Clinical and pathological characterization of tebentafusp-associated skin toxicity: A cohort study with 33 patients

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Background: Tebentafusp is a novel treatment for patients with metastatic uveal melanoma and often causes cutaneous side effects.

Objectives: The aim of this study was to better characterize these heterogenous cutaneous side effects.

Methods: This prospective cohort study evaluated all patients from a tertiary hospital center who were treated with tebentafusp between January 2019 and June 2023 clinically and assessed skin biopsies histologically.

Results: In total, 33 patients were analyzed. Skin toxicity was observed in 78.8% of patients and was classified into 5 clinical categories: (1) symmetrical erythematous patches (83.8%), (2) hemorrhagic macules (11.8%), (3) urticarial lesions (7.4%), (4) bullous lesions (1.5%), and (5) skin (8.5%) and hair depigmentation (11.4%). Histopathologic features were focal lymphocytic interface dermatitis with epidermal infiltration of CD8-positive lymphocytes. Patients with skin reactions had a significantly longer median overall survival compared to patients without any cutaneous events (34 versus 4 months, $P < .001$).

Limitation: Monocentric study with a limited number of patients.

Conclusion: Tebentafusp frequently induces cutaneous reactions. Pathogenesis is likely due to binding of tebentafusp to stimulated melanocytes in the skin, followed by infiltration and activation of lymphocytes. Development of treatment-induced skin reactions may be associated with survival benefits. (J Am Acad Dermatol 2024;91:1136-42.)

Key words: drug-associated rash; exanthema; gp100; rash; tebentafusp; uveal melanoma.

INTRODUCTION

Tebentafusp is a bispecific antibody and belongs to the new group of immune-mobilizing monoclonal T cell receptors against cancer (ImmTAC) approved by the U.S. Food and Drug Administration and European Medicines Agency for the therapy of

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Patient consent: The authors attest to obtaining written patient consent for publication of recognizable patient photographs or other identifiable material, with the understanding that this information may be publicly available.

IRB approval status: The study was approved by the institutional review board of the medical faculty of the Munich University Hospital (reference number 20-1122) and was conducted in accordance with the principles of the Helsinki Declaration.

Data availability: The main data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author upon reasonable request.

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patients with metastatic uveal melanoma and available in many countries including the United States, Australia, and Europe. It is composed of an HLA-A*02:01-restricted T cell receptor that is specific for the glycoprotein 100 (gp100) peptide and binds with a high affinity to gp100 positive cells, such as melanocytes, uveal melanoma, and cutaneous melanoma cells. After binding to tumor cells, the fused anti-CD3 single-chain variable fragment recruits and activates T cells, leading to the lysis of the tumor cells.

Although exhibiting very low response rates of 9%, tebentafusp has been shown in a phase 3 trial of patients with unresectable or metastatic uveal melanoma to improve survival, with 21.7 months of survival in the treatment group as compared to 16.0 months in the control-group.[1] Treatment-related adverse events include cytokine-related pyrexia (76%), chills (47%), hypotension (38%), and cutaneous side effects, the most frequent being exanthema (83%), pruritus (69%), and erythema (23%). Most of these side effects can be managed well with antipyretics, IV fluids, or topical corticosteroids.[2] Rarely, severe toxicity like tumor lysis syndrome has been observed.[3] Interestingly, the occurrence and severity of side effects are attenuated with repeated dosing. Thus, the current use, according to the prescribing information, is by escalating doses with subsequent inpatient monitoring for the first 3 infusions. In a real-life retrospective multicenter study, we observed skin toxicity in 53.8% of the patients, mostly being mild to moderate with grade 1 (59.5%) and grade 2 (35.7%) according to Common Terminology Criteria of Adverse Events version 5.0. Grade 3 skin toxicity was only reported in 2.4% of patients.[4]

In the first-in-human study, 84 HLA-A*02-positive patients with advanced melanoma (including cutaneous, uveal, and other origins), were treated with tebentafusp in different doses. Among all patients, 82% developed any side effects on the skin, which were not further specified and referred to as "rash." Of note, in a multivariate analysis, those patients survived longer than patients who did not experience any rash, independent of absolute lymphocyte count or prior anti-PD1 treatment (P = .003).[5] In a post hoc analysis of a phase I/II clinical study of tebentafusp in 42 patients with metastatic uveal melanoma, patients with skin toxicity of any grade within 7 days of the first dose (n = 24) were observed to have survived longer than patients without any observed skin reaction (n = 18), with a 1-year overall survival rate of 83% versus 44%. Skin toxicity in this study included the terms rash, pruritus, dry skin, pigment change, erythema, edema, and other changes.[6]

The analysis of the overall survival in patients in whom a rash of any grade had developed within 1 week after tebentafusp treatment initiation was the second primary objective of the phase III study, which included 149 patients who were randomized to the treatment arm with tebentafusp. Finally, onset of a rash within 1 week of treatment initiation was not identified as an independent predictor of overall survival in a multivariate Cox model.[1]

However, the term rash in this study included 40 different and heterogeneous terms, including eczema, erythema multiforme, excoriation, interstitial granulomatous dermatitis, lichenification, papules, psoriasis, seborrhea, solar dermatitis, and urticarial lesions, representing different skin lesions with individual etiology, involved cytokines and lymphocyte subsets, as well as histologic inflammatory patterns.[7]

For the clinical trials investigating tebentafusp, the majority of study sites were led by clinical oncologists and only few by dermatologists with supervision of 321 and 57 patients, respectively.

In our study, we aimed to characterize skin changes that occurred in patients during treatment with tebentafusp clinically and histologically and correlate them with outcome.

CAPSULE SUMMARY

- Skin toxicity was regularly observed in patients treated with tebentafusp but has not yet been described clinically and histologically.
- Skin toxicity can be classified into: symmetrical erythematous patches, hemorrhagic macules, urticarial lesions, bullous lesions, and skin/hair depigmentation. Histopathologic features were focal lymphocytic interface dermatitis with epidermal infiltration of CD8-positive lymphocytes.

PATIENTS AND METHODS

This prospective cohort study included all patients with metastatic uveal melanoma who were treated with at least one dose of tebentafusp at LMU University Hospital from January 2019 to June 2023.

Clinical data at baseline was assessed, including patients' demographics, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, sites of metastases, and previous tumor therapies.

Abbreviation used:

OS: overall survival

Patients who were treated with tebentafusp were hospitalized for the first 3 doses and observed for at least 16 hours. The interval between the doses was 7 days as stated in the prescribing information. Before discharge from the hospital, patients routinely underwent a whole-body examination and were checked for presence of skin changes by a board-certified dermatologist. Time of onset of rash, affected anatomical regions, clinical presentation, and accompanying symptoms were documented. No grading was performed for cutaneous toxicities. Photographs of the skin were taken. Skin biopsies were offered to all patients for routine diagnostic purposes and performed if patients gave their consent. Skin toxicity patients were defined as patients in which at least once erythematous patch after one or more of the first 3 doses of tebentafusp were observed.

Skin biopsies were assessed by H&E and with immunohistochemistry for CD3, CD4, CD8, Melan-A, SOX-10, and HMB-45.

Continuous data are presented as median or ranges and categorical data are presented as percentages. Continuous variables were compared using unpaired Student's t-test. Categorical variables were compared using Fisher's exact test. Overall survival (OS) was defined as the time between first dose of tebentafusp and date of death. For calculation of Kaplan-Meier estimate, survival times were censored at the last follow-up. Log-rank tests were performed to compare OS between the 2 groups. P values $< .05$ were considered statistically significant. Statistical analyses were conducted with SPSS Version 29.

RESULTS

Patients

A total of 33 patients who received treatment with tebentafusp were included in this study. Of these, skin symptoms were observed in 26 of 33 patients (78.8%). Median follow-up was 21.5 months for patients with skin toxicity and 3 months for patients without skin toxicity. Both groups were well balanced with regard to age, performance status according to Eastern Cooperative Oncology Group, metastatic sites, and preceding systemic tumor therapies. Imbalance with regard to sex and elevation of baseline lactate dehydrogenase above the upper limit of normal were observed (Table I).

Table I. Patients' characteristics

	Patients with skin toxicity	Patients without skin toxicity	
	n = 26	*n* = 7	*P*
Age, y			
Median	63.5	62	.484
Range	27-82	48-91	
Sex, no. (%)			
Male	10 (38.5)	7 (100.0)	.007
Female	16 (61.5)	0 (0.0)	
LDH			
Normal	17 (65.4)	0 (0.0)	.003
>ULN	9 (34.6)	7 (100.0)	
ECOG			
0	23 (88.5)	3 (42.9)	.023
1	3 (11.5)	4 (57.1)	
Metastases			
Hepatic only	15 (57.7)	3 (42.9)	.674
Hepatic and extrahepatic	11 (42.3)	4 (57.1)	
Preceding systemic tumor therapy			
Yes	7 (26.9)	1 (14.3)	.652
No	19 (73.1)	6 (85.7)	

ECOG, Eastern Cooperative Oncology Group; *LDH*, lactate dehydrogenase; *ULN*, upper limits of normal.

Clinical features

Altogether, 68 (64.7%) acute skin eruptions were documented after 105 doses of tebentafusp. The predominant anatomical areas in which skin changes were documented were the face (69.1%), the torso (67.6%), followed by the upper extremities (36.7%) and the neck (19.1%). Presence of skin changes on the lower extremities or genitals were observed in 4.4% and 2.9%, respectively. Skin eruptions were accompanied by itch in 47.1% of cases. In all patients, cutaneous eruptions occurred after the first dose of tebentafusp. After the second and third doses of tebentafusp, there was an increase or decrease in intensity or affected body surface area in 15.4% and 84.6%, respectively. Four patients reported recurring skin reactions after the first 3 doses, which gradually decreased in intensity and eventually ceased. The interval between tebentafusp dosing and first onset of skin eruption ranged from 3.5 to 7 hours (median 6.5 hours) in 6 patients, and in most cases (n = 19), skin changes were noted 20 hours after the infusion. There was no treatment discontinuation due to skin toxicities (Fig 1).

The clinical appearance of the skin eruptions was heterogeneous and a coexistence of different manifestations as observed simultaneously in certain patients. (1) Symmetrical erythematous patches on the face, neck, trunk, and/or arms

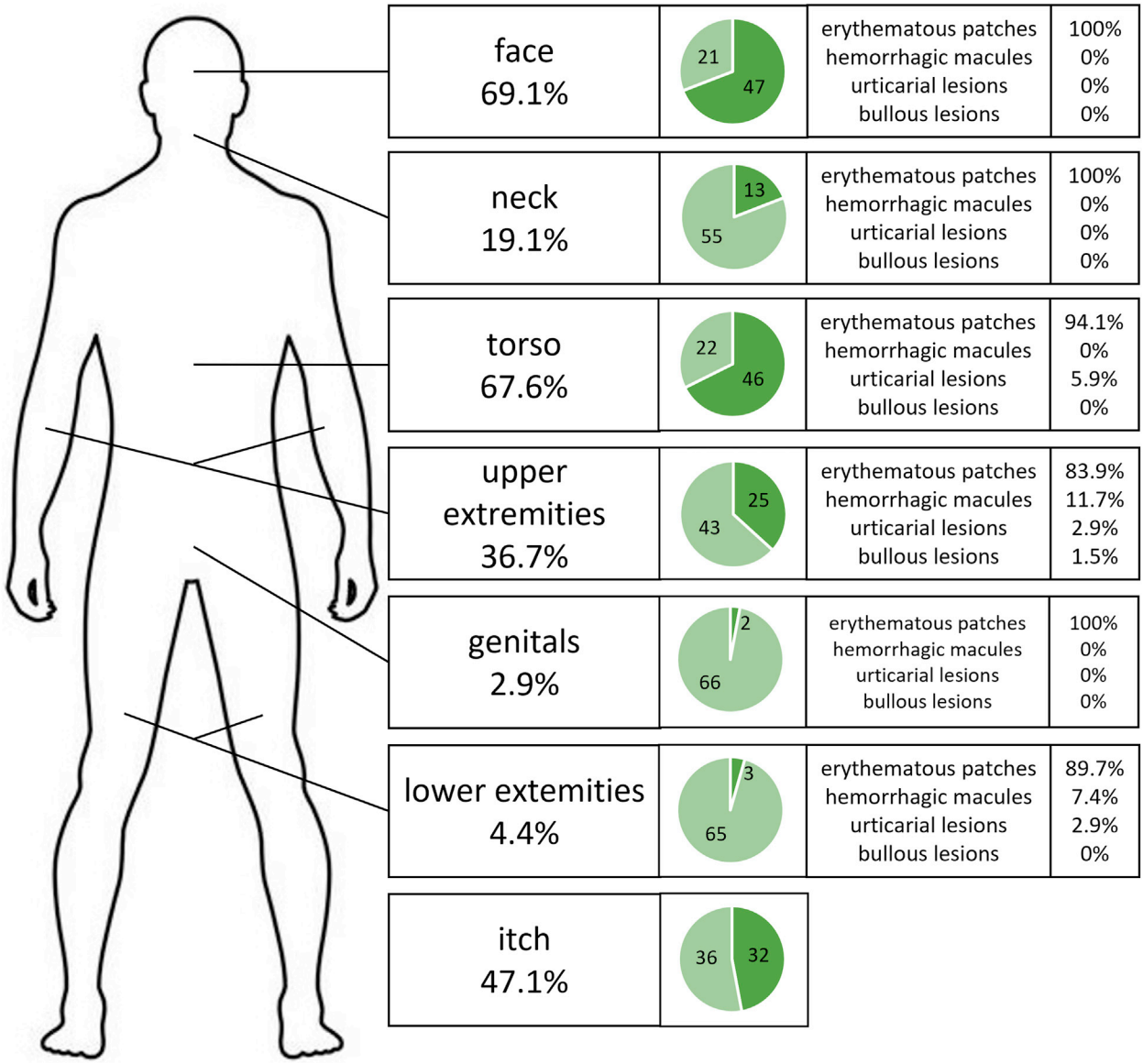

Fig 1. Frequency of skin changes in different anatomical areas. The numbers in the pie chart equate the absolute numbers of observed cutaneous reactions in the corresponding anatomical area (*dark green*) and the observed unaffected corresponding anatomical areas (*light green*).

were observed most frequently (57 of 68 skin eruptions, 83.8%). Involvement of the periorbital area was often accompanied with periorbital edema. (2) Hemorrhagic macules on the distal portion of the upper or lower extremities in 8 of 68 skin eruptions (11.8%). (3) Urticarial lesions were observed in 5 of 68 cases (7.4%), and (4) a bullous detachment of the skin was documented in one patient (1.5%, Fig 2).

Except for blistering changes, which took longer to heal and resulted in the formation of milia, all early skin eruptions resolved without sequelae until the next dosing 7 days later. Only patients with cutaneous symptoms were treated with topical corticosteroids. One patient with pre-existing vitiligo who was treated with tebentafusp had periorbital erythematous patches only in pigmented skin. The erythematous patches that occurred in another patient also spared the depigmented area around pre-existing Sutton nevi on the back.

During the course of treatment with tebentafusp, permanent changes in skin or hair pigmentation occurred. Circumscribed vitiligo-like depigmented macules and patches were observed in 3 patients (8.5%) after 8 to 19 weeks of treatment initiation. In 4 patients (11.4%), a depigmentation of ciliary hair,

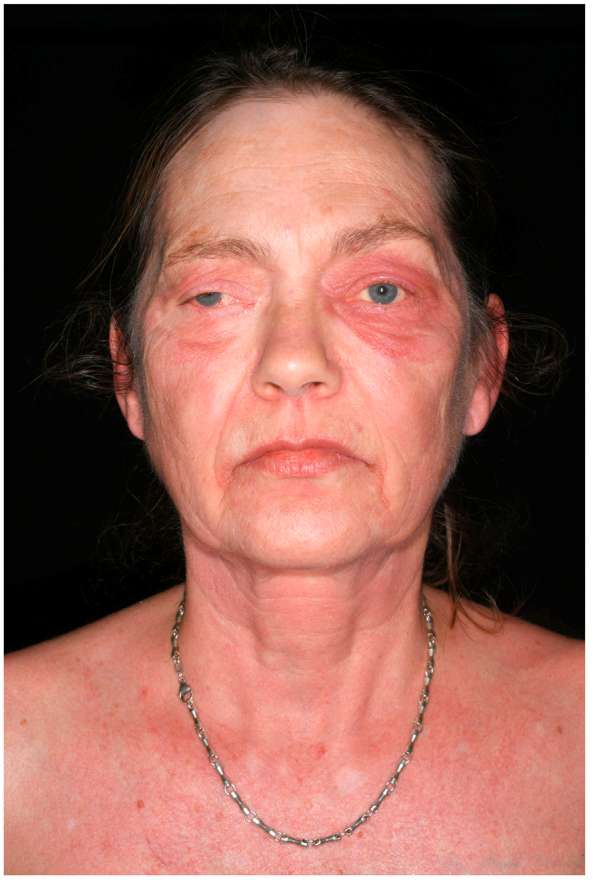

Fig 2. A female patient with typical erythematous patches in the face accompanied by swelling of the eyelids.

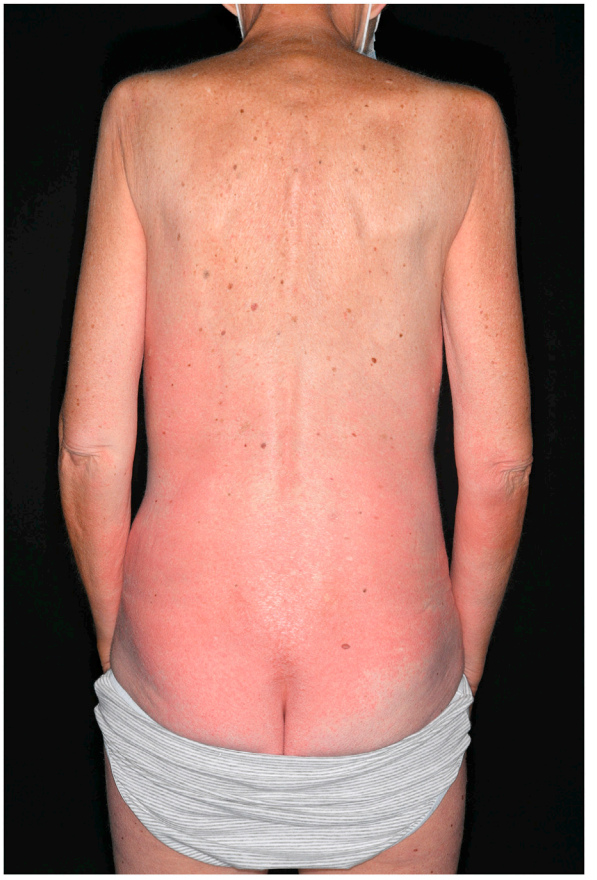

Fig 3. A female patient with erythematous patches on the lower back.

eyebrow hair, beard hair, scalp hair, and/or pubic hair was noticed 8 to 17 weeks after the beginning of therapy (Fig 3).

HISTOPATHOLOGIC FEATURES

In total, 14 skin biopsies were taken from patients with a cutaneous eruption after tebentafusp treatment. Of these, 11 were taken from erythematous patches. The specimen demonstrated a mild perivascular lymphocytic infiltration with a discrete, focal interface dermatitis in all cases (Fig 4). In 3 of the cases, the infiltrate also contained neutrophils, and in 2 of the cases, eosinophils. In immunohistochemistry, the lymphocytes stained positive for CD3 and demonstrated a CD4:CD8 ratio of approximately 5:1. CD8-positive lymphocytes were mainly detected in the epidermis, whereas CD4-positive lymphocytes were detected in the dermo-epidermal junction and around the blood vessels. Melan-A and SOX-10 immunostaining showed a regular staining of melanocytes in the basal layer of the epidermis in 4 specimens and a reduction or absence of Melan-A or Sox-10-positive cells in 5. Only a few HMB-45-positive cells were detected in 3 biopsies.

Two skin biopsies were taken from bullous lesions of the same patient. The perilesional skin showed extensive intracorneal neutrophilic abscesses and a mixed infiltrate in the dermis consisting of lymphocytes, neutrophils, eosinophils, and histiocytes. The biopsy from lesional skin demonstrated a subepidermal detachment with a mixed dermal infiltrate of lymphocytes, neutrophils, eosinophils, and histiocytes.

The skin biopsy that was taken from an urticarial lesion demonstrated a perivascular lymphocytic infiltrate with some eosinophils and neutrophils, focally also in the epidermis.

SURVIVAL

In this small cohort, the presence of treatment-associated skin reactions within the first 3 doses was correlated with a more favorable patient outcome. The median follow-up time was 15 months. All 7 patients without any skin symptoms died (100%) during follow-up, whereas in the skin toxicity group, only 8 deaths were observed (31%). The median overall survival (OS) of 34 months in patients with skin toxicity was significantly longer than the

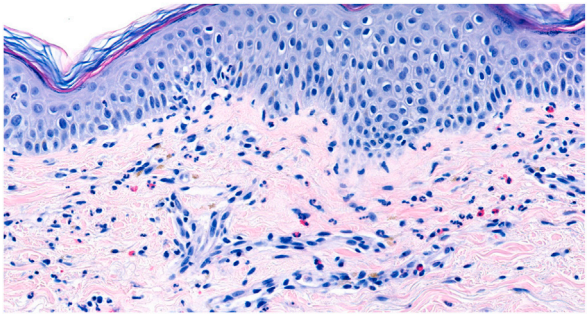

Fig 4. The main histologic reaction pattern showed perivascular lymphocytic infiltration and focal interface dermatitis (hematoxylin-eosin).

4 months in the patient group without skin reactions ($P < .001$).

DISCUSSION

In this clinical study with 33 patients with metastatic uveal melanoma who were treated with tebentafusp, a therapy-associated skin eruption was observed in 78.8% of patients and showed heterogenous clinical and histopathologic features. Skin eruptions could be classified into 5 clinical categories: (1) symmetrical erythematous patches, (2) hemorrhagic macules, (3) urticarial lesions, (4) bullous lesions, and (5) skin and hair depigmentation.

Skin biopsies of erythematous patches, which belonged to the predominant clinical pattern observed, revealed an epidermal infiltration of CD8-positive lymphocytes, and a focal lymphocytic interface dermatitis, which was in some cases accompanied by eosinophils or neutrophils. Immunohistochemistry staining revealed a reduced frequency or absence of melanocytes, which suggests the destruction of melanocytes by the cytotoxic lymphocytes. Of note, the patients with absence of Melan-A and SOX-10-stained melanocytes developed skin depigmentation during the course of treatment.

In early studies with tebentafusp, pathogenesis of the rash was assumed to be caused by targeting T cells to gp100-positive melanocytes.[5] Gp100 refers to the glycoprotein of 100 kDa and is a structural component of melanosomes. It is found in junctional and compound melanocytic nevi, mostly at the dermoepidermal junction, usually with diminished expression from top to bottom. It can be stained by HMB-45 in immunohistochemistry.[8] The expression of gp100 is dependent on melanocyte maturation stage and is low in normal skin and high in melanoma.[9] A clinical study in which normal human epidermal melanocytes were exposed to UVA and UVB showed that UVA radiation caused a slight induction of the activation marker HMB-45 in melanocytes, whereas UVB radiation led to a significant induction.[10] In our cohort, we observed a higher frequency of treatment-associated erythematous patches in sun-exposed skin like face and arms. This predilection might be explained by an UVB-associated melanocyte activation and consecutive binding of the tebentafusp-associated T cell receptor to the gp100 peptide on the stimulated melanocytes, which lead to infiltration and activation of lymphocytes by the fused anti-CD3 single-chain variable fragment.

Of note, in 2 patients with pre-existing skin depigmentation disorders, vitiligo and Sutton's nevi, which are characterized by a loss of melanocytes, the rash spared the depigmented areas and only occurred pigmented skin.[11,12] This observation contributes to the theory of melanocytes being the target of tebentafusp in the skin. However, whether the pathogenesis of the development of urticarial and bullous skin eruptions is caused by the same mechanism or whether hemorrhagic lesions are the consequence of cytokine release remains unclear and needs to be further investigated.

Skin eruptions from the first 4 categories only occurred during the first doses of tebentafusp treatment, were often accompanied by pruritus, and resolved without treatment after a few days. In contrast, pigment disorders were only observed after several weeks of treatment and remained permanently, even beyond the end of treatment with tebentafusp.

In contrast to the phase III study in which onset of rash was not found to be associated with improved OS,[1] patients in our study who developed skin reactions at least once after the first 3 doses of tebentafusp had a significantly longer median OS.

This study has limitations, including a monocentric cohort with restricted amount of patients.

To date, tebentafusp is approved for the treatment of uveal melanoma, which represents a rare tumor. It is currently being investigated for advanced cutaneous melanoma and might be applied more frequently in the future; therefore, knowledge and understanding of the pathogenesis of the tebentafusp-associated rash will be crucial for the treating oncologists and dermatologists.

We thank the patients who participated in this study.

Conflicts of interest

Dr Tomsitz reports consultancy, speaker fees, or travel grants: BMS, Roche, Novartis, Sanofi, Recordati, Kyowa Kirin, Sun Pharma, Recordati, and Pierre Fabre. Dr Heinzerling reports consultancy, speaker fees, travel grants, and/or research funding: BMS, MSD, Merck, Roche, Amgen, Curevac, Novartis, Sanofi, and Pierre

Fabre; clinical studies: BMS, MSD, Merck, Roche, Amgen, GSK, Curevac, and Novartis. Drs Kerl and French have no conflicts of interest to declare.

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JAAD Game Changer

JAAD Game Changers: Clinical and dermoscopic features of combined cutaneous squamous cell carcinoma (SCC)/ neuroendocrine [Merkel cell] carcinoma (MCC)

Jane M. Grant-Kels, MD

Original Article Information: Suarez AL, Louis P, Kitts J, et al. Clinical and dermoscopic features of combined cutaneous squamous cell carcinoma (SCC)/neuroendocrine [Merkel cell] carcinoma (MCC). *J Am Acad Dermatol*. 2015;73(6):968-975. https://doi.org/10.1016/j.jaad.2015.08.041

How did this article change the practice of dermatology?

- Merkel cell carcinomas (MCC), aggressive neuroendocrine skin cancers with no known cure, are nondescript and therefore hard to diagnose and can co-occur with non-MCC tumors, particularly squamous cell carcinoma (SCC).
- This report reviews clinical findings and long-term follow-up data from a series of cutaneous SCC/MCC in comparison with pure MCC and demonstrates the more aggressive nature of combined tumors compared with pure MCC.
- The clinical examination (marked scale and telangiectasia) and dermatoscopic findings (small dotted and short linear irregular peripheral vessels and central milky-red areas with large-diameter arborizing vessels) reported here for SCC/MCC will help in identifying this tumor type, reducing delays in diagnosis and treatment.

Conflicts of interest: None disclosed.

Note: A Game Changer is a short narrative stating how an article that originally appeared in *JAAD* changed the game of dermatology. The Game Changer author is not the author of the original article.

Funding sources: None.

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