Analysis of tumor response and clinical factors associated with vitiligo in patients receiving anti–programmed cell death-1 therapies for melanoma: A cross-sectional study

Léa Dousset, MD, Alize Pacaud, MD, Thomas Barnetche, PhD, Marie Kostine, MD, PhD, Caroline Dutriaux, MD, Anne Pham-Ledard, MD, PhD, Marie Beylot-Barry, MD, PhD, Emilie Gérard, MD, Sorilla Prey, MD, PhD, Nicolas Andreu, BSc, Katia Boniface, PhD, and Julien Seneschal, MD, PhD

Bordeaux, France

Background: Clinical factors associated with vitiligo in patients receiving anti–PD-1 remain unknown.

Objective: To better characterize the occurrence of vitiligo in patients receiving anti–PD-1.

Methods: The present single-center ambispective cohort study included patients with melanoma treated with anti–PD-1. Progression-free survival, overall survival, and objective tumor response were compared between patients with and those without vitiligo using Kaplan-Meier curves and the log-rank test. Demographic and clinical factors associated with vitiligo were evaluated using multivariate logistic regression.

Results: Of the 457 patients included in the study, vitiligo developed in 85 patients. The clinical presentation of vitiligo consisted of the presence of ovalar and multiple flecked white macules, mainly located on chronic sun-exposed areas. The presence of vitiligo was associated with a significant improvement in overall survival and progression-free survival (P < .001). A Cox proportional hazards model estimation demonstrated markedly improved survival in patients with vitiligo compared with those without vitiligo (aHR [overall survival], 0.20; 95% CI, 0.12-0.33; aHR [progression-free survival], 0.33; 95% CI, 0.23-0.47; P < .001). In the multivariate logistic regression analyses, men showed an independent increased risk of the development of vitiligo (odds ratio, 1.66). In contrast, the presence of pulmonary metastases was found to be an independent factor associated with a reduced risk of the development of vitiligo (odds ratio, 0.50).

Limitations: Single-center ambispective cohort.

Conclusion: Vitiligo in patients receiving anti–PD-1 for advanced melanoma is associated with a better outcome. A gender effect associated with the development of vitiligo will need further investigation. (JAAD Int 2021;5:112-20.)

Key words: checkpoint inhibitors; halo phenomenon around cutaneous metastases; immunotherapy; leukotrichia; melanoma; vitiligo.
INTRODUCTION

Immune checkpoint inhibitors (ICIs) have considerably changed the prognosis of patients in many cancer types, including advanced melanoma.\textsuperscript{1,2} However, nonspecific activation of the immune response leads to the occurrence of a myriad of immune-related adverse events (irAEs), in which the skin is the most frequent target.\textsuperscript{3} Among them, the development of vitiligo is of particular interest as an increasing number of studies have shown that it is associated with better clinical response and prolonged survival in patients with stages III and IV melanoma treated with anti–programmed cell death-1 (PD-1) therapies.\textsuperscript{4-6}

The onset of vitiligo in the context of melanoma, especially during treatment, has been widely described, and its incidence ranges from 2.8% to 25.7%,\textsuperscript{5-11} which is much higher than the incidence of spontaneously occurring vitiligo in the general population. However, studies evaluating the occurrence of vitiligo in patients receiving anti–PD-1 therapies are mainly descriptive and involve a limited number of patients, thus in-depth analysis of this issue remains a challenge.

Therefore, we sought to confirm that the occurrence of vitiligo is associated with better outcomes in patients receiving pembrolizumab or nivolumab for advanced melanoma and that their association induces a better response to therapies. The clinical and demographic factors associated with vitiligo occurring in patients receiving pembrolizumab or nivolumab were assessed.

METHODS

This single-center ambispective cohort study was conducted within the Department of Dermatology, University Hospital of Bordeaux, France, with retrospective and prospective data collected. Patients with advanced melanoma who received anti–PD-1 monotherapy treatment were included from January 2015 to December 2019. Demographic, clinical, and pathologic characteristics of all patients were recorded. Patients had documented \textit{BRAF}\textsuperscript{V600} mutation status as established by a clinical mutation test approved by the French national health authority. The study was approved by the local ethics committee (Ethical Committee, University Hospital of Bordeaux, CE-GP-2020/48).

Patients

Eligibility criteria were stage IV or locally advanced unresectable stage III melanoma, according to the 2009 American Joint Committee on Cancer melanoma staging and classification.\textsuperscript{12} All patients were treated with anti–PD-1 monotherapy (nivolumab or pembrolizumab) with 3 months of follow-up. Skin depigmentation, known as “melanoma-associated leukoderma,” appearing before the initiation of PD-1 inhibitors was an exclusion criterion.

Treatment and evaluation

Patients were treated with either nivolumab (3 mg/kg every 2 weeks or a flat dose of 240 mg every 2 weeks or 480 mg every 4 weeks) or pembrolizumab (2 mg/kg every 3 weeks or a flat dose of 200 mg every 3 weeks or 400 mg every 6 weeks), until disease progression, severe toxicity graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (version 4.03), or long-term remission.

The tumor response to anti–PD-1 therapy was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1 and evaluated every 3 months using computed tomography.\textsuperscript{13} An objective tumor response is defined by a partial or complete tumor response. Overall survival (OS) was calculated from the first administration of anti–PD-1 to the occurrence of death from any cause. Progression-free survival (PFS) was defined as the period between the first administration of anti–PD-1 and disease progression or death.

Vitiligo assessment

The date of the diagnosis of vitiligo occurring under anti–PD-1 therapies was defined as the date of the visit when the depigmented areas of skin were first observed. The diagnosis of vitiligo was confirmed systematically by expert physicians from the vitiligo clinic (JS, LD) for both the retrospective and prospective cohort using the same standardized questionnaire and clinical pictures. The skin site involved was defined according to the occurrence on chronic sun-exposed areas (face and neck, neckline, forearms, and hands) or sun-protected areas (trunk, arms, legs, feet, and genital areas).
Statistical analysis
Continuous variables were described using the median and interquartile range and qualitative variables with numbers and percentages. Comparisons were performed using χ² test for qualitative variables or the Fisher’s exact test when needed. Concerning the main objective, we built Kaplan-Meier analysis curves to estimate OS and PFS using the log-rank test. Odds ratios (ORs) were estimated with their 95% CI. A landmark survival analysis was performed at 3 time points (12, 24, and 36 weeks) to control for “the guarantee-time” bias, including only patients who were alive at these follow-up times after the first treatment. Cox proportional hazards regression was also performed to evaluate the impact of vitiligo on OS and PFS. We built a Cox proportional hazards model adjusted on age, sex, disease stage, brain metastasis, hepatic metastasis, pulmonary metastasis, and skin metastasis. Results are presented with adjusted hazard ratios (aHRs) and their associated 95% CI. The main analysis used “developing vitiligo” as a fixed covariate. A secondary analysis for OS and PFS was realized, including vitiligo as a time-varying covariate with a value of 0 before vitiligo onset and 1 after vitiligo onset. To identify factors associated with vitiligo, comparisons between groups were conducted using univariate and multivariate logistic regression factors. Presenting a P value of <.20 in the univariate analysis were introduced into multivariate logistic regression models. P values of <.05 were considered significant. All analyses were performed using 13.1 Stata/SE software (StataCorp LLC).

RESULTS

Patient characteristics
In total, 457 patients with advanced melanoma were included. Data were collected retrospectively for 243 (53%) of the 457 patients. Among all included patients, 439 (96.1%) had stage IV melanoma, and 18 patients (3.9%) had stage III melanoma, not eligible for surgery. The median age was 66 years (range, 24-94 years), and 262 patients (57.3%) were men. Of all patients, 274 (60%) received pembrolizumab and 183 (40%) received nivolumab, with a median follow-up of approximately 16 months (range, 1-63 months). Of all patients, 270 (59.1%) had not received any previous systemic therapies before PD-1 inhibitors (Table I). Vitiligo lesions developed in 85 patients during anti–PD-1 therapy with an estimated cumulative incidence of 18.6% and a median follow-up of 27.5 months. The median duration of anti–PD-1 therapy was 209 days (range, 12-1736 days) in the control group and 608 days (range, 60-1826 days) in the group with vitiligo. Among patients with vitiligo, anti–PD-1 monotherapy was the first-line treatment for 52 (61.2%), 19 (22.4%) received targeted therapy, 6 (7.1%) received chemotherapy, and 18 (21.2%) received ipilimumab before anti–PD-1 monotherapy. IrAEs other than vitiligo were found in 28 patients (32.9%) and included endocrine (n = 7; 8.2%), intestinal (n = 6; 7.1%), hepatic (n = 6; 7.1%), rheumatic (n = 5; 5.9%), and pulmonary (n = 4; 4.7%) side effects.

Vitiligo characteristics
The median time to onset of vitiligo was 6.9 months (range, 1-35.5 months) from the start of anti–PD-1 treatment. Body surface area was ≤5% at the diagnosis of vitiligo in 67 (84.8%) of the 79 patients (Table II). Clinical presentation of vitiligo consisted of the presence of ovalar (n = 48; 58.%) and multiple flecked macules (n = 45; 54.9%) (Fig 1). A halo phenomenon around cutaneous metastases developed in 10 patients (11.8%), and leukotrichia developed in 29 patients (34.1%). Vitiligo occurred at the site of chronically sun-exposed areas in most patients (n = 72; 84.7%). Only 3 patients (3.5%) and 1 patient (1.2%) had a personal and familial history of autoimmune diseases, respectively.

OS, PFS, and response to anti–PD-1
Among the patients with available clinical data in whom vitiligo developed during treatment, 66 (80.5%) were still alive at the end of the study. As shown in Fig 2, patients in whom vitiligo developed under anti–PD-1 had significantly improved OS and PFS compared with patients without vitiligo (P < .001).

The median value of survival (50% of the initial sample size) for OS and PFS was not reached in the group of patients with vitiligo and was 18 months (range, 1-63 months), and it was 4 months (range, 0.5-43 months) in the group of patients without vitiligo. A landmark analysis was subsequently performed to control for the guarantee-time bias. Similar significant OS rates were found in patients in whom vitiligo developed compared with those without vitiligo (P < .001) at 12, 24, and 36 weeks. The analysis using a Cox proportional hazards model

Abbreviations used:
aHR: adjusted hazard ratio
IC: immune checkpoint inhibitor
irAE: immune-related adverse event
OR: odds ratio
OS: overall survival
PD-1: programmed cell death-1
PFS: progression-free survival
estimation produced a similar result with better OS and PFS associated with patients with vitiligo compared with those without vitiligo (aHR [OS], 0.20; 95% CI, 0.12-0.33; P < .001; and aHR [PFS], 0.33; (range).

Table I. Characteristics of patients with or without vitiligo

| Patients characteristics | Patients with vitiligo n = 85 (%) | Patients without vitiligo n = 372 (%) |
|--------------------------|-----------------------------------|--------------------------------------|
| Demographic features     |                                   |                                      |
| Age, mean, y (range)     | 66.5 (24-88)                      | 66.0 (25-94)                         |
| Gender                   |                                   |                                      |
| Men                      | 57 (67.1)                         | 205 (55.1)                          |
| Women                    | 28 (32.9)                         | 167 (44.9)                          |
| Mean BMI, kg/m² (range)  | 26.6 (17.5-49.8)                  | 25.6 (12.1-49.7)                    |
| Melanoma features        |                                   |                                      |
| BRAFV600 mutation presence | 24 (28.2)                        | 151 (40.6)                          |
| Histologic type           |                                   |                                      |
| SSM                      | 34 (40.0)                         | 184 (49.5)                          |
| Nodular                  | 8 (9.4)                           | 42 (11.3)                           |
| Acral lentiginous         | 15 (17.6)                         | 15 (4.0)                            |
| Unknown primary           | 5 (5.9)                           | 37 (9.9)                            |
| Mucous                   | 6 (7.1)                           | 16 (4.3)                            |
| Choroid                   | 3 (3.5)                           | 15 (4.0)                            |
| Others                   | 14 (16.5)                         | 63 (16.9)                           |
| AJCC VIII melanoma staging |                                   |                                      |
| Stage III, unresectable  | 5 (5.9)                           | 13 (3.5)                            |
| Stage IV                 | 80 (94.1)                         | 359 (96.5)                          |
| Metastatic sites (may have multiple) |        |                                      |
| Brain                    | 27 (31.8)                         | 156 (41.9)                          |
| Lung                     | 33 (38.8)                         | 208 (55.9)                          |
| Liver                    | 23 (27.1)                         | 111 (29.8)                          |
| Skin                     | 35 (41.2)                         | 167 (44.9)                          |
| Melanoma treatments      |                                   |                                      |
| Prior line(s) of therapy before PD-1 inhibitors | |                                      |
| 0                        | 52 (61.2)                         | 218 (58.6)                          |
| 1                        | 24 (28.2)                         | 139 (37.4)                          |
| >1                       | 9 (10.6)                          | 15 (4.0)                            |
| Prior melanoma treatment |                                   |                                      |
| Chemotherapy             | 6 (7.1)                           | 18 (4.8)                            |
| Targeted therapy         | 19 (22.4)                         | 116 (31.2)                          |
| Ipilimumab               | 18 (21.2)                         | 33 (8.9)                            |
| Type of immunotherapy   |                                   |                                      |
| Pembrolizumab            | 54 (63.5)                         | 220 (59.1)                          |
| Nivolumab                | 31 (36.5)                         | 152 (40.9)                          |
| Other immune-related adverse events |        |                                      |
| All                      | 28 (32.9)                         | 100 (26.9)                          |
| Endocrine system         | 7 (8.2)                           | 32 (8.6)                            |
| Intestinal               | 6 (7.1)                           | 8 (2.2)                             |
| Hepatic                  | 6 (7.1)                           | 12 (3.2)                            |
| Rheumatologic            | 5 (5.9)                           | 6 (1.6)                             |

Table I. Cont’d

| Patients characteristics | Patients with vitiligo n = 85 (%) | Patients without vitiligo n = 372 (%) |
|--------------------------|-----------------------------------|--------------------------------------|
| Patients characteristics |                                   |                                      |
| Pulmonary                | 4 (4.7)                           | 4 (1.1)                              |
| Others                   | 7 (8.2)                           | 49 (13.2)                           |
| Follow-up duration from initiation of anti–PD-1 antibody, median, mo (range) | 27.5 (6-63) | 12.5 (1-62) |

AJCC, American Joint Committee on Cancer; BMI, body mass index; PD-1, programmed cell death-1; SSM, superficial spreading melanoma.

Table II. Clinical characteristics of patients in whom vitiligo developed

| Vitiligo features | Patients with vitiligo n = 85 (%) |
|-------------------|-----------------------------------|
| Time to vitiligo onset after anti–PD-1 initiation, median, mo | 6.9 (1-35.5) |
| Vitiligo body surface area at diagnosis of vitiligo ≤5% | 67/79 (84.8) |
| Vitiligo body surface area after 6 mo ≤5% | 43/68 (63.2) |
| Vitiligo body surface area after 12 mo ≤5% | 31/59 (52.5) |
| Vitiligo type | 45/82 (54.9) |
| Multiple flecked macules | 48/82 (58.5) |
| Ovalar macules | 11/82 (13.4) |
| Both | 29/85 (34.1) |
| Leukotrichia | 10/85 (11.8) |
| Halo phenomenon around cutaneous metastases | 4/85 (4.7) |
| Koebner phenomenon | 72/85 (84.7) |
| Localization according to sun exposure | 50/85 (58.8) |
| Chronic exposure | 3/85 (3.5) |
| Sun-protected areas | 1/85 (1.2) |

PD-1, Programmed cell death-1.
The positive impact of vitiligo was consistent when defining vitiligo as a time-varying covariate (aHR [OS], 0.53; 95% CI, 0.39-0.72; \( P < .001 \); and aHR [PFS], 0.27; 95% CI, 0.18-0.40; \( P < .001 \)).

Fifty-eight patients with vitiligo (68.2%) had an objective response, with a complete remission for 24 patients (28.2%) and a partial response for 34 patients (40.0%) (Supplemental Table I).

Only 4 patients (4.7%) had progressive disease and 22 (25.9%) had stable disease. The response rate in the group without vitiligo was 28.2% (\( n = 104 \)) and a partial response for 34 patients (40.0%) (Supplemental Table I).

On examining additional clinical features associated with vitiligo that could be correlated with increased OS, PFS, or response rate to anti–PD-1, we observed that patients in whom a halo phenomenon around cutaneous metastases developed (\( n = 10 \)) were still alive with a median follow-up of 28 months (range, 12.6-59 months). Additionally, the mortality rate was 10.3% (3 of 29 patients) in patients in whom leukotrichia developed with a median follow-up of 30 months (range, 2-47 months). However, OS, PFS, and response rate to anti–PD-1 in patients with vitiligo presenting a halo phenomenon around cutaneous metastases or leukotrichia were not significantly improved compared with patients with vitiligo who were free of these clinical features (Supplemental Figs 1 and 2).

**Factors associated with the occurrence of vitiligo in patients receiving anti–PD-1**

We next assessed whether clinical and/or biologic factors were associated with the occurrence of vitiligo in patients receiving anti–PD-1. The results of the univariate and multivariable analyses of patients with vitiligo compared with those without vitiligo are presented in Table III.

Men had a higher risk of the development of vitiligo than women (\( P = .035 \)). Patients bearing the \( \text{BRAF}^{V600} \) mutation status (\( P = .037 \)) or having pulmonary metastases (\( P = .005 \)) had a significantly reduced risk of the development of vitiligo. Previous treatment with ipilimumab (\( P = .001 \)) was significantly associated with the occurrence of vitiligo.

In multivariate analysis (Table III), male sex (OR, 1.66; 95% CI, 1.00-2.78; \( P = .05 \)) was an independent factor associated with a higher risk of the development of vitiligo, whereas the presence of pulmonary metastases (OR, 0.50; 95% CI, 0.3-0.8; \( P = .007 \)) was an independent factor associated with a reduced risk of the development of vitiligo.
DISCUSSION

This study in a large population of patients with advanced melanoma with up to a 5-year follow-up demonstrated that the occurrence of vitiligo in patients receiving anti–PD-1 therapies (pembrolizumab or nivolumab) is associated with increased OS and PFS, even when the guarantee-time bias was controlled for at different time points. It was important to avoid a selection bias because patients in whom vitiligo develops may receive the treatment for long
enough and live long enough for skin irAEs to develop.

These findings are of clinical relevance because the association of vitiligo with increased survival is still debated, mainly due to the low number of patients reported. The incidence of vitiligo in patients treated with anti-PD-1 therapies was estimated to be 18.6%, similar to that found in a previous prospective real-life study. The mean time of 6.9 months before vitiligo onset after the initiation of the treatment in our study was similar to or even lower than that in previous studies. The development of vitiligo appears to be an IrAE specific to patients treated with anti–PD-1 for metastatic melanoma. Only a few cases of vitiligo have been reported in patients treated with anti–PD-1 for other cancers, such as bronchial adenocarcinoma and myeloid leukemia, thus melanoma cells and melanocytes might share similar antigens targeted by CD8+ T cells reinvigorated by anti–PD-1 therapies. Vitiligo occurring in patients receiving anti–PD-1 therapies follows a generalized pattern with ovalar and/or multiple flecked lesions mainly located on sites of chronic sun exposure, such as the face, neck, neckline, and forearms. The link between ultraviolet impregnation and the development of vitiligo in patients with metastatic melanoma treated with anti–PD-1 therapies has been investigated. Lo et al found that tumor samples from patients with advanced melanoma who responded well to ICI were enriched for gene sets related to pigmentation, including expression of melanocyte antigens. The authors then showed that inducing mutations using ultraviolet lights in murine melanomas in combination with ICI resulted in T cell responses to the induced mutations. To date, no study has analyzed the clinical factors associated with the occurrence of vitiligo in patients receiving anti–PD-1. We found that men had a significant independent higher likelihood of the development of vitiligo, suggesting the presence of a gender effect. Although gender-related differences have been observed for the efficacy of ICI, the issue remains a matter of debate as gender has not been used to stratify patients in clinical trials. A recent meta-analysis showed a relative reduction in the risk of death resulting from immunotherapy compared with standard therapies that was significantly higher in men than in women. These results were not confirmed in additional meta-analyses conducted. However, pooling data from different clinical trials including all cancer types may not be appropriate to assess this effect. Indeed, a broader analysis showed a difference in gender effects in patients with melanoma treated with ICI. Another important finding of our study is that the presence of lung metastases was independently associated with a reduced risk of the development of vitiligo. The hypothesis that the tumor microenvironment could differ between lung and skin, leading to a different immune reaction in response to anti–PD-1, requires further investigation.

Table III. Univariate and multivariate analyses of factors associated with the occurrence of vitiligo in patients treated with programmed cell death-1 inhibitors

| Melanoma features                     | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | OR (95% CI)         | P value               |
|                                       |                     | OR (95% CI)           | P value               |
| Male sex                              | 1.70 (1.00-2.90)    | .035                  |
|                                       |                     | 1.66 (1.00-2.78)      | .050                  |
| BRAF V600+ mutation                   | 0.58 (0.33-0.99)    | .037                  |
|                                       |                     | 0.63 (0.29-1.39)      | .252                  |
| Lung metastasis                       | 0.50 (0.30-0.83)    | .005                  |
|                                       |                     | 0.50 (0.3-0.8)        | .007                  |
| Brain metastasis                      | 0.65 (0.38-1.10)    | .089                  |
|                                       |                     | 0.77 (0.45-1.34)      | .360                  |
| Prior melanoma treatment ≥            | 0.90 (0.54-1.50)    | .035                  |
|                                       |                     | 0.90 (0.31-2.64)      | .649                  |
| Prior ipilimumab treatment            | 2.79 (1.39-5.44)    | .001                  |
|                                       |                     | 3.48 (0.91-13.2)      | .068                  |
| Prior BRAF/MEK targeted therapy       | 0.63 (0.34-1.13)    | .110                  |
|                                       |                     | 1.14 (0.3-4.3)        | .650                  |
| Stage IV vs stage III                 | 0.62 (0.20-2.26)    | .367                  |
| Skin metastasis                       | 0.85 (0.51-1.40)    | .499                  |
| Liver metastasis                      | 0.87 (0.49-1.51)    | .618                  |
| Prior chemotherapy                    | 1.51 (0.47-4.13)    | .417                  |
| Nivolumab vs pembrolizumab            | 1.20 (0.72-2.03)    | .456                  |
| Other immune-related adverse events   | 1.31 (0.76-2.24)    | .282                  |

Significant P values are shown in bold.
OR, Odds ratio.
When symptoms associated with the occurrence of vitiligo were analyzed, the presence of a halo phenomenon around cutaneous melanoma metastases or leukotrichia was associated with the absence or a low rate of mortality, respectively. However, due to the lack of power, no significant association was observed between these symptoms and increased OS, PFS, or response rate. Larger clinical surveys will be necessary to demonstrate this trend toward an association. Until now, these clinical symptoms have been reported only in small cohorts and/or case reports.

This study has some limitations. First, as a single-center study, it may not reflect the general population of patients in whom vitiligo develops under anti–PD-1. Second, although ours is the largest cohort of patients receiving anti–PD-1 in whom vitiligo developed, the number of patients was probably small when other clinical factors associated with vitiligo (eg, leukotrichia and/or halo phenomenon around cutaneous metastases) were evaluated to assess OS and/or PFS.

In conclusion, the development of vitiligo in patients receiving anti–PD-1 for advanced melanoma is associated with better outcomes. Other clinical factors associated with vitiligo that could be related to an increased response to anti–PD-1 (eg, leukotrichia and halo phenomenon around cutaneous metastases), as well as a putative gender effect, should be investigated further.

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Conflicts of interest

Dr Dousset received fees from MSD, BMS, Novartis, AbbVie, and Pierre Fabre, outside the submitted work. Dr Kostine received fees from AbbVie, BMS, Lilly, Novartis, and Pfizer, outside the submitted work. Dr Beylot-Barry received fees from MSD, outside the submitted work. Drs Pacaud, Barnette, Dutriaux, Pham-Ledard, Gérard, Prey, Boniface, and Seneschal and Author Andreu have no conflicts of interest to declare.

REFERENCES

1. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-1492. https://doi.org/10.1016/S1470-2045(18)30700-9

2. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239-1251. https://doi.org/10.1016/S1470-2045(19)30388-2

3. 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(4):886-894. https://doi.org/10.1158/1078-0432.CCR-15-1136

4. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. 2015;33(7):773-781. https://doi.org/10.1200/JCO.2014.57.4756

5. 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(1):45-51. https://doi.org/10.1001/jamadermatol.2015.2707

6. Nakamura Y, Tanaka R, Asami Y, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: a multi-institutional retrospective study. J Dermatol. 2017;44(2):117-122. https://doi.org/10.1111/1346-8138.13520

7. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death–1 therapies are clinically and biologically distinct from vitiligo. J Am Acad Dermatol. 2017;76(5):863-870. https://doi.org/10.1016/j.jaad.2016.10.044

8. Quaglino P, Marenco F, Osella-Abate S, et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. Ann Oncol. 2010;21(2):409-414. https://doi.org/10.1093/annonc/mdp325.

9. Hwang SJE, 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(3):455-461.e1. https://doi.org/10.1016/j.jaad.2015.10.029

10. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-330. https://doi.org/10.1056/NEJMoa1412082

11. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521-2532. https://doi.org/10.1056/NEJMoa1503093

12. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472-492. https://doi.org/10.3322/caac.21409

13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(22):228-247. https://doi.org/10.1016/j.ejca.2008.10.026

14. Nardin C, Jeand’heur A, Bouiller K, et al. Vitiligo under anti–programmed cell death–1 therapy is associated with increased survival in melanoma patients. J Am Acad Dermatol. 2020;82(3):770-772. https://doi.org/10.1016/j.jaad.2019.11.017

15. Ramondetta A, Ribero S, Conti L, et al. Clinical and pathological relevance of drug-induced vitiligo in patients treated for metastatic melanoma with anti–PD1 or BRAF/MEK inhibitors. Acta Derm Venereol. 2020;100(1):adv00001. https://doi.org/10.1111/1346-8138.1409

16. Zanogouolus P, Huang H, Tsiodra O, et al. Immunotherapy “shock” with vitiligo due to nivolumab administration as third line therapy in lung adenocarcinoma. Respir Med Case Rep. 2017;22:283-286. https://doi.org/10.1016/j.rmcr.2017.10.006

17. Yin ES, Totonchy MB, Leventhal JS. Nivolumab-associated vitiligo-like depigmentation in a patient with acute myeloid leukaemia. 5,7,18,19,20-28
leukemia: a novel finding. JAAD Case Rep. 2017;3(2):90-92. https://doi.org/10.1016/j.jdcr.2016.10.008

18. Dousset L, Boniface K, Seneschal J. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies. G Ital Dermatol Venereol. 2019;154(4):435-443. https://doi.org/10.23736/S0392-0488.18.06254-5

19. Lo JA, Kawakubo M, Juneja VR, et al. Epitope spreading toward wild-type melanocyte-lineage antigens rescues suboptimal immune checkpoint blockade responses. Sci Transl Med. 2021;13(581):ead8636. https://doi.org/10.1126/scitranslmed. aed8636

20. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626-638. https://doi.org/10.1038/nri.2016.90

21. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. Lancet Oncol. 2018;19(3):310-322. https://doi.org/10.1016/S1470-2045(18)30078-0

22. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients’ sex: a systematic review and meta-analysis. Lancet Oncol. 2018;19(6):737-746. https://doi.org/10.1016/S1470-2045(18)30261-4

23. Wallis CJD, Butaney M, Satkunasivam R, et al. Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis. JAMA Oncol. 2019;5(4):529-536. https://doi.org/10.1001/jamaoncol.2018.5904

24. Yang F, Markovic SN, Molina JR, et al. Association of sex, age, and Eastern Cooperative Oncology Group performance status with survival benefit of cancer immunotherapy in randomized clinical trials: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(8):e2012534. https://doi.org/10.1001/jamanetworkopen.2020.12534

25. Ye Y, Jing Y, Li L, et al. Sex-associated molecular differences for cancer immunotherapy. Nat Commun. 2020;11(1):1779. https://doi.org/10.1038/s41467-020-15679-x

26. Bottlaender L, Amini-Adle M, Maucourt-Boulch D, Robinson P, Thomas L, Dalle S. Cutaneous adverse events: a predictor of tumour response under anti-PD-1 therapy for metastatic melanoma, a cohort analysis of 189 patients. J Eur Acad Dermatol Venereol. 2020;34(9):2096-2105. https://doi.org/10.1111/jdv.16311

27. Thomas S, Laino A, Sturm R, et al. Focal regression of a primary melanoma, fading lentigines and poliosis in metastatic melanoma treated with anti-PD-1. J Eur Acad Dermatol Venereol. 2018;32(5):e176-e177. https://doi.org/10.1111/jdv.14678

28. Canestraro J, Jaben KA, Wolchok JD, Abramson DH, Francis JH. Progressive choroidal thinning (leptochoroid) and fundus depigmentation associated with checkpoint inhibitors. Am J Ophthalmol Case Rep. 2020;19:100799. https://doi.org/10.1016/j.ajoc.2020.100799