Immune checkpoint-mediated psoriasis: A multicenter European study of 115 patients from the European Network for Cutaneous Adverse Event to Oncologic Drugs (ENCADO) group

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Background: Immune checkpoint inhibitor (ICI)–mediated psoriasis poses significant diagnostic and therapeutic challenges.

Objective: To report data on ICI-mediated psoriasis, emerging from the largest cohort to date, to our knowledge, and to propose a step-by-step management algorithm.

Methods: The medical records of all patients with ICI-mediated psoriasis were retrospectively reviewed across 9 institutions.

Results: We included a cohort of 115 individuals. Grade 1, 2, and 3 disease severity was reported in 60 of 105 (57.1%, 10 missing data), 34 of 105 (32.4%), and 11 of 105 (10.5%), respectively. The ratio between exacerbation and de novo cases was 1:4.3. The most common systemic therapy was acitretin (23 patients, 20.1%), followed by systemic steroids (8 patients, 7%), apremilast (7 patients, 6.1%), methotrexate (5 patients, 4.3%) and biologics (4 patients, 3.6%). Overall, 29 of 112 patients (25.9%) interrupted and 20 of 111 (18%) permanently discontinued ICIs because of psoriasis. Body surface area of greater than 10% at baseline had a 3.6 increased risk for ICI treatment modification (odds ratio, 3.64; 95% confidence interval, 1.27-10.45; $P = .03$) and a 6.4 increased risk for permanent discontinuation (odds ratio, 6.41; 95% confidence interval, 2.40-17.11; $P < .001$). Guttate psoriasis and grade 2 or 3 disease were significant positive predictors for antitumor response of ICI, whereas pruritus was a negative predictor.

Limitations: Retrospective design.

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Conclusion: Acitretin, apremilast, and methotrexate are safe and effective modalities for ICI-mediated psoriasis. In most cases, ICI can be completed unhindered. A therapeutic algorithm is proposed. (J Am Acad Dermatol 2021;84:1310-20.)

Key words: adverse events; immune checkpoint inhibitors; immunotherapy; nivolumab; pembrolizumab; psoriasis; skin toxicity.

CAPSULE SUMMARY

- Cutaneous toxicities represent a crucial limitation for immune checkpoint inhibitor applicability.
- Psoriasis affecting more than 10% of the body surface area as well as pustular psoriasis increase the risk of treatment modification/interruption. Guttate psoriasis and grade 2 or 3 disease may be significant positive prognostic indicators for antitumoral effect of immune checkpoint inhibitors.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies targeting cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1). Their addition in our armamentarium has radically transformed the therapeutic arena in oncology, providing the potential of high-level and durable responses in a large number of diverse malignancies.

The introduction of ICIs has resulted in the recognition of a new spectrum of immune-related adverse events (irAEs) that may occasionally limit their use.[1] The nature of irAEs has not been completely elucidated; however, it is meaningful that they are mostly immune mediated, resulting from the T-cell activation of cytotoxic $CD4^+/CD8^+$.[2] Skin toxicities are the most prevalent irAEs related to immunotherapy. Lichenoid reactions, maculopapular rashes, vitiligo, and other autoimmune skin diseases, including bullous disorders, have been reported in the literature.[3-5]

Considering that the use of anti–PD-1 anti–PD-L1 antibodies is relatively new, our experience with the management of immune-triggered skin toxicity remains empirical and occasionally exploratory. In the current article, we present our experience with immunotherapy-triggered psoriasis, focusing on disease phenotypic characteristics and management.

PATIENTS AND METHODS

This was a multicenter, retrospective study of psoriasis related to immunotherapy, conducted in the name of the European Network for Cutaneous Adverse Event to Oncologic Drugs (ENCADO) group. For the aims of the study, we used the databases of 9 oncodermatology units from Greece, France, Italy, Spain, and Argentina and searched for psoriasis cases developing through the treatment course with ICI until the end of December 2019. Inclusion criteria were patients developing psoriasis after anti–PD-1 or anti–PD-L1 treatment with available data on sex, age, psoriasis type(s), type of immunotherapy, primary cancer, and the number of ICI doses until the event. We also recorded and analyzed more parameters including personal/family history of the disease, psoriasis grading and pruritus, the need for interruption or ICI discontinuation, the therapeutic interventions, and the treatment outcomes. We recorded epidemiologic data of the patients including sex, age, primary cancer, psoriasis subtype(s), and personal/family history of the disease. The severities of psoriasis and pruritus were classified by using the Common Terminology Criteria for Adverse Events. Disease severity was classified as grade 1 (<10% body surface area [BSA], mild), grade 2 (10%-30% BSA, moderate) and grade 3 (>30% BSA, severe). The type of immunotherapy, number of ICI doses until the event, need for interruption or ICI discontinuation, therapeutic interventions, and treatment outcomes were also recorded. The therapeutic responses to psoriasis treatment were evaluated based on the reduction of BSA, and it was graded as no response (<30% BSA reduction of the initial BSA involved), partial response (30%-80% BSA reduction) and excellent response (>80% BSA reduction). Best oncologic response to immunotherapy was recorded and graded according to the Response Evaluation Criteria in Solid Tumors criteria.[6]

Statistical analysis

For continuous variables, we conducted a descriptive analysis calculating the mean and standard deviation (SD), and we checked for normality using the Kolmogorov-Smirnov test. Also, the Mann-Whitney *t* test and Kruskal-Wallis analysis of variance were used for the comparisons between them. Pairwise comparisons were also conducted. For dichotomous and categorical variables, the Pearson chi-square test was used for the association between the variables. Crude and

Abbreviations used:

BSA: body surface area
CI: confidence interval
ICI: immune checkpoint inhibitors
irAE: immune-related adverse event
OR: odds ratio
PD-1: programmed cell death protein 1
PD-L1: programmed death ligand 1
SD: standard deviation
TNF-α: anti-Tumor Necrosis Factor-α

adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated from univariate and multivariate conditional logistic regression, respectively. An alpha level of 0.10 was used as a cutoff for variable removal in the automated model selection for multivariate logistic regression. A survival analysis with the Kaplan-Meier method and log rank test for the comparison of time to response to psoriatic treatment were also conducted. All the statistical tests were 2 sided, and the level of significance was set at $\alpha = 0.05$. Data analysis was carried out by using SPSS Statistics for Windows, version 25.0 (IBM).

RESULTS

European Network for Cutaneous Adverse Event to Oncologic Drugs group members provided data of 115 patients with anti−PD-1/PD-L1−induced psoriasis that were included in the study. The mean (SD) follow-up period after psoriasis diagnosis was 9.3 (7.09) months.

Demographic characteristics of the study group are listed in Table I. Thirty-three of 115 (30.8%) patients had a personal history of psoriasis; in 20 out of 33 of them, the disease was active and clinically apparent upon ICI initiation. Data about family history of psoriasis were available in only 93 patients and was positive in 32 of them (34.4%).

The mean number (SD) of drug doses until psoriasis onset or exacerbation was 11.2 (14.9). In patients with clinically present psoriasis upon ICI initiation, deterioration of the disease was recorded sooner compared to those with no active psoriatic at baseline (mean number of infusions, 5.4 vs 12.2; $P < .05$) (Table II). No dosage differences were noted among anti−PD-1 and anti−PD-L1 agents or with regard to any other specific drug of this group. Patients with non−small-cell lung cancer developed psoriasis sooner compared to those with melanoma (9.7 vs 20.8 mean number of infusions), but this was not statistically significant (Fig 1, *A*). The number of infusions until psoriasis development or deterioration was higher in women compared to men (14.9 vs 10.1, respectively; $P = .025$).

Thirty of 107 patients (28%) developed additional cutaneous irAEs, namely, macular rash (8 patients), vitiligo (7 patients), and lichen planus (5 patients). Another 20.8% (20/96) of cases were complicated by systemic irAEs.

Clinical characteristics

Plaque psoriasis was the most commonly diagnosed clinical form (49/115, 42.6%), followed by palmoplantar (14/115, 12.2%) (Table I). Interestingly, 30 of 115 (26.1%) patients simultaneously or subsequently developed more than 1 clinical subtype of psoriasis. Nail involvement was recorded in 37 of 115 cases (32.7%), whereas 8.1% reported symptoms of psoriatic arthritis. Pruritus was present in 67 of 115 (58.3%) patients, including 38 (33%) grade 1, 21 (18.3%) grade 2, and 8 (7%) grade 3 reactions. No differences were found regarding number of infusions and type of psoriatic lesion (Fig 1, *B*). The mean (SD) BSA affected at visit 1 was 15.9% (17.22), and the worst mean BSA during follow-up was 16.3% (15.9). Fig 2 illustrates representative cases of different psoriatic phenotypes at baseline.

Psoriasis treatment and outcomes

Sixty-eight of 115 patients (59.1%) were solely treated with topical agents, mainly topical steroids (37 patients), followed by calcipotriol plus betamethasone (26 patients) and topical retinoids (tazarotene gel) plus topical steroids (1 patient). Four patients underwent narrowband ultraviolet B phototherapy combined with topical steroids (2 patients) or with calcipotriol plus betamethasone (2 patients). Forty-seven patients (40.9%) were treated with both systemic and topical agents (Supplementary Table I; available via Mendeley at https://doi.org/10.17632/m7w8sszs6y.2). The most common systemic therapy was acitretin monotherapy (21 patients, 18.3%; 10-25 mg/day), followed by systemic steroids (8 patients, 7%), apremilast (7 patients at standard dose, 6.1%), methotrexate (5 patients, 4.3 %; 7.5-20 mg/week) and biologics (4 patients, 3.5%). Systemic steroids were prescribed at an initial dose of 25 to 50 mg/day, with a gradual decrease in a mean period of 5.8 weeks. Acitretin was used in combination with topical corticosteroids or/and calcipotriol (16 patients, 76.2%) or in combination with phototherapy (narrowband ultraviolet B, 5 patients, 23.8%). Four patients were treated with biologic agents, including 2 with anti-Tumor Necrosis Factor (TNF) - α (adalimumab and infliximab), 1 with ustekinumab and 1 with the combination of acitretin and guselkumab. Eighteen of 23 patients treated with acitretin showed either

Table I. Epidemiologic and clinical characteristics at baseline and therapeutic intervention (N = 115)

Characteristics	Value
Sex, n (%)	
Male	88 (76.5)
Female	27 (23.5)
Age, y, mean (SD)	
Male	68.5 (9.3)
Female	63.7 (11.8)
Primary cancer, n (%)	
NSCLC	69 (60)
Melanoma	17 (14.8)
Head and neck SCC	6 (5.2)
Renal cell carcinoma	6 (5.2)
Urothelial carcinoma	6 (5.2)
Hodgkin lymphoma	2 (1.7)
Merkel cell carcinoma	1 (0.9)
Hepatocellular carcinoma	3 (2.6)
Gastric cancer	2 (1.7)
Mesothelioma	1 (0.9)
Ovarian cancer	1 (0.9)
Pulmonary neuroendocrine cancer	1 (0.9)
Immune checkpoint inhibitor, n (%)	
Anti—PD-1	99 (86.1)
Nivolumab	68 (59.2)
Pembrolizumab	30 (26.1)
Spartalizumab	1 (0.8)
Anti—PD-L1	16 (13.9)
Durvalumab	6 (5.2)
Atezolizumab	9 (7.9)
Avelumab	1 (0.8)
Anti—PD-1/PD-L1 monotherapy, n	
Yes	100
No	15
Ipilimumab	2
Cabozantinib	1
Pazopanib	1
Bevacizumab	1
Capmatinib	1
Anti—lymphocyte activation gene-3	1
Chemotherapy (platinum base)	6
Dabrafenib	2
Psoriasis type, n (%)	
Plaque psoriasis	49 (42.6)
Pustular psoriasis	8 (7)
Palmoplantar psoriasis	14 (12.2)
Guttate psoriasis	8 (7)
Nail psoriasis	2 (1.7)
Inverse psoriasis	1 (0.9)
Erythrodermic psoriasis	3 (2.6)
>1 Type, n	30 (26.1)
Plaque and palmoplantar psoriasis	11
Plaque, palmoplantar, and guttate	11
Plaque, palmoplantar, and pustular	4
Inverse and palmoplantar	2
Pustular, palmoplantar, and guttate	2
Grade (first visit), n (%)	
1 (<10% BSA, mild)	60 (57.1)
2 (10%-30% BSA, moderate)	34 (32.4)
3 (>30% BSA, severe)	11 (10.5)
Treatment, n (%)	
Topicals monotherapy	68 (59.1)
Acitretin	21 (18.3)
Apremilast	7 (14.8)
Methotrexate	5 (4.3)
Steroids	8 (7)
Anti—TNF-α	2 (1.7)
Ustekinumab	1 (0.9)
Acitretin + guselkumab	1 (0.9)
Acitretin followed by methotrexate	1 (0.9)
Acitretin followed by apremilast	1 (0.9)

BSA, Body surface area; *NSCLC,* non—small-cell lung cancer; *PD-1,* programmed cell death protein 1; *PD-L1,* programmed death ligand 1; *SCC,* squamous cell carcinoma; *SD,* standard deviation; *TNF,* tumor necrosis factor.

excellent response of psoriasis with complete clearance of the lesions (6/23, 26%) or partial response (12/23, 52.1%). A significant clinical improvement (excellent response or partial response) was also reported in all patients treated with apremilast. All patients treated with systemic steroids also showed a positive clinical response. Regarding biologics, partial response was observed in 1 patient treated with infliximab and in 1 patient treated with ustekinumab, whereas 2 individuals did not response to adalimumab and guselkumab. The first nonresponder had intolerable grade 2 disease presenting with plaques and inverse and guttate lesions, and the palms, soles, and nails were also involved. The second nonresponder had grade 3 plaque psoriasis with nail and palmoplantar involvement as well. The median time (95% CI) to response to psoriasis treatment was 8 months (7.02-8.98) for acitretin, 14 months (1.16-26.8) for apremilast, 6 months (4.30-7.69) for methotrexate, and 3 months (1.17-4.28) for steroids. Patients treated with systemic steroids showed a quicker response to psoriasis treatment, and this was the only statistically significant comparison (steroids vs other therapies: log rank test, $P = .01$).

Impact on ICI continuation

Overall, 29 of 112 patients (25.9%) interrupted ICI treatment because of psoriasis, whereas 20 of 111 patients (18%) permanently discontinued

Table II. Number of infusions until psoriasis

Characteristics	Number of infusions, mean (SD)	*P* value*
Sex		.025
Male	10.1 (13.7)	
Female	14.9 (18.1)	
Psoriasis type		.09
Plaque psoriasis	10.3 (9.63)	
Pustular psoriasis	17.8 (35.1)	
Palmoplantar psoriasis	10.5 (8.33)	
Guttate psoriasis	16.6 (17.9)	
Nail psoriasis	23.5 (13.4)	
Inverse psoriasis	10	
Erythrodermic psoriasis	14 (17.3)	
>1 Type	8.83 (15.8)	
Personal history of psoriasis		.076
No	11.5 (13.2)	
Yes	9.82 (17.9)	
ICI		.615
Anti–PD-1	11.3 (15.4)	
Anti–PD-L1	10.9 (12.0)	
Active psoriasis at initiation		.019
No	12.2 (15.8)	
Yes	5.43 (3.87)	
Family history		.808
No	11.3 (13.6)	
Yes	11.9 (18.3)	
Type of cancer		.773
NSCLC	9.87 (10.4)	
Melanoma	20.8 (29.3)	
Head and neck SCC	6.5 (5.24)	
Renal cell carcinoma	7.33 (4.63)	
Urothelial carcinoma	15.3 (18.3)	
Hodgkin lymphoma	6.5 (0.70)	
Merkel cell carcinoma	18	
Hepatocellular carcinoma	7 (5.00)	
Gastric cancer	5 (4.24)	
Mesothelioma	5	
Ovarian cancer	9	
Pulmonary neuroendocrine	4	

ICI, Immune checkpoint inhibitor; *NSCLC,* non–small-cell lung cancer; *PD-1,* programmed cell death protein 1; *PD-L1,* programmed death ligand 1; *SCC,* squamous cell carcinoma; *SD,* standard deviation.

**P* value for dichotomous variables (sex, ICI, etc) is based on Mann-Whitney *t* test and for nominal variables (type of psoriasis and cancer) is based on Kruskal-Wallis analysis of variance.

immunotherapy. No differences regarding the need for oncologic treatment discontinuation were recorded between patients treated exclusively with topical regimens and patients treated with systemic therapies (8 [12.5%] patients with topical treatment only vs 12 [26.7%] patients with systemic treatment; $P = .128$). Patients with psoriasis affecting more than 10% of the BSA had 3.6 times increased risk for treatment modification (OR, 3.64; 95% CI, 1.27-10.45; $P = .03$) and 6.4 times increased risk for treatment interruption (OR, 6.41; 95% CI, 2.40-17.11; $P < .001$). The presence of pustular psoriasis also increased the risk of treatment interruption (OR, 4.9; 95% CI, 1.41-16.96; $P < .012$).

Antitumoral effect of ICI

Overall, 67.7% of the treated patients improved after immunotherapy, by either complete (19/99, 19.2%) or partial (48/99, 48.5%) response. From univariate regression, Guttate psoriasis and disease affecting greater than 10% of BSA were found to be positive predictors leading to a 2.73-fold ($P = .05$; 95% CI, 0.98-7.55) and 2.55-fold ($P = .03$; 95% CI, 1.05-6.22) increased probability for response, respectively. In contrast, patients with pruritus had a decreased probability for response, and the relationship was statistically significant (OR, 0.38; $P = .03$; 95% CI, 0.16-0.91). From multivariate logistic regression, only severity (positive predictor for response to ICI: OR, 3.15; 95% CI, 1.18-8.41) and pruritus (negative predictor for response to ICI: OR, 0.35; 95% CI, 0.12-0.97) were statistically significant (Table III).

DISCUSSION

Psoriatic lesions have been reported in various case series of ICI treatment.[7-12] Several studies report that the majority of these patients are complicated with psoriasis on the setting of exacerbation of a pre-existing condition.[10,13-15] We present, to our knowledge, the largest series to date of patients with cancer treated with ICIs, complicated with psoriasis. According to our analysis, 70% of the cases were affected by psoriasis de novo with unique disease features. Based on our data, as well as current European guidelines,[16-18] we propose an algorithmic approach regarding proper management of psoriasis in this setting (Fig 3).

Our study supports that the development of psoriasis occurs later than other skin toxicities. According to recent literature, in patients treated with nivolumab, skin irAEs presented after a median of 5 weeks, and similar results (6.4 weeks) were reported in lung cancer studies.[19,20] Phillips et al,[21] in a large study of 285 patients with cutaneous adverse reactions, also reported that psoriasiform rashes presented in a median time of 61 days for 21 of 285 patients with recorded skin toxicities.[21] In our population, the minimum period until psoriasis diagnosis was significantly longer (12 weeks). Nevertheless, there was a noticeable difference between the group of patients with a prior psoriasis history versus the de novo group, with the former

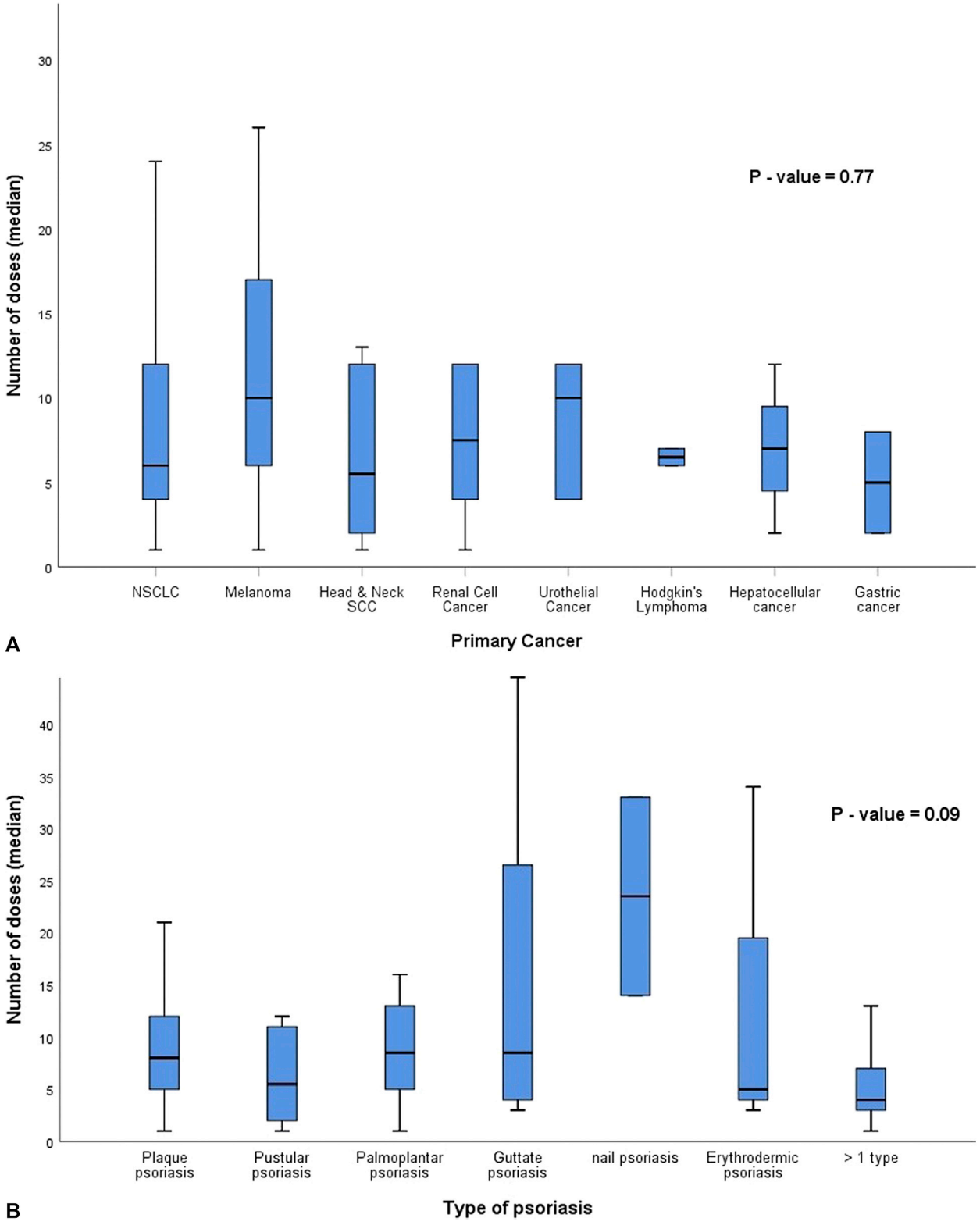

Fig 1. A, Boxplot of the number of doses by primary cancer. There was not a statistically significant difference between the number of doses to an adverse event and the primary cancer (analysis of variance, $P = .77$; pairwise comparisons, $P > .05$) **B**, Boxplot of the number of doses by type of psoriasis. There was not a statistically significant difference between the number of doses to an adverse event and the type of psoriasis (analysis of variance, $P = .09$; pairwise comparisons, $P > .05$). *NSCLC,* Non—small-cell lung cancer; *SCC,* squamous cell carcinoma.

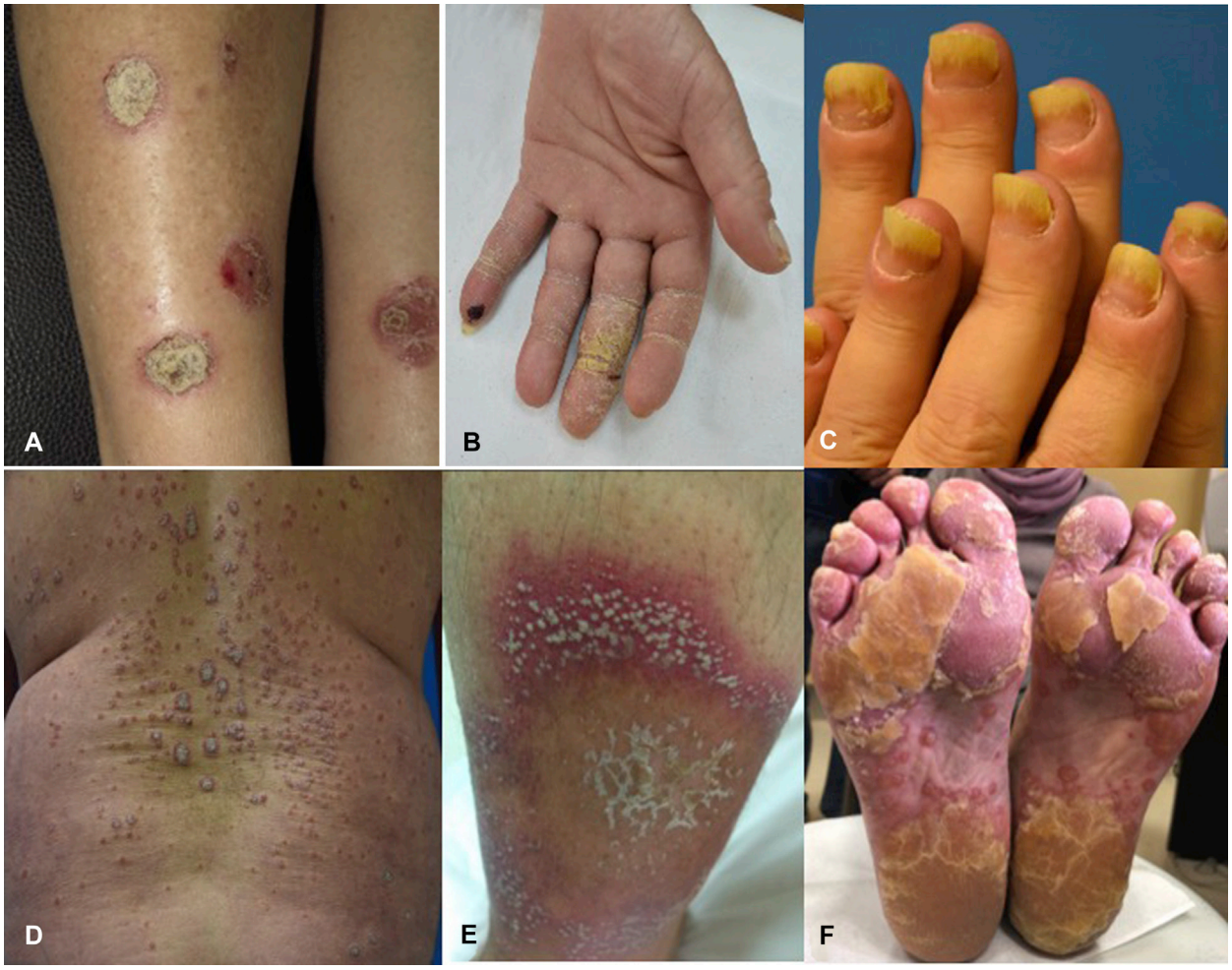

Fig 2. **A**, Plaque-type psoriasis. **B**, Palmar psoriasis. **C**, Nail psoriasis. **D**, Guttate psoriasis. **E**, Pustular psoriasis. **F**, Plantar pustulosis.

Table III. Possible predictors affecting the antitumoral effect of ICI

	Response vs no response (stable or progressive disease)		
Predictors	**Odds ratio**	***P* value**	**Confidence interval**
Univariate analysis			
Guttate psoriasis	2.73	.05	0.98-7.55
Pruritus	0.38	.03	0.16-0.91
Severity	2.55	.03	1.05-6.22
Systemic therapy	1.42	.39	0.62-3.26
Acitretin	1.20	.71	0.42-3.42
Steroids	2.13	.30	0.49-9.11
Treatment modification	1.30	.56	0.53-3.19
Multivariate analysis			
Pruritus	0.35	.04	0.12-0.97
Severity	3.15	.02	1.18-8.41

ICI, Immune checkpoint inhibitor.

being affected significantly earlier. For both groups, close skin surveillance and early expert consultation should be part of standard care.

Regarding response to immunotherapy, our rates were quite positive, reaching overall response rates of 67.7%. Previous studies on patients with

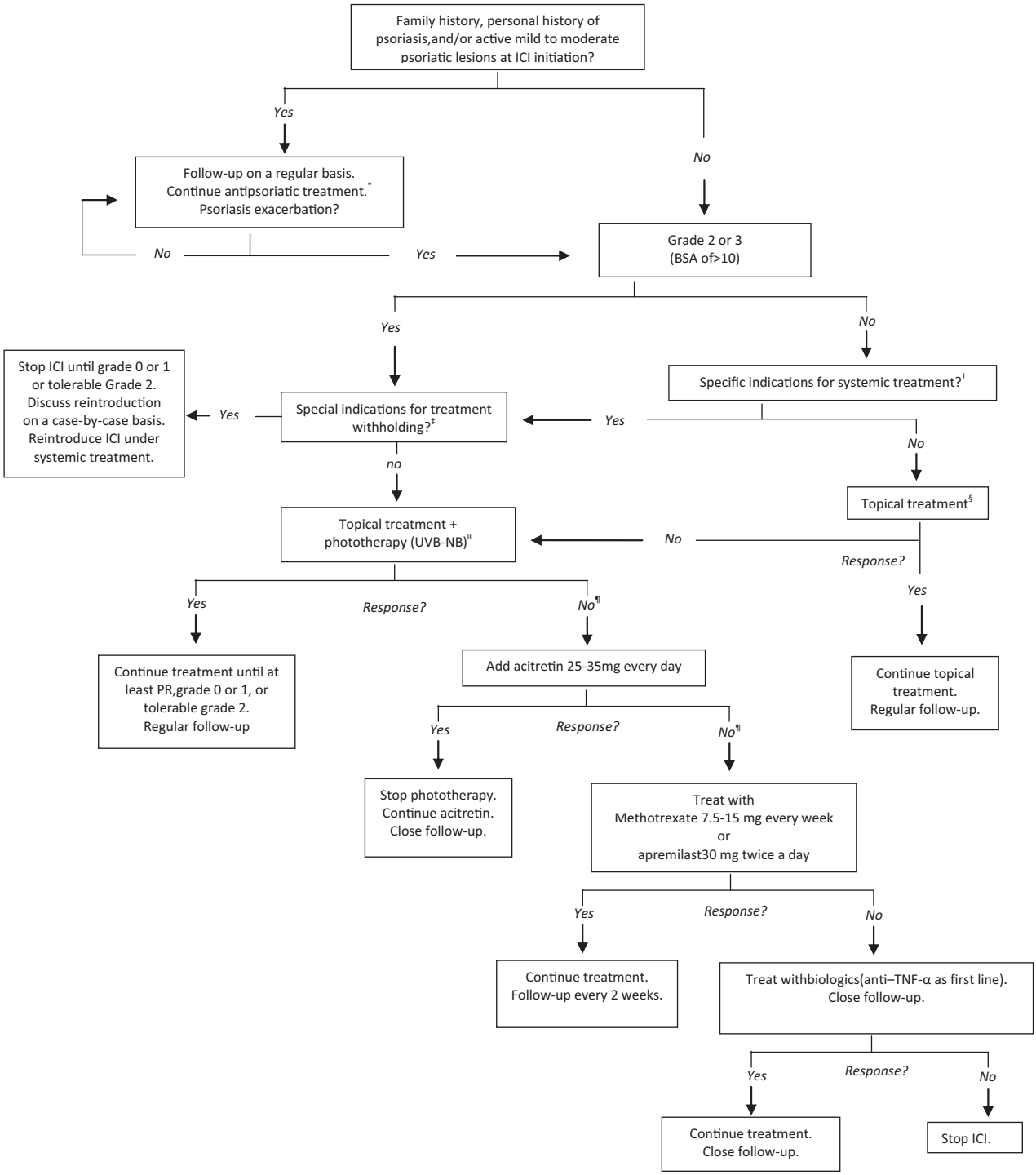

Fig 3. Treatment algorithm for anti—PD-1/PD-L1—induced psoriasis.*Patients with active psoriasis under systemic treatment can start ICI under close follow-up:

- Patients receiving acitretin, apremilast, or methotrexate can start ICI under close surveillance.
- Patients receiving cyclosporine should be referred to a dermatology expert for treatment modification.
- Patients receiving biologics should be discussed case by case in a multidisciplinary approach with oncologists.

†Special indications for systemic treatment include the following:

- involvement of sensitive areas such as face, hands, genitals, nails, and scalp;
- disseminated lesions;

melanoma and lung cancer have supported that skin reactions are analogically related to therapeutic efficacy.[22,23] Our study, also mainly based on patients with melanoma and lung cancer, is in line with this latter observation. Moreover, in our study, the presence of guttate lesions as well as psoriasis affecting more than 10% of BSA were both associated with better response rates to immunotherapy compared with other types of psoriasis and mild symptomatology, respectively. On the contrary, the presence of pruritus was a negative predictor. However, larger prospective studies are needed to safely confirm if these clinical signs could be viable prognostic factors.

Apart from the epidemiologic and disease characteristics, in our cohort, we attempted to focus on therapeutic aspects of this novel type of irAE. The most common systemic agent administered was acitretin. Acitretin, as opposed to many other antipsoriatic drugs, does not harbor immunosuppressive properties, and in this context, it does not interfere with ICI treatment.[24] In our sample, response rates were satisfactory, and the treatment was well tolerated, with no unpredicted adverse events; therefore, we recommend acitretin as one of the first-line options in ICI-induced psoriasis.

Our study included 7 individuals with moderate to severe psoriasis successfully treated with apremilast. All patients responded well, with 2 of 7 achieving excellent response and 5 achieving partial response. An important advantage of apremilast is that, based on the summary of product characteristics of the drug, there is no contraindication or specific warning for patients with cancer. Likewise, there is evidence of optimal outcomes in similar scenarios.[25,26] Without overlooking the weaknesses of a small sample, we believe that apremilast may represent a valuable therapeutic weapon against anti–PD-1–induced psoriasis.

Methotrexate was administered in only 5 patients in our group, with all of them achieving excellent or partial responses. Recent psoriasis guidelines from the French group[8] reviewed the risk of cancer associated with systemic therapies and reported that there does not seem to be an increased risk for cancer in patients treated with methotrexate except for a possible increase of nonmelanoma skin cancer. However, further studies are needed to obtain solid evidence.

The role of systemic steroids in the treatment of psoriasis is controversial. In our daily clinical practice, we avoid systemic steroids, because it is well known that rapid withdrawal of systemic steroids may lead to a rebound phenomenon. To date, only 1 case report has been published, reporting a patient with pembrolizumab-induced psoriatic dermatitis that was successfully treated with systemic steroids without exacerbation after discontinuation.[27] In our cohort, 8 individuals were managed with systemic steroids, resulting in satisfactory response. However, because systemic steroids might interfere with ICI treatment, in 5 of 8 cases, immunotherapy was discontinued. Despite our small sample and based on the relatively large number of available antipsoriatic agents, we recommend that systemic steroids be preserved for cases resistant to other interventions.

Our experience with biologics was limited, because these agents are not recommended in patients with active malignancies. However, a recent meta-analysis of 9 studies, assessing the risk of carcinogenesis or cancer recurrence in 11,679 patients exposed either to anti–TNF-α or to nonbiologic disease-modifying antirheumatic drugs,

- mild to moderate psoriatic arthritis;
- Dermatology Life Quality Index greater than 10;
- severe symptoms (eg, itch or burning); and
- intolerable grade 2.

‡Special indications for ICI cessation or withholding include the following:

- grade 3 (BSA of >30%),
- erythrodermic psoriasis: consider introducing systemic corticosteroids (prednisolone 0.2-0.5 mg/kg),
- generalized pustular psoriasis: consider introducing systemic corticosteroids (prednisolone 0.2-0.5 mg/kg), and
- severe symptoms (eg, itch or burning).

§Topical treatments include topical steroids, calcipotriol, tazarotene, and UVB-NB.ⁿPatients treated for melanoma are excluded. ¶Discuss with cancer specialists on a case-by-case basis. *BSA,* Body surface area; *ICI,* immune checkpoint inhibitors; *PD-1,* programmed cell death protein 1; *PD-L1,* programmed death ligand 1; *PR,* partial response; *UVB-NB,* narrowband ultraviolet B.

did not detect any increased risk for the former.[28] Moreover, the prophylactic administration of anti−TNF-α concomitantly with ICI therapy has been reported to be capable of resolving several shortcomings of the latter while retaining its antitumor efficacy.[29] Phillips et al[21] reported that interleukin 23a and interleukin 12/23 inhibition might be beneficial in patients with steroid-refractory irAEs, whereas antitumoral response was maintained in 2 patients treated with guselkumab and ustekinumab, respectively. On the other hand, Esfahani et al[30] reported loss of antitumor efficacy in a patient with pembrolizumab-induced psoriasis treated with secukinumab.[30] In our study, 4 patients were treated with biologic agents, of whom 2 responded well and the other 2 had to discontinue immunotherapy because of adverse effects and despite clinical improvement. Given the increased disease severity, response rates were satisfying; however, the decision for biological therapy should be always individualized.

The effect of systemic immunomodulatory treatments on ICIs remains controversial. Recent studies in groups with pre-existing autoimmune disease, have shown that the median progression-free survival was shorter in patients receiving immunosuppressive therapy at ICI initiation.[16] Although there were differences with our study related to the initiation time of immunomodulators, our results indicate that coadministration of systemic treatment for psoriasis and ICIs did not effect the overall therapeutic effect of the latter. This indicates that treatment of psoriasis is of great clinical value even with the use of systemic therapies, which do not seem to compromise immunotherapy's overall efficacy.

Some of the major limitations of our study are due to its retrospective nature. Therefore, significant parameters, like Psoriasis Area and Severity Index scores, cannot be evaluated, resulting in missing data that could have led to more accurate patient categorization. Future prospective studies including pathology data will lead to further analysis and better understanding of this unique irAE.

In conclusion, we present, to our knowledge, the largest series of patients experiencing complicates with psoriasis during anti−PD-1/PD-L1 treatment. The clinical characteristics of this entity are highly diverse. Early diagnosis and adequate management with agents that do not interfere with immunotherapy, or with the underlying malignancy, are crucial. In this context, we introduce a practical therapeutic algorithm that we consider useful for both dermatologists and oncologists. In most cases, ICI treatment can be completed, as long as strict dermatologic surveillance is present throughout treatment.

Conflicts of interest

None disclosed.

REFERENCES

1. O'Reilly A, Hughes P, Mann J, et al. An immunotherapy survivor population: health-related quality of life and toxicity in patients with metastatic melanoma treated with immune checkpoint inhibitors. *Support Care Cancer*. 2020;28:561-570.
2. Berner F, Bomze D, Diem S, et al. Association of checkpoint inhibitor-induced toxic effects with shared cancer and tissue antigens in non-small cell lung cancer. *JAMA Oncol*. 2019;5:1043-1047.
3. Sibaud V, Meyer N, Lamant L, et al. Dermatologic complications of anti-PD-1/PDL1immune checkpoint antibodies. *Curr Opin Oncol*. 2016;28:254-263.
4. Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. *Curr Probl Cancer*. 2017;41:125-128.
5. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicity and immunotherapy. *Am J Clin Dermatol*. 2018;19:345-361.
6. Schwartz LH, Litiere S, De Vries E, et al. RECIST 1.1- Update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132-137.
7. Bonigen J, Raynaud-Donzel C, Hureaux J, et al. Anti-PD1-induced psoriasis. A study of 21 patients. *J Eur Acad Dermatol*. 2017;31:e254-e257.
8. Voudouri D, Nikolaou V, Laschos K, et al. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer*. 2017;41:407-412.
9. Ruiz-Banobre J, Perez-Pampin E, Garcia-Gonzalea J, et al. Development of psoriatic arthritis during nivolumab therapy for metastatic non-small cell lung cancer, clinical outcome analysis and review of the literature. *Lung Cancer*. 2017;108:217-221.
10. Guven DC, Kilickap S, Guner G, Taban H, Dizdar O. Development of de novo psoriasis during nivolumab therapy in a patient with small cell lung cancer. *J Oncol Pharm Pract*. 2020;26:256-258.
11. Chujo S, Asahina A, Itoh Y, et al. New onset psoriasis during nivolumab treatment for lung cancer. *J Dermatol*. 2018;45:e55-e56.
12. Coleman E, Ko C, Dai F, et al. Inflammatory eruptions associated with immune checkpoint inhibitor therapy: a single-institution retrospective analysis with stratification of reaction by toxicity and implications for management. *J Am Acad Dermatol*. 2019;80:990-997.
13. DeBock M, Hulstaert E, Kruse V, Brochez L. Psoriasis vulgaris exacerbation during treatment with a PD-1 checkpoint inhibitor: case report and literature review. *Case Rep Dermatol*. 2018;10:190-197.
14. Scarfi F, Lacava R, Patrizi A, et al. Follicular psoriasis induced by pembrolizumab in a patient with advanced non-small-cell lung cancer. *Int J Dermatol*. 2019;58:e151-e152.
15. Matsumura N, Ohtsuka M, Kikuchi N, et al. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. *Acta Derm Venereol*. 2016;96:259-260.
16. Nast A, Gisondi P, Ormerod AD, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris—update 2015; Short version—EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol*. 2015;29:2277-2294.
17. Amatore F, Villani AP, Tauber M, et al. French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. *J Eur Acad Dermatol Venereol*. 2019;33:464-483.

18. Gisondi P, Altomare G, Ayala F, et al. Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31:774-790.
19. Weber JS, Hodi FS, Wolchock JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785-792.
20. Aso M, Toi Y, Sugisaka J, et al. Association between skin reaction and clinical benefit in patients treated with anti-programmed cell death 1 monotherapy for advanced non-small cell lung cancer. *Oncologist*. 2019;24:1-9.
21. Phillips GS, Wu J, Hellmann MD, et al. Treatment outcomes of immune related cutaneous adverse events. *J Clin Oncol*. 2019;37:2746-2758.
22. Min Lee CK, Li S, Tran DC, et al. Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: a retrospective case-control study. *J Am Acad Dermatol*. 2018;79:1047-1052.
23. Chan L, Hwang SJE, Byth K, et al. Survival and prognosis of individuals receiving programmed cell death 1 inhibitor with and without immunology cutaneous adverse events. *J Am Acad Dermatol*. 2020;82:311-316.
24. Rademaker M, Rubel DM, Agnew K, et al. Psoriasis and cancer. An Australian/New Zealand narrative. *Australas J Dermatol*. 2019;60:12-18.
25. Fattore D, Annuziata MC, Panariello L, et al. Successful treatment of psoriasis induced by immune checkpoint inhibitors with apremilast. *Eur J Cancer*. 2019;110:107-109.
26. Apalla Z, Psarakis E, Lallas A, et al. Psoriasis in patients with active lung cancer: is apremilast a safe option? *Dermatol Pract Concept*. 2019;9:300-301.
27. Suzuki M, Matsumoto S, Takeda Y, Sugiyama H. Systemic psoriasiform dermatitis appeared after the administration of pembrolizumab. *Intern Med*. 2020;59:871-872.
28. Micic D, Komaki Y, Alavanja A, et al. Risk of cancer recurrence among individuals exposed to antitumor necrosis factor therapy: a systematic review and meta-analysis of observational studies. *J Clin Gastroenterol*. 2019;53:e1-e11.
29. Alvarez M, Otano I, Minute L, et al. Impact of prophylactic TNF blockade in the dual PD-1 and CTLA-4 immunotherapy efficacy and toxicity. *Cell Stress*. 2019;3:236-239.
30. Esfahani K, Miller WH Jr. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. *N Engl J Med*. 2017;376:1989-1991.