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ORIGINAL ARTICLE

Cutaneous manifestations induced by check point inhibitors in 120 melanoma patients—The European MelSkinTox study

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Abstract

Background: Checkpoint inhibitors provide an effective approach for the melanoma treatment. They prolong lymphocyte effects, which explains the cytotoxicity underlying immune-related adverse events (irAEs). Cutaneous irAEs affect nearly 40% of PD-1i and 50% of CTLA4i-treated patients. Severe cutaneous irAE do not often occur but could be life-threatening and may persist despite treatment discontinuation.

Methods: We aimed to investigate cutaneous irAEs in a cohort of patients treated with ICI across Europe in an effort to characterize the reactions in a real-world, phase IV, post-marketing study using a follow-up questionnaire.

Data since November 2016 until March 2021 were obtained from the Melskintox database, a European multicentric biobank dedicated to the follow-up of melanoma and cutaneous adverse events, supported by EADO. The dermatoses reported were pooled into four categories: inflammatory dermatosis, bullous diseases, drug-related eruptions and pigmentary diseases.

Results: Inflammatory benign dermatoses ($n=63$) represented the most common group of reactions (52.5%), followed by drug-related eruptions ($n=24$, 20%),

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pigmentary diseases ($n=23$, 19.2%) and bullous diseases ($n=10$, 8.3%). Grade II ($n=41$, 34.2%) are represented by bullous pemphigoid, eczema, hypodermatitis, lichenoid eruption, maculopapular rash, pruritus, psoriasis-like rash, urticarial eruption and vitiligo. Grade III ($n=18$, 15.0%) are represented by bullous pemphigoid, lichenoid eruption and rashes. Grade IV ($n=2$, 1.7%) is only represented by bullous disease. Most cutaneous irAEs led to immunotherapy continuation ($n=95$, 88.0%). CR is associated with more severe the cutaneous irAEs. We report an average time-to-onset of 208 days and some late-onset events.

Conclusion: Our study has characterized the clinical spectrum of cutaneous irAEs, their timing and severity and their relationship with tumour response. Grade I–II cutaneous irAE are easily managed allowing ongoing anticancer treatment. Severe late-onset cutaneous irAE are not uncommon. A dermatological follow-up helps mitigate the risk of life-threatening adverse events. These findings highlight the importance of oncodermatological involvement in management of patients with melanoma receiving immunotherapy.

INTRODUCTION

Cutaneous melanoma develops from pigment-containing cells known as melanocytes¹ and represents nearly 2%–3% of all cancers²; it is a highly aggressive cancer but has been shown to be highly responsive to immunotherapy, especially immune checkpoints inhibitors (ICI).³

Immune checkpoints regulate the outcome of lymphocyte engagement with antigen-presenting cells and tumour cells.⁴ They downmodulate the intensity of the adaptive immune response, thus providing a new gold standard in the treatment of metastatic melanoma.^{3,5}

PD-1 inhibits the proliferation of immune cells that downmodulate effector functions^{6,7} and promotes self-tolerance.¹ Engagement of PD-1 by PD-L1 leads to the inhibition of T cell receptor–mediated lymphocyte proliferation and cytokine secretion,⁸ and consequently increased tolerance.

Checkpoint inhibitors (ICI) such as ipilimumab (CTLA-4 inhibitor) or nivolumab or pembrolizumab (PD-1 inhibitors) provide an effective approach⁹ for the melanoma treatment preventing cancer cells from evading immune detection and then enabling their destruction.¹⁰

Immune-related adverse events and cutaneous adverse events

Treatment by ICI prolong lymphocyte effects, which explains the cytotoxicity underlying irAE. The irAE are graded according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE displays grades I (asymptomatic or mild symptoms) through 5 (death related to AE) with unique clinical descriptions of severity for each AE. Nearly 70% of patients receiving ICI will experience an irAE and of those nearly 10% will experience severe irAE (grade III–IV).^{11,12} The occurrence of severe irAE may be as high as 55%–60% with combination immunotherapies.¹³

These may have varying phenotypes and may involve multiple organs, including the skin. Most adverse events occur during or after the first cycle of treatment at a median time of 40 days¹⁴ and include gastrointestinal, rash, hyperglycaemia, thyroiditis, hepatitis and musculoskeletal disorders.¹⁵

Cutaneous irAEs in ICI-treated patients with metastatic melanoma affect nearly 40% of PD-1i and 50% of CTLA4i-treated patients.^{11,12} Severe cutaneous irAE do not often occur and are reported in under 3% of patients¹³; however, these irAE may be life-threatening and may persist despite treatment discontinuation.¹⁶ Pruritus, eczema and vitiligo are the most frequent skin manifestations reported with ICI use, across all cancers.

Recently, the EADV task force ‘Dermatology for cancer patients’ has edited phenotype-specific treatment recommendations for cutaneous irAEs including levels of evidence and grades of recommendation.¹⁷

Rationale and aim of the study

Cutaneous irAE are probably underestimated and diagnosis is often delayed because of a lack of recognition. If diagnosed early, cutaneous irAE—particularly lower intensity grade I–II reactions—may be managed without interruption of anti-cancer treatment. ICI may result in severe grade III–IV cutaneous manifestations in the absence of previous skin pathology and rapid diagnosis is crucial. Recognition and management of all grade cutaneous irAE is important, as this may facilitate continuation of ICI for anti-cancer treatment.¹³

The clinical presentations of cutaneous irAE are diverse and our knowledge of their clinical course, pathophysiology and impact on disease course is poorly understood.

We aimed to investigate cutaneous adverse events in a cohort of patients treated with ICI across Europe in an effort to characterize the reactions in a real-world, phase IV, post-marketing study using a follow-up questionnaire.

MATERIALS AND METHODS

Data on patients with advanced melanoma since November 2016 until March 2021 were obtained from the Melskintox database, a European multicentric biobank dedicated to the follow-up of melanoma patients and cutaneous adverse events, supported by the European Association of Dermato Oncology (EADO). The study complies with the ethical standards resulting from the Declaration of Helsinki. An information sheet was given to each patient to collect their consent to the study, and none of them refused to participate.

The Melskintox database gathers data from 21 participating centres in different European countries (France $n=39$, United Kingdom $n=21$, Italy $n=20$, Serbia $n=17$, Austria $n=15$, Greece $n=4$, Belgium $n=2$ and Germany $n=2$) represented by different dermatological unit all around Europe as Nantes ($n=33$), Rome Catholic University ($n=19$), Belgrade ($n=17$), London NHS ($n=16$), Vienna ($n=13$), Paris APHP ($n=6$), London ($n=5$), Athens ($n=4$), Brussel ($n=2$), Graz ($n=2$), Tuebingen ($n=2$) and Modena ($n=1$).

The inclusion criteria were as follows:

- Patients with unresectable stage IV melanoma
- Patients treated with anti-PD-1 or combination therapy
- Patients who experienced cutaneous irAE with the administered immunotherapy.

We only included patients in whom the drug was started for clinical indication in real life experience. Atezolizumab, cemiplimab and avelumab delivered in melanoma clinical trials ($n=10/130$) have been excluded. Patients who received intravenous anti-PD-1 or a combination of PD-1 and anti-CTLA4 or anti-LAG3 were selected and the type, occurrence of cutaneous adverse events were analysed thanks a questionnaire. All cutaneous adverse events have been registered.

It is a prospective study for which a questionnaire was filled in to characterize the dermatosis and follow its evolution. Data were collected by an oncodermatologist at onset of the cutaneous adverse event (i.e. at inclusion of patients) and at 3, 6 and 12 months after the onset. Templates are given in [Appendix 1](#).

The cutaneous adverse events reported were pooled into four categories as follows:

- *Benign inflammatory dermatosis*: psoriasis vulgaris; inverse psoriasis; pruritus; sarcoidosis cutis; lichen planus; urticarial eruption; acneiform rash; photosensitive eruption; xerosis; lichenoid eruption; folliculitis; prurigo; eczema; eczema; palmoplantar hyperkeratosis
- *Bullous diseases*: Steven–Johnson–Lyell syndrome/toxic epidermal necrolysis; bullous pemphigoid
- *Drug-related maculopapular rashes*: maculopapular eruption; morbilliform rash; papulomatous rash
- *Pigmentary diseases*: vitiligo.

Grades III and IV cutaneous IrAEs were pooled in the analysis.

Skin biopsies were not routinely performed since clinical presentation was considered sufficient for diagnosis in most cases.

The primary endpoint of our study was to describe and characterize cutaneous adverse events induced by checkpoint inhibitors, type and delay of appearance. In a second time, we studied tumoral response regarding type and grades of cutaneous irAEs. Each delay of appearance of cutaneous irAEs was studied regarding sub-types of dermatitis to determine if some sub-types of dermatitis have special issue and need special follow-up.

Statistical analysis

Baseline characteristics are presented as n (%) for categorical data.

The associations of response to treatment and of tumour grade with sex, type of lesion and treatment strategy were evaluated in two sequential bivariate analyses by the chi-squared test with simulated p -value. The value of p was computed by Monte Carlo simulation when the chi-square test conditions for validity were not met.

The associations between the grade (independent variable) and the response to treatment at 3rd and 6th month assessments (dependent variable) were evaluated by two multinomial logistic regression models and odds ratios (ORs) and corresponding 95% intervals were calculated. Considering the sample size and the relatively high number of classes of grade and response variables, no adjustment variable was included in the final model.

All analyses were realized on R (version 4.2.1) and Rstudio (2022.07.1).

RESULTS

A total of 120 patients were recruited across the centres between November 2016 and March 2021: Nantes ($n=33$, 27.5%), Rome Catholic University ($n=19$, 15.8%), Belgrade ($n=17$, 14.2%), London NHS ($n=16$, 13.3%), Vienna ($n=13$, 10.8%), Paris APHP ($n=6$, 5.0%), London ($n=5$, 4.2%), Athens ($n=4$, 3.3%), Brussel ($n=2$, 1.7%), Graz ($n=2$, 1.7%), Tuebingen ($n=2$, 1.7%) and Modena ($n=1$, 0.8%).

Immunotherapies included PD-1i (pembrolizumab $n=52$, 43.3%, nivolumab $n=43$, 35.9%) or CTLA-4i (ipilimumab $n=2$, 1.7%) or combination of immunotherapies (nivolumab + ipilimumab $n=20$, 16.7% and nivolumab+relatlimab $n=3$, 2.5%). There was no statistical difference between all these immunotherapies.

Male:female ratio was 2.75 (88/32) that is, 73.3% of males of 120 cases.

Inflammatory benign dermatoses ($n=63$) represented the most common group of reactions (52.5%), followed by drug-related maculopapular rashes ($n=24$, 20.0%), pigmentary

diseases ($n=23$, 19.2%) and bullous diseases ($n=10$, 8.3%). The diversity of cutaneous events under immunotherapy is represented in [Figures 1](#) and [2](#).

Of the 120 cases, 49.2% ($n=59$), 34.2% ($n=41$), 15.0% ($n=18$) and 1.7% ($n=2$) were grade I, grade II, grade III and grade IV cutaneous adverse events, respectively. Grade II ($n=41$, 34.2%) were represented by bullous pemphigoid, eczema, hypodermatitis, lichenoid eruption, maculopapular rash, pruritus, psoriasis-like rash, urticarial eruption and vitiligo. Grade III ($n=18$, 15.0%) were represented by bullous pemphigoid, dry skin, lichenoid eruption, maculopapular rash, morbilliform rash and psoriasis-like rash. Grade IV ($n=2$, 1.7%) was only represented by bullous disease.

Most cutaneous irAEs led to immunotherapy continuation ($n=95$, 88.0%). The first tumour assessment 3 months after cutaneous event reported partial response (PR, $n=39$, 34.2%), followed by stable disease (SD, $n=36$, 31.6%), progression (PD, $n=25$, 21.9%) and complete response (CR, $n=14$, 12.3%).

Grades III–IV were significantly associated with partial response (PR), stable disease (SD) and progressive disease (PD) at 3 and 6 months with all OR <1 which means making a non-complete response after immunotherapy is protective from severe cutaneous irAEs. These results were summarized in [Table 1](#).

The effects of clinicopathological factors on tumour response to immunotherapy at 3 and 6 months and grade of cutaneous irAEs were assessed by bivariate analysis and are presented in [Tables 2](#) and [3](#), respectively.

CR was numerically associated with more severe the cutaneous irAEs: the percentage of CR rose from 5.3% for

grade I irAEs to 12.8% for grade II and 31.6% for grade III/IV irAEs, $p=0.100$. These results were similar for the 6 months assessment.

The proportion of presentations with bullous disease increased with increasing irAE grade (1.7%, 12.2% and 20.0%, respectively, for grade I, grade II and grade III + IV), whereas vitiligo significantly decreased (30.5%, 9.8% and 5.0%, respectively, grade I, grade II and grade III + IV).

Treatment of cutaneous irAEs was summarized in [Table 4](#).

We pooled all cutaneous irAEs into three categories according to time of onset after implementation of immunotherapy: late-onset events occurring 1 year or more; early events occurring less than 3 months; and medium-onset events occurring at >3 months to <1 year.

We found an average time-to-onset of 208 days that is, 7 months and mean time-to-onset of 140 days [0; 1222] i.e., 4.7 months [0; 40.7].

Late-onset events occurred in 25 cases (20.8%); early events in 44 (36.6%); and medium onset events in 51 (42.5%) cases.

There was no association between time-of-onset of cutaneous events and the tumour response to immunotherapy ($p=0.522$ at 3 months and $p=0.5658$ at 6 months) as shown in [Table 5](#).

There was no association between the time-of-onset of cutaneous events and the type of cutaneous event (inflammatory benign dermatoses, pigmentary disease, bullous disease or drug-related maculopapular rash), $p=0.128$ ([Table 6](#)). Inflammatory diseases were more likely to appear early whereas vitiligo is more often a medium-onset event.



FIGURE 1 Clinical pictures of skin adverse reaction to immunotherapies: (a, b, c) palmo-plantar lichenoid eruption; (d) maculopapular rash; (e) psoriasis-like palmar hyperkeratosis, courtesy of Dr. Ketty Peris.

DISCUSSION

Our study confirms the diversity of cutaneous irAE and describe the way to manage these adverse events. Inflammatory diseases are more likely to appear early whereas vitiligo is more often a medium-onset event. Complete response is associated with severe cutaneous irAE.

Adverse events are commonly observed in melanoma patients treated with ICI, and almost 10%–20% of patients experience grade III–IV irAE.^{11,12} The most common adverse events are gastrointestinal or pulmonary.^{12,18} In our real-world study focused on cutaneous irAEs, we reported mainly 24 rashes most of which morbilliform rashes, 23 vitiligo, 19 psoriasiform, 15 lichenoid, 8 eczematous, 6 bullous, 6 urticarial eruptions and only 1 Steven–Johnson–Lyell syndrome/toxic epidermal necrolysis overlap syndrome.

We report a sex ratio of 2.7 (88/32, 73% of males), which is higher to Bottlaender et al.¹⁹ which reported 57.7% of males.

In cancer centres, ICI are commonly administrated by oncologists and metastatic melanoma treatment does not routinely involve dermatologists. Cutaneous irAEs may therefore not be systematically recognized and diagnosed. Rash is a widely misused term by oncologists which has a very precise definition in dermatology. Our data provide an argument to routinely involve organ specialists in oncological treatment: this would facilitate early diagnosis and

treatment of cutaneous irAEs, and continuation of ICI treatment.¹³ Consistent with this we show that low-grade cutaneous irAE are usually easily managed and patients are less likely to discontinue treatment.

In the literature of the approval studies and in former literature, cutaneous irAEs were the most common side-effects of anti-PD-1 or anti-CTLA-4 up to 50% of the patients suffer from pruritus and rash with very few grade III–IV adverse skin reactions.^{20–22} However, these cutaneous irAEs were poorly described. Previous real-life studies reported cutaneous irAE in of 8% to 49%.^{19,23} The most common reactions in these two large series were eczematous eruptions (38% and 9.5%, respectively), and vitiligo (26% and 8.5%, respectively).^{19,23} In our real-life study, we identified vitiligo in 19% ($n=23$) of cases and the prevalence of rashes ($n=24$, 20%) and eczemas ($n=8$, 6%), was similar. We found no difference in occurrence of cutaneous irAE between various ICI or combination treatment, whereas other studies reported that anti-CTLA4 therapy is associated with higher rates of cutaneous irAE than anti-PD1 therapies.¹³ Our real-life study reports a different incidence rate of cutaneous irAEs from the one in literature of the approval studies. It highlights the importance of characterization and reporting of these reactions in a real-world, phase IV, post-marketing to make our scientific knowledge evolve with more hindsight.

Rates of grade III–IV cutaneous irAE have been reported in 1%–4% of patients receiving CTLA-4i²⁴ and 0.6% ($n=3/496$) of those receiving PD-1i immunotherapy.²³ Grade III–IV cutaneous irAE reached 0.6% (3/496) were represented by lichenoid skin reaction and Sweet syndrome in Hofmann study,²³ whereas Bottlaender et al.¹⁹ reported more severe or life-threatening grade cutaneous effects (around 2.6%, 5/189). We found around 15% ($n=18$) of grade III and 1.7% of grade IV cutaneous irAE. As we did, Bottlaender et al., Hofmann and Gault¹³ reported that higher grade cutaneous irAE lead to the interruption ICI therapy.

Our study suggests a positive association between high-grade cutaneous irAE and complete response to treatment as we reported 5.4%, 12.8% and 31.6% of complete response rates, respectively, with grades I, II and III–IV irAE. However, these elements must be considered with caution, because the longer the duration of drug use (correlating with longer OS), the greater the possibility of any adverse event, including severe irAE, occurring. Given the mechanism of action of ICI, which promotes T-cell activation and enhances T-cell activity, it is plausible that immune-related irAE are

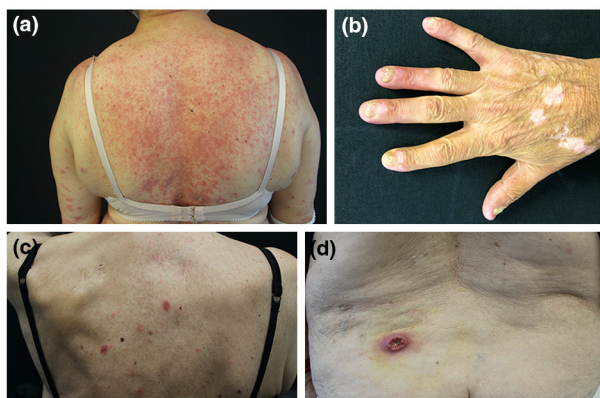


FIGURE 2 Clinical pictures of skin adverse reaction to immunotherapies: (a) relapse and worsening of previous psoriasis; (b) lichenoid nail dystrophy and vitiligo-like eruption; (c) neutrophilic sweet-like eruption; (d) pyoderma gangrenosum, courtesy of Dr. Ketty Peris.

TABLE 1 OR (95%CI) for immunotherapy response at first and second assessment after cutaneous event according to grade, with CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

	3rd month assessment		6th month assessment	
	Grade II	Grades III and IV	Grade II	Grade III and IV
CR	Ref	Ref	Ref	Ref
PR	0.42 [0.08; 2.05]	0.12 [0.02; 0.68]	0.44 [0.10; 1.99]	0.11 [0.02; 0.60]
SD	0.47 [0.09; 2.3]	0.11 [0.02; 0.65]	0.57 [0.013; 2.58]	0.09 [0.02; 0.54]
PD	0.24 [0.04; 1.33]	0.13 [0.02; 0.78]	0.43 [0.09; 2.14]	0.18 [0.03; 0.93]

TABLE 2 Association of tumoral response at first and second assessment with tumour characteristics, bivariate, with irAEs: immune-related adverse events; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

	Tumour response at 3 months					Tumour response at 6 months					<i>p</i>
	CR	PD	PR	SD	SD	CR	PD	PR	SD	SD	
<i>n</i>	14	25	39	36	34	16	24	35	34	34	
Sex = male (%)	11 (78.6)	19 (76.0)	28 (71.8)	26 (72.2)	24 (70.6)	11 (68.8)	18 (75.0)	26 (74.3)	24 (70.6)	24 (70.6)	0.959
<i>Type of cutaneous irAEs (%)</i>											0.428
Inflammatory benign dermatosis	7 (50.0)	13 (52.0)	24 (61.5)	18 (50.0)	16 (47.1)	8 (50.0)	14 (58.3)	22 (62.9)	16 (47.1)	16 (47.1)	0.447
Bullous diseases	3 (21.4)	3 (12.0)	1 (2.6)	2 (5.6)	1 (2.9)	3 (18.8)	3 (12.5)	1 (2.9)	1 (2.9)	1 (2.9)	
Pigmentary diseases	1 (7.1)	3 (12.0)	8 (20.5)	9 (25.0)	9 (26.5)	3 (18.8)	3 (12.5)	6 (17.1)	9 (26.5)	9 (26.5)	
Drug-related maculopapular rashes	3 (21.4)	6 (24.0)	6 (15.4)	7 (19.4)	8 (23.5)	2 (12.5)	4 (16.7)	6 (17.1)	8 (23.5)	8 (23.5)	
Treatment of cutaneous irAEs (%) ^y	11 (78.6)	21 (84.0)	25 (64.1)	25 (69.4)	23 (64.7)	12 (75.0)	19 (79.2)	24 (68.6)	23 (64.7)	23 (64.7)	0.651
<i>Cutaneous irAEs resolution (%)</i>											0.288
Improvement	4 (36.4)	11 (55.0)	16 (72.7)	14 (56.00)	12 (54.5)	5 (45.5)	10 (52.6)	16 (69.6)	12 (54.5)	12 (54.5)	
Progression	0 (0.0)	1 (5.0)	2 (9.1)	1 (4.0)	2 (9.1)	0 (0.0)	1 (5.3)	1 (4.3)	2 (9.1)	2 (9.1)	
Resolved	7 (63.6)	8 (40.0)	4 (18.2)	11 (40.0)	8 (36.4)	6 (54.5)	8 (42.1)	6 (26.1)	8 (36.4)	8 (36.4)	
<i>Grades of event</i>											0.100
Grade I	3 (21.4)	15 (60.0)	20 (51.3)	18 (50.0)	18 (52.9)	4 (25.0)	13 (54.2)	20 (57.1)	18 (52.9)	18 (52.9)	
Grade II	5 (35.7)	6 (24.0)	14 (35.9)	14 (38.9)	13 (38.2)	5 (31.2)	7 (29.2)	11 (31.4)	13 (38.2)	13 (38.2)	
Grade III or IV	6 (42.9)	4 (16.0)	5 (12.8)	4 (11.1)	3 (8.8)	7 (43.8)	4 (16.7)	4 (11.4)	3 (8.8)	3 (8.8)	
<i>Action taken on IT after cutaneous irAEs (%)</i>											0.651
Continuation	9 (90.0)	20 (87.0)	32 (86.5)	29 (87.9)	25 (83.3)	10 (83.3)	19 (86.4)	31 (91.2)	25 (83.3)	25 (83.3)	
Discontinuation	1 (10.0)	2 (8.7)	2 (5.4)	3 (9.1)	2 (6.7)	2 (16.7)	3 (13.6)	1 (2.9)	2 (6.7)	2 (6.7)	
Interruption	0 (0.0)	1 (4.3)	3 (8.1)	1 (3.0)	3 (10.0)	0 (0.0)	0 (0.0)	2 (5.9)	3 (10.0)	3 (10.0)	

TABLE 3 Association between tumour grades and type of cutaneous event, and follow-up, bivariate, with CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

	Grade I <i>n</i> = 59	Grade II <i>n</i> = 41	Grade III + IV <i>n</i> = 20	<i>p</i>
Sex = Male (%)	46 (78.0)	27 (65.9)	15 (75.0)	0.397
<i>Event (%)</i>				0.006
Inflammatory benign dermatosis	28 (47.5)	26 (63.4)	9 (45.0)	
Bullous diseases	1 (1.7)	5 (12.2)	4 (20.0)	
Pigmentary diseases	18 (30.5)	4 (9.8)	1 (5.0)	
Drug-related maculopapular rashes	12 (20.3)	6 (14.6)	6 (30.0)	
Treatment of cutaneous irAES (%)	34 (57.6)	32 (78.0)	18 (90.0)	0.009
<i>Cutaneous irAES resolution (%)</i>				0.103
Improvement	16 (50.0)	21 (70.0)	8 (47.1)	
Progression	0 (0.0)	2 (6.7)	2 (11.8)	
Resolved	16 (50.0)	7 (23.3)	7 (41.2)	
<i>Action taken on IT after cutaneous irAES (%)</i>				<0.001
Continuation	54 (94.7)	31 (91.2)	10 (58.8)	
Discontinuation	2 (3.5)	2 (5.9)	4 (23.5)	
Interruption	1 (1.8)	1 (2.9)	3 (17.6)	
<i>Response at 3M (%)</i>				0.100
CR	3 (5.4)	5 (12.8)	6 (31.6)	
PD	15 (26.8)	6 (15.4)	4 (21.1)	
PR	20 (35.7)	14 (35.9)	5 (26.3)	
SD	18 (32.2)	14 (35.9)	4 (21.1)	
<i>Response at 6M (%)</i>				0.065
CR	4 (7.3)	5 (13.9)	7 (38.9)	
PD	13 (23.6)	7 (19.4)	4 (22.2)	
PR	20 (36.4)	11 (30.6)	4 (22.2)	
SD	18 (32.7)	13 (36.1)	3 (16.7)	

Bold values are significant when $p < 0.05$.

associated with better response of the tumour to ICI therapy. Vitiligo induced by ICI is a favourable prognostic factor in patients with melanoma.²⁵ This may be as a result of melanocyte destruction by autoreactive CD8⁺ T cells. Vitiligo is due to T cells infiltration, also involved in microenvironment of tumour, and explaining a better response to immunotherapy.²⁵ More broadly, it has been reported that any cutaneous irAE are significantly associated with a better overall survival,¹⁹ and we may assume, associated with enhanced response to immunotherapy.

Severe late-onset irAE have been described with a median onset time of 128 days for all organ-grade III–IV irAEs.²⁶ In our study, we report a median onset time of 208 days for all-grades cutaneous irAEs suggesting that appearance of cutaneous irAE could be delayed. Gault et al.¹³ reported a delay of appearance of 10 months for eczematous reactions and 50 days for psoriasis. It seems to be consistent with our study since we reported respectively 46.6% and 34.9% of inflammatory diseases which occur early (i.e. within the first 3 months of treatment) or medium-onset (i.e. after 3 months

and before 1 year). However, as we pooled all inflammatory cutaneous irAEs, we did not distinguish delay of appearance psoriasis from other inflammatory dermatosis.

We found that nearly 21% of cutaneous irAE were late-onset events appearing more than a year after immunotherapy initiation. Such late-onset irAEs may be difficult to formally impute as resulting from ICI, and are difficult to distinguish from coincidental dermatological disease.¹³ Drug-related rashes (20%) and bullous conditions (8.3%) are more likely to be life-threatening adverse effects and could appear more than 1 year after treatment initiation in patients with a long treatment duration.

It highlights the value of long-term dermatological follow-up after immunotherapy. Because the longer immunotherapy is administered, the higher the risk of a drug associated rash, the potential late-onset grade III–IV cutaneous irAEs encourages discontinuation of immunotherapy when oncological conditions permit.²⁶ It should be noted that discontinuation of immunotherapy must always be weighed against the risk of melanoma, since

TABLE 4 Description of treatment used to recover cutaneous irAEs regarding the type of cutaneous event.

	Inflammatory benign dermatosis	Bullous diseases	Pigmentary diseases	Drug-related maculopapular rashes
No Treatment of cutaneous irAEs received	11	0	20	5
Treatment of cutaneous irAEs received	53	10	2	19
Topic steroids or TS + emollients	27 (8 bethametasone; 7 NS; 4 mometasone; 2 MPA; 2 clobetasol; 1 triamcinolone; 1 diflucortolone + emollient; 1 clobetasone + emollient)	2 (2 clobetasol)	0	7 (3 bethametasone; 2 NS; 1 diflucortolone; 1 mometasone)
Antihistamine	4 (1 chloropyramine; 1 desloratadine; 1 cetirizine; 1 desloratadine + hydroxyzine)	0	0	5 (2 desloratadine; 1 cetirizine; 1 chloropyramine; 1 cetirizine + desloratadine)
Topic steroids + antihistamine	4 (2 bethametasone + cetirizine; 1 clobetasol + chlorphenine + emollient; 1 TS NS + desloratadine + hydroxyzine)	0	1 (1 mometasone + cetirizine)	3 (2 bethametasone + desloratadine; 1 diflucortolone + desloratadine)
Antibiotics	2 (1 lymecycline + prednisone; 1 lymecycline + benzoyl peroxide)	0	0	0
Steroids	7 (2 methylprednisolone + bethametasone; 2 prednisolone + cetirizine + fexofenadine + hydroxyzine + clobetasol; 1 prednisolone + mometasone; 1 prednisolone; 1 prednisone)	5 (2 methylprednisolone; 1 prednisolone; 1 methylprednisolone + prednisolone + hydrocortisone; 1 prednisone + TS NS)	0	1 (1 methylprednisolone + clobetasol + prednisolone)
Immunosuppressive treatment	0	3 (1 rituximab + methylprednisolone; 1 methotrexate + prednisolone + doxycycline; 1 methotrexate + salazopyrin + UVB therapy)	1 (1 tacrolimus)	1 (1 tacrolimus + prednisolone + bilastine)
Vitamin D + topic	3 (2 enstilar + emollient; 1 calcipotriol + bethametasone)	1 (1 Dovobet + emollient)	0	0
Retinoids	3 (1 acitretin + mometasone; 1 acitretin + daivobet; 1 keracutan + UVA therapy)	0	0	0
Other systemic treatment	1 (1 apremilast)	0	0	0
Emollient	1	0	0	2

Note: Diprosone as betamethasone; Elocom as mometasone; Advantan as Methylprednisolone aceponate (MPA); Dermoval and Clarelux as Clobetasol; Nerisone as Diflucortolone; trimovate as clobetasone; Aeries as desloratadine; Atarax as hydroxyzine; eumovate and dermovate as clobetasol; Tetralysal as lymecycline; cortancyl as prednisone; Eclaran as benzoyl peroxide.

Abbreviations: NS, non-stipulated; TS, Topic steroids.

TABLE 5 Association of delay of appearance of cutaneous irAEs with tumoral response, with CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

	Early-onset event		Medium-onset event		Late-onset event		<i>p</i>
	At 3 M <i>n</i> (%)	At 6 M <i>n</i> (%)	At 3 M <i>n</i> (%)	At 6 M <i>n</i> (%)	At 3 M <i>n</i> (%)	At 6 M <i>n</i> (%)	
CR	5 (11.4)	5 (11.6)	8 (16.7)	9 (19.6)	1 (4.5)	2 (10.0)	0.522
PD	12 (27.3)	12 (27.9)	10 (20.8)	10 (21.7)	3 (13.6)	2 (10.0)	0.5658
PR	16 (36.4)	14 (32.6)	15 (31.3)	14 (30.4)	8 (36.4)	7 (35.0)	0.5658
SD	11 (25.0)	12 (27.9)	15 (31.3)	13 (28.3)	10 (45.5)	9 (45.0)	0.5658

TABLE 6 Association of delay of appearance of cutaneous irAEs with type of cutaneous irAEs.

	Early-onset event <i>n</i> (%)	Medium-onset event <i>n</i> (%)	Late-onset event <i>n</i> (%)	<i>p</i>
Inflammatory benign dermatosis (<i>n</i> = 62)	29 (65.9)	22 (43.1)	12 (48.0)	0.12
Bullous diseases (<i>n</i> = 7)	2 (4.55)	6 (11.8)	2 (8.0)	
Pigmentary diseases (<i>n</i> = 23)	3 (6.82)	13 (25.9)	7 (28.0)	
Drug-related maculopapular rashes (<i>n</i> = 19)	10 (22.7)	10 (19.6)	4 (16.0)	

Bold values are significant when $p < 0.05$.

the risk of grade III-IV cutaneous toxicity is more often smaller than risk of death of stage III-IV melanoma. It suggests increased monitoring even after immunotherapy is discontinued.

CONCLUSIONS

In conclusion, our European multi-centre prospective cohort of patients with melanoma has characterized the clinical spectrum of cutaneous irAEs, their timing and severity and their relationship with tumour response. We show that grade I-II cutaneous irAE are easily managed allowing ongoing anti-cancer treatment and avoid potential progression to grade III-IV irAE that may lead to treatment discontinuation.

We reported late-onset events which means cutaneous side effects may appear a long time after the immunotherapy has been stopped or a long time after its initiation. When the cutaneous irAEs occurs at a later stage than the discontinuation of the immunotherapy, it is not easy to distinguish between a cutaneous side effect and a dermatosis with another aetiology.

This pleads for a reinforced dermatological follow-up, either by an oncodermatologist, or via a care pathway where the oncologist is linked with a dermatologist. These findings highlight the importance of specialist oncodermatological involvement in management of patients with melanoma receiving immunotherapy.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request or from the Melskintox data scientist in charge: julie.cassecuel@chu-nantes.fr.

ETHICAL STATEMENT

The study complies with the ethical standards resulting from the Declaration of Helsinki. An information sheet was given to each patient to collect their non-opposition to the study, and none of them was opposed to it. The patients in this manuscript have given written informed consent to the publication of their case details.

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APPENDIX 1

Templates of formula

**MELSKINTOX: Cutaneous rash induced by check point inhibitors
INCLUDING GRADE I-II-III-IV
Initial report**

Date ___/___/___

Center No. _____

Patient code number _____

Year of birth: _____ Sex M F

Previous anti cancer treatment (name of the drug)	Treatment start date	Treatment dose	Treatment schedule dose	Treatment end date	Cutaneous or other AE related to treatment		If YES CTCAE grade *				
					Yes	No	1	2	3	4	5
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Current anti cancer treatment (name of the drug)	Treatment start date	Treatment dose	Treatment schedule dose	Treatment end date	AE other than skin related to treatment		If YES CTCAE grade *				
					Yes	No	1	2	3	4	5
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*AE should be classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 or new VS when published)

1. Does the patient have a medical history of:

- Autoimmune disease NO YES Unknown if yes, what type? _____
- EBV infection NO YES Unknown
- HIV infection NO YES Unknown
- HSV6 infection NO YES Unknown
- Previous skin disease (except melanoma) NO YES Unknown if yes, what type? _____

Skin AE:

2. Date of onset: ___/___/___

CTCAE grade 1 2 3 4 5

VERSION 4 10/MAY/2017

3. Aspect of cutaneous lesions related to drug eruption (please tick one or more box) with grading of cutaneous lesions according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 or new V 5.0 when published)

	NO	YES	If YES CTCAE grade				
			1	2	3	4	5
Aspect of Steven-Johnson- Lyell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aspect of Sweet's syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aspect of DRESS syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aspect of erythema multiforme	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vasculitis-like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bullous disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lichenoid eruption	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acneiform rash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Urticarial eruption	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psoriasis-like rash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Erythema nodosum-like eruption	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vitiligo	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Morbilliform rash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other: Please provide a detailed dermatological description of the skin manifestation if you would like to point out any other specific aspect/sign/symptom: ----- ----- -----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 4. Location:** head/neck
 anterior trunk
 posterior trunk
 upper extremities
 lower extremities

- 5. Surface involved**
 covering <10% BSA
 covering 10 - 30% BSA
 covering >30% BSA

- 6. Involvement of** palms NO YES CTCAE grade 1 2 3 4 5
Soles NO YES CTCAE grade 1 2 3 4 5

- 7. Nail involvement:** NO YES CTCAE grade 1 2 3 4 5
If yes, please provide a description of the nail abnormalities:

- 8. Hair involvement**
Alopecia NO YES CTCAE grade 1 2 3 4 5
Modification of the structure or color of hair NO YES CTCAE grade 1 2 3 4 5

9. Mucosal involvement NO YES

	NO	YES	If YES CTCAE grade				
			1	2	3	4	5
Eye	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mouth	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genitalia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. Pruritus NO YES If yes: mild moderate severe
CTCAE grade 1 2 3 4 5

11. Burning NO YES If yes: mild moderate severe
CTCAE grade 1 2 3 4 5

12. Scaling/dryness NO YES If yes: mild moderate severe
CTCAE grade 1 2 3 4 5

13. Photosensitivity NO YES If yes: mild moderate severe
CTCAE grade 1 2 3 4 5

-- Location on sun-exposed areas (e.g. face, back of the hands): _____

-- Extension to sun protected area NO YES

Note: _____

14. Photographic documentation NO YES if yes, specify the date: _____

15. Associated Systemic symptoms

	NO	YES	If YES CTCAE grade				
			1	2	3	4	5
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Arthralgia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diarrhea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Others: please specify ----- -----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

16. Associated biological abnormalities

	NO	YES	If YES CTCAE grade				
			1	2	3	4	5
Renal failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Elevation in aminotransferase	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hyper eosinophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lymphopenia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thrombopenia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Others: please specify ----- -----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

17. Biological Material

- Skin biopsy NO YES if Yes specify date of biopsy: ___/___/___

- Histopathologic diagnosis _____

- Bacterial samples NO YES if Yes specify date of bacterial samples: ___/___/___

Results _____

- Cutaneous tests (Patch, Pricks) NO YES if Yes specify date of cutaneous tests: ___/___/___

Results _____

- Phototests NO YES if Yes specify date of phototests: ___/___/___

Results _____

- Others: _____ NO YES if Yes specify date of tests: ___/___/___

Results _____

18. Material in biobank for future studies

Signed consent NO YES

Frozen tissue NO YES

Formalin tissue NO YES

Blood Sample NO YES

19. Treatment of cutaneous lesions:

Date	Drug/surgery	Treatment schedule (dosage and time)	Result / Comments

20. Impact on melanoma treatment:

Continuation NO YES

Discontinuation NO YES

Reduction NO YES

Interruption NO YES

Resumption after discontinuation NO YES

Please email the document within 1 week of adverse event onset to Nantes onco-dermatology department to julie.cassecul@chu-nantes.fr

In case of medical discussion, you can send an email to ibtissam.moustaghfir@chu-nantes.fr

Brief follow-up forms will be sent at 3, 6 and 12 months

**MELSKINTOX: Cutaneous rash induced by check point inhibitors
INCLUDING GRADE I-II-III-IV
Follow-up at 3 months**

Date __/__/__

Center No.

Patient code number

Year of birth:

Sex M

F

Cutaneous adverse event

Resolved? NO YES

If yes, date __/__/__

With Without sequelae

If no, precise current grade _____

Impact on melanoma treatment:

Continuation NO YES

Discontinuation NO YES

Reduction NO YES

Interruption NO YES

Resumption after discontinuation NO YES

Is the patient still treated with immunotherapy NO YES

Is the patient still alive NO YES

Did the patient have any other cutaneous toxicity? NO YES

If yes, what type? _____

Please email the document to Nantes onco-dermatology department to julie.casseciel@chu-nantes.fr

In case of medical discussion, you can send an email to ibtissam.moustaghfir@chu-nantes.fr

Brief follow-up forms will be sent at 6 and 12 months

**MELSKINTOX: Cutaneous rash induced by check point inhibitors
INCLUDING GRADE I-II-III-IV
Follow-up at 6 months**

Date ___/___/___

Center No. _____

Patient code number _____

Year of birth: _____ Sex M F

Is the patient still treated with immunotherapy NO YES

Is the patient still alive NO YES

Did the patient have any other cutaneous toxicity? NO YES

If yes, what type? _____

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Brief follow-up forms will be sent at 12 months

**MELSKINTOX: Cutaneous rash induced by check point inhibitors
INCLUDING GRADE I-II-III-IV
Follow-up at 12 months**

Date ___/___/___

Center No. _____

Patient code number _____

Year of birth: _____ Sex M F

Is the patient still treated with immunotherapy NO YES

Is the patient still alive NO YES

Did the patient have any other cutaneous toxicity? NO YES

If yes, what type? _____

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In case of medical discussion, you can send an email to lucie.peuvrel@chu-nantes.fr