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POSITION STATEMENT

European recommendations for management of immune checkpoint inhibitors-derived dermatologic adverse events. The EADV task force 'Dermatology for cancer patients' position statement

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Abstract

The introduction of immune checkpoint inhibitors (ICIs) opened a new era in oncologic therapy. The favourable profile of ICIs in terms of efficacy and safety can be overshadowed by the development of immune-related adverse events (irAEs). Dermatologic irAEs (dirAEs) appear in about 40% of patients undergoing immunotherapy and mainly include maculopapular, psoriasiform, lichenoid and eczematous rashes, auto-immune bullous disorders, pigmentary disorders, pruritus, oral mucosal lesions, hair and nail changes, as well as a few rare and potentially life-threatening toxicities. The EADV task force Dermatology for Cancer Patients merged the clinical experience of the so-far published data, incorporated the quantitative and qualitative characteristics of each specific dirAEs, and released dermatology-derived, phenotype-specific treatment recommendations for cutaneous toxicities (including levels of evidence and grades of recommendation). The basic principle of management is that the interventions should be tailored to serve the equilibrium between patients' relief from the symptoms and signs of skin toxicity and the preservation of an unimpeded oncologic treatment.
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Conflict of interest

Azael Freites-Martinez received honoraria for lectures from L' Oreal France and Leo Pharma and travel grands from ISDIN. Gabriella Fabbrocini participated in advisory boards held by ABBVIE SRL, BEIERSDORF SPA, BOEHRINGER INGELHEIM ITALIA SPA, DIFA COOPER SPA, GALDERMA ITALIA SPA, GALDERMA INTERNATIONAL SAS, JANSENN, L'OREAL ITALIA SPA, LEO PHARMA A/S, LILLY, LDV SR, MEDA PHARMA SPA, MERTZ PHARMA ITALIA SRL, NOVARTIS, PIERRE FABRE DERMO-COSMETIQUE, PIERRE FABRE ITALIA SPA, SANOFI, SIFARMA SPA, VALETUDO SRL. Elizabeth Lazaridou received honoraria and travel grands from Abbvie, Janssen, Leo-Pharma, Novartis, Lilly, Galderma, UCB, Loreal. Alexandros Stratigos received honoraria from Novartis, Abbvie, Regeneron, BMS, Janssen Cilag, Sanofi

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Highlights

- This European clinical practice recommendations, released from the *EADV task force Dermatology for Cancer Patients*, provides fundamental information for the diagnosis/management of dermatological toxicities from immune checkpoint inhibitors (ICIs)
- Authorship includes a multidisciplinary group of onco-dermatology experts from different institutions and countries in Europe and abroad
- Recommendations refer to diagnosis/management of pruritus, maculopapular, psoriasiform, and lichenoid rashes, bullous pemphigoid, mucosal and hair/nail changes, as well as rare and potentially life-threatening checkpoint inhibitor-related adverse events.
- Recommendations are provided, including levels of evidence and grades of recommendation.

Introduction

Immune checkpoint inhibitors (ICIs) reinvigorate anticancer immune surveillance, via the inhibition of certain regulatory proteins, namely cytotoxic T lymphocyte protein 4 (CTLA-4), programmed death (PD)-1 and PD-ligand (L)1.[1,2] The desirable, immune-mediated oncologic response is often achieved at the cost of immune-related adverse events (irAEs) that may potentially affect any organ system.[1,2] With an approximate overall incidence of 30%–40% for PD-1/PDL1 and 50% for CTLA-4 inhibitors, dermatologic irAEs (dirAEs) are among the most common and include maculopapular, psoriasiform, lichenoid and eczematous rashes, auto-immune bullous disorders (AIBD), depigmentation, pruritus, hair/nail and mucosal changes, as well as a few rare and potentially life-threatening toxicities (Figs 1–8).[1,3,4] In the majority of cases, diagnosis of dirAEs is set on clinical presentation. Histopathological examination is preserved for severe, atypical or persistent forms. Even though development of skin toxicities has been associated with increased survival and tumour response,[3,5–9] the prognostic significance of specific dirAE phenotypes remains unclear.[2,6]

A majority of current treatment guidelines for dirAEs (NCCN version 1.2020) uses generic terms like 'skin rash' or 'bullous dermatitis' to encompass a wide and diverse range of dirAEs, without considering their substantial disparity in terms of pathogenesis, phenotypical and immunohistopathological characteristics.[1] There are several proposed immunopathogenic mechanisms responsible for skin toxicities, possibly involving generation of autoreactive T and B cells during ICI treatment, excessive release of pro-inflammatory cytokines promoting tissue-specific immune-mediated damage, or exposure of host antigens from tumour cells due to cytotoxic attack.[2,10,11] In this context, systemic corticosteroids remain the cornerstone of medical management of grade 3 and 4 skin toxicities, whilst a list of classic immune-suppressive drugs serve as second-line options. Wide applicability of the aforementioned recommendations in ICI-induced dermatologic AEs is not always feasible, if not questionable. Potential drawbacks include the possible antagonistic effects of the proposed treatments on cancer immune surveillance,[1,12–15] the exclusion of skin-specific therapies that are less or non-immunosuppressive and could benefit these patients and the lack of licensed approval of certain drugs in dedicated indications (e.g. omalizumab and rituximab in bullous pemphigoid (BP)).

Furthermore, it is worth to mention that, opposed to irAEs in other organ-systems, and with the exception of toxic epidermal necrolysis (TEN) and severe forms of immunobullous disorders, life-threatening cutaneous toxicity is an unlikely event, even in the scenario of >30% BSA involvement. In this context, depending on the patient's profile and the rash phenotype, maintenance of ICI might be potentially feasible in most cases. Early detection and appropriate intervention are fundamental to minimise treatment interruption or discontinuation and preserve patients' health status and quality of life (QoL).

The EADV 'Dermatology for Cancer Patients' Task Force (representing an international expert panel of dermatologists from the academic and public sectors working together for three years on supportive oncodermatology for cancer patients), merged the clinical experience of the so-far published data, incorporated the quantitative and qualitative characteristics of each specific dermatologic symptoms/manifestations, appearing in the context of irAEs, and released dermatology-derived, phenotype-specific treatment recommendations for cutaneous toxicities. The basic principle of management is that the interventions should be tailored to serve the equilibrium between patients' relief from the symptoms and signs of skin toxicity and the preservation of an unimpeded oncologic treatment.[16]

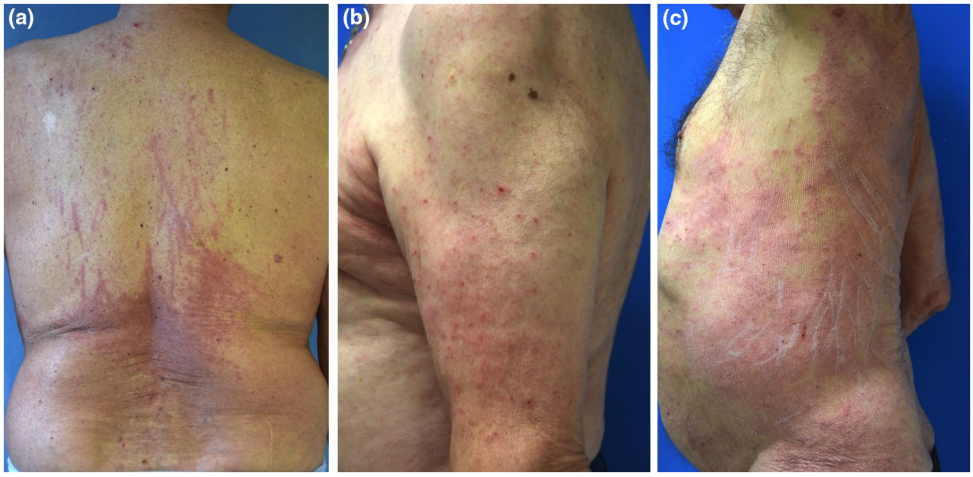

Figure 1 Grade 2 pruritus resulting in secondary excoriations (a). Grade 1 (a) and grade 3 (b) maculopapular eruption. Maculopapular eruption is usually pruritic.

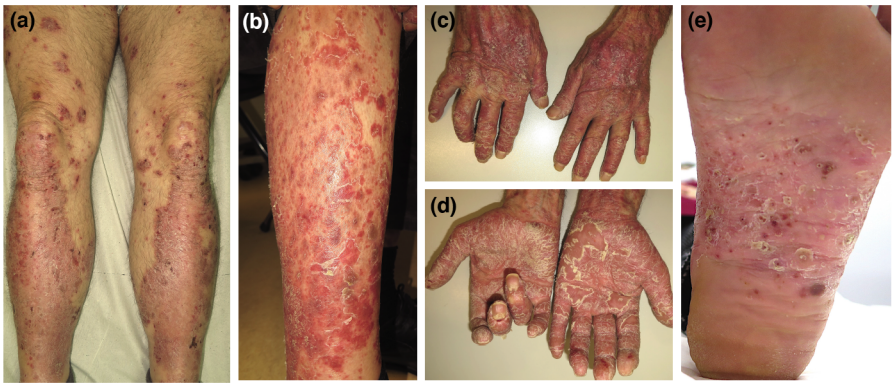

Figure 2 Grade 2 psoriasis-like rash (plaque-type) in a patient under nivolumab (a). Grade 3 pustular psoriasis-like rash and psoriatic arthritis in a patient under pembrolizumab (b–d). Palmoplantar pustulosis-like rash is a usual dermatologic immune-related adverse event (e).

Methodology

A kick-off meeting took place virtually on 1 October 2020, that was open to all members belonging to the European Task Force of the EADV 'dermatology for cancer patients' The scope and methodology for the development of these recommendations were first defined, based on both evidence-based medicine and expert opinion. The main topics to be addressed in these recommendations were defined at this first meeting.

A thorough literature search was then carried out. Search strategy and selection criteria included Pubmed and Embase databases analyses with identification of articles published in European languages, with no limitations in time of publication. The following terms and keywords were used: one referring to cancer (carcinoma, tumour, cancer, neoplasm), one characterising the ICI (anti-CTLA-4, anti-PD-1, anti-PD-L1, ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, tremelimumab), and one related to the event (skin toxicity, dermatologic adverse event, cutaneous toxicity) connected by the word 'and'.

The final reference list with the relevant identified articles was generated based on their relevance to the broad spectrum of the article review and was fully reviewed and their corresponding findings were considered.

Three additional joint meetings were held, bringing together the 20 experts ultimately involved in the development of these recommendations and representing ten European or overseas

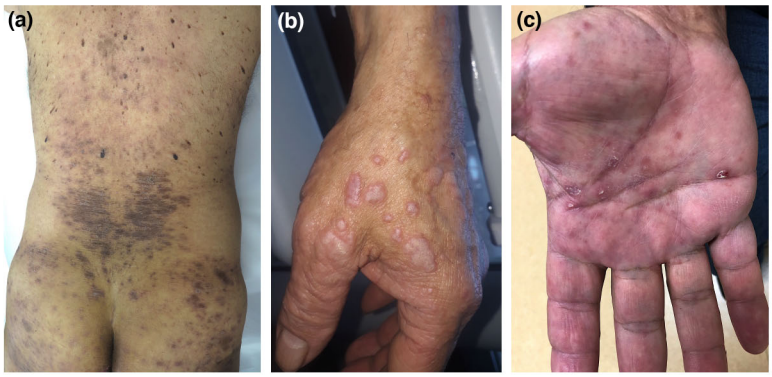

Figure 3 Grade 2 pigmented lichenoid lesions (a). Hypertrophic variants (b) and palmoplantar involvement (c) are not unusual.

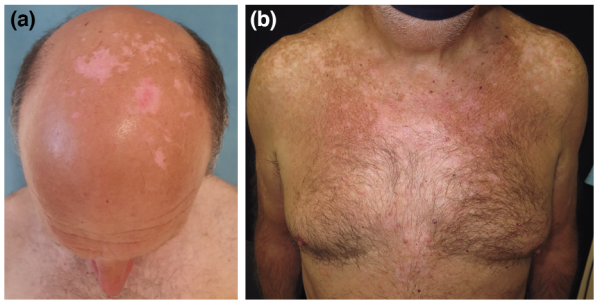

Figure 4 Classic, grade 1 (a) and confetti-like, grade 2 (b) vitiligo-like lesions.

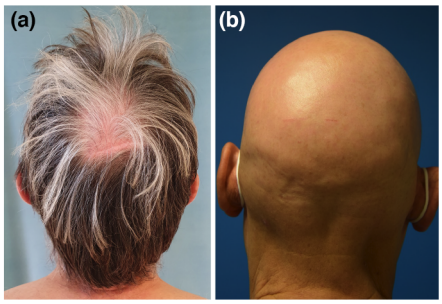

Figure 6 Poliosis (a) and alopecia areata totalis (b) in patients under treatment with ICIs.

countries (USA, Argentina, Israel). All experts were dermatologists or oncodermatologists, except one who was an oral medicine practitioner (EV). Levels of evidence and grades of recommendation were structured by our working group and were based on evidence and/or expert opinion (Table 1).

All the content of the recommendations was subsequently reviewed by two supervising authors (ZA and VS). At the final stage, a critical appraisal was performed by three experts (AF, GF and RD) of our Task Force. A recommendation was included if at least 70% of experts (including the experts in charge of each

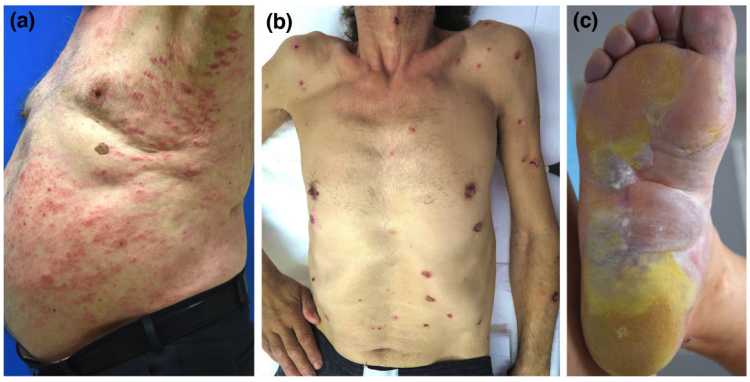

Figure 5 Pre-bullous phase of BP, characterised by urticarial and eczematoid plaques. Intense pruritus is a constant symptom (a) BP in a patient under nivolumab (b). Lichen planus pemphigoides is a rare adverse event (c).

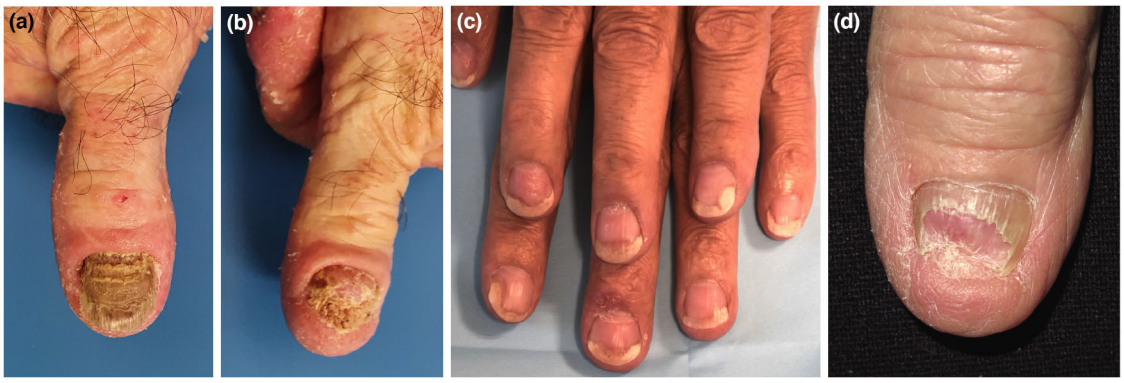

Figure 7 Nail involvement in a patient developing Hallopeau disease (a) and in a patient developing psoriasis during treatment with anti-PD1 (b). Pterygium as a clinical manifestation of lichen planus derived from checkpoint inhibitors (c).

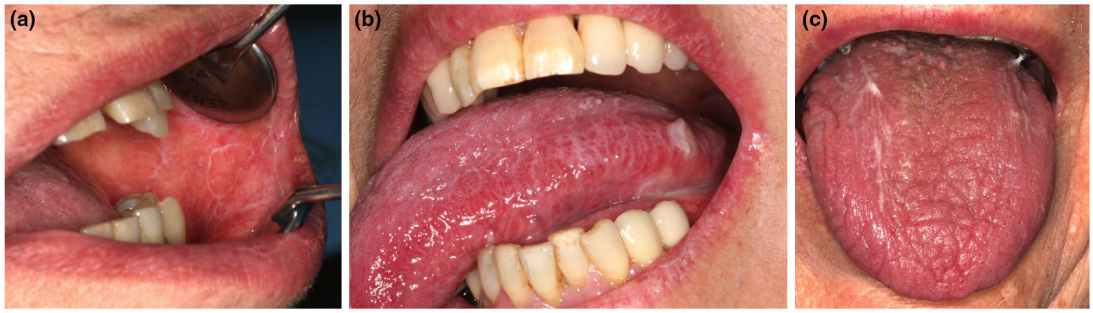

Figure 8 Oral mucosal lichenoid reaction (a), lichen planus pemphigoides-like eruption involving the tongue (b), and sicca syndrome (c) during the course of immunotherapy.

sub-chapter as well as the two supervising authors (VS, ZA) and the final three experts (AF, GF and RD) agreed with this recommendation. All authors approved the content of the final manuscript.

Pruritus

Immune checkpoint inhibitors-induced pruritus can develop either without apparent skin changes, or in association with other dirAEs.[17,18] In a recent cohort of 285 patients referred for dirAEs, 138 (32%) experienced isolated pruritus.[19]

A meta-analysis reported pruritus in 13.2% and 20.2% of patients treated with nivolumab and pembrolizumab, respectively. Grade 3 pruritus was rarely reported, with 0.5% and 2.3% respectively.[20] Incidences for anti-CTLA4-based regimens reach 47%.[21] Pruritus, along with maculopapular eruptions typically appear early (3–10 weeks) during treatment.[22] Table 2 summarises the incidence, time to onset and need for histologic confirmation of the most common dirAEs, including pruritus.

Grade 2 or 3 pruritus can significantly impact patients' QoL, illustrated by a mean ItchyQoL score of 2.29, which is higher than described in haemodialysis patients with uraemic pruritus.[23]

Pruritus is diagnosed clinically, based on a thorough anamnesis and a full-body inspection, for detecting excoriations (Fig. 1a), skin superinfection and other secondary skin changes that may suggest an associated dirAE. In patients experiencing persistent ICI-related pruritus, a standard of care laboratory analyses should be performed, with special attention to the absolute eosinophil counts, glomerular filtration rate, total IgE and hepatic parameters.[24] Furthermore, a pre-bullous stage of an AIBD should always be considered. If suspected, histologic examination, enzyme-linked immunosorbent assay (ELISA) and direct/indirect immunofluorescences should be performed.

Management should be adapted to CTCAE grade (Table 3).[25] For mild (G1) pruritus, regular application of topical moisturisers, with or without a medium to high-potency corticosteroid, should be prescribed.[26] If instrumental activities of daily living are impacted (Grade 2), non-sedating anti histamines and/or GABA agonists such as pregabalin, or gabapentin should be added. In more severe cases (Grade3), ICI generally needs to be

Table 1 Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended

held until pruritus improves at least to G1. Other medications with anti-pruritic effect, such as the neurokinine 1 receptor agonist aprepitant, should also be considered.[27,28] For patients with refractory pruritus, low doses of oral corticosteroids (10 mg a day of prednisone or equivalent) or immunomodulators such as omalizumab and dupilumab may be advisable. In this respect, it should be noted that IgE blockade with omalizumab has very recently been shown to be very effective in patients treated with ICIs who had grade 2/3 refractory to topical steroids and at least one additional systemic intervention.[28]

Maculopapular rash

Development of a maculopapular rash (MR, syn. spongiotic dermatitis or eczema-like rash) represents the most prevalent dirAE.[19,29] MR of any grade can affect up to 68% of patients treated with anti-CTLA-4 therapy and up to 20% of patients treated with anti-PD-1/PD-L1 therapy.[30,31]

The precise pathophysiology driving the development of ICI-related maculopapular rashes remains unknown. It has been speculated, however, that it could be related to an aberrant targeting by reactivated $CD4^+/CD8^+$ T cell clonotypes recognising simultaneously antigens shared by cancer cells and healthy skin, including desmocollin 3 and keratin 6.[2,11]

MR appears early during immunotherapy, commonly 3–6 weeks after initial dose, although cases of very early[21,29] or delayed onset have been reported (Table 2).[20,32] The clinical presentation is nonspecific and consists of a rapid onset of multiple minimally scaly, erythematous macules and papules, congregating into plaques. Lesions are mostly located on trunk and extensor surfaces of the extremities and the face is generally spared.[20,21,29,32] MR is typically pruritic, although asymptomatic rash can also occur (Fig. 1b,c).[33]

Histopathologic features are characterised by superficial perivascular CD4-prodominant T lymphocytic infiltrate with eosinophils, epidermal spongiosis and papillary dermal oedema.[12,21,29,34,35]

Management of MR adjusts to the severity of the eruption, based on CTCAE criteria.[18] Systematic dermatologic consultation should be considered in atypical, refractory or severe presentation. Grade 1 management includes symptomatic measures, such as topical moisturisers and topical potent or super-potent corticosteroids applied on the affected areas.[21,23,29,31,36–39] Oral antihistamines are added to treatment in grade 2.[21,29,36] Immunotherapy is maintained in up to Grade

Table 2 Frequency, time to appearance and need for histologic confirmation of the most common dirAEs observed with anti-CTLA4, anti-PD1/PDL-1 and the combination

Side effect	Frequency			Requirement of biopsy (yes/no)	Time of appearance in weeks, median and/or range
	Anti-CTLA4	Anti-PD1 Anti-PDL-1	Combination		
Pruritus	Up to 47%	13.2%–20.2%	Up to 47%	No§	3–10
Maculopapular rash	Up to 68%	Up to 20%	Up to 68%	No†	3–6
Psoriasis-like rash	Not determinated	3.5%	Not determinated	No†	5–12
Lichen planus-like rash	Not determinated	Not determinated	Not determinated	Yes	Not determinated (after several months)
Vitiligo-like rash	<3%	8%–25%	8%–25%	No	After several months
Bullous pemphigoid-like rash	Not determinated two reported cases	1%–5%	1%–5%	Yes	20 (range 1–88)
Alopecia areata	5%	1%–5%	1%–5%	No	20 (range 2–92)
Oral lichenoid reactions	Not determinated	Not determinated	Not determinated	No†	Not determinated
SCARs	Not determinated#	Not determinated#	Not determinated#	Yes	Not determinated

dirAEs, dermatologic immune related adverse events; SCARs, Severe cutaneous adverse reactions.
§A skin biopsy maybe recommended on an individualized basis for exclusion of an early phase of a SCAR or a pre-bullous phase of a bullous pemphigoid.
†A skin biopsy maybe recommended on an individualized basis, in atypical, persistent, or severe cases.
#Up to date, about 150 cases of checkpoint inhibitors related SCARs have been reported in the literature.

Table 3 Pruritus: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1	**Skin-directed therapy**		
Mild or localized; topical intervention indicated	Fragrance-free moisturizers	V	B
	Potent or superpotent topical corticosteroids (e.g. triamcinolone 0.1% or clobetasol 0.05% cream in pruritic areas)	IV†	B
	Systemic therapy	IV†	B
	Non-sedating antihistamines such as cetirizine 10 mg or loratadine 10 mg od		
	Continue ICI at current dose		
	Reassess after 2–4 weeks; if reactions worsen or do not improve, proceed to next step		
Grade 2	**Skin-directed therapy**		
Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Reinforce grade 1 management	V/IV†	B
	Systemic therapy	IV†	B
	Non-sedating antihistamines such as cetirizine 10 mg or loratadine 10 mg od		
	Consider replacing antihistamines with GABA analogs, e.g., gabapentin 100–300 mg tid or pregabalin, 50–100 mg tid (titrate)	IV†	B
	Continue ICI at current dose		
	Reassess after 2–4 weeks; if reactions worsen or do not improve, proceed to next step		
Persistent Grade 2	**Additional systemic antipruritics**		
	Consider neurokinine 1 receptor antagonists e.g., aprepitant 125 mg day 1, 80 mg day 3, 80 mg day 5	V	C
	or		
	Consider omalizumab 300 mg s.c. every 4 weeks‡	IV§	B
	Reassess after 2–4 weeks; *if reactions worsen or do not improve, proceed to next step*		
Grade 3	**Skin-directed therapy**		
Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	Reinforce grade 2 management	IV†	B
	Systemic therapy		
	Consider systemic corticosteroids (e.g. prednisone 0.5–1 mg/kg body weight/day, 14-day taper)†,#	IV†	B
	GABA analogs, e.g. gabapentin 100–300 mg tid or pregabalin, 50–100 mg tid (titrate)	IV†	B
	If lesions worsen or do not improve, consider omalizumab 300 mg s.c. every 4 weeks†,#	IV§	B
	Discontinue or withhold ICI (at least improvement to grade 0/1)#		

ADL, activities of daily life; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors; s.c., subcutaneously; tid, 3 times a day.
†Ref. [23].
‡Prior to initiation of systemic immunomodulators (including prednisone and omalizumab), a skin biopsy with direct immunofluorescence is recommended.
§Ref. [33].
#A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.

2.[21,29,36,37] Systemic corticosteroids (0.5–1 mg/kg/day of prednisone equivalent), in addition to symptomatic measures used in grade 1–2, are preserved for grade 3 rashes and only after ruling out other dirAEs requiring a specific management (e.g. psoriasis). Oral steroids are tapered over 4 weeks after MR improvement.[21,36,38]

Recommendations with level of evidence are provided in Table 4.

Psoriasis-like rash

Psoriasis is considered one of the most common ICI-induced dirAEs. Both psoriasis exacerbation and de novo psoriasis have been reported.[40] Personal and familial history are significant risk factors and must be investigated prior to any ICI initiation.[41,42] The lesions occur after a median of 5–12 weeks after treatment initiation (Table 2).[23,41,43] Patients with psoriasis history are being affected earlier, as recently shown by Nikolaou et al. (mean

Table 4 Maculopapular rash: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1† macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning)	**Skin-directed therapy** Potent or superpotent topical corticosteroids (e.g., betamethasone dipropionate 0.05%, triamcinolone 0.1% or clobetasol 0.05% cream, over the skin lesions) Oral antihistamines – fragrance-free moisturizers (applied to full body surface) Continue ICI at current dose	IV‡	A
Grade 2† macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning); limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	*Reassess after 2–4 weeks; if reactions worsen or do not improve, proceed to next step*		
Persistent or intolerable grade 2† or **Grade 3**† macules/papules covering >30% BSA with moderate or severe symptoms (e.g., pruritus, burning); limiting self-care ADL	Reinforce grade 2 management Consider oral corticosteroids (0.5–1 mg/kg/day or equivalent with dose increase up to 2 mg/kg/day if no improvement†,§) Withhold ICI§ *Reassess after 2–4 weeks:* *- if reactions worsen or do not improve, proceed to next step* *- if reactions improve, start oral corticosteroids tapering* *- Rechallenge ICI when Grade ≤1, and after tapering oral corticosteroids at a dose ≤10 mg/d*	IV‡	A
Grade 4† Life-threatening consequences, urgent intervention needed.	Methylprednisolone 2 mg/kg/day or equivalent Permanently discontinue and urgent supportive measures	IV‡	A

ADL, activities of daily life; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†Check for rash-associated dermatosis and other skin disorders induced by immune checkpoint inhibitors (including lichenoid reactions, psoriasis, Grover's disease, bullous pemphigoid, or life-threatening cutaneous drug reactions).
‡Ref. [23].
§A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.

number of infusions 5.4 vs. 12.2, $P < 0.05$).[41] Psoriasis vulgaris with plaques (Fig. 2a) is the most common ICI-related type; however, all clinical variants (Fig. 2b–e) have been recorded, including inverse, scalp or pustular psoriasis.[41] Pathogenesis of ICI-induced psoriasis remains controversial. However, it has been hypothesised that overexpression of Th1/Th17-specific cytokines, such as IL-17 and IL-22 that follows PD1-blocking by ICIs may be involved.[44] Dermatological follow-up for initial diagnosis and management is required. Topical agents (corticosteroids, Vitamin D analogues) are prescribed in Grades 1/2 and supplementary to systematic treatment for patients with grade 3 or recalcitrant lesions.[41] If skin-directed therapies fail to provide symptomatic control, systematic treatment and narrow band UVB phototherapy should be considered (Table 5).

Data on systemic treatments in ICI treated patients remain scarce. Acitretin represents a first-line option among conventional therapies, since it can be safely used in cancer patients.[40,41,45] Methotrexate carries no increased risk for cancer recurrence, or development of a second tumour, with the slight exception of non-melanoma skin cancers.[46] Therefore, methotrexate is also deemed a safe option at low doses (10–25 mg/week). Cyclosporine has potential tumour-promoting effects and should be preferably avoided.

The use of novel antipsoriatic agents should be examined on a case-by-case basis. Apremilast therapy has been presented in small case series.[41,47,48] The hypothesis supporting its safety is based on the fact that it mostly interacts with the innate immune system.[49] However, we recommend the cautious use of apremilast since long-term safety data are lacking.[50] The decision for biologic treatments should be made on an individualised basis. However, since anti-TNFa have been routinely used for the treatment of gastrointestinal toxicity we support their use as first choice, until further evidence.[51]

Lichen planus-like rash (LPLR)

Lichen planus-like rash represents one of the most prevalent dirAEs, with a reported incidence ranging from 25% to almost 100% of all pruritic maculopapular rashes.[32,52,53] In our and

Table 5 Psoriasis-like rash: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 psoriatic plaques covering <10% BSA with or without symptoms	**Skin-directed therapy** Potent topical corticosteroids; vitamin D analogues; tazarotene 0.05%; coal tar; salicylic acid Multiple topical treatment modalities can be combined Continue ICI at current dose *Reassess after 2–4 weeks; if reactions worsen or do not improve, proceed to next step*	IV†	A
Grade 2 psoriatic plaques covering 10–30% BSA with or without symptoms or **Intolerable Grade 1**‡	Reinforce grade 1 management consider other treatments: narrowband ultraviolet B phototherapy§, acitretin 10–30 mg qd, methotrexate 10–25 mg/week ± apremilast 30 mg bid Withhold or continue ICI at current dose* *Reassess after 2 weeks:* *- If reactions worsen or do not improve, proceed to next step* *- If reactions improve, continue or rechallenge ICI when Grade≤1*	IV†	A
Intolerable Grade 2‡ or **Grade 3** Psoriatic plaques covering >30% BSA with or without symptoms Psoriatic plaques covering >30% BSA with or without symptoms	Reinforce grade 2 management Consider methotrexate 15–25 mg/week If reactions worsen or do not improve, consider biologics**,***: - anti-TNFa (infliximab, adalimumab) - IL-23 targeting agents (risarkizumab, guselkumab, ustekinumab) Discontinue or withhold ICI (at least improvement to grade 0/1)*	IV	B

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors; TNF, tumoral necrosis factor.
†Refs [40, 41].
§Narrowband UVB should be limited to patients with solid cancers other than melanoma. A shared-decision process is recommended for melanoma patients.
*A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.
‡Intolerable grade 1 or grade 2: Involvement of sensitive areas such as face, hands, genitals, nails, scalp; Disseminated lesions; mild to moderate psoriatic arthritis; DLQI > 10; severe symptoms (e.g. itch, burning).
**IL17 targeting agents should be generally avoided due to the known GI side effects.
***Short-term systemic corticosteroids (prednisolone 0.5mg/kg/day) should be preserved only for refractory Grade 3 lesions after a shared-decision process.

other investigators' experience, however, the overall incidence of LPLR is lower, representing <10% of all dirAEs.[6,21,23,37,54]

Lichen planus-like rash is particularly seen with anti-PD-1/PD-L1 agents used alone or in combination with anti-CTLA-4.[21,32,37,52,53,55] The lesions tend to be delayed, appearing after several weeks or months after treatment initiation (Table 2). Development of LPLR after ICI discontinuation has also been observed and lesions that last for months after the discontinuation of immunotherapy may also be encountered.[6,37,53–56]

The clinical presentation is variable, ranging from typical LP to hypertrophic, atrophic, ulcerative, bullous or papulosquamous lesions (Fig. 3a–c). Lesions mainly occur on the trunk and the limbs although dissemination is possible.[6,21,32,37,55] Predominant palmoplantar, hair and nail, mucosal, or distinct inverse involvement has been also described.[21,29,32,37,57] Pruritus can be severe and debilitating.[32,53]

Hypertrophic forms of LPLR may resemble squamous cell carcinoma (SCC).[21] Taking into account that eruptive SCCs and keratoacanthomas have been described with anti-PD-1, histopathologic examination should be considered in clinically ambiguous lesions.[58] Bullous LPLR can be distinguished from lichen planus pemphigoid with use of immunofluorescence studies.[21,52,59]

Histopathologic features include band-like lymphohistiocytic infiltrate along the dermal-epidermal junction, with patchy-to-florid vacuolar interface dermatitis and apoptotic keratinocytes, associated with variable parakeratosis, hypergranulosis, acanthosis, spongiosis, and dermal eosinophils.[12,21,32,33,37,52,55,57] Contrary to idiopathic LP, immunostaining individualise a mixed $CD4^+/CD8^+$ or a predominantly $CD4^+$ T-cell infiltrate.[12,32,55] However, LPLR induced by anti-PD-1/PD-L1 can be histologically indistinguishable from classic LP.[12]

Lesions are usually self-limiting and can be adequately managed with skin-directed therapy. First-line treatment involves conservative management with potent and very potent topical corticosteroids and treatment can be maintained in most

cases.[21,32,37,53,60] Intralesional triamcinolone acetonide injections may represent an alternative for localised, or hypertrophic lesions.[58]

In patients with refractory or severe lesions (grade 3) or concomitant mucosal involvement, systemic treatments, including corticosteroids (0.5–1 mg/kg/day for 4–6 weeks followed by a progressive tapering) and/or oral retinoids (20–30 mg/day, alitretinoin or acitretin) can be prescribed as second-line modalities.[21,23,32,37,53,55,61] Immunosuppressive drugs (methotrexate, azathioprine) have been sporadically proposed. Narrowband UVB should be restricted to patients with solid cancers other than melanoma.[32,52,62] Table 6 summarises the management recommendations for LPLR.

Vitiligo-like rash

Vitiligo-like lesions (VLL; Fig. 4a,b) consist of multiple, usually bilateral, depigmented macules, mostly appearing in association to anti-PD-1/anti-PD-L1, with a large predilection for melanoma patients.[29,37] By meta-analyses, the overall incidence was estimated as 8.3% for pembrolizumab and 7.5% for nivolumab in patients with melanoma.[20,37] However, a higher incidence (about 25%) has been reported in prospective studies.[37,63] The incidence is significantly lower with anti-CTLA-4.[21]

Vitiligo-like lesions develop after several months of treatment and can be preceded by an inflammatory phase.[21,37,63,64] Combination treatment is associated with a shorter time of onset.[52] Apart from large confluent white patches of classic vitiligo, small, multiple, asymmetric and more localised macules can be observed.[21,64] Histology is characterised by mild lymphocytic infiltrate along the basement membrane with few or no melanocytes in the epidermis and rare melanophages in the dermis.[12] Pathogenesis of VLL is not fully elucidated, but is deemed to result from a cross-reaction against antigens shared by melanoma cells and normal melanocytes (e.g. GP100, MART-1, TRP1–2 or tyrosinase).[21,63] Infiltration of same clonal $CD8^+$ T-cells was found both in melanoma tumour lesions and in vitiligo areas.[63]

Immune checkpoint inhibitors discontinuation because of VLL is not required (Table 7). VLL may anyhow persist despite treatment discontinuation.[21] Repigmentation after discontinuation was associated in several cases with disease progression or tumour recurrence.[8]

Table 6 Lichen planus-like rash: Management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning) **Grade 2** macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning); limiting instrumental ADL; rash covering>30% BSA with or without mild symptoms	**Skin-directed therapy** Potent or superpotent topical corticosteroids (e.g., betamethasone dipropionate 0.05%, triamcinolone 0.1% or clobetasol 0.05% cream, over the skin lesions) Oral antihistamines – fragrance-free moisturizers Continue ICI at current dose *Reassess after 2–4 weeks; if reactions worsen or do not improve, proceed to next step*	IV†	A
Persistent or intolerable Grade 2 or **Grade 2 with severe mucosal lesions**‡ or **Grade 3** macules/papules covering >30% BSA with moderate or severe symptoms (e.g., pruritus, burning); limiting self-care ADL	**Reinforce grade 2 management** consider oral corticosteroids (0.5–1 mg/kg/day for 4/6 weeks) and high-potency or very high-potency topical corticosteroids ± oral retinoids (alitretinoin, acitretinoin – 20–30 mg/day)§ Withhold ICI* *Reassess after 2–4 weeks:* - *If reactions worsen or do not improve, proceed to next step* - *If reactions improve, start oral corticosteroids tapering* - *Rechallenge ICI when G ≤ 1, and after tapering oral corticosteroids at a dose ≤10 mg/d*	IV†	A
/ **Recalcitrant lesions**	**Reinforce grade 3 management** Maintain oral corticosteroids (1 mg/kg/day) withhold or discontinue ICI* Consider other steroid-sparing agents: narrowband ultraviolet B phototherapy**, immunosuppressive drugs (e.g. methotrexate)* consider hospitalization until control of disease activity	V	B/C

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†Refs [19, 53].
‡Oral, perianal or vulvovaginal ulcerative lesions.
§The addition of oral retinoids will be decided according to the clinical presentation.
*A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.
**Narrowband UVB should be limited to patients with solid cancers other than melanoma.A shared-decision process is recommended for melanoma patients.

Topical treatments with corticosteroids or tacrolimus can be considered for localised lesions. Photoprotective measures and camouflaging limit the impact on QoL.

Autoimmune bullous disorders

Drug-induced AIBD (Fig. 5a–c) have been also described in association with ICI.[65,66] They are mostly linked to anti PD-1/PD-L1 agents.[59,67] BP is the predominant phenotype. The overall incidence of bullous dermatoses with anti-PD-1/anti-PD-L1 agents is estimated about 1%,[59] whereas the reported incidence for anti-PD-L1 agents alone ranges from 1.3% to 5%, raising concerns of a higher risk with the use of the latter.[68] Lichen planus pemphigoides, pemphigus, dermatitis herpetiformis, linear IgA bullous dermatosis or mucous membrane pemphigoid have been much more rarely reported in association with ICIs.[59,67,69–74]

Pathogenesis of ICI-induced BP is vague, but it more likely represents a secondary consequence of both B- and T-cell activation in the context of immune stimulation. PD-1 inhibition may activate antibody-secreting B cells and inhibit immunosuppressive B regulatory cells. Furthermore, ICI-induced BP may result by the cross-reaction of BP180 and BP230 antigens of the dermoepidermal junction of the skin with those expressed by the neoplastic cells.[10] Finally, PD-1/PD-L1 inhibition may unmask incipient BP, which may partially explain persistence of BP after cessation of immunotherapy in a few patients.[1,66]

The eruption develops from weeks to several months after treatment initiation and manifests with tense bullae and vesicles involving the trunk and extremities.[59,65,67,71,72] A pre-bullous phase, characterised by intractable pruritic and non-specific maculopapular or urticarial plaques may precede bullae formation.[69,73] Mucosal involvement is more common as compared to classic BP, with an incidence close to 40% in the most recent series.[65,73]

Histopathology is characterised by subepidermal clefting containing fibrin and eosinophils and dermal infiltrates composed of lymphocytes, eosinophils and often neutrophils.[12,69] Direct immunofluorescence (DIF and salt-split DIF), demonstrating linear deposits of IgG and C3 to the epidermal part of the clefting and ELISA studies, mostly detecting BP180 and less often BP230 antibodies, are of high diagnostic value and should be included in the workup.[59,65,73]

Bullous pemphigoid has a profound impact on ICI therapy, resulting in permanent discontinuation in 20%–50% of patients.[59,65,67,69] Early diagnosis and appropriate intervention seem to facilitate adequate control of BP, limiting treatment withdrawals. ICI-triggered BP may rarely persist for several months after discontinuation, demanding long-term monitoring.[67]

Recommended therapeutic strategy for BP is analytically shown in Table 8. Management decisions for the rare immunobullous diseases should be made on an individualised basis.

Hair dirAEs

The overall incidence of ICI-induced alopecia is low (1.03% for PD-1/PD-L1 and ~5.1% for anti-CTLA-4).[75,76] Any grade of alopecia may negatively impact patients' QoL,[77] underscoring the need for effective supportive care.

Immune checkpoint inhibitors-related common hair disorders include in order of frequency; non-scarring alopecia [alopecia areata, alopecia totalis, and alopecia universalis (Fig. 6b)],[76,78] hair depigmentation or poliosis[29] (Fig. 6a), hair repigmentation[79] and persistent changes of hair texture.[80] Diagnosis is based on thorough medical history and clinical examination including trichoscopy. Biopsy is recommended in case of diagnostic uncertainty.

Table 7 Vitiligo-like rash: Management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	UVA/UVB photoprotection No treatment† or potent topical corticosteroids ± topical calcineurin inhibitors Continue ICI at current dose *Reassess after several weeks and monitor for change in severity, clinical improvement, patient satisfaction and psychologic impact; consider camouflage if needed* *If reactions worsen or do not improve, proceed to next step*	III-IV	A
Grade 2 Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	UVA/UVB photoprotection No treatment† or potent topical corticosteroids and/or topical calcineurin inhibitors and/or narrowband ultraviolet B phototherapy‡ Continue ICI at current dose *Reassess after several weeks and monitor for change in severity, clinical improvement, patient satisfaction and psychologic impact; consider camouflage if needed*	III–IV	A

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.
‡Narrowband UVB should be limited to patients with solid cancers other than melanoma.A shared-decision process is recommended for melanoma patients.

Table 8 Bullous pemphigoid: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 (<10% BSA)	Superpotent topical corticosteroids (30–40 g/day of clobetasol propionate applied, bid, over the whole body area for up to 15 days from disease control) continue ICI at current dose	IV	A
	Reassess after 2–4 weeks; if reactions do not improve, consider the addition of oral prednisolone at a dose ≤< 10 mg/day *If reactions worsen, proceed to next step*		
Grade 2 (10%–30% BSA)	Consider oral corticosteroids (0.5 mg/kg/day, prednisolone) and superpotent topical corticosteroids wound care with petrolatum-based emollients and non-stick dressings are recommended withhold ICI†	IV	A
	Reassess after 2–4 weeks : *if reactions worsen or do not improve, increase the dose of oral prednisolone to 1 mg/kg/day or proceed to next step* *- if reactions improve, start oral corticosteroids tapering* *- Rechallenge ICI when G ≤ 1, and after tapering oral corticosteroids at a dose ≤ 10 mg/d*		
Grade 3‡ (>30% BSA)	Oral corticosteroids (0.5–1.0 mg/kg/day, I prednisolone) Consider a steroid-sparing agent†,‡ Withhold or discontinue ICI† consider hospitalization until control of disease activity	IV	A
	Reassess after 2 weeks: *- if reactions worsen proceed to next step* *- if reactions improve start oral corticosteroids tapering;* *- Re-challenge ICI when G ≤ 1, and after tapering oral corticosteroids at a dose ≤ 10 mg/d*		
Grade 4§ (>30% BSA; with fluid and/or electrolyte abnormalities)	Hospitalize (intensive care or burn unit) the patient and use IV methylprednisolone 1–2 mg/kg/day until control of disease activity, then switch to prednisolone 0.5–1 mg/kg/day and start tapering discontinue ICI†	V	A

BSA, body surface area; CTCAE, Common terminology criteria for adverse event; ICI, immune checkpoint inhibitor.
†A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.
‡Tetracycline, niacinamide, dapsone, methotrexate, omalizumab, rituximab.
§Cultures of skin and/or blood samples are mandatory if there are signs of infection.

It has been hypothesised that the inflammatory state rendered by PD-1/PD-L1 immunotherapy and cytotoxic tumour destruction may result in a proinflammatory state, collapsing the immune privilege of the hair follicle, culminating in hair shaft pigment changes,[79] or even switch to a profoundly pro-inflammatory reaction provoking non-scarring alopecia.[81]

Management is mostly based on case series, case reports, and expert opinion (level of evidence V). Current treatment recommendations for alopecia areata include intralesional and topical high-potency steroids, and systemic immunomodulators (Table 9).[82] For patients treated with ICIs, we recommend a shared-decision process that involves a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting) and treatments risks and benefits. For hair colour changes, camouflage techniques can be offered (e.g. crayons, powder, hair dye).[83]

Nail dirAEs

Nail irAEs are usually underreported. Although not systemically investigated, they are characterised by a late time of onset, extended up to several months. In some cases, lesions may persist after drug ICI discontinuation.[84] A wide range of nail changes (Fig. 7a–c) has been reported in association to ICI treatment: lunular erythema, onychorrhexis, thinning of the nail plate, fragility, longitudinal fissures, splitting in layers, onycholysis and onychomadesis. The condition may affect few to several finger- or toenails. However, classification of nail toxicity remains to be determined, since most physicians are reluctant to biopsy the nail unit. In a review article, it has been hypothesised that the majority of the nail changes were psoriasiform or lichenoid in nature.[21] Accordingly, histopathologic findings reported recently in two patients with onycholysis were consistent with a lichenoid reaction.[85] There are also several reports of new-onset or exacerbations of nail psoriasis associated to ICI treatment.[40,41] De novo, histologically confirmed, nail psoriasis, presenting as nail thickening along with periungual erythema has been also seen with nivolumab.[84,86]

If several nails are involved, or the nail lesions are not responding to topical therapy or are associated with skin involvement, systemic therapy should be discussed. In this context, oral retinoids (acitretin, alitretinoin) represent the first-line therapy.[85,87]

Oral mucosal dirAEs

Oral irAEs are reported in about 7% of individuals under ICI treatment[88] but their overall incidence is probably

Table 9 Alopecia areata: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hairpiece to camouflage	No treatment† or Intralesional corticosteroids (triamcinolone) ± potent or superpotent topical corticosteroids (e.g., betamethasone dipropionate 0.05%, triamcinolone 0.1% or clobetasol 0.05% lotion) + topical minoxidil 5% solution or foam. continue ICI at current dose Reassess after 4 weeks and monitor for change in severity, improvement, patient satisfaction and psychologic impact; continue dermatologic therapy as needed if success ful response *if reactions worsen or do not improve, proceed to next step*	V‡	A
Grade 2 Hair loss more than 50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	No treatment† or intralesional corticosteroids (triamcinolone) ± potent or superpotent topical corticosteroid (e.g. betamethasone dipropionate 0.05%, triamcinolone 0.1% or clobetasol 0.05% lotion) + topical minoxidil 5% solution or foam. Other therapies could be considered† including topical immunotherapy with diphenylcyclopropenone ± Janus kinase inhibitors. Continue dermatologic therapy as needed if successful response continue ICI at current dose Reassess after 4 weeks and monitor for change in severity, clinical improvement, patient satisfaction and psychologic impact; consider scalp prothesis or camouflage if needed *If reactions worsen or do not improve, proceed to next step*		
Recalcitrant alopecia (any grade) (to intralesional corticosteroids and topical therapies)	No treatment† or Consider other steroid-sparing agents/immunosuppressive drugs† (e.g. methotrexate) monitor for change in severity, clinical improvement, patient satisfaction and psychologic impact; or scalp prothesis or camouflage if needed continue ICI at current dose if positive cancer outcome, with psychological support if needed	V‡	C

CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.
‡Ref. [82].

underestimated due to the lack of systematic oral examination.[89] Oral changes mainly develop within the first 12 months.[88,90] Typical oral lichenoid reactions (OLR) can develop with both anti-PD-1/PD-L1 antibodies (Fig. 8a,b).[29,32,55,89–93] They can be accompanied by cutaneous, genital and/or ungueal lichenoid lesions.[21,57,89] OLR can display typical reticulated white streaks, together with papular, plaque-like, ulcerative, or atrophic/erythematous lesions[21,29,57,92] involving both keratinised and nonkeratinised mucosae. They mostly occur 3 months after treatment initiation.[21,32,89,93]

Histological findings and ancillary immunostaining reveal patchy and/or florid lichenoid interface dermatitis in the upper lamina propria with predominantly CD4/CD8-positive band-like T cell infiltrates.[12,21,57,92,93] DIF should be systematically performed in case of suspected lichen planus pemphigoid or AIBD with mucosal involvement.[21,74,90]

Oral lichenoid reactions are generally mild, self-limited and manageable with mucosa-directed therapy (Table 10). First-line treatment involves maintenance of good oral hygiene and topical corticosteroids (dexamethasone 0.1 mg/ml solution, prednisolone mouth-rinse, clobetasol 0.05% cream, or flucinonide 0.05% gel).[57,90,93] In severe cases, systemic corticosteroids (0.5–1 mg/kg/day for 2–4 weeks followed by a progressive tapering) can be discussed on a case-by-case basis, in an effort to maintain ICI treatment.[21,90]

Sicca syndrome with xerostomia (Fig. 8c) is probably the most frequent oral irAE, seen in 2%–6% of patient.[88,90] It generally develops abruptly, within 3 months after treatment initiation, with a predilection for elderly males.[94,95]

Xerostomia remains of mild intensity in most cases but severe cases can also occur.[21,89,94,95] Xerostomia can be accompanied by thirstiness, mucosal and dental hypersensitivity.[21,89,92,94,95] Secondary mucosal ulcerations may result in burning sensation. Salivary glands biopsy reveals mild-to-severe sialadenitis, distinct from Sjögren's Syndrome, with a diffuse T-cell infiltrate. A slight predominance of $CD4^+$ over $CD8^+$ and scattered $CD20^+$ B cells are usually noted.[94–96] Anti-SSA/SSB antibodies are typically negative but sporadic cases of Sjögren's syndrome have been also reported.[97]

Table 10 Oral mucosal lichenoid reactions: Management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Prevention/Grade 1 asymptomatic oral mucosal lichenoid reactions or mild symptoms	Pre-therapeutic screening to eliminate potential sources of trauma (restorative material, prosthesis), identify dental or periodontal outbreaks and ensure proper treatment Maintain good oral hygiene with basic oral care interventions† Continue ICI at current dose	V IV	B A
Grade 2 Oral lesions with moderate pain, modified diet may be required; reticulated white streaks together with papular, plaque-like, ulcerative, or atrophic/erythematous lesions	Reinforce grade 1 management Oral coating, lubricating, wetting agents Mucosa-directed therapy: first-line treatment with potent or superpotent topical corticosteroids (dexamethasone 0.1 mg/ml solution, prednisolone mouth rinse, topical clobetasol 0.05% cream, topical flucinonide 0.05% gel), tacrolimus gel Continue ICI at current dose *Reassess within 2–4 weeks; if reactions worsen or do not improve, proceed to next step*		
Persistent or intolerable grade 2 or **Oral Grade 2 associated with extra oral lichenoid reactions**‡ or **Grade 3** Ulcerative oral lichenoid lesions, severe pain interfering with oral intake	Reinforce grade 2 management consider oral corticosteroids (0.5–1 mg/kg/day) for 2–4 weeks ± oral retinoids (alitretinoin, acitretinoin – 20–30 mg/day)§ Withhold ICI** Reassess after 2–4 weeks: *- if reactions worsen or do not improve, proceed to next step* *- if reactions improve, start oral corticosteroids tapering* *- Rechallenge ICI when G ≤ 1, and after tapering oral corticosteroids at a dose ≤10 mg/d*	V	A***
/ **Recalcitrant oral mucosal reactions**	Reinforce grade 3 management Oral corticosteroids (1 mg/kg/day) withhold or discontinue ICI** Consider other steroid-sparing agents: immunosuppressive drug (e.g. methotrexate) Supportive care, support oral intake, nutritional status evaluation	V	A***

CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†Educational measures based on tooth and mucosal brushing, mouth rinsing, interdental flossing to improve oral hygiene and alleviate oral discomfort.
‡Cutaneous, perianal or vulvovaginal ulcerative lesions
§The addition of oral retinoids will be decided according to the clinical presentation (hyperkeratotic and reticular lesions).
***Ref. [21].
**A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.

Oral basic care and supportive measures (hydration, lubrication, artificial saliva, saliva substitute, spa water) are recommended to limit oral reaction.[90,98] Oral corticosteroids (0.5 mg/kg/day) for 2–4 weeks followed tapering should be considered in recalcitrant or severe cases (Table 11). Monitoring for dental hypersensitivity, vitamin deficiency (B12, folates, iron), or candidiasis superinfection is advised.[94,95] The efficacy of oral pilocarpine in this context remains to be evaluated. ICIs is usually maintained but temporary interruption may be required in severe cases.

Rare dirAEs

Therapeutic guidelines for rare dirAEs are elaborated using the scarce published data and the authors' personal experience. In all cases, management of such AE should always be discussed in a multi-disciplinary way, involving a dermatologist.

- Whereas pulmonary granulomata and hilar/mediastinal lymphadenopathy are a well-established irAE, cutaneous granulomatous/sarcoid-like eruptions (GE) have been also described in the context of ICI treatment.[99,100]

Eighty cases of ICI-induced GE have been reported with both anti-CTLA-4, anti-PD-1 or in combination, and mostly in patients with melanoma. Exclusive cutaneous/subcutaneous involvement is uncommon, noted in only 8/80 patients.[99,100] The median time of onset is 6 months.[100] The most common site of skin involvement is upper and lower extremities. As in primary sarcoidosis, localisation to prior scars or tattoos has been described, as well as panniculitis.[12] Cutaneous biopsy typically reveals non-caseating epithelioid granulomas.[12]

If cutaneous involvement remains isolated, ICI should not be interrupted and topical corticosteroids primarily considered.

- Suprabasal acantholytic dermatoses are sporadically reported in the literature.[101] The most common

Table 11 Sicca syndrome: management algorithm and recommendations

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Pre-therapeutic screening to eliminate potential sources of trauma (restorative material, prosthesis), identify dental or periodontal outbreaks and ensure proper treatment. Maintain good oral hygiene with Basic oral care interventions† Continue ICI at current dose Reinforce grade 1 management Dietary recommendations	V V	B B
Grade 2 Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1–0.2 ml/min	Reinforce saliva stimulation and hydration‡, avoid places with dry ambient air, maintain nasal hygiene (regular cleaning with saline solution) to facilitate nasal breathing (and thus limit dry mouth breathing), lubricate lips several times a day Discuss introduction of saliva stimulants§ Screen dental hypersensitivity and implement caries prevention measures (topical fluoride) Continue ICI at current dose *Reassess within 2–4 weeks; if reactions worsen or do not improve, proceed to next step*		
Persistent or intolerable grade 2 or **Grade 3** Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	Reinforce grade 2 management Accessory salivary glands biopsy, anti- SSA/SSB serum screening (to rule out ICI-induced Sjögren's syndrome) oral corticosteroids (0.5 mg/kg/day) for 2–4 weeks In case of associated burning sensation ± dysesthesia screening for iron and vitamin deficiencies (B12, folates) Detect herpetic/candidiasis superinfection Manage speech and taste associated disorders with dietary education, Supportive care, support oral intake Withhold ICI* *Reassess after 2–4 weeks:* *- if reactions worsen or do not improve, proceed to next step* *- if reactions improve, start oral corticosteroids tapering* *- Rechallenge ICI when G ≤ 1, and after tapering oral corticosteroids at a dose ≤10 mg/d*	IV	A*
Recalcitrant sicca syndrome	Reinforce grade 3 management Oral corticosteroids (1 mg/kg/day) Withhold or discontinue ICI**	IV	A*

CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.
†Educational measures based on tooth and mucosal brushing, mouth rinsing, interdental flossing to improve oral hygiene and alleviate oral discomfort.
‡Sugar-free gum or candy stimulants, artificial saliva, saliva substitutes, Spa water.
§Pilocarpine (dose 30 mg/day), cevimiline.
*Refs [94, 95].
**A shared-decision process is recommended, involving a careful consideration of patient's preferences, psychologic impact, tumour stage (adjuvant vs. metastatic setting), response to ICI and treatments risks and benefits.

manifestation is the development of, erythematous papules or papulovesicular lesions with severe pruritus on the trunk, mimicking Grover's disease. Histological examination is characterised by suprabasal clefts with acantholytic cells and dyskeratosis involving the epidermis. However, a spectrum of other acantholytic dermatologic disorders has been also described with anti-PD-1 and diagnosis can be challenging.[12] In most cases, ICI should not be interrupted and topical steroids considered as first-line therapy.[101]

- Only a few ICI-induced scleroderma and scleroderma-like cases have been reported, predominantly occurring with anti-PD-1.[102,103] Both morphea and limited/diffuse cutaneous systemic sclerosis have been observed, with sometimes unusual clinical features.[102] Scleroderma-like changes appear after at least 3 months of ICI initiation. Autoantibodies are repeatedly negative. Worsening of previously known morphea has also been reported.[102] All reported patients so far were effectively treated with systemic corticosteroids, when needed, together with ICI interruption.[102] Other proposed treatments include methotrexate, mycophenolate mofetil, intravenous immunoglobulins, and hydroxychloroquine.[102] In our opinion, in non-severe forms, ICI may be maintained with close monitoring.
- In the same way, eosinophilic fasciitis (EF) can also occur, with a median onset of 11 months. Most reported patients had peripheral eosinophilia.[104] All patients discontinued ICI, and 9 of 10 started on systemic immunosuppressive therapy, including prednisone with different regimens

ranging from 0.5 to 1 mg/Kg daily, methylprednisolone pulse, infliximab, mycophenolate mofetil, methotrexate or sirolimus.[104]

- Systemic and cutaneous leukocytoclastic vasculitis have been scarcely reported with anti-PD-1. Lesions can be debilitating with skin necrosis.[105] Screening for autoantibodies and serum markers of autoimmunity are usually negative. Extracutaneous involvement must always be ruled out and oral corticosteroids considered regarding to the severity of AE.[105] The decision of maintaining, withholding or discontinuing the oncologic therapy depends on the severity of involvement and should be taken on an individualised basis.
- Development of inflammatory acne-like lesions has been sporadically reported with both anti-CTLA-4 and anti-PD-1, sometimes with microbial superinfection.[106]

Potentially life-threatening dirAEs

Severe cutaneous adverse reactions (SCARs) such as drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), Stevens-Johnson syndrome (SJS)/TEN, and acute generalised exanthematous pustulosis (AGEP) have occasionally been associated with ICIs. Incidence of SCARs remains unknown. In PubMed/MEDLINE database, Maloney et al. recently identified 12 cases of SJS, 5 TEN and 1 SJS/TEN.[107] Cases with newly approved anti-PD-1 and anti PD-L1 are also registered in VigiAccess (http://www.vigiaccess.org/ date of consultation October the 1st 2021). ICI-associated DRESS has been described with the use of ipilimumab, nivolumab, pembrolizumab, cemiplimab and atezolizumab. At VigiAccess database 48 cases are reported to date.[108]

Immune checkpoint inhibitors-related SCARs usually present with delayed onset and the initial manifestation may be that of a non-specific maculopapular rash. The mean time of onset for DRESS ranges from 40 to 164 days.[108–111] Presentation can delay up to 12 weeks for AGEP and SJS/TEN, with longest recorded latencies of 197 days for TEN and 251 days for SJS.[107,112,113] Considering the prolonged lag time in the latter cases, a definite aetiologic link remains to be demonstrated.

Although the RegiSCAR and EuroSCAR diagnostic criteria for DRESS and AGEP may facilitate diagnosis it is still unclear whether these criteria remain valid with ICIs. The cornerstone of treatment is early recognition, skin biopsy, hospitalisation and discontinuation of the offending agent. Multidisciplinary approach and supportive care are recommended. Pharmacokinetic properties of ICI with long half-lives must be taken into consideration. Plasmapheresis has been proposed to improve drug elimination, although its efficacy remains to be determined.[107]

The dose of corticosteroids may be adapted to the severity of DRESS. The therapeutic benefit of systemic corticosteroids in the management of SJS/TEN remains controversial and some authors favour treatment with cyclosporine.[113,114] However, the use of corticosteroids in this context of ICI treatment appears reasonable and should be proposed. Short courses of steroids seem also effective in AGEP.[112,113]

Immune checkpoint inhibitors-induced TEN carries a higher mortality rate. No cases of mortality due to SJS or AGEP are reported to date.[107] Re-challenging with the offending drug is not recommended.[115]

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Data availability statement

Data available on request from the authors.

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