Bei Plaque-Psoriasis und Psoriasis-Arthritis*

* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0.0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®.
2. Reich K et al. Lancet. 2019;394(10201):831-839.
3. Griffiths CEM et al. Poster Presentation Coastal Dermatology Symposium 2020, October 15-16th.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

TREMFYA® 100 mg Injektionslösung in einer Fertigspritze/ in einem Fertigpen. Wirkstoff: Guselkumab. **Zusammensetz.:** Fertigspritze/Fertigpen enth. 100 mg Guselkumab. Sonst. Bestandt.: Histidin, Histidinmonohydrochlorid-Monohydrat, Polysorbat 80, Sucrose, Wasser f. Injektionszw.. **Anw.geb.:** Für d. Bhdlg. erw. Pat. m. mittelschwerer bis schwerer Plaque-Psoriasis indiziert, d. für e. syst. Therapie in Frage kommen. Als Monotherapie od. in Komb. m. Methotrexat für d. Bhdlg. erw. Pat. m. Psoriasis-Arthritis indiziert, d. auf e. vorherige nicht-biolog. kranheitsmodifiz. antirheumat. (DMARD)-Therapie unzureich. angesprochen od. diese nicht vertragen haben. **Gegenanz.:** Schwerwieg. Überempfindl. gg. Guselkumab od. e. d. sonst. Bestandt., klin. relev. aktive Infektionen (einschl. aktive Tuberkulose), Schwangersch., Stillzeit. **Bes. Warnhinw. u. Vorsichtsmaßn.:** Um d. Rückverfolgbark. b. biolog. Arzneim. zu verbessern, sollten Name u. Ch.-Bez. d. verabreich. Prod. deutl. protokoll. werden. Vors. b. Infektionen, Tuberkulose, Impfungen (vor Anw. v. Lebendimpfst. muss d. Bhdlg. m. Tremfya nach d. letzt. Gabe f. mind. 12 Wo. ausgesetzt werden). B. Erhöh. v. Leberenzymwerten (ALT/AST) u. Verdacht auf arzneimittelinduz. Leberschädig. sollte d. Bhdlg. vorüberg. unterbr. werden. B. schwerwieg. Überempfindl.reakt. sollte d. Anw. v. Tremfya unverzügl. abgebrochen u. e. geeign. Bhdlg. eingel. werden. Frauen im gebärfäh. Alter sollen währ. u. f. mind. 12 Wo. nach d. Bhdlg. e. zuverläss. Verhütgs.meth. anw.. Arzneim. f. Kdr. unzugängl. aufbewahren. **Nebenwirk.:** *Sehr häufig* (≥ 1/10), *Häufig* (≥ 1/100 bis < 1/10), *Gelegentlich* (≥ 1/1.000 bis < 1/100). *Sehr häufig:* Atemwegsinfekt.. *Häufig:* Kopfschm., Diarrhoe, Arthralgie, Reakt. a. d. Injektionsst., Transamin. erhöht. *Gelegentlich:* Herpes-simpl-Infekt., Tinea-Infekt., Gastroenteritis, Überempfindl.reakt., Anaphylaxie, Urtikaria, Hautausschlag, Neutrophilenzahl erniedr.. Verschreibungspflichtig. **Pharmazeut. Unternehmer:** JANSSEN-CILAG International NV, Turnhoutseweg 30, B-2340 Beerse, Belgien. **Örtl. Vertreter für Deutschland:** Janssen-Cilag GmbH, Johnson & Johnson Platz 1, D-41470 Neuss. **Stand d. Inform.:** 12/2020.

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Clinical Letter

Four cases of erysipelas-like inflammation in patients with metastatic melanoma treated with checkpoint inhibitors

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Dear Editors,

Checkpoint inhibitors (CPI) can activate an antitumoral immune response [1]. Immune-related adverse effects (irAE) occur in more than 80% of CPI-treated patients [1–3]. Rare irAEs are often only detected at a late stage, and fatal outcomes have been described [4, 5]. Although monitoring and therapy of autoimmune side effects have led to increased safety, the range of newly discovered and described autoimmune phenomena is constantly increasing. We report on four patients receiving therapy with CPI for metastatic melanoma who developed an erysipelas-like inflammation in areas with cutaneous and subcutaneous metastases.

Case 1

A 71-year-old man presented with amelanotic melanoma metastasis (*BRAF* mutation V600E) with unknown primary. A lymph node dissection (LAD) showed that 4/22 removed lymph nodes had metastasized. After adjuvant radiotherapy of the supraclavicular, infraclavicular and left axillary lymphatic drainage pathways (total dose 60 Gy), adjuvant therapy with interferon-alpha was administered. Upon progression of the disease with osseous metastases, lymph node metastases and a pulmonary metastasis, treatment with encorafenib and binimetinib was initiated. The best response to this regimen was stabilization of the disease with subsequent progression, prompting treatment with nivolumab. Within 16 days of therapy initiation, a warm redness developed in the area of the cutaneous and subcutaneous metastases in the axilla, on the chest and on the left thoracic wall (Figure 1a). There was no leukocytosis, C-reactive protein was not elevated, and the patient did not have fever. Histological examination of a biopsy revealed dilated lymphatic vessels and

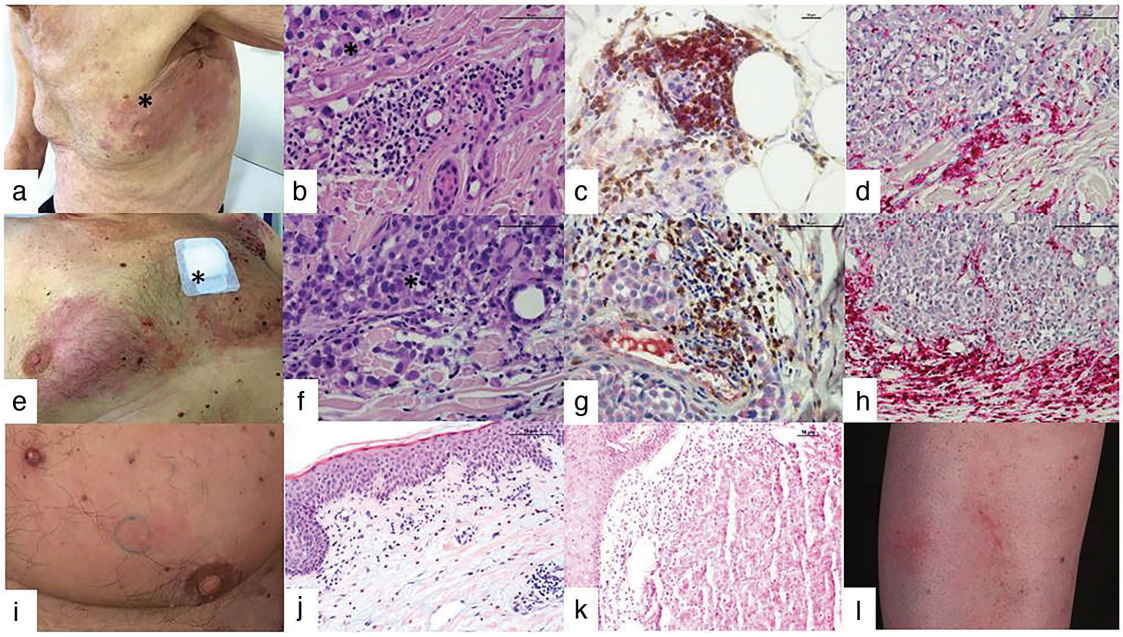

Figure 1 Patient 1 (a). Hematoxylin-eosin (HE)-staining of a biopsy specimen taken from the infiltrate (*localization of biopsy in (a)) (b). Immunohistochemistry, CD_4 (red), $FoxP_3$ (brown) (c). CD8-positive T cells (re) at the edge of an accumulation of melanoma cells (d). Patient 2 (e). HE-staining of a biopsy specimen taken from the infiltrate (*localization of biopsy in (e)) (f). Immunohistochemistry for CD_4 (red), and $FoxP_3$ (brown) (g). CD8-positive T cells (red) form a wall around a subcutaneous metastasis (h). Patient 3 (i). HE-staining of a tissue sample taken from the infiltrate (j). The infiltrate in (i) and (j) shows many eosinophils (k). Patient 4 (l).

a perivascularly accentuated, peritumoral T cell dominated inflammatory response with CD4+ Tregs (CD4+/FoxP3+) and CD8-positive cytotoxic T cells, without infiltrating tumor cells. Eosinophilic granulocytes were not observed in the infiltrate (Figure 1b–d). The histological findings provided no evidence of pathogen-induced inflammation. Even with dabrafenib and trametinib treatment and whole-brain radiotherapy, the disease progressed with a fatal outcome nine months after initiation of nivolumab therapy.

Case 2

In a 53-year-old patient with a primary on the left shoulder and left axillary lymph node metastasis, adjuvant radiotherapy (5 Gy) and adjuvant therapy with interferon-alpha was terminated upon progression of multiple cutaneous and subcutaneous in-transit metastases. Therapy with nivolumab was initiated, under which, after 41 days, a warm, flaring redness developed in the area of the metastases on the chest (Figure 1e). Histologically, a discrete infiltration of the tumor tissue by lymphocytes was observed, which could be characterized by immunohistochemistry as CD4+ Tregs (CD4+/FoxP3+). CD8-positive T cells appeared to wall in conglomerates of melanoma cells, but did not infiltrate them (Figure 1h). There was no infiltration by eosinophil granulocytes (Figure 1e–h). After three months, therapy was discontinued due to disease progression. The patient showed no response to subsequent therapies (chemotherapy with carboplatin and paclitaxel and electrochemotherapy). The patient died six months later.

Case 3

In an 80-year-old patient, disseminated metastases appeared on the flank almost two years after excision of the breast primary. Intralesional interleukin-2 therapy was discontinued after one week due to poor tolerability. Four weeks after termination of the IL-2 injections, therapy with pembrolizumab was initiated. After 31 days, redness and hyperthermia developed in the area of the cutaneous and subcutaneous metastases (Figure 1i). A biopsy from this area showed an infiltrate with abundant eosinophils, both in the tumor itself (Figure 1k) and in its extensions (Figure 1j). The best response to this therapy was a partial remission that lasted for two years. Pembrolizumab treatment was discontinued. One year later, there was a renewed progression of the left axillary lymph node metastases. Re-exposure to pembrolizumab failed to achieve further remission. Figure 2 shows the percentage of eosinophilic granulocytes throughout this process.

Case 4

A 44-year-old woman was diagnosed with melanoma of the back of the foot, at the same time micrometastases in three

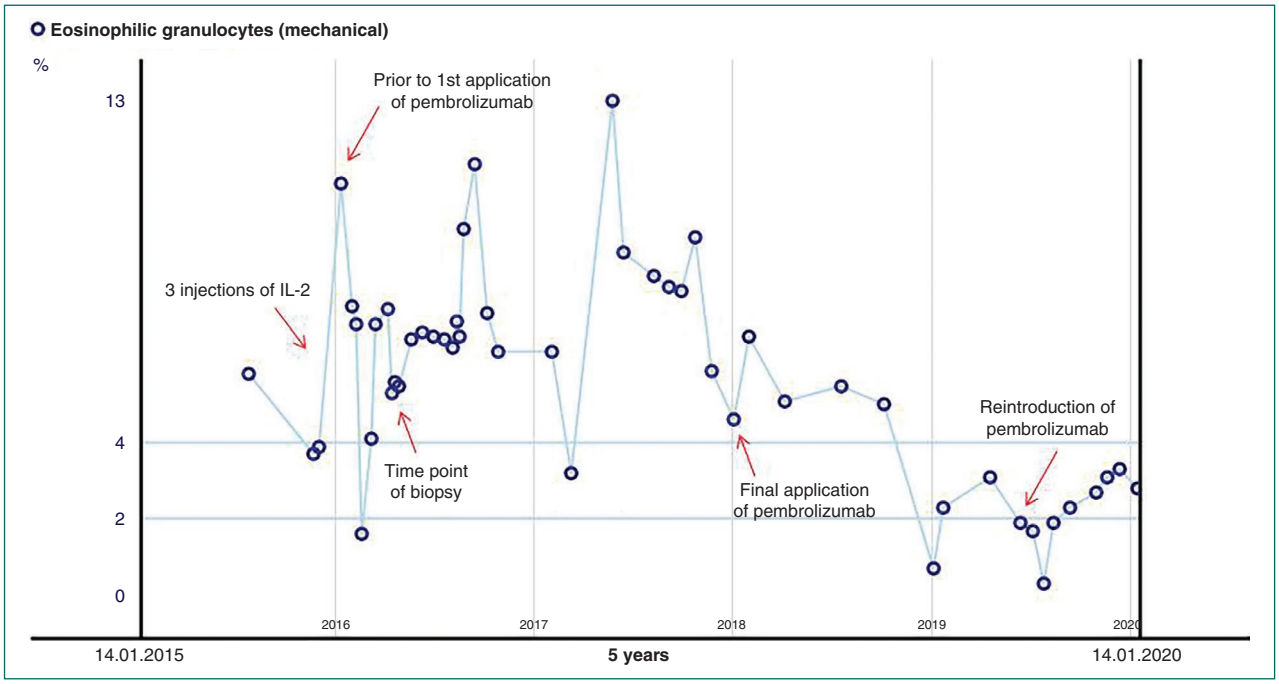

Figure 2 Eosinophils in percent (x-axis) over time (y-axis) in Patient 3.

inguinal lymph nodes were observed. After excision of the primary and LAD, adjuvant therapy with interferon-alpha was administered. During this time, inguinal, iliac and obturatorial in-transit metastases and lymph node metastases arose and were operated on and adjuvantly irradiated (55 Gy). A few months later, multiple cutaneous and subcutaneous metastases formed on the leg; in addition, inguinal lymph node metastases appeared. Combination therapy with dacarbazine and topical dinitrobenzene was followed by four rounds of immunotherapy with ipilimumab. Dabrafenib and trametinib were administered upon disease progression, resulting in a transient response. Upon suspicion of a developing resistance, treatment was switched to pembrolizumab. After 28 days, a flaring, hyperthermic redness developed along the entire right leg (Figure 1l) with simultaneous occurrence of pulmonary metastases. At no time was there a constellation of infection. A biopsy of the erythematous area was not performed. Pembrolizumab therapy was supplemented by the administration of ipilimumab, resulting in a mixed response. The redness persisted mainly in the area of the responsive metastases. Upon progression the patient was administered treatments with vemurafenib and cobimetinib as well as carboplatin and paclitaxel, none of which produced a response. The patient died as a result of tumor progression.

Table 1 summarizes the characteristics of all four patients.

Discussion

We describe erysipelas-like inflammation in four patients who received immunotherapy with CPI for advanced melanoma. All patients developed a flaring redness in the area of the cutaneous and subcutaneous metastases within weeks of therapy initiation, suggestive of a bacterial infection as in erysipelas or an intralymphatic spread of melanoma cells as in erysipelas melanomatosum. In three patients tissue samples of the erythematous area were taken.

Whereas erysipelas melanomatosum is defined by the infiltration of dermal lymphatic vessels by melanoma cells, erysipelas-like inflammation is understood to be clinically similar to erysipelas [6]. Erysipelas melanomatosum can appear long after diagnosis of the primary tumor and may be a sign of progression or recurrence [7, 8]. Often, the clinical picture is of an orange peel-like thickening of the skin. Papular and nodular changes in the sense of a cutaneous or subcutaneous metastasis are often visible, histologically appearing as tumor cell aggregates. An infection is often suspected in cases of erysipelas-like inflammation. Histologically, varyingly dense intratumoral or peritumoral infiltration by T lymphocytes of different immunophenotypes, without tumor cell invasion in lymphatic vessels, can be observed. The composition of the infiltrate excludes suppurative inflammation. It is important to differentiate infiltrates from cutaneous autoimmune side effects caused by pembrolizumab or nivolumab, which occurs in 15–26% of cases and which may appear locally rather than in a generalized manner [9, 10]. Histologically, such exanthema displays CD4-positive and melan-A-specific CD8-positive T cells in the vicinity of apoptotic melanocytes [10].

In the patients presented here, erythema in the area of the cutaneous or subcutaneous metastases generally appeared within the first four weeks (range 16–41 days) of therapy with pembrolizumab or nivolumab. Three of our patients were men. In these, the thorax was always affected. In two men (Patients 1 and 2) the disease progressed rapidly. Biopsies of the erysipelas-like inflamed skin showed T cell infiltrates, predominantly composed of regulatory T cells. Tumor infiltrating cytotoxic T lymphocytes were not represented. Where CD8-positive T cells were present, these surrounded the melanoma formations without infiltrating them. Patient 3 responded to immunotherapy; in his case, the infiltrate was mainly eosinophilic. Corresponding eosinophilia was found in the blood, which became manifest and persisted following intralesional administration of interleukin-2. Upon recurrence and repeated administration of pembrolizumab, to which no new response was observed, an increase in eosinophilic granulocytes ensued, though not to the same extent as previously seen. In Patient 4, no biopsy was taken from the erythematous area that developed after PD-1 blockade. It is noteworthy, however, that erythema occurred mainly in areas of responsive metastases and not in areas where only stabilization or progression was observed. The extent to which pre-therapies have an effect on the development of erysipelas-like inflammation is unclear. In three cases, however, radiotherapy and therapy with interferon-alpha had been performed previously, and in one case a short-term intralesional application of interleukin-2 had been conducted. A recall phenomenon after radiotherapy seems unlikely, since the erythemas were found far beyond the irradiated areas. Animal experimentation has shown that a combination of radiotherapy and PD-1 blockade can lead to tumor cell resistance, caused by regulatory T cell expansion [11]. In Patients 1 and 2, this type of resistance is conceivable. The clinical picture of erysipelas-like inflammation under therapy with CPI may form the basis of various, histologically differentiable inflammation patterns. Immunohistological characterization of biopsies with infiltrate from erythematous tissue enables further classification and allows statements to be made on immunotherapy responsiveness.

Acknowledgements

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Table 1 Clinical and histological characteristics of the patients.

Patient	Sex	Age at first diagnosis of melanoma	Histological type of primary tumor	Tumor depth (mm)	Primary tumor ulceration	Mutation status	Localization of the primary tumor	Localization of the erysipelas-like inflammation	PD-1 blockade with	Days between initial application of the checkpoint inhibitor and appearance of erysipelas-like redness	Best response to checkpoint inhibition	Pre-therapy with
1	m	71	MUP	–	–	*BRAF* V600E, *NRAS* wt, c-*KIT* wt	Unknown	Chest	Nivolumab	16	PD	Irradiation Interferon-α
2	m	53	SSM	5,5	Yes	*BRAF* wt, *NRAS* wt, c-*KIT* wt	Upper back	Chest	Nivolumab	41	PD	Irradiation Interferon-alpha
3	m	80	SSM	2,2	No	*BRAF* wt, *NRAS* wt, c-*KIT* wt	Chest	Chest	Pembrolizumab	31	PR	Intralesional Interleukin-2
4	f	44	NM	7,0	Yes	*BRAF* V600E, *NRAS* wt, c-*KIT* wt	Foot	Leg	Pembrolizumab	28	PR	Irradiation Interferon-α DTIC + DNCB Ipilimumab Dabrafenib + Trametinib

Abbr.: MUP, melanoma of unknown primary; SSM, superficial spreading melanoma; NM, nodular melanoma; wt, wild type; PD, progressive disease; PR, partial remission.

Conflict of interest

Claudia Pföhler declares consultancy or advisory fees from Novartis, BMS, Roche, MSD, Amgen, Merck Serono and Pierre Fabre. Jessica Hassel declares consultancy or advisory fees from MSD, Sunpharma and BMS. Research Funding to Institution was obtained from BMS. Lucie Heinzerling declares consultancy or advisory fees from BMS, Roche, Novartis, MSD, Amgen, Curevac, Sanofi, Pierre-Fabre. Research funding to institution was obtained from Novartis. Cornelia Müller received advisory fees from UCB.

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