Clinical associations and classification of immune checkpoint inhibitor-induced cutaneous toxicities: a multicentre study from the European Academy of Dermatology and Venereology Task Force of Dermatology for Cancer Patients

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Bulleted statements

What's already known about this topic?

- Cancer patients treated with different immune checkpoint inhibitors carry an increased risk of developing various types of skin toxicities.

What does this study add?

- In this multicentric cohort study we showed that immune checkpoint inhibitor_related skin toxicities do not share a unanimous pattern and may depend on several factors, including the specific agent administered, as well as the underlying malignancy.
- Among patients with macular rash, vitiligo and multiple skin toxicities patients received immune checkpoint inhibitors more frequently for melanoma than for NSCLC
- The combination of ICI and chemotherapy compared to ICI monotherapy occurred to a lesser extent in patients with psoriatic rash, lichenoid and eczematous reactions compared to patients with pruritus.
- Clinical awareness and specialized dermatologic consultation should be advocated.

Abstract

Background: Cutaneous immune-related adverse events (irAEs) represent the most frequent toxicities induced by immune checkpoint inhibitors (ICI).

Objectives: To investigate clinical associations of cutaneous toxicities induced by different ICI therapies.

Methods: Multi-centric retrospective international cohort study of cancer patients, who developed cutaneous irAEs under ICI. Rates and basic characteristics analysis of all cutaneous toxicities and identification of any associations, using univariate and multivariate models were performed.

Results: 762 patients who developed 993 cutaneous toxicities were included. Forty different types of skin toxicities were identified. Psoriasis (175 patients, 23%) and pruritus (171 patients, 22.4%) were the most common toxicities followed by macular rash (161 patients, 21.1%) and eczematous-type reactions (150 patients, 19.7%).
Multivariate analysis showed that among patients with macular rash, vitiligo, and multiple toxicities, patients with melanoma received ICI more frequently than for NSCLC. Moreover, anti-CTLA4 was less frequent than anti-PD1 treatment in patients with macular rash (OR 0.11, 95%CI 0.01 - 0.76) and vitiligo (OR=0.07, 95%CI 0.006 – 0.82). The same significant association was shown in patients with psoriasis (OR 0.08, 95%CI 0.02- 0.31) , lichenoid (OR 0.15, 95%CI 0.03 – 0.77) and eczematous reactions (OR 0.24, 95%CI 0.07 – 0.78), all compared to pruritic rash, who received combination of ICI plus chemotherapy and compared to ICI monotherapy.

Conclusions: Our study showed that skin-oriented toxicities do not share a unanimous pattern and are related to several factors, including the specific agent administered and the underlying malignancy treated. Follow-up plans should be individualized, in order to minimize the risk for severe reactions that could compromise optimum therapeutic outcome.

Introduction

Immune checkpoint inhibitors (ICI) have been approved for the treatment of various types of cancer – including non-small cell lung cancer (NSCLC), renal cell carcinoma, melanoma and non-melanoma skin cancers –, becoming a significant weapon in the armamentarium of late-stage cancer therapies. They are characterized by a unique pattern of action which aims to enhance the host's immune response against cancer. However, these same properties of ICI are responsible for a novel group of adverse events, also known as immune related adverse events (irAEs). Approximately 60% of patients receiving immunotherapy will experience at least one irAE during, or even after their course of treatment, mainly involving diarrhoea, colitis, hepatitis, mucosal-cutaneous reactions, and thyroid dysfunction.[1] Considering these agents have been approved as a first-line treatment for a wide range of malignancies, irAEs attributed to ICI management have turned into a growing challenge of great clinical importance.
Cutaneous toxicities are among the most common irAEs events in patients treated with ICI.[2] Although cutaneous life-threating reactions remain exceptional, they may lead to treatment interruption or even discontinuation and may have a significant negative impact on patients' quality of life.[3] Lichenoid dermatitis, eczematous reaction, maculopapular rash, pruritus, vitiligo, bullous pemphigoid, and psoriasis are the most frequently reported cutaneous toxicities.[4] However, a remarkably wide range of uncommon skin reactions have also been reported. In this large, multicentric study conducted by the EADV-Task Force of Dermatology for Cancer Patients, we aimed to identify the clinical characteristics and the overall incidence of each skin toxicity among cancer patients with cutaneous irAEs and to identify clinical associations for each toxicity.

Methods

The design of this study was a multi-centric retrospective analysis of, cutaneous toxicities induced by immune checkpoint inhibitors, under the EADV-Task Force of Dermatology for Cancer Patients. Eleven Oncodermatology Units from Greece (3), Italy (4), Spain (3) and Argentina (1) participated. All centers provided all cases of irAEs attributed to ICI referred to each department in a specific time frame, set by each center individually (all between 2016-2020, from 6 months to 5 years, Suppl Table 1). ICI drugs included in this study were Anti – CTLA4 (ipilimumab 5mg/ml), Anti- PD-1 [Pembrolizumab (25mg/ml), Nivolumab (10mg/ml), Cemiplimab (50mg/ml)], Anti- PD-L1 [Atezolizumab (60mg/ml), Avelumab (10 mg/ml), Durvalumab (50mg/ml)]. Each regime was administered as per the EMA established dosing scheme for the malignancy indication. The severity of cutaneous toxicities was based on the Common Terminology Criteria for Adverse Events, version 5 (CTCAEv5) and was classified as grade-1 (<10% Body Surface Area [BSA], mild), grade-2 (10-30% BSA, moderate), grade-3 (>30% BSA, severe) and grade-4 (life-threatening consequences, urgent intervention needed).[5] Pruritus was defined likewise, as grade-1 (mild or localized), grade-2 (widespread and intermittent skin changes from scratching, such as excoriations and lichenification), and grade-3 (widespread and constant, limiting self-care, activities of daily living [ADL] or sleep). The CTCAEv5 grade of each case was the highest one recorded during patient's follow-up.

Patients' characteristics (i.e., age, gender), type of immunotherapy and combination treatments, the type of cancer, the number and types of cutaneous toxicities and the number of ICI doses until the event were recorded for each patient. Lichenoid reaction was determined as a clinical rash resembling lichen planus, characterized by pink-violaceous papules with an overlying white network of scale, and/or lichenoid lesions in mucosal membranes. Eczematous reactions were defined as erythematous or erythematosquamous plaques or crusted macules and papules that coalesce into plaques, accompanied by pruritus and macular rash as erythematous morbilliform, maculopapular rash on the trunk and /or extremities. The remaining cutaneous irAEs (e.g. vitiligo, psoriasis) were diagnosed based on typical clinical manifestations. Pathohistological confirmation was performed when necessary.

Statistical analysis

First, a descriptive analysis was conducted in order to calculate the mean and standard deviation of continuous variables and the frequencies of categorical variables. Also, in order to investigate different associations between toxicities, univariate and multivariate multinomial logistic regression analyses were conducted, comparing a reference toxicity with others.

Pruritus was selected as the index toxicity, since it was the most frequent cutaneous reaction. Because some patients developed two or more cutaneous toxicities, a new variable referring to multiple toxicities was included in the multinomial analyses. Number of doses, the type of primary cancer, type of ICI given and the combination of ICI with immunotherapy, chemotherapy or targeted therapy were the independent variables in the model. Age and gender were not selected in the multivariable model, because there was not any significant association in both descriptive and univariate multinomial analysis. NSCLC and anti-PD1 were the most frequent type of cancer and the most widely used ICI in the sample, respectively, and were therefore set as our reference level. Moreover, missing values analysis was conducted (Table 1), and multiple imputation was used to handle missing data. Ten multiply imputed datasets were developed using fully conditional specification and predictive mean matching applied for scale variables. All the statistical tests were two–sided and the level of significance was set at a=0.05. Data analysis was carried out using SPSS Statistics for Windows, version 25.0 (IBM Corp).

Results

Eleven centers provided data corresponding to 762 cancer patients under ICI (Suppl table 1). There were 466 males (61.1%) and 296 females (38.9%) with a mean age (SD) of 66.3 (11.5) and 61.8 (12.4) years, respectively. The most common malignancy treated was lung cancer (385 patients, 50.6%) followed by melanoma (199 patients, 26.1%). Six hundred and twenty-five patients (82.1%) received ICI in monotherapy and 136 patients (17.9%) received combination therapy, including combination immunotherapy, ICI therapy plus chemotherapy or ICI treatment plus Tyrosine Kinase Inhibitors (TKI). One hundred and ninety-seven patients (25.9%) developed more than one cutaneous toxicity during treatment's course (Table 1).

Cutaneous toxicities

Nine hundred ninety-three cutaneous toxicities were overall recorded (Table 2). Skin toxicities developed after a mean number of 6.7 doses (range 1-46, Figure 1). Psoriasis and pruritus were the most frequent toxicities (175 and 171 patients, corresponding to 23% and 22.4% of the study population, respectively), followed by macular rash (161 patients, 21.1%), eczematous-type reactions (150 patients, 19.7%), lichenoid dermatitis (83 patients, 10.9%), vitiligo (46 patients, 6 %) and bullous pemphigoid (29 patients, 3.8%). One hundred and seventy eight patients (total number) (23.4%) developed less typical/frequent (forming the "uncommon toxicities" group) cutaneous irAEs (suppl table 2). In total, 40 different morphologies of

cutaneous toxicity were identified. Finally, histological confirmation of clinical diagnosis was available in 207 cases (20%).

Clinical associations of skin toxicities

Macular rashes developed after a lower number of doses compared to other toxicities (mean number of doses 4.25, p<0.001) (Fig.1) and was the most frequent cutaneous irAE in melanoma patients, with sixty-four cases (32.2%). The most frequent skin toxicity in patients with renal cancer was pruritus (15 out of 39 patients, 38.5%) (Table 2). Psoriasis developed after a mean number of 8.75 doses (range 1-36) which was significantly higher compared to the dosage of other toxicities (p<0.001) (Fig. 1). Psoriasis complicated mainly NSCLC patients (111 patients out of 175 with psoriasis, 63.4%).

Multinomial analysis - *Univariate analysis*

Macular rash (OR 3.10, p=0.006, 95%CI 1.37 – 6.93), vitiligo (OR>44 p<0.001, 95%CI 9.02 – 222) and multiple type of cutaneous toxicities (OR 3.99, p<0.001, 95%CI 1.76 – 9.01) developed more frequently in melanoma patients who received immune checkpoint inhibitors compared to NSCLC patients, both compared to pruritic rash.

Psoriatic rash and multiple types of toxicities occurred in a lesser extent in patients who received anti-PD-L1 therapy compared to anti-PD1 and, in comparison with pruritus (OR 0.41, p=0.02, 95%CI 0.18 – 0.89 and OR 0.40, p=0.04, 95%CI 0.17 – 0.96, respectively). In addition, macular rash presented less frequently than pruritus in patients who received combination of immunotherapy with chemotherapy compared to ICI-monotherapy (OR 0.36, p=0.03, 95%CI 0.14 – 0.93). Similar significant association among combined ICI-chemotherapy and ICI-monotherapy was also demonstrated in psoriatic rash and multiple toxicities, compared to pruritus (Supp. Table 3 & 4).

Multinomial analysis - *Multivariate analysis*

Patients treated with combination of ICI and chemotherapy, developed less frequently eczematous, psoriatic and lichenoid reactions, compared to pruritus (OR 0.24, p=0.02, 95%CI 0.07 – 0.78, OR 0.08, p<0.001, 95%CI 0.02 – 0.31 and OR 0.15, p=0.02, 95%CI 0.03 – 0.77, respectively) (Table 3).

Moreover, among patients with macular rash, vitiligo and multiple cutaneous toxicities, patients received ICI more frequently for melanoma than for NSCLC, in multivariable model. As for type of ICI, macular rash (OR 0.11, p=0.02, 95%CI 0.01 – 0.76) and vitiligo (OR 0.07, P=0.03, 95%CI 0.006 – 0.78), both compared to pruritus, occurred to a lesser extent in patients treated with anti-CTL4, compared to anti-PD1.

Grading

Available data about grading were noted in 967 toxicities: 453 were classified as grade1 (46.8%), 370 as grade2 (38.3%) and 140 as grade3 (14.5%). Only four patients (0.5%) developed grade-4 rashes. Melanoma and the combination of chemotherapy with ICI were associated to a 0.62-fold (OR=0.38, 95%CI 0.16 – 0.94) and a 0.11-fold (OR=0.89, 95%CI 0.01 – 0.96) decreased risk for grade 2 and 3 disease respectively. Melanoma patients also showed a decreased probability for high grade pruritus compared to NSCLC patients (OR=0.21, 95%CI 0.09 – 0.47). Patients with hepatocellular cancer had an increased probability for high grade eczematous rash development, compared to NSCLC patients (OR= 11.14, 95%CI 1.27 – 97.23).

Other toxicities

One hundred and seventy-eight cases presented with uncommon toxicities (<3% of the total cases), including acneiform rashes (27 cases), granulomatous reactions (9 cases), hair disorders (14 cases) and autoimmune diseases (22 cases) (Suppl table 2). The latter involved 4 cases of cutaneous lupus erythematosus, 5 cases of dermatomyositis, 6 cases of scleroderma-like reactions and 7 cases of vasculitis.

Eight patients (4 males and 4 females) were complicated with life threatening reactions, involving 4 Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS) and 4 Steven Johnson/Toxic Epidermal Necrolysis (SJS/TEN) cases. Five patients had received anti-PD-1 monotherapy, one anti-PD-L1 and two combination treatment with anti-CTLA-4 and anti-PD-1 agents. All cases were histologically confirmed. These cutaneous reactions presented early during treatment course, after a median number of 3 doses for both DRESS and SJS/TEN reactions.

Twenty-two cutaneous malignancies were also recorded, with squamous cell carcinomas/keratoacanthomas being the most common among them (9 cases).

Discussion

The wide use of ICI has been related with a novel profile of irAEs among cancer patients. Approximately 30-50% of patients treated with either anti-CTLA-4 or anti PD-1/PD-L1 agents, will experience a cutaneous complication. [6] In recent years, there has been an urgent need for the development of specialized dermatooncology units for the treatment of these demanding cases. One of the main strengths of our analysis is that all patients included were diagnosed and treated by dermatologists specialized in supportive oncodermatology exclusively. We strongly believe that this is of great importance since although skin eruptions induced by ICI show a wide clinical diversity and often unique features, these toxicities have been widely described by many large-scale oncologic studies with the generic term of "rash", without any further specifications. We managed to identify 40 different cutaneous irAEs, confirming an extremely wide clinical spectrum, potentially mirroring the diverse pathogenesis of these toxicities and underlining the need of oncodermatology consultation as part of standard care of cancer patients.

In our cohort, psoriasis and pruritus were the most frequent skin toxicities recorded, followed by macular rashes. We believe that psoriasiform rashes may be over-represented in our cohort, probably due to the fact that the participating centers are all Oncodermatology units, and therefore referrals mainly involve cases with skin lesions more complex and difficult to identify than macular rash. However, the association between ICI and psoriasis development has been well established, as reported by our group and other researchers. [7] [8] [9] In a previous study, we reported the development of all clinical subtypes of psoriasis, as well as several unstable forms of the disease.[6]

To our knowledge, this is the first study showing that different malignancies have different cutaneous toxicities patterns. To date , the only well recognized correlation was that of vitiligo in patients treated for melanoma; [1] although there are recent reports of sporadic vitiligo cases in other types of cancer.[10] [11] In agreement with these data, the majority of vitiligo cases in our study were also seen in ~~the~~ melanoma patients. Moreover, in our cohort among patients with macular rashes patients were treated more frequently for melanoma compared to NSCLC. According to recent literature, macular rash is the most common reaction to ICI.[12] [13] [14] In our cohort, macular rash was indeed among the most frequent skin toxicities (21.1% of the study population). Given that anti-CTLA-4 agents are predominantly used to treat melanoma patients, the high rate of melanoma cases in the group of patients who developed macular rashes was sensibly expected. However, multivariate analysis showed that melanoma retains

its significance independently. This may suggest that melanoma pathogenesis and macular rash development share common immunologic pathways on which ICI treatments could lead to further deterioration. Further investigation is definitely warranted since the prognostic and therapeutic implications of this will be of great clinical importance.

Clinical profiles of adverse events associated with anti-PD-L1 therapies do not differ significantly from anti-PD-1 therapies since both types of antibodies target the PD-1-PD-L1 interaction during immune responses. However, a recent meta-analysis suggested that possible differences might exist regarding the risk of irAEs and this also applies to skin toxicities: the authors reported a 4-fold increased risk of any grade rash with anti-PD-1 compared to anti-PD-L1 antibodies. [15] In our study we showed that patients treated with anti-PD-L1 developed less frequently psoriasis or multiple skin toxicities compared to patients treated with anti-PD-1 antibodies, while there was no difference between anti-PD-1 and antit-PD-L1 for other skin toxicities.

The relations between specific cutaneous toxicities and time exposure to immunotherapy has not yet been fully elucidated.[16] [17] [18] In our study, we confirmed that the interval between immunotherapy initiation and first appearance of rash is wide and can occur up to 46 doses after treatment introduction. We also confirmed the earlier appearance of pruritus and macular rash compared to other skin toxicities. Moreover, and in agreement with our previous findings, it was confirmed that the mean number of drug dosages until psoriasis onset is higher compared to other cutaneous irAEs.[7] Another interesting point that should be stressed, is that cutaneous irAEs – unlike their counterparts related to other novel oncological treatments, such as TKIs or epidermal growth factor receptor inhibitors (EGFRIs) – may first appear after many months of therapy.[19] Therefore, patients should be closely monitored throughout their treatment course and even after discontinuation of ICI.[20]

Cutaneous irAEs attributed to combination ICI treatments have been widely studied and are similar to those related to monotherapy, although a higher rate of more severe toxicities (grade 3 and 4) has been reported. [21] Although combination treatment regimens of chemotherapy or targeted agents with ICIs are now widely used in oncology therapeutics, data on their cutaneous toxicity profiles are limited. Our study concluded that the combination of chemotherapy plus ICI had a protective effect against psoriasis development, lichenoid reactions, eczematous reactions as well as against high grade (2 and 3) rashes. This could be attributed to the chemotherapy-induced direct inhibition of epidermal hyperplasia, by arrest of mitosis in the rapidly dividing epidermal cells observed especially in psoriatic patients. Preemptive measures

including emollients could be suggested to cancer patients, especially for those being treated with combination therapies.

One limitation of this study was the retrospective design. Large prospective multicentric studies are needed in order to define the exact rates of the different skin toxicities – especially of the uncommon presentations –, as well as their effect on overall prognosis. However, we have presented a large cohort of patients that allowed the characterization of significant clinical patterns and frequency rates of cutaneous irAEs attributed to ICI. Another limitation of our analysis is that we were unable to estimate the cumulative incidence rates of different cutaneous toxicities among all patients treated with ICI and to calculate predictive factors of cutaneous irAES after ICI initiation. Recently, Wongvibulsin S et al in a large retrospective study of 8637 ICI patients and 8637 matched controls showed that between the wide range of cutaneous toxicities recorded only 10 occurred more frequently in ICI recipients.[22] These included SJS/TEN, maculopapular eruption, vitiligo, mucositis, pruritus, erythema multiform and Grover diseases. However, among the most common reported cutaneous irAEs "nonspecific drug reaction" "rash and other non-specific eruption" were included emphasizing the difficulties in recognizing and characterizing cutaneous irAEs by nondermatology providers. We believe, that identifying the occurrence rates of specific skin toxicities in patients presenting with a cutaneous iRAE is of great importance in the clinical setting. Large prospective multicentric studies would be more conclusive in assessing the incidence rates of each cutaneous toxicity.

In conclusion, this study highlighted the wide clinical range of skin toxicities in patients receiving ICI. We also found specific cutaneous toxicity profiles in patients with different cancer types. Our analysis indicated that among patients under ICIs with macular rashes, vitiligo and multiple cutaneous toxicities, melanoma cases are predominant. The etiology and pathogenesis behind these differences, as well as the prognostic significance of each toxicity should be further investigated. Considering the diversity and high frequency rates of cutaneous irAEs, together with the wide use of ICI, dedicated referral Oncodermatology clinics are required to ensure effective diagnosis and management. Until then, close surveillance of these patients by specialized dermatologists, should be included as part of their standard care.

Table 1: Baseline characteristics

Number of patients	**762**	**Missing Values, n (%)**
Age [mean (SD)]	64.5 (12.1)	33 (4.4)
Number doses to AE [mean (SD)]	6.73 (6.89)	27 (3.5)
Gender (%≠)		0
Male	466 (61.1)	
Female	296 (38.9)	
Mean age (SD)		
Male	66.3 (11.5)	
Female	61.8 (12.4)	
Primary Cancer (%≠)		1 (0.1)
NSCLC	385 (50.6)	
Melanoma	199 (26.1)	
Head & Neck SCC	27 (3.5)	
Renal cell carcinoma	39 (5.1)	
Urothelial carcinoma	34 (4.5)	
Hodgkin's lymphoma	6 (0.8)	
Merkel cell carcinoma	5 (0.7)	
Hepatocellular carcinoma	21 (2.8)	
Other	45 (5.9)	
ICI (%≠)		0
Anti – CTLA4	20 (2.6)	
Anti- PD-1	581 (76.2)	
Anti- PD-L1	109 (14.3)	
Anti-CTLA4 + Anti-PD-1 or Anti-PD-L1	52 (6.9)	
Combined therapy (%≠)		1 (0.1)
Monotherapy	625 (82.1)	
Immunotherapy	52 (6.9)	
Chemotherapy	57 (7.5)	
TKI	27 (3.5)	
No of skin toxicities per patient (%≠)		0
1	565 (74.1)	
2	165 (21.7)	
>3	32 (4.2)	
Skin Toxicities	**No=993 (%≠)**	
Eczematous reaction	150 (19.7)	
Macular rash	161 (21.1)	
Psoriasis	175 (23)	
Lichen planus like rash	83 (10.9)	
Pruritus	171(22.4)	
Vitiligo	46 (6.0)	
Bullous Pemphigoid	29 (3.8)	
Uncommon	178 (23.4)	
Grading (%≠)	**No=967 (%‡)**	26 (2.6‡)
Grade-1	453 (46.8)	
Grade-2	370 (38.3)	
Grade-3	140 (14.5)	
Grade-4	4 (0.4%)	

SD: Standard Deviation, AE: Adverse Event, NSCLC: Non-Small Cell Lung Cancer, SCC: Squamous Cell Carcinoma, ICI: Immune Checkpoint Inhibitor TKI: Tyrosine Kinase Inhibitor, anti-CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4, anti-PD-1: Programmed cell death protein 1, anti-PDL1: programmed cell death-1 ligand 1 (PD-L1), **≠:** *percentages calculated based on total number of patients,* ‡ *percentages calculated based on total number of skin toxicities*

Table 2: Frequencies and baseline characteristics of the main cutaneous toxicities

	Macular (N=160)	**Psoriasis (N=175)**	**Eczema (N=150)**	**Pruritus (N=171)**	**Lichenoid (N=83)**	**Vitiligo (N=46)**
Age (mean, SD)	62.1 (13.4)	66.5 (10.9)	64.8 (11.3)	62.9 (11.9)	65.7 (11.7)	63.6 (13.3)
Number of doses (mean, SD)	4.25 (3.33)	8.75 (7.94)	6.49 (7.47)	5.71 (5.89)	7.53 (5.48)	7.90 (6.16)
Gender (%⊥)						
Male	92 (19.8)	116 (24.9)	94 (20.2)	98 (21.1)	47 (10.3)	29 (6.2)
Female	68 (23.0)	59 (19.9)	56 (18.9)	73 (24.7)	36 (12.2)	17 (5.7)
Primary Cancer (%⊥)						
NSCLC	58 (15.1)	111 (28.8)	84 (21.8)	84 (21.8)	47 (12.2)	6 (1.6)
Melanoma	64 (32.2)	25 (12.6)	29 (14.6)	42 (21.1)	18 (9)	37 (18.6)
Head and neck SCC	5 (18.5)	8 (29.6)	6 (22.2)	9 (33.3)	2 (7.4)	0
Renal	10 (25.6)	7 (17.9)	4 (10.3)	15 (38.5)	5 (12.8)	2 (5.1)
Urothelial	9 (26.5)	11 (32.4)	6 (17.6)	9 (26.5)	1 (2.9)	1 (2.9)
Hodgkin	2 (33.3)	1 (16.7)	0	2 (33.3)	2 (33.3)	0
Merkel cell	2 (40)	1 (20)	0	2 (40)	0	0
Hepatocellular	1 (4.8)	5 (23.8)	7 (33.3)	4 (19)	5 (23.8)	0
ICI (%⊥)						
Anti -CTL4	11 (55)	0	4(20)	12 (60)	0	2 (10)
Anti-PD1	99 (17)	148 (25.5)	118 (20.3)	118 (20.3)	69 (11.9)	38 (6.5)
Anti-PDL1	25 (22.9)	20 (18.3)	23 (21.1)	24 (22)	9 (8.3)	1 (1.0)
Combination (%⊥)						
Monotherapy	117 (18.7)	158 (25.3)	126 (20.2)	131 (21)	72 (11.5)	41(6.9)
Immunotherapy	25 (48.2)	7 (13.5)	6 (11.5)	18 (34.6)	5 (9.6)	4 (7.7)
Chemotherapy	9 (17.5)	6 (10.5)	17 (29.8)	19 (33.3)	5 (8.8)	0
Targeted	8 (29.6)	4 (14.8)	1 (3.7)	3 (11.1)	1 (3.7)	1 (3.7)

N: number of patients, SD: Standard Deviation, ⊥: percentages calculated based on number of patients in each category from the total sample, NSCLC: Non-Small Cell Lung Cancer, SCC: Squamous Cell Carcinoma, ICI: Immune Checkpoint Inhibitor, anti-CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4, anti-PD-1: Programmed cell death protein 1, anti-PDL1: programmed cell death-1 ligand 1 (PD-L1)

Table 3: Multinomial multivariate analysis for associations between cutaneous toxicities and predisposing factors. Pruritus was set as the index toxicity for the comparisons. Values represent Odds Ratios (ORs) with 95% Confidence Intervals (CIs).

Factors	**Cutaneous toxicities**					
	Eczema (N=98)	**Macular (N=112)**	**Psoriasis (N=160)**	**Lichenoid (N=56)**	**Vitiligo (N=26)**	**Multiple toxicities (N=124)**
Age						
Number of doses	1.02 (0.95 – 1.09)	0.95 (0.88 – 1.03)	1.05 (0.99 – 1.12)	1.00 (0.93 – 1.08)	1.10 (0.91 – 1.12)	1.01 (0.94 – 1.07)
Gender						
Male						
Female						
Primary Cancer						
NSCLC	Ref	Ref	Ref	Ref	Ref	Ref
Melanoma	1.39 (0.45 – 4.29)	**3.63 (1.23 – 10.72)**	0.95 (0.32 – 2.83)	1.21 (0.34 – 4.30)	**91 (9.8 – 852)**	**3.73 (1.26 – 11.03)**
Head and neck SCC	Inf	2.86 (0.30 – 27.32)	2.46 (0.28 – 21.23)	0.96 (0.05 – 16.35)	Inf	6.18 (0.71 – 53.13)
Renal	0.25 (0.05 – 1.22)	0.33 (0.07 – 1.58)	0.25 (0.06 – 1.01)	0.33 (0.05 – 1.95)	5.13 (0.25 – 103)	1.86 (0.55 – 6.28)
Urothelial	0.54 (0.10 – 2.98)	1.07 (0.23 – 4.87)	0.70 (0.16 – 3.06)	0.30 (0.02 – 3.16)	Inf	1.22 (0.24 – 6.15)
Other	1.01 (0.21 – 4.83)	0.78 (0.13 – 4.44)	0.70 (0.15 – 3.24)	1.87 (0.38 – 9.23)	Inf	1.79 (0.39 – 8.22)
ICI treatment						
Anti -CTL4	0.17 (0.02 – 1.19)	**0.11 (0.01 – 0.76)**	Inf	Inf	**0.07 (0.006 – 0.78)**	0.43 (0.09 – 1.90)
Anti-PD1	Ref	Ref	Ref	Ref	Ref	Ref
Anti-PDL1	0.77 (0.28 – 2.16)	1.30 (0.50 – 3.38)	0.60 (0.23 – 1.61)	0.79 (0.24 – 2.54)	Inf	0.41 (0.13 – 1.29)
Combination therapy						
Monotherapy	Ref	Ref	Ref	Ref	Ref	Ref
Immunotherapy	Inf	Inf	Inf	Inf	Inf	Inf
Chemotherapy	**0.24 (0.07 – 0.78)**	0.35 (0.11 – 1.04)	**0.08 (0.02 – 0.31)**	**0.15 (0.03 – 0.77)**	Inf	**0.25 (0.07 – 0.90)**
Targeted	2.33 (0.20 – 26.13)	1.79 (0.16 – 19.77)	1.52 (0.13 – 16.62)	1.17 (0.06 – 21.46)	1.53 (0.07 – 31.52)	0.34 (0.01 – 5.94)

Pruritus was set as the index toxicity. NSCLC, anti-PD1 and ICI monotherapy were the reference lever for the independent variables. [OR: Odds Ratio, CI: Confidence Interval, NSCLC: Non-Small Cell Lung Cancer, ICI: Immune Checkpoint Inhibitor, anti-CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4, anti-PD-1: Programmed cell death protein 1, anti-PDL1: programmed cell death-1 ligand 1 (PD-L1), N: numbers of patients included in the multinomial analysis, other cancer type: Merkel cell, hepatocellular carcinoma, Hodgkin Lymphoma]

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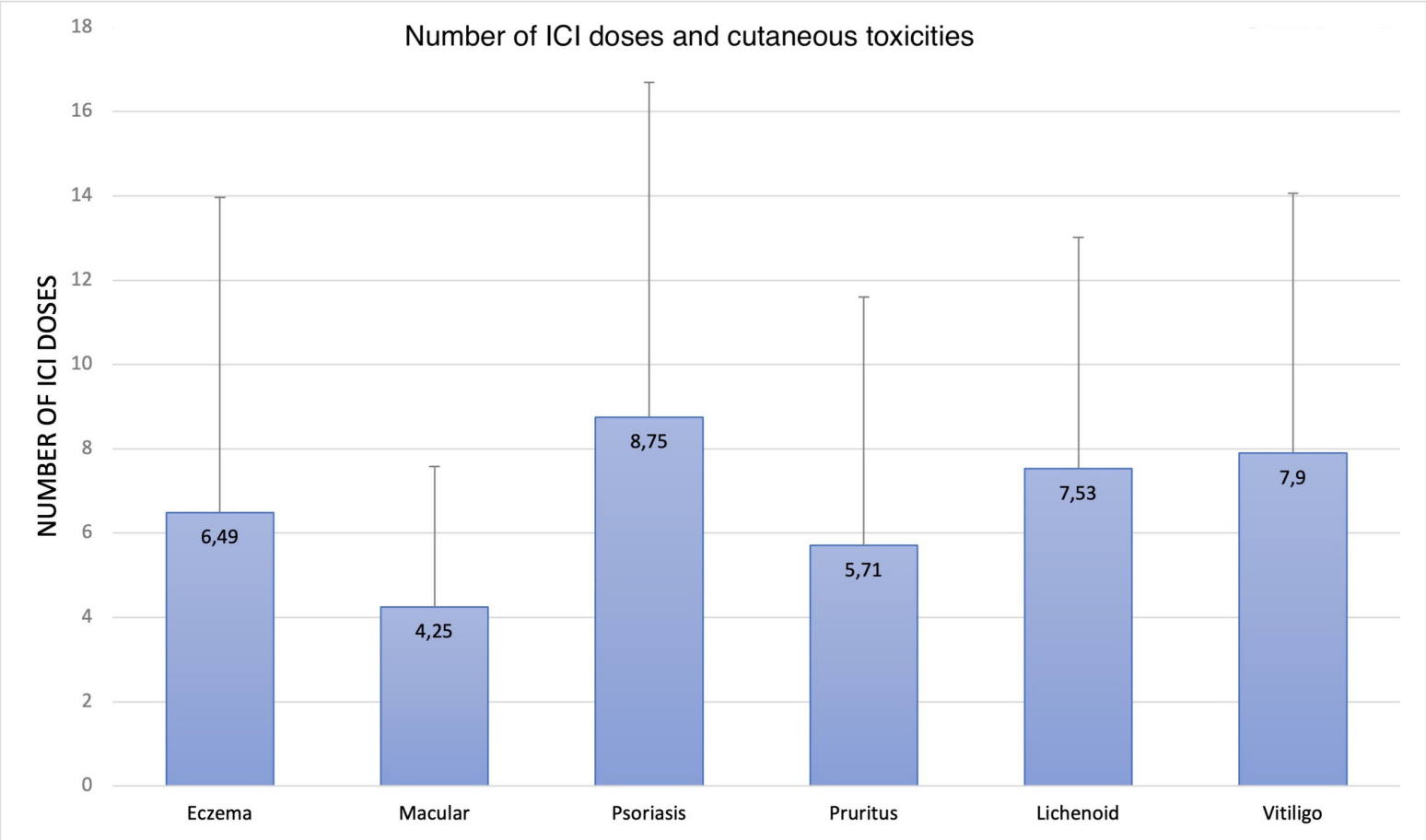
Figure legends

Figure 1: Bar plots presenting the main cutaneous toxicities and the mean number of Immune Checkpoint Inhibitors (ICI) doses (Standard Deviation as shown as error bars).



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