Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma

Martina Sanlorenzo, MD,[a,b] Aditi Choudhry, MD,[a] Igor Vujic, MD,[a,c] Christian Posch, MD,[a,c] Kim Chong, MD,[a] Katia Johnston, BSc,[a] Melissa Meier, MD,[a] Simona Osella-Abate, MSc,[b] Pietro Quaglino, MD,[b] Adil Daud, MD,[a] Alain Algazi, MD,[a] Klemens Rappersberger, MD,[c] and Susana Ortiz-Urda, MD, PhD[a]
San Francisco, California; Turin, Italy; and Vienna, Austria

Background: BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi) frequently cause cutaneous adverse events.

Objective: We sought to investigate the cutaneous safety profile of BRAFi versus BRAFi and MEKi combination regimens.

Methods: We performed a retrospective cohort study, collecting data from 44 patients with melanoma treated either with BRAFi (vemurafenib or dabrafenib) or BRAFi and MEKi combination regimens (vemurafenib + cobimetinib or dabrafenib + trametinib). Patient characteristics, and the occurrence and severity of cutaneous adverse events, are described.

Results: The development of cutaneous adverse events was significantly less frequent (P = .012) and occurred after longer treatment time (P = .025) in patients treated with BRAFi and MEKi combination regimen compared with patients treated with BRAFi monotherapy. Among patients who received both BRAFi and the combination of BRAFi and MEKi at different time points during their treatment course, the development of squamous cell carcinoma or keratoacanthoma was significantly less frequent when they received the combination regimen (P = .008). Patients receiving vemurafenib developed more cutaneous adverse events (P = .001) and in particular more photosensitivity (P = .010) than patients who did not.

Limitations: There were a limited number of patients.

Conclusion: Combination regimen with BRAFi and MEKi shows fewer cutaneous adverse events and longer cutaneous adverse event-free interval compared with BRAFi monotherapy. (J Am Acad Dermatol 2014;71:1102-9.)

Key words: cutaneous adverse event; histology; inflammation; rash; squamous cell carcinoma; therapy.

Pharmacologic inhibition of the mitogen-activated protein kinase (MAPK) pathway by targeting the mutant BRAF is a milestone in the management of metastatic melanoma. BRAF inhibitors (BRAFi), such as vemurafenib and dabrafenib, have been associated with prolonged progression-free and overall survival.[1,2] MEK inhibitors (MEKi), such as cobimetinib[3] and trametinib,

From the University of California—San Francisco, Mt Zion Cancer Research Center[a]; Department of Medical Sciences, Section of Dermatology, University of Turin[b]; and Department of Dermatology, Rudolfstiftung Hospital, Academic Teaching Hospital, Medical University Vienna.[c]

This study was supported by the National Cancer Institute of the National Institutes of Health (NIH) under award number K08CA155035. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors are also grateful to Timothy Dattels; the Melanoma Research Alliance; and the National Center for Advancing Translational Sciences, NIH (through University of California—San Francisco Clinical and Translational Science Institute Grant Number UL1 TR000004) for their generous support.

Conflicts of interest: None declared.

Accepted for publication September 2, 2014.

Reprint requests: Martina Sanlorenzo, MD, Department for Dermatology, University of California—San Francisco, Mt Zion Cancer Research Center, 2340 Sutter St, N461, San Francisco, CA 94115. E-mail: martina.sanlorenzo@hotmail.it.

Published online October 15, 2014.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.09.002

have also been associated with improved progression-free and overall survival in BRAF[4] mutant melanoma and NRAS[5] mutant melanoma. Despite these advances in melanoma treatment, disease progression occurs in approximately 50% of patients within 6 to 7 months of commencing therapy with either a BRAFi or MEKi.[1,2,4,6] This is a result of several mechanisms of resistance, most of which seem to rely on reactivation of the MAPK pathway.[7-9] Therefore, to avoid or delay resistance to a single drug, combination therapies with BRAFi and MEKi have been explored.[10] In phase I and II studies, combination regimens showed improved progression-free survival over single inhibitor therapy.[10] Vemurafenib and dabrafenib are approved by the Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, as detected by an FDA-approved test. The recommended dosages of vemurafenib and dabrafenib are 960 mg and 150 mg, respectively, both taken orally twice a day (bid). Trametinib is approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations, as detected by an FDA-approved test, and the recommended dose is 2 mg orally once daily. Ongoing clinical trials are exploring these drugs in an adjuvant setting for patients with stage III (American Joint Committee on Cancer) disease.[11] Treatment with vemurafenib causes a multitude of cutaneous adverse events, such as exanthema, photosensitivity, palmar-plantar dysesthesia or hand-foot syndrome, alopecia, pruritus, keratosis pilaris–like eruptions, actinic keratosis (AK), hyperkeratosis, skin papillomas, keratoacanthomas (KA), and cutaneous squamous cell carcinomas (SCC).[1,6,12-14] The most frequent cutaneous adverse events of dabrafenib are hyperkeratosis, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. Trametinib is more frequently related with the development of acneiform dermatitis or alopecia.[4,15] Less is known about the cutaneous adverse events related to cobimetinib. In a phase Ib trial where cobimetinib was administered in combination with a pan-PI3K inhibitor, 50% of the patients developed a rash.[16] Interestingly, when BRAFi and MEKi drugs are combined, the development of cutaneous adverse events specific for each drug appear to be reduced.[4,10]

The number of patients treated with BRAFi and MEKi combination is increasing, and a better understanding of the type and morphology of related cutaneous adverse events and their management is needed. In this retrospective study, we collected data on 44 patients treated with either a BRAFi alone or the combination of a BRAFi and a MEKi. We have clinically and histologically characterized the cutaneous adverse events of BRAFi monotherapy and of combination regimens.

CAPSULE SUMMARY

- BRAF and MEK inhibitors frequently cause cutaneous adverse events.
- Combination of BRAF and MEK inhibitors shows fewer cutaneous adverse events and longer cutaneous adverse event-free interval compared with BRAF inhibitor monotherapy.
- The knowledge of expected cutaneous adverse events can help clinical decision-making during follow-up.

METHODS

We performed a retrospective cohort study, and included patients with stage IV or unresectable stage III melanoma[17] who received BRAFi monotherapy or BRAFi + MEKi combination therapy. All patients were treated and followed up at the University of California–San Francisco between November 2009 and August 2013. In all, 32 patients received treatment with a BRAFi and 23 patients received BRAFi + MEKi combination. Eleven patients received both BRAFi monotherapy and BRAFi + MEKi regimen at different time points during their treatment. Among the patients treated with a BRAFi: 27 received vemurafenib (PLX4032) at a dose of 960 mg bid (phase III clinical trial, NCT01006980), and 5 received dabrafenib (GSK2118436) at a dose of 150 mg bid (phase III clinical trial, NCT01227889). In the BRAFi + MEKi group, 15 patients received a combination of dabrafenib at 150 mg bid and trametinib (GSK1120212) at 2 mg daily (phase II clinical trial, NCT01072175), and 8 patients received a combination of vemurafenib at 960 mg bid on days 1 to 28 of each cycle and cobimetinib (GDC-0973) at 60 mg daily on days 1 to 21 of each cycle (phase Ib clinical trial, NCT01271803). All treatment decisions were made by the patient's medical oncologist. Collected data included patient demographics, course of the disease, medications (previous chemotherapy and immunotherapy—including interleukin 2, interferon, or anti-CTLA 4 antibodies), cutaneous adverse events, the treatment of those adverse events, and the response to treatment. Patients were evaluated at baseline by a dermatologist with full-body skin examinations and followed up at 4- to 6-week

Abbreviations used:

AK: actinic keratosis
bid: twice a day
BRAFi: BRAF inhibitor
CI: confidence interval
FDA: Food and Drug Administration
KA: keratoacanthoma
MAPK: mitogen-activated protein kinase
MEKi: MEK inhibitor
SCC: squamous cell carcinoma

intervals or upon patient request, in case of development of cutaneous adverse events. All cutaneous adverse events were ascertained by a dermatologist based on clinical and histologic findings. Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (June 14, 2010)[18] (Supplemental Table I, available at http://www.jaad.org). The study design was reviewed and approved by the Committee on Human Research of the University of California—San Francisco.

Statistical analyses were performed using Stata 12.0 statistical software (Stata, College Station, TX). Comparisons between independent groups were performed using Fisher exact test. The confidence interval (CI) calculation was performed for the estimated frequencies, considering the variable as binomial (0/1) and using an exact binomial CI. Comparisons between correlated groups were performed using McNemar exact test. Kaplan-Meier curves were used to analyze the time of development of cutaneous adverse events, and the statistical comparisons between groups were done using the log rank test. To analyze the safety profile of vemurafenib, either as monotherapy or in combination, we compared patients who received vemurafenib with those who did not receive the drug, assessing if they ever developed the event of interest. A *P* value less than .05 was considered significant.

RESULTS

A total of 44 patient charts were reviewed. In all, 32 patients were treated with a BRAFi as monotherapy (27 with vemurafenib, 5 with dabrafenib) and 23 were treated with a combination of BRAFi and MEKi (8 with vemurafenib + cobimetinib, 15 with dabrafenib + trametinib). The baseline characteristics of the patients in the study groups are outlined in Table I. None of the patients included in the study experienced grade-4 or -5 cutaneous adverse events. Grade-3 cutaneous adverse events were recorded in 8 patients treated with the single agent vemurafenib, and in 2 patients during BRAFi + MEKi combination therapy (1 treated with vemurafenib + cobimetinib, and 1 treated with dabrafenib + trametinib).

In all, 33 patients received single treatment regimen (either BRAFi or BRAF + MEKi combination but not both) during their disease history; a detailed list of all the cutaneous adverse events recorded in these patients is reported in Table II, and representative clinical pictures are presented in Fig 1. Eleven patients received both a BRAFi alone and a BRAFi + MEKi combination at different time points during their treatment course. A detailed description of their cutaneous adverse events is reported in Table III. Of these 11 patients, 8 received the same BRAFi (vemurafenib or dabrafenib) both as monotherapy and in combination with MEKi.

Among the patients who received only single treatment regimen (either BRAFi monotherapy or BRAF + MEKi combination treatment) during their disease history, we observed that cutaneous adverse events occurred more frequently during BRAFi monotherapy than during BRAFi + MEKi combination therapy (N = 21/21, 100%, 95% CI 83.9-100 vs N = 8/12, 66.67%, 95% CI 34.9-90.1; P = .012). Kaplan-Meier curves showed a significant difference in the time of development of cutaneous adverse events between BRAFi monotherapy and BRAFi + MEKi combination therapy (P = .0246). The median cutaneous adverse event-free interval was 28 (range 7-470) days for BRAFi monotherapy, and 122.5 (range 7-341) days for BRAFi + MEKi combination therapy. Kaplan-Meier curves comparing all 4 treatment groups also demonstrated a significant difference (P = .0002); the median cutaneous adverse event-free interval was 28.5 (range 7-470) days for vemurafenib, 26 (range 14-106) days for dabrafenib, 10 (range 7-13) days for vemurafenib + cobimetinib, and 150.5 (range 19-341) days for dabrafenib + trametinib (Fig 2).

Among the 11 patients who received both BRAFi monotherapy and BRAFi + MEKi combination treatment at different time points during their disease course, 10 developed cutaneous adverse events during BRAFi monotherapy (90.9%, 95% CI 58.7-99.8), and 5 developed cutaneous adverse events during BRAFi + MEKi combination therapy (45.5%, 95% CI 16.7-76.6) (P = .2188). Four of 11 patients developed AK during BRAFi monotherapy and no one developed it during combination treatment (36.4%, 95% CI 10.9-69.2 vs 0%, 95% CI 0-28.5; P = .0156). Three of 11 patients developed SCC or KA during BRAFi monotherapy, and no one developed SCC or KA during combination treatment (27.3%, 95% CI 6-61 vs 0%, 95% CI 0-28.5; P = .0078).

Of 44 patients, 29 received vemurafenib either in monotherapy or in combination. They developed

Table I. Characteristics of patients included in the study

	BRAFi (N = 32)		BRAFi + MEKi (N = 23)	
	Vemurafenib (N = 27)	Dabrafenib (N = 5)	Vemurafenib + cobimetinib (N = 8)	Dabrafenib + trametinib (N = 15)
Median age at beginning of treatment, y (range)	60.2 (18.3-87.9)	60.4 (48.9-72.5)	56.49 (19.9-70.3)	55.1 (33.9-70.1)
Median duration on treatment, mo (range)	8.2 (1-33.8)	5.1 (0.9-9.3)	5.9 (1.4-14.5)	13.0 (1.8-30.3)
Sex				
Female	10 (37%)	3 (60%)	4 (50%)	9 (60%)
Male	17 (63 %)	4 (40%)	4 (50%)	6 (40%)
BRAF mutation				
V600E	19 (70.4%)	3 (60%)	8 (100%)	13 (86.7%)
V600K	4 (14.8%)	2 (40%)	-	2 (13.3%)
V600R	1 (3.7%)	-	-	-
K601E	2 (7.4%)	-	-	-
L597R	1 (3.7%)	-	-	-
Stage of disease				
IIIB	1 (3.7%)	-	-	-
IIIC	1 (3.7%)	-	-	-
IV	25 (92.6%)	5 (100%)	8 (100%)	15 (100%)
Previous chemotherapy	14 (51.9%)	2 (40%)	4 (50%)	6 (40%)
Previous immunotherapy*	15 (55.6%)	-	5 (62.5%)	7 (46.7%)
Current immunotherapy	3 (11.1%)	1 (20%)	-	-
History of nonmelanoma skin cancer	9 (33.3%)	1 (20%)	5 (62.5%)	-

BRAFi, BRAF inhibitor; *MEKi*, MEK inhibitor.
*Immunotherapy included interleukin 2, interferon, or ipilimumab (anti-CTLA 4 antibody).

Table II. Cutaneous adverse events reported during BRAF inhibitor monotherapy and during BRAF inhibitor + MEK inhibitor combination therapy in patients who received single treatment regimen (either BRAF inhibitor monotherapy or BRAF inhibitor + MEK inhibitor combination treatment but not both)

	BRAFi (N = 21)		BRAFi + MEKi (N = 12)	
	Vemurafenib (N = 18)	Dabrafenib (N = 3)	Vemurafenib + cobimetinib (N = 2)	Dabrafenib + trametinib (N = 10)
	No. (% [95% CI])			
Any cutaneous side effect	18 (100 [81.5-100])	3 (100 [29.2-100])	2 (100 [15.8-100])	6 (60 [26.2-87.8])
Photosensitivity	4 (22.2 [6.4-47.6])	1 (33.3 [0.8-90.6])	2 (100 [15.8-100])	0 (0 [0-30.8])
Actinic keratosis	8 (44.4 [21.5-69.2])	2 (66.7 [9.4-99.2])	1 (50 [1.3-98.7])	1 (10 [2.5-44.5])
Cutaneous squamous cell carcinoma and keratoacanthoma	4 (22.2 [6.4-47.6])	0 (0 [0-70.8])	1 (50 [1.3-98.7])	0 (0 [0-30.8])
Alopecia	2 (11.1 [1.4-34.7])	0 (0 [0-70.8])	0 (0 [0-84.2])	0 (0 [0-30.8])
Macular-papular rash	8 (44.4 [21.5-69.2])	0 (0 [0-70.8])	0 (0 [0-84.2])	3 (30 [6.7-65.2])
Acneiform rash	1 (5.6 [0.1-27.3])	1 (33.3 [0.8-90.6])	1 (50 [1.3-98.7])	2 (20 [2.5-55.6])
Eczema	0 (0 [0-18.5])	0 (0 [0-70.8])	0 (0 [0-84.2])	3 (30 [6.7-65.2])
Pruritus	6 (33.3 [13.3-59])	1 (33.3 [0.8-90.6])	0 (0 [0-84.2])	0 (0 [0-30.8])
Xerosis	2 (11.1 [1.4-34.7])	0 (0 [0-70.8])	0 (0 [0-84.2])	3 (30 [6.7-65.2])
Panniculitis-like reaction	3 (16.7 [3.6-41.4])	1 (33.3 [0.8-90.6])	0 (0 [0-84.2])	3 (30 [6.7-65.2])
Keratosis pilaris	3 (16.7 [3.6-41.4])	1 (33.3 [0.8-90.6])	0 (0 [0-84.2])	1 (10 [2.5-44.5])
Warts	4 (22.2 [6.4-47.6])	0 (0 [0-70.8])	1 (50 [1.3-98.7])	1 (10 [2.5-44.5])
Palmar-plantar erythrodysesthesia or hand-foot syndrome	1 (5.6 [0.1-27.3])	0 (0 [0-70.8])	1 (50 [1.3-98.7])	1 (10 [2.5-44.5])
Nevi changes	1 (5.6 [0.1-27.3])	0 (0 [0-70.8])	0 (0 [0-84.2])	0 (0 [0-30.8])
Acrochordon (skin tag)	1 (5.6 [0.1-27.3])	0 (0 [0-70.8])	0 (0 [0-84.2])	2 (20 [2.5-55.6])
Oral blisters	1 (5.6 [0.1-27.3])	0 (0 [0-70.8])	0 (0 [0-84.2])	0 (0 [0-30.8])

BRAFi, BRAF inhibitor; *CI*, confidence interval; *MEKi*, MEK inhibitor.

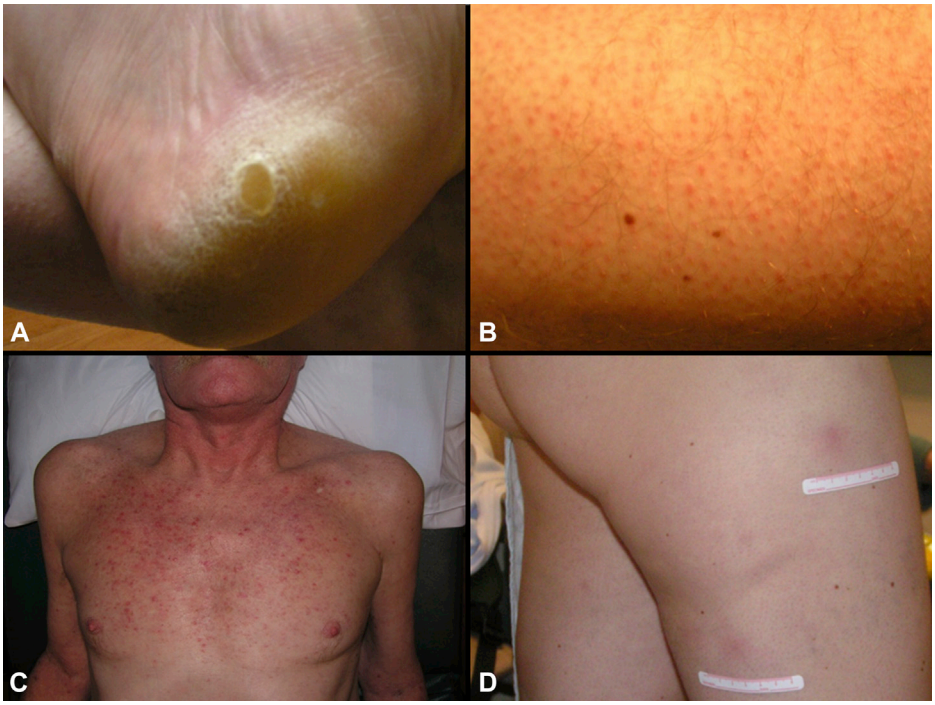


Fig 1. Cutaneous adverse events developed during BRAF inhibitor (BRAFi) monotherapy (palmar-plantar erythrodysesthesia [**A**] and keratosis pilaris [**B**]) and during BRAFi and MEK inhibitor combination therapy (acneiform rash [**C**] and erythema nodosum [**D**]).

cutaneous adverse events significantly more frequently than patients who never received vemurafenib (N = 29/29, 100%, 95% CI 88.1-100 vs N = 10/15, 66.7%, 95% CI 38.4-88.2; $P = .001$). Thirteen of 29 patients treated with vemurafenib (44.8%, 95% CI 26.4-64.3) and 1 of 15 patients who did not receive vemurafenib (6.7%, 95% CI 0.2-31.9) developed photosensitivity ($P = .010$).

DISCUSSION

After approval by the FDA, targeted inhibitors have become an important treatment modality for patients with BRAF mutant melanoma. It is anticipated that the number of patients receiving a single or combination inhibitor treatment will increase significantly in the near future. For this reason, knowledge about the incidence and the appearance of cutaneous adverse events associated with targeted inhibitor therapy is critical for optimal patient care. In this study we present the data on patients treated with 2 different BRAFi (vemurafenib or dabrafenib) and with 2 different combination regimens of a BRAFi and MEKi (vemurafenib + cobimetinib or dabrafenib + trametinib).

Among our patients who received single treatment regimen (either BRAFi monotherapy or BRAFi + MEKi combination treatment), cutaneous adverse events occurred more frequently and faster during BRAFi therapy than during BRAFi + MEKi combination therapy. In particular, we observed a longer cutaneous adverse event-free interval during treatment with a combination of dabrafenib and trametinib.

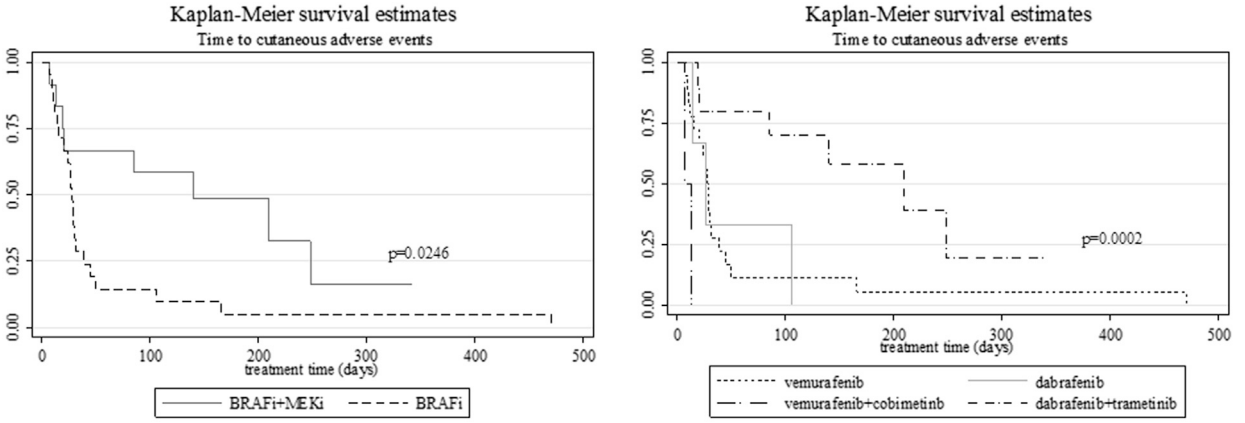
The development of AK, a well-known precursor of SCC, was frequent during monotherapy with both BRAFi. It has be reported that the development of cutaneous SCC during BRAFi therapy is caused by activation of the MAPK pathway in keratinocytes with pre-existing RAS mutations commonly found in chronically sun-damaged skin. Although BRAFi potently reduce RAF signaling in BRAF mutant cells, leading to apoptosis and tumor shrinkage, they cause increased CRAF signaling in wild-type cells, leading to the development of SCC.[19-21] The concomitant administration of a MEKi reduces this activation and therefore has preventive effects on the development of SCC and KA.[10] Interestingly, the 11 patients who received both BRAFi and BRAFi + MEKi at different time points developed AK and SCC or KA significantly less frequently during the combination treatment.

Photosensitivity is another well-known adverse event experienced during vemurafenib treatment.[1,6,12] Previous studies speculated that this is a result of the chemical structure of the drug and

Table III. Cutaneous adverse events reported in patients who received at different time points during their treatment course both BRAF inhibitor monotherapy and BRAF inhibitor + MEK inhibitor combination therapy

	BRAFi (N = 11)		BRAFi + MEKi (N = 11)	
	Vemurafenib (N = 9)	Dabrafenib (N = 2)	Vemurafenib + cobimetinib (N = 6)	Dabrafenib + trametinib (N = 5)
	No. (% [95%CI])			
Any cutaneous side effect	9 (100 [66.4-100])	1 (50 [1.3-98.7])	3 (50 [11.8-88.2])	2 (40 [5.3-85.3])
Photosensitivity	7 (77.8 [40-97.2])	0 (0 [0-84.2])	1 (16.7 [0.4-64.1])	0 (0 [0-52.2])
Actinic keratosis	4 (44.4 [13.7-78.8])	0 (0 [0-84.2])	0 (0 [0-45.9])	0 (0 [0-52.2])
Cutaneous squamous cell carcinoma and keratoacanthoma	3 (33.3 [7.5-70.1])	0 (0 [0-84.2])	0 (0 [0-45.9])	0 (0 [0-52.2])
Alopecia	3 (33.3 [7.5-70.1])	0 (0 [0-84.2])	0 (0 [0-45.9])	0 (0 [0-52.2])
Macular-papular rash	2 (22.2 [2.8-60])	0 (0 [0-84.2])	0 (0 [0-45.9])	2 (40 [5.3-85.3])
Acneiform rash	2 (22.2 [2.8-60])	0 (0 [0-84.2])	1 (16.7 [0.4-64.1])	0 (0 [0-52.2])
Eczema	0 (0 [0-33.6])	0 (0 [0-84.2])	1 (16.7 [0.4-64.1])	2 (40 [5.3-85.3])
Xerosis	3 (33.3 [7.5-70.1])	1 (50 [1.3-98.7])	1 (16.7 [0.4-64.1])	1 (20 [0.5-71.6])
Panniculitis-like reactions	2 (22.2 [2.8-60])	0 (0 [0-84.2])	2 (33.3 [4.3-77.7])	0 (0 [0-52.2])
Keratosis pilaris	3 (33.3 [7.5-70.1])	0 (0 [0-84.2])	1 (16.7 [0.4-64.1])	0 (0 [0-52.2])
Warts	2 (22.2 [2.8-60])	0 (0 [0-84.2])	1 (16.7 [0.4-64.1])	0 (0 [0-52.2])
Palmar-plantar erythrodysesthesia or hand-foot syndrome	1 (11.1 [0.3-48.2])	1 (50 [1.3-98.7])	0 (0 [0-45.9])	0 (0 [0-52.2])

BRAFi, BRAF inhibitor; *CI*, confidence interval; *MEKi*, MEK inhibitor.



Patients who developed cutaneous adverse events at different time points of treatment

	BRAFi (N=21)	BRAFi+MEKi (N=12)
30 days	13 (61.9%)	4 (33.3%)
60 days	17 (81.0%)	4 (33.3%)

A

	vemurafenib (N=18)	dabrafenib (N=3)	vemurafenib + cobimetinib (N=2)	dabrafenib + trametinib (N=10)
30 days	12 (66.7%)	2 (66.7%)	2 (100%)	2 (20%)
60 days	16 (88.9%)	2 (66.7%)	2 (100%)	2 (20%)

B

Fig 2. Kaplan-Meier curves. **A**, The onset of cutaneous adverse events is at an earlier time point in patients treated with BRAF inhibitor (*BRAFi*) than patients treated with BRAFi and MEK inhibitor (*MEKi*) combinations. **B**, Patients treated with dabrafenib + trametinib have longer adverse-free events interval.

ultraviolet A exposure,[22] rather than a result of BRAF inhibition and the subsequent consequences on MAPK signaling. In our experience, also, photosensitivity was more frequent in patients treated with vemurafenib. Regardless of the treatment regimen, anytime a patient receives vemurafenib, particular attention should be given to sun-exposure prevention measures.

The most common adverse event previously reported during trametinib monotherapy is acneiform dermatitis.[5,10,15,23] The mechanism triggering this reaction is still unknown, but a fundamental role of the PI3K/AKT pathway has been hypothesized. Indeed, MEKi relieves a negative feedback loop in the PI3K/AKT pathway leading to increased AKT signaling[24] that is known to play a central role in acne pathogenesis.[25,26] Another hypothesis previously reported is that these acneiform eruptions could be a result of drug-induced apoptosis of keratinocytes disturbing epidermal homeostasis.[15] In our study, trametinib was only administrated in combination with a BRAFi, and as reported previously, acneiform eruptions appeared to be less frequent with this combination compared with historical data pertaining to MEKi alone.[10,15]

Eight patients treated with BRAFi and only 2 treated with the combination regimen had to reduce the inhibitor dosage or interrupt the treatment because of cutaneous adverse events. In the BRAFi group, dosage reduction or interruption of treatment had to be done for patients treated with vemurafenib who developed the following cutaneous adverse events: macular-papular rash (4 patients), acneiform rash (3 patients), and oral blisters (1 patient). Two patients in the BRAFi + MEKi group developed panniculitis-like reaction, which did not respond to nonsteroidal anti-inflammatory drugs. Interestingly, 1 patient treated with the combination of vemurafenib (days 1-28 of each cycle) and cobimetinib (days 1-21 of each cycle) reported a correlation between the severity of xerosis, acneiform rash, and pre-existing psoriasis with the drugs' schedule. The skin condition improved during combination regimen and worsened when the MEKi was withheld.

From the results of this study, we conclude that each inhibitor and each combination has a particular cutaneous safety profile. Knowledge of expected cutaneous adverse events can help clinical decision-making during follow-up.

We are indebted to Ann Lazar, PhD (assistant professor, Clinical and Translational Science Institute, University of California—San Francisco) for her help in the statistical analysis.

REFERENCES

1. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364:2507-16.
2. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicenter, open-label, phase 3 randomized controlled trial. Lancet 2012;380:358-65.
3. LoRusso P, Shapiro G, Pandya SS, Kwak EL, Jones C, Belvin M, et al. A first-in-human phase Ib study to evaluate the MEK inhibitor GDC-0973, combined with the pan-PI3K inhibitor GDC-0941, in patients with advanced solid tumors. J Clin Oncol 2012;30(15 suppl):abstr2566.
4. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107-14.
5. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P, et al. MEK162 for patients with advanced melanoma harboring NRAS or Val600 BRAF mutations: a non-randomized, open-label phase 2 study. Lancet Oncol 2013;14:249-56.
6. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366: 707-14.
7. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS up-regulation. Nature 2010;468:973-7.
8. Poulikakos PI, Persaud Y, Janakiraman M, Kong X, Ng C, Moriceau G, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature 2011; 480:387-90.
9. Johannessen CM, Boehm JS, Kim SY, Thomas SR, Wardwell L, Johnson LA, et al. COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. Nature 2010;468: 968-72.
10. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012; 367:1694-703.
11. US National Institutes of Health. Clinicaltrials.gov. Available from: URL:http://clinicaltrials.gov/. Accessed August 27, 2014.
12. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010;363:809-19.
13. Manousaridis I, Mavridou S, Goerdt S, Leverkus M, Utikal J. Cutaneous side effects of inhibitors of the RAS/RAF/MEK/ERK signaling pathway and their management. J Eur Acad Dermatol Venereol 2013;27:11-8.
14. Mattei PL, Alora-Palli MB, Kraft S, Lawrence DP, Flaherty KT, Kimball AB. Cutaneous effects of BRAF inhibitor therapy: a case series. Ann Oncol 2013;24:530-7.
15. Anforth R, Liu M, Nguyen B, Uribe P, Kefford R, Clements A, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. Australas J Dermato doi: http://dx.doi.org/10.1111/ajd.12124. Published online December 9, 2013.
16. Shapiro G, LoRusso P, Kwak EL, Cleary JM, Musib L, Jones C, et al. Clinical combination of the MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941: a first-in-human phase Ib study testing daily and intermittent dosing schedules in patients with advanced solid tumors. J Clin Oncol 2011;29(suppl): abstr3005.
17. Balch CM, Gershenwald JE, Soong S-J, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009; 27:6199-206.
18. National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS; 2009: NIH publication #09-7473.
19. Hatzivassiliou G, Song K, Yen I, Brandhuber BJ, Anderson DJ, Alvarado R, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature 2010;464:431-5.

20. Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 2012;366:207-15.
21. Oberholzer PA, Kee D, Dziunycz P, Sucker A, Kamsukom N, Jones R, et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. J Clin Oncol 2012;30:316-21.
22. Dummer R, Rinderknecht J, Goldinger SM. Ultraviolet A and photosensitivity during vemurafenib therapy. N Engl J Med 2012;366:480-1.
23. Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, DeMarini DJ, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:782-9.
24. Turke AB, Song Y, Costa C, Cook R, Arteaga CL, Asara JM, et al. MEK inhibition leads to PI3K/AKT activation by relieving a negative feedback on ERBB receptors. Cancer Res 2012;72:3228-37.
25. Smith TM, Gilliland K, Clawson GA, Thiboutot D. IGF-1 induces SREBP-1 expression and lipogenesis in SEB-1 sebocytes via activation of the phosphoinositide 3-kinase/Akt pathway. J Invest Dermatol 2008;128:1286-93.
26. Melnik BC. FoxO1—the key for the pathogenesis and therapy of acne? J Dtsch Dermatol Ges 2010;8:105-14.

Supplemental Table I. Adverse events grading system based on National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (v4.03: June 14th 2010)[18]

Grade 0	No adverse event
Grade 1	Mild adverse event (any of the following): • Minor • Mild symptoms and intervention not indicated • Nonprescription intervention indicated • No specific medical intervention • Asymptomatic laboratory finding only • Radiographic finding only • Marginal clinical relevance
Grade 2	Moderate adverse event (any of the following): • Intervention indicated • Minimal, local, noninvasive intervention (eg, packing, cautery) • Limiting instrumental ADL (eg, shopping, laundry, transportation, ability to conduct finances)
Grade 3	Severe adverse event (any of the following): • Medically significant but not life-threatening • Inpatient or prolongation of hospitalization indicated • Important medical event that does not result in hospitalization but may jeopardize the patient or may require intervention either ○ to prevent hospitalization or ○ to prevent the adverse event from becoming life-threatening or potentially resulting in death • Disabling - results in persistent or significant disability or incapacity ○ Limiting self-care ADL (eg, getting in and out of bed, dressing, eating, getting around inside, bathing, using the toilet)
Grade 4	Life-threatening adverse event (any of the following): • Life-threatening consequences • Urgent intervention indicated • Urgent operative intervention indicated • Patient is at risk of death at the time of the event if immediate intervention is not undertaken
Grade 5	Fatal adverse event: • Death

ADL, Activities of daily living.