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ORIGINAL RESEARCH ARTICLE

# Occurrences and Outcomes of Immune Checkpoint Inhibitors-Induced Vitiligo in Cancer Patients: A Retrospective Cohort Study

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## Abstract

**Background** The use of immune checkpoint inhibitors (ICI) in melanoma and non-small cell lung cancer patients is associated with the onset of vitiligo. However, previous studies have suggested conflicting results on the conditions of occurrence of ICI-induced vitiligo.

**Objective** The aim of this study was to describe the occurrences and outcomes of several cases of ICI-induced vitiligo.

**Methods** A retrospective study was carried out using the French Pharmacovigilance Database (FPD) between the beginning of the commercialization of ICI in France and 1 January 2019, selecting for analysis the vitiligo reactions of patients due to treatment with ICI.

**Results** Among the 95 case patients identified in the FPD, the median times to onset of vitiligo after the start of pembrolizumab, nivolumab and ipilimumab therapies were 5.4, 5.0, and 3.8 months, respectively. Furthermore, 37 patients (45%) discontinued ICI treatment due to disease progression. The median follow-up time of all patients was 33 months (interquartile range 2–56).

**Conclusions** This study provided an overall picture of ICI-induced vitiligo in daily medical practice on a large number of pharmacovigilance observations of case patients. Among the observations of ICI-induced vitiligo, the diagnosed cancer was melanoma for almost all patients. Most patients in the study experienced other associated adverse drug reactions (ADRs), such as colitis, pruritus, hypothyroidism, hyperthyroidism, thyroiditis, pancreatitis, and gastritis. Furthermore, our data suggest that the resolution of pembrolizumab- or nivolumab-induced vitiligo could be a marker of disease progression. Future studies evaluating vitiligo outcomes are warranted.

**Key Points**

Among the observations of immune checkpoint inhibitor (ICI)-induced vitiligo, the diagnosed cancer was melanoma for almost all patients.

Most patients in the study experienced other associated adverse drug reactions, such as colitis, pruritus, hypothyroidism, hyperthyroidism, thyroiditis, pancreatitis, and gastritis.

The resolution of ICI-induced vitiligo could be a marker of disease progression. Future studies evaluating vitiligo outcomes are warranted.

## 1 Introduction

### 1.1 Context

Pembrolizumab and nivolumab are monoclonal antibodies targeting programmed cell death-1 (PD-1) receptors, avelumab and atezolizumab target programmed cell death-ligand 1 (PD-L1) receptors, and ipilimumab targets cytotoxic T-lymphocyte antigen-4. These immune checkpoint inhibitors (ICI) are effective in the treatment of several types of cancer [1] and some of the adverse effects of these ICI are described as immune-related adverse effects (IrAE) [2]. Vitiligo-like depigmentation is a well-described irAE in melanoma patients receiving immunotherapy with PD-1 inhibitors [3–8]. However, some studies showed

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conflicting results on the time to vitiligo occurrence and on the patient's outcomes [4, 6]. Furthermore, published studies were conducted on a small sample of patients, and suggested that the occurrence of vitiligo was associated with a favorable clinical response in melanoma patients treated with nivolumab or pembrolizumab [4, 9].

### 1.2 Aim of the Study

The aim of this retrospective study was to describe the occurrences and outcomes of several case patients with ICI-induced vitiligo.

## 2 Methods

### 2.1 Data Source

The French Pharmacovigilance System was first established in 1973 and consists of a network of 31 Regional Pharmacovigilance Centers (CRPVs). The French Pharmacovigilance Database (FPD) has registered all adverse drug reactions (ADRs) spontaneously reported by health professionals to the 31 CRPVs since 1985 [10]. For each report, information on the patient (i.e. age, sex, and medical history), the ADRs (i.e. date of occurrence and outcome), and exposure to the drug (i.e. date of introduction and withdrawal) are recorded in the FPD. A detailed summary of the clinical description is added at the end of each pharmacovigilance case report. ADRs are coded according to the Medical Dictionary for Drug Regulatory Activities (MedDRA®) [11], and all drugs are recoded according to the Anatomical Therapeutic Chemical (ATC) classification system.

In the FPD, each spontaneous report is followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.

### 2.2 Data Analysis

In the present study, spontaneous reports of vitiligo with ICI (pembrolizumab, nivolumab, ipilimumab, atezolizumab, and avelumab) considered as 'suspect' according to the FPD were extracted from 1 January 2008 to 1 January 2019, and updated until 30 April 2019. The cases in the FPD were selected using the MedDRA prefered term 'vitiligo' and the presence of one or more ICI in the report.

In this study, spontaneous adverse reaction reports lacked complete information because the ADRs were still ongoing. A median duration follow-up of 33 months [interquartile range (IQR) 2–56] was realized from the date of onset of ICI-induced vitiligo, and the observations were systematically updated in the FPD.

The Kaplan–Meier method was used to estimate progression-free survival (PFS) in both pembrolizumab and nivolumab treatment. PFS was usually defined as the length of time, during and after the treatment of a disease such as cancer, that a patient lives with the disease and it does not get worse. In this study, PFS was defined as the time from the onset of ICI therapy to the first documented progressive disease. Statistical analyses were performed using XLSTAT software.

## 3 Results

From the beginning of the commercialization of ICI in France to 1 January 2019, a total of 96 reports of ICI-induced vitiligo were recorded in the FPD. One case was excluded from the analysis because vitiligo onset was diagnosed during the clinical exam prior to the initiation of pembrolizumab treatment and no vitiligo aggravation occurred during treatment with this agent. Fifty-three patients were male (56%) and 42 were women, with a median age of 69 years (IQR 26–86) at the occurrence of the lesions. The diagnosed cancer was melanoma for 94 patients and non-small cell lung cancer (NSCLC) for one patient.

The only patient with NSCLC was a 67-year-old male with squamous cell carcinoma of the right metastatic bronchus diagnosed in 2009, but the disease progressed to hepatic, pleural, ganglionic, supraclavicular, and mediastinal levels. Fourteen months after starting nivolumab treatment (28 cycles), the patient experienced a hyperpigmentation of the face, with frontal and nasal confetti depigmentation. A diagnosis of vitiligo was made and nivolumab therapy was continued without corrective treatment.

Before the initiation of ICI-induced vitiligo, 46 patients (48%) had a previous course of drug treatment and 22 patients (23%) had received previous radiotherapy treatment for melanoma or NSCLC. Among the 46 patients with a previous course of drug treatment, 28 patients received at least one previous treatment with ICI; the median number of previous courses of cancer treatments was 1 (IQR 0–4) (Table 1).

Of the 95 case patients, two involved the same patient. Therefore, we report the case of a 76-year-old male patient with a metastatic melanoma who developed two episodes of ICI-induced vitiligo at different drug treatment periods.

The first episode of vitiligo occurred 6 months after nivolumab treatment and was resolved 2 months after stopping treatment. Nivolumab was switched with ipilimumab and, after 3 months of treatment, the worsening metastatic melanoma involved the discontinuation of treatment with ipilimumab. The second episode of vitiligo occurred on

the whole body 4 months after ipilimumab withdrawal; the patient's progress was unknown.

Among the 95 vitiligo cases, 74 (78%) occurred with pembrolizumab, 13 (14%) with nivolumab, 6 with ipilimumab, and 2 with ipilimumab/nivolumab. No cases of atezolizumab- or avelumab-induced vitiligo were registered in the FPD during the period of analysis. Five patients had pre-existing vitiligo induced by ipilimumab or pembrolizumab, which had worsened with the readministration of ICI. Furthermore, seven other patients had a pre-existing auto-immune disease prior to the occurrence of ICI-induced vitiligo.

**Table 1** Characteristics of patients with immune checkpoint inhibitors-induced vitiligo in the French Pharmacovigilance Database

| No. of case patients (*n*) | 95 |
|---|---|
| Age, years [median (IQR)] | 69 (26–86) |
| Males | 53 (56) |
| Labeled indication | 95 |
| Melanoma | 94 (99) |
| NSCLC | 1 (1) |
| Other cancers | 0 |
| Patients with previous treatment by radiotherapy | 22 (23) |
| Patients with a previous course of treatment | 46 (48) |
| Previous treatment with ICI | 28 |
| Patients without a previous course of treatment | 39 (41) |
| Previous treatment not specified | 10 (11) |
| Total | 95 (100) |
| Previous courses of treatment [median (IQR)] | 1 (0–4) |

Data are expressed as *n* (%) unless otherwise indicated

*IQR* interquartile range, *NSCLC* non-small cell lung cancer, *ICI* immune checkpoint inhibitors

Despite the occurrence of vitiligo, ICI were maintained for all patients. The median number of months/cures of therapy duration was 11 months/20 cures with pembrolizumab, 9 months/17.5 cures with nivolumab, 2 months/4 cures with ipilimumab, and 15 days with ipilimumab and nivolumab. Eleven treatments with pembrolizumab, two with nivolumab, and one with ipilimumab plus nivolumab were still ongoing in patients at the time of follow-up. The median dose of ICI treatment was 150 mg/cycle with pembrolizumab, 234 mg/cycle with nivolumab, and 237 mg/cycle with ipilimumab.

Eighty-one patients (85%) had to discontinue ICI treatment (the reasons for discontinuation are summarized in Table 2). The most common reasons for ICI withdrawals were due to disease progression in 37 cases (45%), a complete response in 17 cases (21%), partial or stable response in 12 cases (15%), the occurrence of ADRs other than vitiligo in 16 cases (18%), and death in 2 cases. No patients experienced complete response with ipilimumab or ipilimumab plus nivolumab. Among the 37 patients with disease progression, the outcome was death for 20 patients. Of the 28 exposed patients who had undergone at least one previous treatment with ICI, 14 patients died and 3 patients showed a complete melanoma response.

The time to onset of vitiligo-like lesions with pembrolizumab ranged from 0.7 to 36 months (median 5.4 months or seven cures), and from 0.4 to 23 months (median 5 months or five cures) with nivolumab. The time to onset of vitiligo-like lesions with ipilimumab ranged from 1 to 6.2 months (median 3.8 months or four cures) and from 1.8 to 3 months (median 2.4 months or two cures) with ipilimumab plus nivolumab (Table 3).

Vitiligo outcome was not resolved in 81 cases and was unknown in three cases. Only six patients receiving ICI

**Table 2** Therapy duration and treatment discontinuation

| | Pembrolizumab | Nivolumab | Ipilimumab | Ipilimumab + nivolumab | Total |
|---|---|---|---|---|---|
| Therapy duration, months [median (IQR)] | 11 (1–33) | 9 (0.03–31) | 2 (0.7–4) | 0.5 | 10 (0.03–33) |
| Therapy duration cures, *n* [median (IQR)] | 20 (2–40) | 17.5 (1–58) | 4 (4–4) | 1 | 18 (1–58) |
| Median dosage, mg/cycle (IQR) | 150 (90–230) | 234 (156–300) | 237 (141–240) | Nivolumab: 75 (60–90)<br>Ipilimumab: 230 (190–270) | |
| Treatment discontinuation, yes [*n* (%)] | 63 (85) | 11 (85) | 6 (100) | 1 (50) | 81 (85) |
| Due to disease progression | 29 | 6 | 2 | 0 | 37 |
| Due to complete response | 14 | 3 | 0 | 0 | 17 |
| Due to AE | 14 | 1 | 1 | 0 | 16 |
| Due to partial response | 4 | 0 | 2 | 1 | 7 |
| Due to stability | 4 | 0 | 1 | 0 | 5 |
| Due to death | 1 | 1 | 0 | 0 | 2 |
| Unspecified | 4 | 1 | 1 | 0 | 6 |

*IQR* interquartile range, *AE* adverse event

therapy showed a favorable outcome of their vitiligo, and four died at the end of the follow-up period (Table 4).

Clinical features of vitiligo-like lesions occurring in patients receiving ICI were reported. Among the 95 patients with vitiligo, 34% of patients had lesions localized on the face and hair, 17% on the trunk, 13% on the back, 12% on the hands, 12% on the arms, 9% on the legs, 2% on the pelvic region, and 1% on the feet. The median number of vitiligo-like lesions was three lesions per patient using ICI.

Fifty-six patients (59%) with ICI-induced vitiligo presented 168 associated ADRs occurring before or after the first vitiligo lesions. All associated ADRs occurred during the same ICI treatment that involved the vitiligo occurrence. The average number of ADRs per patient with ICI-induced vitiligo was three, and the main System Organ Classes (SOCs) involved were skin and subcutaneous tissue disorders (21%), endocrine disorders (20%), and gastrointestinal disorders (18%). The most frequent ADRs associated with vitiligo were colitis, pruritus, hypothyroidism, hyperthyroidism, thyroiditis, pancreatitis, and gastritis. Additionally, 16 patients discontinued ICI treatment due to the occurrence of ADRs. Treatment-related ADRs leading to discontinuation that were reported more than once included pancreatitis (two patients) and renal failure (two patients) in patients treated with pembrolizumab.

Median PFS was 22.4 months (95% CI 15.6–27.4) for pembrolizumab and 20.1 months (95% CI 11.2–31.2) for nivolumab (Fig. 1). The median follow-up time of all patients was 33 months (IQR 2–56). At the end of the follow-up period, 65 patients were alive and 30 deceased. Disease progression was the main cause of death for 20 patients (65%), while other causes of death were sepsis, pneumopathy, and general health deterioration.

## 4 Discussion

To the best of our knowledge, this study was the first to describe ICI-induced vitiligo on such a large number of observations of 95 case patients. The main strength of the present investigation was that it reported data from a heterogeneous population of non-selected patients, including a patient with non-melanoma cancer, highlighting the association between vitiligo and ICI. Indeed, among 95 vitiligo case patients, the diagnosed cancer was melanoma for 94 patients and NSCLC for one patient. ICI-induced vitiligo was rarely reported in non-melanoma malignancies. In this study, we report a single case of ICI-induced vitiligo in a patient with NSCLC; other reports have already been published [9, 12]. The risk of melanoma patients developing vitiligo has been estimated to be seven- to tenfold higher compared with the general population [5]. However, the overrepresentation of ICI-induced vitiligo in patients with melanoma can also be explained by the fact that vitiligo is an easily recognized disorder for dermatologists.

The median time to vitiligo onset following pembrolizumab or nivolumab initiation was approximately 5 months, and almost half of ICI-induced vitiligo lesions in patients were observed in photo-exposed areas such as the face, hair, and hands. These results confirmed the findings of the multi-institutional retrospective study of melanoma patients treated with nivolumab [6]. However, it appeared that ipilimumab-induced vitiligo had a shorter onset than pembrolizumab- or nivolumab-induced vitiligo. In our study, 30% of patients were previously treated with an ICI and almost one-quarter of patients were exposed to radiotherapy prior to the onset of vitiligo [13, 14]. These results suggest that previous treatments should be considered as contributing factors in the onset of vitiligo.

A large meta-analysis of multiple melanoma immunotherapy modalities found that vitiligo was significantly associated with PFS, with a two- to fourfold reduction in the risk of disease progression in patients who develop vitiligo [8]. In our study, the median PFS of nivolumab and pembrolizumab was similar, i.e. approximately 1½ years. In an open-label, phase III study (KEYNOTE-006), the median PFS was 5.6 months for pembrolizumab every 2 weeks in advanced melanoma patients [15]. However, further epidemiological

**Table 3** Time to onset and outcome of immune checkpoint inhibitors-induced vitiligo

| | Pembrolizumab | Nivolumab | Ipilimumab + nivolumab | Ipilimumab | Total |
|---|---|---|---|---|---|
| *N* (%) | 74 (78) | 13 (14) | 2 (2) | 6 (6) | 95 (100) |
| Time to onset of vitiligo, months [median (range)] | 5.4 (0.7–36) | 5 (0.4–23) | 2.4 (1.8–3) | 3.8 (1–6.2) | 4.9 (0.4–36) |
| No. of injections before the onset of vitiligo [median (range)] | 7 (1–37) | 5 (1–28) | 2 (1–3) | 4 | 6.5 (1–37) |
| Vitiligo non-resolved | 63 | 11 | 2 | 5 | 81 |
| Vitiligo resolved | 5 | 1 | 0 | 0 | 6 |

**Table 4** Favorable outcome of immune checkpoint inhibitors-induced vitiligo

| Patient | Patient | | | | | Drug | | | | Vitiligo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age (years) | Sex (M/F) | Melanoma diagnosed (time before ICI-induced vitiligo) | ICI stopping | Death occurrence | Suspected drug | Dose amount per cure, mg | Duration of treatment (months) | No. of cures | Localisation | Other adverse effect(s) | Time to onset | Outcome | Time to regression |
| 1 | 37 | F | 3 years | Remission of melanoma | No | Pembrolizumab | 100 | 14 | 21 | Face and hair | – | 4.6 months | Resolved | 3 months |
| 2 | 64 | M | NA | Melanoma progression | 4 months after drug stopping | Pembrolizumab | 198 | 8 | 6 | Face and hair | Hypophysitis | 2.5 months | Resolved | NA |
| 3 | 49 | M | NA | Melanoma progression | 23 months after drug stopping | Pembrolizumab | 194 | 3 | 5 | Trunk and arms | – | 2 months | Resolved | 14 days |
| 4 | 68 | F | 17 years | Melanoma progression | 7 months after drug stopping | Pembrolizumab | 140 | 26 | 37 | NA | – | 16.8 months | Resolved | 3.8 months |
| 5 | 84 | M | 2 months | Melanoma progression | 3 months after drug stopping | Pembrolizumab | 148 | 4 | 5 | Hands, trunk, face | – | 21 days | Resolved | 1.3 months |
| 6 | 76 | M | 4 years | Melanoma progression | No | Nivolumab | 246 | ? | 11 | Ankle, close to metastasis | Lichen planus, cheilitis, purpura | 6.9 months | Resolved | 1.42 months |

*M* male, *F* female, *ICI* immune checkpoint inhibitor, *NA* not available

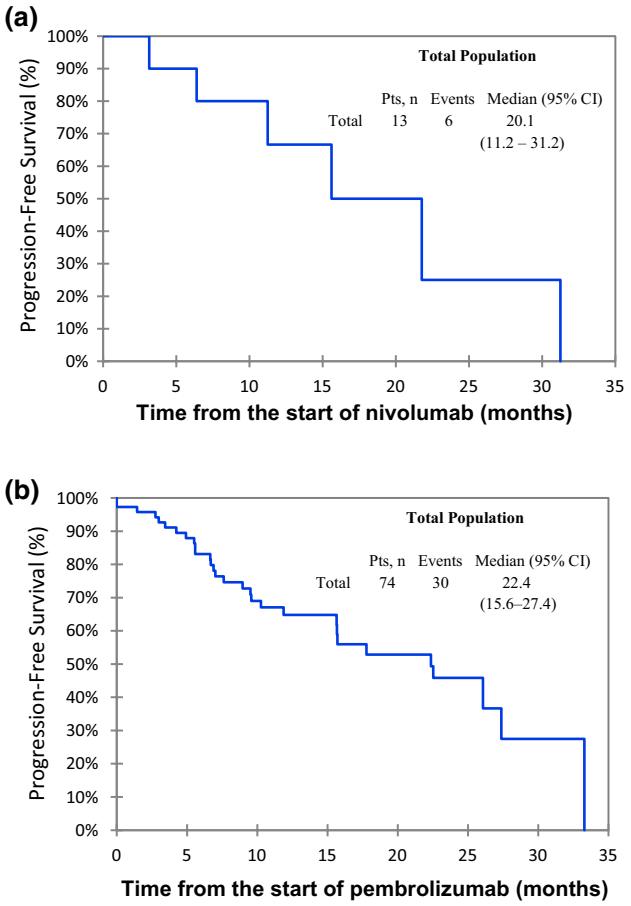


**Fig. 1** Progression-free survival outcomes on vitiligo patients. **a** Treatment with nivolumab. **b** Treatment with pembrolizumab

studies are needed to compare the outcomes of patients treated with ICI with those of untreated patients.

As well as the occurrence of vitiligo being a marker of tumor response in patients exposed to pembrolizumab and nivolumab, the resolution of vitiligo could be a marker of melanoma progression. Indeed, data suggested that the resolution of pembrolizumab- or nivolumab-induced vitiligo could be a marker of disease progression. Future studies evaluating vitiligo outcomes are warranted (Table 4).

Several studies indicate that the occurrence of vitiligo after melanoma immunotherapy has been associated with increased clinical efficacy as a manifestation of melanoma immunity [16, 17]. Compared with earlier published results [3–6], in our study, pembrolizumab or nivolumab provided a better complete response in patients with melanoma, while data are insufficient to establish an association between complete remission and exposure to previous treatment with ICI.

Vitiligo is often known to be associated with other autoimmune diseases, such as autoimmune thyroiditis and type 1 diabetes [18], but our data did not allow us to evaluate the presence of autoimmune diseases because information was not systematically recorded in the case patients. However, more than half of the patients with vitiligo experienced other ADRs, such as colitis, pruritus, hypothyroidism, hyperthyroidism, thyroiditis, pancreatitis, and gastritis. These findings are consistent with several studies showing that common IrAE with ICI are dermatological, gastrointestinal, or endocrine adverse effects [19–21] and underlined the association between the occurrences of multiple IrAE and survival outcomes from anti-PD1 therapy [22].

In France, reporting ADRs to CRPVs allows high-quality analysis of pharmacovigilance signals so they can be brought to the attention of the national agency responsible for making decisions about drugs, i.e. the French Health Products Agency (ANSM) [23]. However, this analysis underlines the limitations of our study due to the spontaneous reporting system in the field of pharmacovigilance. This study did not allow epidemiological extrapolation to the general population with vitiligo and treated with ICI. However, vitiligo has been reported in 11% of patients treated with pembrolizumab [4], but this adverse event could be underreported because a total body skin examination is not always performed in patients treated for melanoma. According to INCA (Institut National du Cancer) data, 1567 patients were treated with pembrolizumab in 2016, knowing that skin cancer accounts for 95% of patients [24]. Therefore, the number of vitiligo reports with ICI in the FPD was relatively low, in comparison with the number of patients treated with pembrolizumab in France. Underreporting can affect the validity of results since it can be related to either the drug or to the degree of seriousness of reactions [25]. 'Serious' adverse events are defined as any untoward medical occurrence that, at any dose, results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, is life-threatening, and results in cancers, congenital anomalies, or birth defects, as well as any medical event that would be regarded as serious if they had not responded to acute treatment [26]. However, in our study, vitiligo is considered a non-serious event. Furthermore, there is a trend to report serious events more frequently than non-serious events [27]. Despite these limitations, we were able to identify some interesting points regarding ICI-induced vitiligo.

## 5 Conclusions

This study provided an overall picture of ICI-induced vitiligo in daily medical practice on a large number of pharmacovigilance observations of case patients. Among the observations of ICI-induced vitiligo, the diagnosed cancer was melanoma for almost all patients. The median time to vitiligo onset following pembrolizumab or nivolumab initiation was

approximately 5 months, while ipilimumab-induced vitiligo had a shorter onset. Almost half of the ICI-induced vitiligo lesions in patients were observed in photo-exposed areas such as the face, hair, and hands. Most patients included in the study experienced other associated ADRs, such as colitis, pruritus, hypothyroidism, hyperthyroidism, thyroiditis, pancreatitis, and gastritis. Furthermore, our data suggest that the resolution of pembrolizumab- or nivolumab-induced vitiligo could be a marker of disease progression. Future studies evaluating vitiligo outcomes are warranted.

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**Data availability** The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Compliance with ethical standards

**Funding** No sources of funding were used to assist in the preparation of this study.

**Conflict of interest** Samy Babai, Anne-Laure Voisin, Célia Bertin, Amandine Gouverneur and Hervé Le Louet have no conflicts of interest that are directly relevant to the content of this article.

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