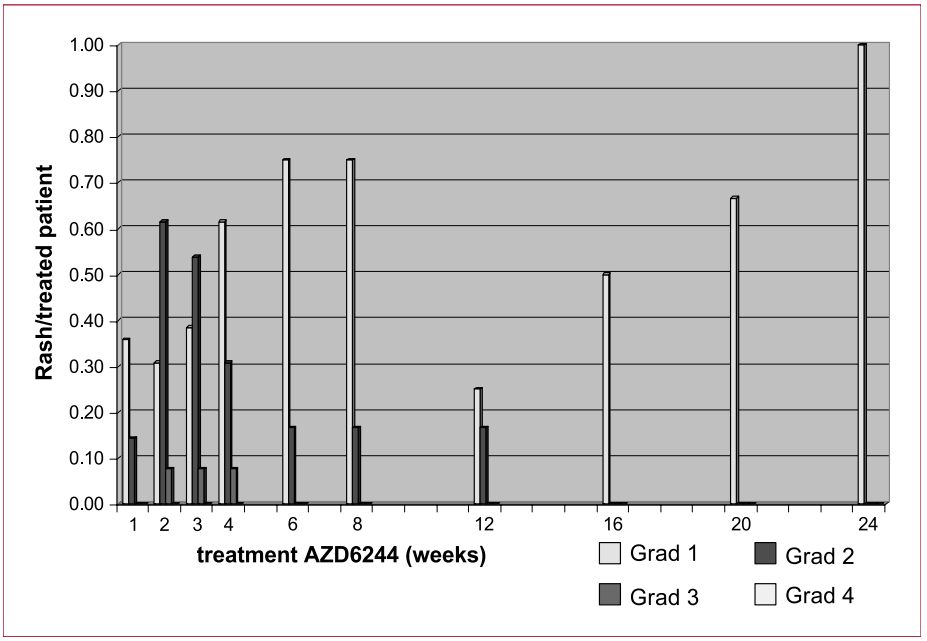

Fig. 2. Time course of acute papulopustular rash according to CTC grading.

and 10 mg/g triclosan, and either erythromycin gel or cream (2% or 4%) or fusidine acid cream showed an obvious lessening of rash after 1 week of halomethason-monohydrat and triclosan cream treatment (Supplementary Fig. S7A and B). With topical erythromycin treatment, the skin became dry, irritated, and elicited intense burning sensations.

Discussion

This is the first detailed investigation of AZD6244-induced skin reactions analyzing the clinical and histologic reaction patterns. Cutaneous toxicity may be interpreted as a stress response that affects epidermal homeostasis (17). Stress signals are transmitted to effectors in the cell, which may drive an inflammatory response (18). EGFR signal inhibition in a clinical setting often yields outcomes that resemble cutaneous reactions (19). Our findings emphasize that this is partly due to a common signaling pathway. Three different pathways downstream of EGFR have been identified; however, the RAS-RAF-MEK signal pathway is the one most commonly identified (20). Downstream signaling results in the activation of transcription factors, modulation of the cell cycle, growth, apoptosis, and angiogenesis.

Physiologically, EGFR signaling suppresses p53 expression in keratinocytes. This in turn downregulates Notch1, which is involved in regulating keratinocyte differentiation and thus protects the epithelial stem cell pool (21). Accordingly, the number of apoptotic keratinocytes (p53 positive) was increased under MEK inhibition compared with controls.

Under physiologic conditions, cell proliferation is mainly restricted to the undifferentiated basal cell layer of the epidermis, sweat gland apparatus, and hair follicle epithelium. In these cell compartments, EGFR is strongly expressed (22, 23). As keratinocytes exit the basal layer, EGFR is reduced. Interestingly, during MEK inhibition, we observed a shift in Ki67 positivity from the basal layer to the suprabasal keratinocyte layers. We propose that MEK inhibition mainly affects the basal keratinocytes characterized by high EGFR expression, resulting in early Notch1-dependent differentiation. The reduced basal proliferation is compensated by increased suprabasal proliferation possibly by self-amplifying cells residing in this layer (21).

Because EGFR signals through RAS-RAF-MEK, it is reasonable to expect a spectrum of skin reactions similar to EGFR inhibition. Indeed, there was clinically a biphasic cutaneous side effect profile as reported for EGFR inhibition. In the early phase, a papulopustular rash mainly in the seborrhoic area was observed. In the late phase, however, xerosis cutis, paronychia, and fissured finger tips as is typical of EGFR inhibition was observed (13, 14). In addition, disturbances of pigmentation of hair and vitiligo-like discoloration were seen.

As papulopustular rash is more significant in sun-exposed skin, UV light might be another cofactor initiating cutaneous eruptions. Indeed, we observed definite photodistribution of skin lesions in one patient (Supplementary Fig. S8). The histology of early phase skin reactions showed large numbers of p53-positive apoptotic keratinocytes with a neutrophil-rich infiltrate similar to acutely UV-exposed skin (24). Keratinocytes stressed by UV light and/or growth factor deprivation attract neutrophils secreting chemokines and active enzymes including elastases and matrix metalloproteinases, which contribute to tissue damage (21). We suggest that long-term

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Table 1. Skin reactions in MEK-treated patients

A. Acute skin reactions (≤6 wks of treatment)

	Patient no. (%) 22 (100%)	AZD first 13 of 22 (59%)	AZD second 9 of 22 (44%)
Rash	17 (77)	9 (41)	8 (36)
No rash	5 (23)	4 (18)	1 (5)

B. Chronic skin reactions (>6 wks of treatment)

	Patient no. (%) 17 (100%)	AZD first 13 of 17 (53%)	AZD second 9 of 17 (47%)
Xerosis cutis	6 (35)	4 (24)	2 (12)
Fissured finger tips	4 (24)	2 (12)	2 (12)
Paronychia	2 (12)	2 (12)	0
Hair depigmentation	2 (12)	2 (12)	0

C. Total of skin reactions

	Patient no. (%) 22 (100%)	AZD first 13 of 22 (59%)	AZD second 9 of 22 (41%)
Total side effects (skin or adnexis)	19 (86)	11 (50)	8 (36)

NOTE: Total patients treated with AZD, $n = 22$. AZD first, patients initially treated with AZD; AZD second, patients initially treated with temozolomide until progression, then changed to AZD treatment.

MEK inhibition may accelerate normal aging processes and thus decrease epidermal proliferative capacity and depth. Both endogenous and exogenous aging share some fundamental pathways, including a decrease of ERK-dependent mitogen-activated protein kinase signaling, resulting in stress-related responses and apoptosis (25).

In addition to the expected cutaneous side effects reported during EGFR inhibition, MEK inhibition affected pigmentation. In two patients, we observed reduced pigmentation (resembling vitiligo) and transient hair pigment reduction correlating with the length of the treatment period. Similar findings have been seen in patients treated with c-Kit–inhibiting agents (26). Inhibition of c-Kit leads to reduced mitogen-activated protein kinase activity and a diminished expression of its downstream transcription factor microphthalmia-associated transcription factor

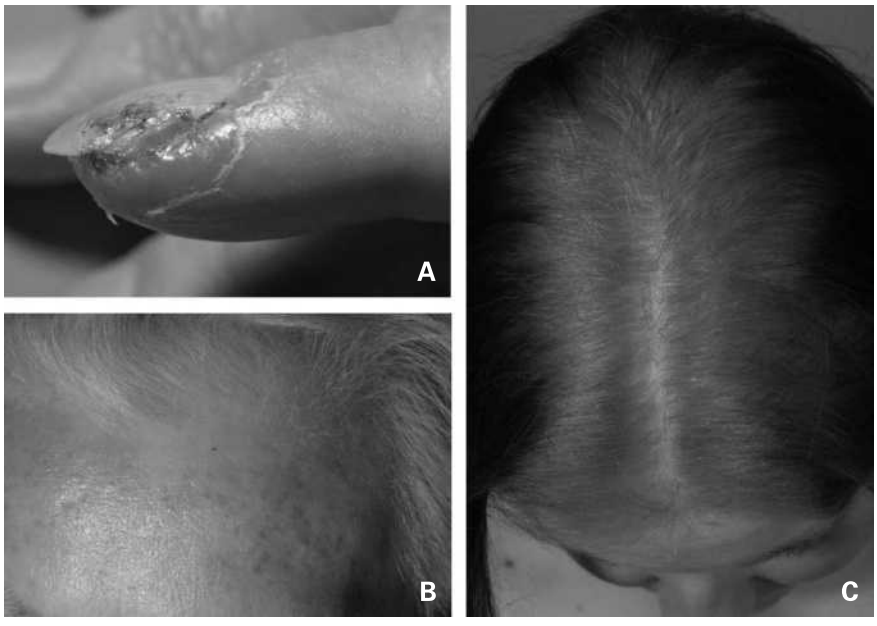

Fig. 3. Chronic skin changes: A, paronychia Dig 2 right hand in 75-y-old woman, 6 wks after the beginning with the MEK inhibitor; B, reduced pigmentation of skin in a 59-y-old woman treated with the MEK inhibitor for 27 wks; C, reduced pigmentation of hair in a 21-y-old woman treated with the MEK inhibitor for 22 wks.

(regulating the expression of tyrosinase mRNA), which regulates both melanocyte proliferation and melanogenesis. We hypothesize that the imbalance in epidermal homeostasis, as shown by upregulated p53 and Notch1, may affect melanocytic pigment production and/or transfer to keratinocytes.

Treatment strategies. According to the results of our clinical and dermatohistopathologic correlation, our treatment strategies were adapted to the stage of the rash. Several authors still interpret acute rash as acneiform and suggested retinoids or other acne medications. The current concept of the mechanism of skin toxicity of EGFR-targeting drugs (23) and the findings presented in this article do not support acne-like events. In contrast, irritating local medications such as benzoylperoxide may worsen the situation. In our half-side treatment comparisons with topical corticosteroids on one side of the face and topical antibiotics (Fusidine acid or Erythromycin) on the other, we show as shown in Supplementary Fig. S7 that the application of anti-inflammatory steroids led to a faster improvement of the rash.

Based on the observations above, it seems that the acute skin damage is mainly caused by neutrophils, suggesting the importance of an anti-inflammatory approach. There is evidence that the calcineurin inhibitor pimecrolimus is another treatment option for EGFR-treated patients (27). Acne medication can aggravate dry skin and should therefore not be used. With continued treatment and drying of the skin as a side effect of long-term treatment with AZD6244, it might be necessary to use unmedicated creams for skin care.

In addition, as UV may mediate additional stress signals to keratinocytes, use of UV protection and antioxidative compounds such as green tea catechines (28) should be explored.

In conclusion, the sudden interruption of the RAS-RAF-MEK signaling pathway by MEK inhibition with AZD6244 results in an acute keratinocyte stress response including a disturbed epidermal homeostasis associated with inflammation and tissue damage. After several weeks, adaptation controls inflammatory tissue damage but leads to epidermal dysfunction in the skin (18). MEK inhibition with AZD6244 shows a biologically significant effect on the targeted pathway in the epidermis, revealed by increased p53 and Notch1 expression, and a shift of proliferative keratinocytes from the basal to the suprabasal layer of the epidermis. Melanocytic function is also affected as shown by reduced pigmentation of hair and skin in contrast to EGFR targeting.

Disclosure of Potential Conflicts of Interest

R. Dummer, commercial research grants from AstraZeneca, Novartis, Cephalon, MSD, Trisgene, Bayer; advisory board member, AstraZeneca, Novartis, Cephalon, MSD, Trisgene, Genfa, Bayer; participated in advisory board meetings and received an honorarium from Astra Zeneca. The other authors disclosed no potential conflicts of interest.

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