Received: 4 March 2022 | Revised: 2 June 2022 | Accepted: 27 July 2022

DOI: 10.1111/dth.15747

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Dermatological adverse events under programmed cell death-1 inhibitors as a prognostic marker in metastatic melanoma

Rony Shreberk-Hassidim[1] | Lilach Aizenbud[2] | Shalev Lussheimer[3] | Elena Thomaidou[4] | Tali Bdolah-Abram[5] | Sharon Merims[6] | Aron Popovtzer[6] | Alex Maly[7] | Michal Lotem[6] | Abraham Zlotogorski[1]

[1]Department of Dermatology, Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Jerusalem, Israel

[2]Department of Medicine (Medical Oncology), Yale University School of Medicine, New Haven, Connecticut, USA

[3]Department of Internal Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

[4]University of Nicosia Medical School, Nicosia, Cyprus

[5]The Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

[6]Sharett Institute of Oncology, Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Jerusalem, Israel

[7]Department of Pathology, Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Jerusalem, Israel

Correspondence
Rony Shreberk-Hassidim, Department of Dermatology, Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Kiryat Hadassah, POB 12000, Jerusalem 9112001, Israel.
Email: rshreberk@gmail.com

Abstract

Melanoma is widely treated with programmed cell death-1 (PD-1) inhibitors. As part of their anti-tumor immunity effect, they increase the susceptibility to cutaneous immune-related adverse events (cIRAE) among other autoimmune effects. To characterize the manifestations of cIRAE in melanoma patients treated with PD-1 inhibitors, and evaluate the correlation with tumor response. A retrospective study of 95 metastatic malignant melanoma patients treated with PD-1 inhibitors at the Hadassah Medical Center during 2013–2016. The most common cIRAE was pruritus reported by 39 (41%) patients. All other cIRAE were noted in 34 patients (35.8%), of which the most common cutaneous manifestation was vitiligo, demonstrated in 17 patients (17.9%) followed by various rashes (7.4%, including erythema multiforme, oral lichen planus, photosensitive rash, insect bite-like reaction, and urticaria), psoriasiform rash (3.2%), bullous pemphigoid (3.2%), and eczema (1%). Interestingly, higher response rates to immunotherapy were demonstrated in patients who developed pruritus (85%) and cIRAE (88%), with lower mortality rates in the cIRAE group (38.2%) versus the non-cIRAE group (70.5%, $p = 0.002$). cIRAE are common among malignant melanoma patients treated with PD-1 inhibitors and may be a marker for favorable prognosis.

KEYWORDS
adverse events, immunotherapy, melanoma, programmed cell death-1 inhibitors

1 | INTRODUCTION

Immunotherapy is one of the most innovative therapeutic approaches to cancer. It is based on checkpoint inhibitors (CPI) as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1).[1,2] These receptors are over-expressed by cancer cells, allowing them to evade the immune system's regulation.

Anti-CTLA-4 antibody (Ipilimumab, Yervoy) was the first CPI approved for metastatic melanoma thanks to a significant increase in survival rate demonstrated in clinical trials.[3,4] Later on, PD-1 inhibitors (Pembrolizumab, Keytruda, Nivolumab, Opdivo) were approved.

Rony Shreberk-Hassidim and Lilach Aizenbud contributed equally to the manuscript

However, along with the expected stimulation of the immune system against malignant cells, these immunotherapeutic agents may also induce a variety of immune-related adverse events (IRAE), most commonly involving the skin. The cutaneous immune-related adverse events (cIRAE) typically include pruritus and rash, usually with no specific association between tumor and rash type, with melanoma and vitiligo as an exception.[5] Previous clinical studies have concluded that around 50% of patients treated with Ipilimumab (anti-CTLA-4) will develop some form of cIRAE,[6] while an estimated 40% of patients will have cutaneous involvement under PD-1 inhibition (Pembrolizumab/Nivolumab).[7,8] A meta-analysis calculated that the risk of developing a rash under Ipilimumab treatment is around 24%, with a 2.4% risk of severe cutaneous reaction.[9]

On the bright side, some studies suggest that IRAE might correlate with better treatment results, especially regarding vitiligo in melanoma.[7,10,11]

Although it is widely agreed that cIRAE are very common, data regarding the specific manifestation in Melanoma patients is still lacking. This study aims to estimate the rate of cIRAE in metastatic melanoma patients treated with PD-1 inhibitors, and identify potential risk factors for them. Additionally, the study aims to strengthen the status of vitiligo as a marker for favorable results, and assess a possible correlation between other cIRAE and patients' response to therapy and survival.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a retrospective analytic-descriptive study, of histologically-diagnosed metastatic melanoma patients who received treatment with at least one PD-1-inhibitor agent at the Hadassah-Hebrew University Medical Center, a tertiary medical center in Israel.

The study was approved by the Hadassah-Hebrew University Medical Center institutional review board. Informed consent was waived due to this being a retrospective deidentified research.

The inclusion criteria were 18-year-old and older patients, who were treated between the years 2013–2016.

2.2 | Data extraction and definitions

Information was collected from the electronic medical records. The diagnosis of cutaneous adverse reactions and additional cutaneous findings were made and recorded by an oncologist and/or dermato-oncologist. For this study, pruritus, which is a dermatological symptom reported by patients, was analyzed separately from other cIRAE which were observed in physical examination and/or biopsy.

The endpoint of the study was set to January 1, 2019. The oncological response, oncological level of disease and mortality rate were recorded then. The oncological response is based on radiological findings (CT/MRI) as follows: (a) Complete response—gradual or complete remission; (b) Partial response—temporary radiological remission in all disease sites followed by recurrence/complete remission in some sites parallel to progression in others/clinical improvement recorded by the oncologist with steady radiological disease distribution, followed by clinical deterioration; and (c) No response—natural progression of the disease. The oncological level includes no evident disease, alive with disease and deceased.

2.3 | Statistical analysis

All data were summarized and displayed as a number (percentage) of patients in each group for categorical variables and as a mean (±standard deviation) for continuous variables. Categorical variables were compared using a Chi-square or Fisher's exact test. Comparison of quantitative variables between two categories of categorical variables was made using the T-test or the non-parametric Mann–Whitney test. Variables that were found to have significant statistical association to the independent variable (development of cIRAE) in the univariate analyses, were entered into a multivariate logistic regression model using the stepwise, forward, likelihood method. The Kaplan–Meier survival model with the log-rank test for the comparison of survival curves was applied to assess the effect of side effects on survival. All statistical tests were two-tailed, and the threshold for statistical significance was set to p-values ≤ 0.05. All analyses were performed with the SPSS 25.0 software (SPSS Inc., Chicago, IL).

3 | RESULTS

3.1 | Study population

The study included 95 patients, 63 (66%) of them were male. The mean age at diagnosis was 60.4 (±14.4) years and the mean follow-up duration was 54.2 (±42.1) months. The most common primary tumor location was cutaneous (81%). About a third (35.8%) of the patients were treated with PD-1 inhibitors as first line. In addition, 75 (78.9%) of the patients were treated with either radiation, chemotherapy or anti-MEK and anti-BRAF therapies, before, after or combined with the PD-1 inhibitors. At the study endpoint, the mortality rate was 58.4%. The demographic and clinical characteristics of the study population are detailed in Table 1.

3.2 | Dermatological manifestations

Pruritus was the most common dermatological symptom, reported by 39 (41%) patients. All other objective cIRAE were noted in 34 patients (35.8%). There was an overlap of 24 patients between the two groups, thus the overall rate of cutaneous findings and/or pruritus was 51%. Among the cIRAE, the most common cutaneous manifestation was vitiligo, demonstrated in 17 patients (17.9% of the total cohort). Other dermatological manifestations included various rashes (7.4%, including

TABLE 1 Demographic and clinical characteristics of study population ($n = 95$)

Variable	Number (%) or value ± SD
Male/female	63 (66%)/32 (33%)
Mean age at diagnosis, years	60.4 ± 14.4
Mean follow-up duration, months (median)	54.2 ± 42.1 (45.5)
Source of primary tumor	
Cutaneous	77 (81%)
Choroidal	5 (5%)
Ocular	4 (4%)
Unknown	7 (7%)
Attributions of selected therapies	
Anti-PD-1 as first-line treatment	34 (35.8%)
Radiation	61 (63.6%)
Chemotherapy[a]	45 (47.9%)
Dermatological manifestations	
Pruritus	39 (41.1%)
cIRAE manifesting as skin lesions[b]	34 (35.4%)
Vitiligo	17 (17.9%)
Specific rash[c]	7 (7.4%)
Non-specific rash	5 (5.3%)
Psoriasiform rash	3 (3.2%)
Bullous pemphigoid	3 (3.2%)
Eczema	1 (1.0%)
Oncological status at study endpoint	
No evidence of disease	21 (21.9%)
Alive with disease	13 (13.5%)
Deceased	56 (58.4%)
Oncological response to anti-PD-1	
Complete response	26 (27.1%)
Partial response	33 (35.4%)
No response	36 (37.5%)

Abbreviations: cIRAE, cutaneous immune-related adverse events; PD-1, programmed cell death-1.
[a]Including Paclitaxel (Taxol), Cyclophosphamide (Cytoxan), Temozolomide (Temodal), Dacarbazine (DTIC).
[b]Two patients developed two types of cIRAE including rash and vitiligo.
[c]Including erythema multiforme, oral lichen planus, photosensitive rash, insect bite-like reaction, urticarial rash.

erythema multiforme, oral lichen planus, photosensitive rash, insect bite-like reaction, and urticaria), psoriasiform rash (3.2%), bullous pemphigoid (3.2%), and eczema (1%). Interestingly, cIRAE appeared at different latency periods: vitiligo followed a prolonged latency period of 37.8 weeks, while the latency period for all other types of cIRAE was only 7.3 weeks, suggesting that different types of cIRAE have various mechanisms.

In four patients (4.2%), the cIRAE was graded as severe (grades 3–4) and necessitated treatment with systemic corticosteroids. Cessation of immunotherapy was required in only one patient due to the severity of the reaction.

3.3 | Risk factors

Several factors were found to be associated with the development of cIRAE, as detailed in Table 2. Cutaneous source of the primary tumor was strongly associated with cIRAE, as no cIRAE were noted in non-cutaneous primary tumor sources ($p = 0.031$). Lack of radiotherapy was associated with increased risk for cIRAE ($p = 0.008$), suggesting that this may serve as a risk factor. Administration of PD-1 inhibitors as first-line therapy was associated with cIRAE as well ($p = 0.015$).

3.4 | Treatment response and survival

Higher response rates to immunotherapy were demonstrated in patients who developed pruritus and cIRAE. As seen in Figures 1, 88% of patients with cIRAE showed complete or partial response (a). The rates of no response were about fourfold higher in the group who did not have cIRAE compared to the one who did (b). Similar results are observed in pruritus (Figure 2), with 85% of patients showing a complete or partial response (a), and rates of no response about threefold higher in the group without cIRAE (b).

To determine whether these differential effects may be associated with clinical outcomes, survival analyses were performed. Indeed, lower mortality rates were recorded in the cIRAE group (38.2%) versus the non-cIRAE group (70.5%, $p = 0.002$). Furthermore, the median survival time for patients with cIRAE was 145.6 months (mean 96 months) as compared to 59.6 months (mean 48 months) in patients without cIRAE (Figure 3). These findings yielded an adjusted HR = 1.85 (CI 0.982–3.485, $p = 0.057$). The result remained significant in a sub-analysis done in the cIRAE group excluding patients with vitiligo ($p = 0.002$). The results for the pruritus versus the no pruritus groups demonstrated a trend but were not statistically significant.

4 | DISCUSSION

This is a retrospective study on metastatic melanoma patients treated with PD-1 inhibitors. The study aimed to characterize the incidence and clinical manifestations of dermatological IRAE in these patients, assess the possible correlation between them and favorable results as well as explore risk factors.

4.1 | Dermatological manifestations

Among the 95 participants, 41% reported pruritus and 35.8% developed cIRAE manifesting as skin lesions. Overall these rates are similar to the findings reported in the literature, which estimates that under

TABLE 2 Comparison between patients without cutaneous immune-related adverse events and patients with cutaneous immune-related adverse events to anti-PD-1 immunotherapy

Variable	Patients without cIRAE ($n = 61$)	Patients with cIRAE ($n = 34$)	p Value
Gender			0.546
Male	39 (61.9%)	24 (38.1%)	
Female	22 (68.8%)	10 (31.1%)	
Source of primary tumor			**0.031**
Cutaneous	45 (58.4%)	32 (41.6%)	
Ocular	5 (100%)	0	
Mucosal	4 (100%)	0	
Unknown	5 (71.4%)	2 (28.6%)	
Other therapies			
Chemotherapy			0.092
No	28 (56.0%)	22 (44.0%)	
Yes	33 (73.3%)	12 (26.6%)	
Radiation			**0.008**
No	16 (47.1%)	18 (52.9%)	
Yes	45 (73.8%)	16 (26.3%)	
Anti-MEK and anti-BRAF			0.569
No	47 (62.6%)	28 (37.3%)	
Yes	14 (70.0%)	6 (30.0%)	
Anti-PD-1 as first-line therapy			**0.015**
No	44 (73.3%)	16 (26.6%)	
Yes	17 (48.5%)	18 (51.4%)	
Oncological response to anti-PD-1 therapy			**0.001**
No response	32 (52.5%)	4 (11.8%)	
Partial response	17 (27.9%)	16 (47.1%)	
Complete response	12 (19.7%)	14 (41.2%)	
Oncological status at study endpoint			**0.002**
No evident disease	9 (14.8%)	12 (35.3%)	
Alive with disease	5 (8.2%)	8 (23.5%)	
Deceased	43 (70.5%)	13 (38.2%)	

Note: Bold values represents statistical significance at p-values ≤ 0.05.
Abbreviations: cIRAE, cutaneous immune-related adverse events; PD-1, programmed cell death-1.

PD-1 inhibition, pruritus or rash of any grade develop in 27.5–44.7% of patients, without regard to tumor origin.[12,13]

The most common cIRAE was vitiligo (17.9%). The rates of vitiligo in the literature ranges from 3% to 25%, with an estimated rate of 8% in a meta-analysis.[8,10,14,15] Many studies show low rates of vitiligo since they usually include a variety of tumors and vitiligo is rarely described in other types of cancer besides melanoma.[8,16] Indeed, a recent study by Phillips et al. analyzed cIRAE under CPI in a large spectrum of tumors, and assessed vitiligo as 3%, though when calculated only in the melanoma sub-group, the rate is as high as 14.5%.[15] This rate is supported by another study that reviewed 82 melanoma patients treated with PD-1 inhibitors therapy and found that 14.6% developed vitiligo.[17]

Other subtypes of cIRAE are relatively similar to known rates. One study observed psoriasiform rash in 5% of the participants.[15] A systematic review of cIRAE under PD-1 inhibitors gathered reports of 33 psoriasis cases which calculates to 13% of total cIRAE.[16] However, when adjusting our study results to the same sub-population, the outcome is 8.8% which is more resembling. Similar data is present for bullous pemphigoid, with rates up to 5%. The low rates of bullous pemphigoid are clinically crucial. As most cIRAE are low-grade, bullous pemphigoid might necessitate cessation of treatment, among other more rare and serious cIRAE as Stevens–Johnson syndrome, which may even result fatally.[16,18]

The remaining cIRAE are harder to compare with existing literature since studies either assort subtypes differently or use the term "maculopapular rash" as a bulk. Another obstacle for reliable comparison is that different studies include a variety of patients and treatment plans.

As for the latency period of cIRAE, the range is wide. The time to onset for vitiligo among our patients was 37 weeks, which correlates with existing data that report vitiligo development progressively after several months of treatment.[19] The time to onset for all other types of cIRAE was only 7.3 weeks. The literature suggests a wide range of latency periods for each cIRAE, which hints at risk factors or moderators yet to be identified.[5]

4.2 | Risk factors and favorable response

Our study explored the clinical risk factors to cIRAE development. Among different treatments including chemotherapy, radiotherapy, biological treatment and immunotherapy, both lack of radiotherapy and PD-1 inhibitors as a first-line treatment showed correlation with cIRAE development. Since the study spanned from 2013 to 2016, it included both patients who received PD-1 inhibitors in the context of a clinical trial (following the failure of multiple treatment lines), as well as patients who received it as first-line therapy after FDA approval in 2014. When comparing the two sub-groups, administration of PD-1 inhibitors as first-line treatment was associated with higher rates of cIRAE. This result might have an immunological basis, but might be biased by the increase of awareness of adverse effects over time. The clinical implication is still unclear due to the suspected bias. The association between cIRAE and lack of radiotherapy was surprising since the little literature on the area implies that ionizing radiation may have a contributing effect on the systemic anti-tumor immunity, therefore increased cIRAE was expected.[20] Our data suggest that lack of radiotherapy might be a risk factor for adverse events. If that is indeed the case, it should be another point to consider when adjusting the patient's plan of care, among other risk factors. However, this area needs more research before any strong conclusions are made.

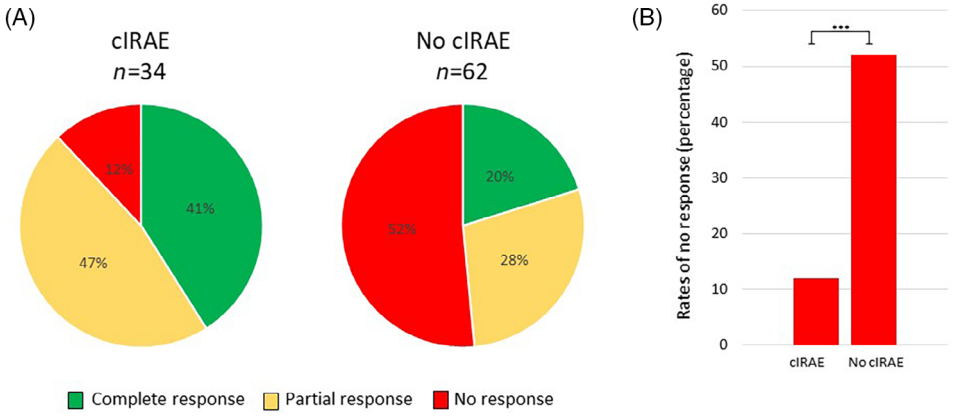

FIGURE 1 Response rate to immunotherapy of patients with and without cutaneous immune-related adverse events (cIRAE). ***$p < 0.001$. Determined by Pearson Chi square

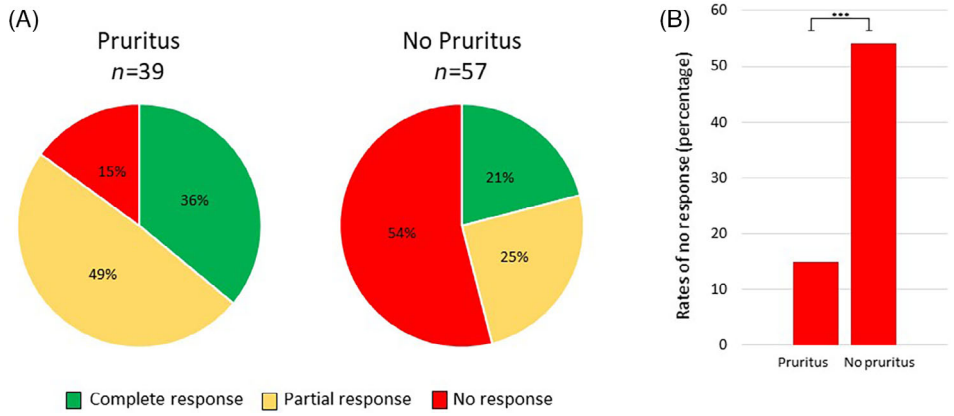

FIGURE 2 Response rate to immunotherapy of patients with and without pruritus. ***$p < 0.001$. Determined by Pearson Chi square

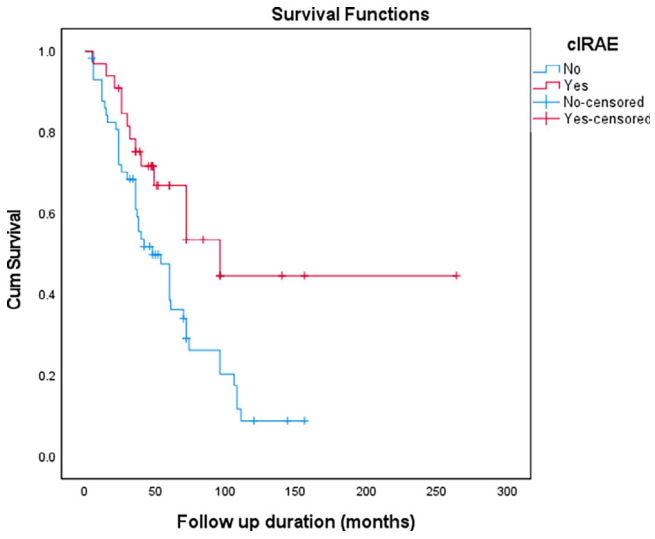

FIGURE 3 Kaplan Meier survival functions comparing patients with (red line, $n = 33$) and without (blue line, $n = 58$) cutaneous immune-related adverse events (cIRAE) ($p = 0.01$)

Excitingly, patients with either pruritus or cIRAE had a significantly better oncological response to the treatment and better oncological status at the endpoint of the study. Not only that, mortality rates were lower in the patients with cIRAE, and the mean median survival time was 96 months compared to 48 months in patients without cIRAE. The concept of cIRAE as a marker for better response to treatment or longer survival time has been established in studies over the past few years, especially with vitiligo in patients with melanoma.[7,10,21] The reports on the relation between cIRAE and improved response to treatment can be attributed to a more powerful activation of the immune system by the administered agent, leading to both phenomena. More specifically, since most melanoma tumors originate in the skin tissue, cIRAE may reflect a more successful response at the primary tumor site. This study not only strengthens the status of vitiligo as a marker but suggest other cIRAE might be markers as well, especially since the correlation remains significant when omitting vitiligo from the cIRAE.

Unfortunately, patients with primary non-cutaneous melanoma (ocular or mucosal) are distinct from these results. As mentioned before, cIRAE was correlated with the cutaneous origin of the primary tumor only. The literature shows low response to PD-1 inhibitors in non-cutaneous melanoma, which might support a common mechanism between cIRAE and response to treatment.[22,23]

5 | CONCLUSION

In conclusion, pruritus and cIRAE are prevalent under PD-1 inhibitors immunotherapy in melanoma patients. Fortunately, the majority of

cIRAE are not severe and do not require cessation of immunotherapy, and may be an indicator for favorable outcomes.

6 | LIMITATIONS

This is the retrospective study of a single medical institution. Therefore, the analyzed data is based on physicians' medical records documentation, which may lead to incomplete information or bias.

AUTHOR CONTRIBUTIONS

Rony Shreberk-Hassidim, Lilach Aizenbud, Shalev Lussheimer, Elena Thomaidou, Tali Bdolah-Abram, Sharon Merims, Aron Popovtzer, Alex Maly, Michal Lotem, and Abraham Zlotogorski meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available upon request

ORCID

Elena Thomaidou https://orcid.org/0000-0002-8029-0209

REFERENCES

1. Dong Y, Sun Q, Zhang X. PD-1 and its ligands are important immune checkpoints in cancer. *Oncotarget*. 2017;8:2171-2186.
2. Rivera GA, Saramipoor Behbahan I, Greenberg PL. Immune checkpoint pathways: perspectives on myeloid malignancies. *Leuk Lymphoma*. 2016;57:995-1001.
3. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
4. Callahan MK, Wolchok JD. At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy. *J Leukoc Biol*. 2013;94:41-53.
5. Coleman E, Ko C, Dai F, Tomayko MM, Kluger H, Leventhal JS. Inflammatory eruptions associated with immune checkpoint inhibitor therapy: a single-institution retrospective analysis with stratification of reactions by toxicity and implications for management. *J Am Acad Dermatol*. 2019;80:990-997.
6. Lacouture ME, Wolchok JD, Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol*. 2014;71:161-169.
7. Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. *JAMA Dermatol*. 2015;151:1206-1212.
8. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. 2016;60:12-25.
9. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol*. 2013;69:e121-e128.
10. Hua C, Boussemart L, Mateus C, et al. Association of Vitiligo with Tumor Response in patients with metastatic melanoma treated with Pembrolizumab. *JAMA Dermatol*. 2016;152:45-51.
11. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and Unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. 2016;22:886-894.
12. Kottschade L, Brys A, Peikert T, et al. A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy. *Melanoma Res*. 2016;26:469-480.
13. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443-2454.
14. Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. 2020;83:1255-1268.
15. Phillips GS, Wu J, Hellmann MD, et al. Treatment outcomes of immune-related cutaneous adverse events. *J Clin Oncol*. 2019;37:2746-2758.
16. Simonsen AB, Kaae J, Ellebaek E, Svane IM, Zachariae C. Cutaneous adverse reactions to anti-PD-1 treatment-a systematic review. *J Am Acad Dermatol*. 2020;83:1415-1424.
17. Hwang SJ, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. *J Am Acad Dermatol*. 2016;74:455-461.
18. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119-iv142.
19. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy. *Am J Clin Dermatol*. 2018;19:345-361.
20. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst*. 2013;105:256-265.
21. Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol*. 2019;30:582-588.
22. Rossi E, Schinzari G, Zizzari IG, et al. Immunological backbone of uveal melanoma: is there a rationale for immunotherapy? *Cancers (Basel)*. 2019;11:1055.
23. Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? *Ther Adv Med Oncol*. 2018;10:1758834018757175.

How to cite this article: Shreberk-Hassidim R, Aizenbud L, Lussheimer S, et al. Dermatological adverse events under programmed cell death-1 inhibitors as a prognostic marker in metastatic melanoma. *Dermatologic Therapy*. 2022;35(10):e15747. doi:10.1111/dth.15747