

# Immune Checkpoint Inhibitor Induced Vitiligo in Non-Melanoma Patients: Characterization and Management

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## Research Article

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# Abstract

**Purpose:** This study highlights the range of non-melanoma cancers where ICI-induced vitiligo can be present and challenges the exclusivity of this phenomenon to melanoma. We believe our manuscript will encourage awareness in our colleagues and stimulate interest in further studies to elucidate the mechanisms of ICI-induced vitiligo in both melanoma and non-melanoma cancers, and to understand whether this phenomenon holds the same positive prognostic value in both cancer groups.

**Methods:** This is a retrospective cohort study from a single-institution's electronic medical record for cancer patients treated with ICIs who subsequently developed vitiligo.

**Results:** We identified 151 patients with ICI-induced vitiligo, 19 (12.6%) non-melanoma and 132 (77.4%) melanoma patients. Time to onset of vitiligo was nearly doubled in the non-melanoma cohort, however, this is confounded by possible delayed diagnosis or under reporting of this asymptomatic condition in patients who do not regularly receive skin exams. The majority of patients had a stable course of vitiligo with 91.4% receiving no treatment in this largely Caucasian cohort. Two patients with non-melanoma cancers and Fitzpatrick type IV or above skin received treatment with narrowband ultraviolet B light therapy and topical steroids with near-complete response.

**Conclusions:** This study highlights the occurrence of ICI-induced vitiligo in a variety of non-melanoma cancers, where skin of color patients will be more prevalent and the need for treatment will potentially be more urgent. Further study is needed to elucidate the mechanism of ICI-induced vitiligo and determine if non-melanoma cancers have the same association between vitiligo and increased tumor response.

## Introduction:

Immune checkpoint inhibitors (ICIs) are targeted inhibitors of T-lymphocyte surface receptors resulting in T-cell stimulation and subsequent upregulation of host anti-tumor response. The immunomodulatory effects of ICIs also lead to various immune-mediated adverse events. Cutaneous adverse events (CAEs) have a wide range of presentations and are among the most common with incidence as high as 44% with use of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monotherapy and > 50% on combination anti-CTLA-4 and anti-programmed cell death 1/anti-programmed cell death-ligand 1 (PD-1/PD-L1) therapy [1]. Vitiligo is a well-documented phenomenon that has long been associated with melanoma and viewed as a positive prognostic factor indicating the body's heightened immune response towards melanocytes [2]. This has also been observed in the ICI-induced setting for melanoma patients, and although the mechanism remains unclear, it is commonly thought to occur because of melanocyte antigen sensitization to the melanoma resulting in subsequent off-target autoimmune response in benign melanocytes [2]. This mechanism comes into question as there are scattered case reports in the literature describing ICI-induced vitiligo in a variety of non-melanoma cancers [3–8] but not nearly at the same incidence as is seen in melanoma patients. Furthermore, there have been multiple reports where ICI-induced vitiligo has been associated with increased progression-free survival, overall survival, and

complete or partial response to treatment in melanoma patients [9–11]. Whether or not this association holds true for non-melanoma patients remains to be elucidated. Here we present and examine a cohort of melanoma and non-melanoma cancer patients representing from a single institution with documented ICI-induced vitiligo.

## **Materials And Methods:**

We identified patients between January 23rd, 2014 and September 24th, 2020 through our institutional electronic medical records system using natural language processing (NLP) to search for patients with multiple mentions of checkpoint inhibitor names or abbreviations as well as the words “depigmented”, “depigmentation”, or “vitiligo” under an internal institutional review board approved protocol. These words were used delineate a diagnosis of vitiligo. Charts were manually reviewed to examine timing and determine causation. Data collected includes patient characteristics, cancer type, staging and response, ICI type and treatment information, and vitiligo characteristics, treatment, and outcome. CAE severity was determined through the Common Terminology Criteria for Adverse Events (CTCAE). The Kruskal-Wallis method was used to test statistical significance for time to onset.

## **Results:**

We identified 151 consecutive, standard of care and clinical trials patients with ICI-induced vitiligo, of which 19 (12.6%) patients were being treated for non-melanoma cancers and 132 (87.4%) for melanoma. Demographics information, primary cancer type, and ICI data are summarized in Table 1.

Table 1  
Demographics of Patients with ICI-Induced Vitiligo

<b>Age</b>	<b><i>median (range), y</i></b>	<b>64 (27-89)</b>
<b>Sex</b>	<i>Male, n</i>	107
	<i>Female, n</i>	44
<b>Race</b>	<i>White, n</i>	108
	<i>Hispanic or Latino, n</i>	19
	<i>Black, n</i>	14
	<i>Asian, n</i>	7
	<i>Others, n</i>	3
<b>Primary Cancer Type</b>	<i>Melanoma, n</i>	132
	<i>NSCLC, n</i>	6
	<i>RCC, n</i>	5
	<i>Breast carcinoma, n</i>	2
	<i>Cutaneous SCC, n</i>	2
	<i>Angiosarcoma, n</i>	1
	<i>Hodgkin's Lymphoma, n</i>	1
	<i>MF, n</i>	1
	<i>SCLC, n</i>	1
<b>ICI Therapy</b>	<i>Ipilimumab + Nivolumab, n</i>	53
	<i>Nivolumab, n</i>	45
	<i>Pembrolizumab, n</i>	39
	<i>Ipilimumab, n</i>	8
	<i>Ipilimumab + Pembrolizumab, n</i>	2
	<i>Spartalizumab, n</i>	2
	<i>Atezolizumab, n</i>	1
	<i>Avelumab, n</i>	1

y = year; n = number of patients; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer; MF = mycosis fungoides

Time to onset, vitiligo outcome and treatments, time to next treatment (TTNT), and overall survival for the three most common melanoma ICI treatment groups are summarized in Table 2. Patients were stratified by primary cancer type into melanoma versus non-melanoma groups for relevant calculations. One patient was excluded from the non-melanoma group for overall survival calculation due to unknown date of passing. Two patients were excluded from the melanoma group, one for overall survival alone due to unknown date of passing and one for TTNT plus OS as patient was lost to follow-up. For melanoma and non-melanoma patients, median TTNT was very similar, with 797 and 983 days respectively. Overall survival was assessed for the three most common treatment arms within our melanoma group. Median OS in melanoma patients was 28.8 months, 34.9 months, and 48.8 months in patients treated with ipilimumab-plus-nivolumab, nivolumab monotherapy, and pembrolizumab monotherapy respectively. Overall, 5-year survival within the melanoma group was highest for patients treated with pembrolizumab (87.0%), followed by nivolumab (79.7%) and ipilimumab-plus-nivolumab therapy (56.8%). OS at 2 years showed a smaller variation among the same three treatment arms at 90.0%, 97.5% and 96.3% respectively. The comparison of each treatment arms' 1, 2, and 5-year OS to previously reported clinical trial data can be found in Table 3.

Table 2  
Disease Outcome and Treatments of Patients with ICI-Induced Vitiligo

		All patients (n = 151)	Melanoma (n = 132)	Non-Melanoma (n = 19)
<b>Time to vitiligo onset post ICI initiation</b>	<i>median (range), d</i>	229 (17-1961)	209 (17-1961)	382 (28-1394)
<b>TTNT post ICI initiation*</b>	<i>median (range), d</i>	837.5 (14-4873)	797 (14-4873)	983 (120-1895)
<b>OS post ICI initiation**</b>	<i>median (range), d</i>	1039 (175-4855)	1029 (175-4855)	1146 (294-2256)
<b>Vitiligo Outcome*</b>	<i>stable, n</i>	117	103	14
	<i>worsened, n</i>	26	25	1
	<i>improved, n</i>	7	3	4
	<i>Lost to follow up, n</i>	1	1	0
<b>Treatments, non-exclusive</b>	<i>Sun protection only, n</i>	139	127	12
	<i>Topical Steroids, n</i>	11	4	7
	<i>NB-UVB, n</i>	2	0	2
	<i>Hydroquinone cream, n</i>	1	1	0
	<i>Ketoconazole cream, n</i>	1	0	1
d= days; ICI = immune checkpoint inhibitor; n = number of patients; NB-UVB = Narrowband Ultraviolet-B; OS = overall survival; TTNT = time to next systemic treatment post CPI-initiation				
*1 patient excluded, lost follow-up				
**3 patients excluded, 2 deceased with date of death unknown, 1 lost to follow-up				

Table 3

## Overall Survival Comparison of Melanoma Treatment Arms to Prior Studies

<b>Ipilimumab + Nivolumab</b> <sup>14,15</sup>		
	Prior Study (n=95, 314)	Our cohort (n= 49)
Median OS (months)	-	28.8 (5.8-65.2)
1-year OS (%)	-	100
2-year OS (%)	63.8	90
5-year OS (%)	52	56.8
<b>Nivolumab</b> <sup>15, 16</sup>		
	Prior Study (n= 316,107)	Our cohort (n= 40)
Median OS (months)	16.8, 36.9	34.9 (12.1-74.6)
1-year OS (%)	62	100
2-year OS (%)	43	97.5
5-year OS (%)	44	97.9
<b>Pembrolizumab</b> <sup>17,18</sup>		
	Prior Study (n=279,277, 655)	Our cohort (n= 30)
Median OS (months)	23.8	48.8 (10.6-94.2)
1-year OS (%)	74.1, 68.4*	100
2-year OS (%)	55, 55*	96.3
5-year OS (%)	34	87
OS = overall survival; *two numbers indicate Pembrolizumab treatment every 2 or 3 weeks respectively		

**Discussion:**

In this single institution series of ICI-induced vitiligo, we reviewed 151 consecutive patients with melanoma and non-melanoma cancers. In our cohort, all Food and Drug Administration (FDA)-approved ICIs have the capacity to induce vitiligo. ICIs are most frequently used in melanoma therapy and ICI-induced vitiligo is most strongly associated with melanoma [2]. As expected, our cohort had mostly melanoma patients (132, 87.4%), with the most prevalent race overall being Caucasians (108, 71.5%). Our cohort of 19 (12.6%) non-melanoma patients, however, definitively challenges the previously held notion that ICI-induced vitiligo is limited to melanoma patients. Specifically, ICI-induced vitiligo in patients with

angiosarcoma, Hodgkin's lymphoma, and mycosis fungoides were not previously reported in the literature. Thus, it appears that ICI-induced vitiligo can be caused by a much wider range of cancers than previously expected, and the mechanism of ICI-induced vitiligo deserves further exploration.

We noted that non-melanoma patients had a statistically significant difference ( $p = 0.005$ ) in median time to onset of vitiligo compared to melanoma patients with 382 days versus 209 days, respectively. As ICI-induced CAEs generally occur on average within 4 weeks after ICI initiation [1], it is interesting to note the delayed onset. It is, however, unclear if ICI-induced vitiligo truly has a delayed onset like ICI-induced bullous pemphigoid, or if vitiligo has a delayed diagnosis. The low acuity and asymptomatic nature of vitiligo increase the risk of delayed diagnosis and under reporting. It is especially prone to delays in diagnosis in lighter skin types where vitiligo is more difficult to detect and there is a lower cosmetic impact. Of note, the majority of the patients in our cohort were Caucasian (71.5%). In combination, these factors likely result in an erroneously low number of reported patients with vitiligo secondary to ICI. Further, patients with non-melanoma cancers' longer time to onset may be explained by these patients not receiving regular full-body skin exams from a dermatologist as their melanoma counterparts do. Definitive incidence and time to onset data would require more standardized skin exams and ideally, prospective reporting.

Vitiligo outcomes in our cohort showed 117 patients (78%) had stable disease, while 26 (17.3%) worsened and 7 (4.7%) improved. This supports vitiligo as a predominantly non-progressive disease. The majority (91.4%) of our patients were not treated for their vitiligo and were offered reassurance with sun protection alone. As many patients also opted not to treat the vitiligo, it is difficult to discern precisely whether no treatment was desired or no treatment was offered. This is not unexpected as vitiligo is predominantly an asymptomatic disease in fair-skinned patients, and thus low priority in the setting of metastatic melanoma. With the expanding use of checkpoint inhibitors for non-melanoma cancers, however, the diversity of patients' skin color is also expected to increase, leading to a greater impact of vitiligo on quality of life and greater importance of vitiligo outcomes. Of note, two African American patients were treated with narrowband ultraviolet B (NB-UVB). Both experienced vitiligo improvement, with one patient experiencing dramatic re-pigmentation. In a previous report, a Hispanic male with renal cell carcinoma experienced improvement of his ICI-induced vitiligo after being treated with NB-UVB in combination with topical steroids, after lack of improvement on topical steroids alone [12]. This points to the effectiveness of the current gold standard treatment of topical steroids and UV light therapy for vitiligo in the ICI-induced variant. In addition, one patient in our cohort was depigmented with topical hydroquinone. It is important for clinicians to keep in mind that for some patients with severe vitiligo, depigmentation therapy can prove a better cosmetic alternative, if the patient is amenable, than repigmentation. Overall, it is reasonable to not treat patients, especially if the vitiligo is asymptomatic and patients are not impacted cosmetically. As studies in skin-of-color (SOC) patients have shown that vitiligo can have a variety of negative impacts on mental health [13], treating vitiligo with NB-UVB alone or in combination with topical steroids can prove fruitful in this setting. As ICIs are increasingly utilized in non-melanoma cancers where there is greater diversity of patients, physicians should be aware of potential quality of life impacts of ICI-induced vitiligo and potential effective treatment options.

It has been hypothesized that vitiligo secondary to ICI therapy in melanoma patients is associated with increased tumor response as it indicates the therapy is effectively targeting melanocytes. This is reflected through the association of ICI-induced vitiligo with increased progression-free survival, overall survival, and complete or partial response to treatment in melanoma patients [9–11]. The ICIs supposedly induce a tumor response against antigens that are present on both benign and malignant melanocytes resulting in vitiligo [10, 11]. This theory, however, bears further exploration in light of the variety of non-melanoma cancers similarly associated with ICI-induced vitiligo. The heterogeneity and small size of our cohort does not allow for this analysis.

Time to next treatment (TTNT) is defined as the time between start date of vitiligo-inducing ICI and the start date of next systemic treatment. This metric represents the clinical benefit of therapy by accounting for both tumor response as well as toxicity profile in disease or treatments which are highly symptomatic. In our cohort, TTNT was similar in melanoma and non-melanoma patients, with a median TTNT of 797 and 983 days respectively. This raises the question of whether ICI-induced vitiligo could be associated with increased clinical benefit in non-melanoma patients and would be worth further prospective analysis.

In comparing our cohort of melanoma patients with vitiligo to that of previously studied consecutively treated standard of care melanoma patients from our institution, we noticed a trend toward higher median TTNT in the vitiligo patients (Table 4). Because of the disparity in sample sizes, meaningful time-dependent analysis was not possible with our data. Of note, in our sub-group of melanoma patients treated with combination ICI therapy, the median TTNT was almost three times longer than in previous studies with 623 and 210 days respectively (Table 4).

Table 4  
Time to Next Treatment Comparison of Melanoma Treatment Arms to Prior Studies

<b>Melanoma Combination Therapy</b>		
	Prior Study (n=155)	Our Cohort (n=53)
Median TTNT (days)	210	623
Range TTNT	21-1273	42-2089
<b>Melanoma Nivolumab Therapy</b>		
	Prior Study (n=63)	Our Cohort (n=39)
Median TTNT (days)	289	784
Range TTNT	20-1523	91-1878
<b>Melanoma Pembrolizumab Therapy</b>		
	Prior Study (n=215)	Our Cohort (n=31)
Median TTNT (days)	429	1386
Range TTNT	13-2108	14-2854
<b>Melanoma Total</b>		
	-	Our Cohort (n=132)
Median TTNT (days)	-	797
Range TTNT	-	14-4873
<b>Non-Melanoma</b>		
	-	Our Cohort (n=19)
Median TTNT (days)	-	983
Range TTNT	-	120-1895
TTNT = Time to next treatment		

Based on our data alone, overall 5-year survival within the melanoma group was highest with pembrolizumab therapy, followed by nivolumab and ipilimumab-plus-nivolumab therapy. As our cohort includes mainly standard of care patients, it is likely that ipilimumab-nivolumab combination therapy was used to treat those with aggressive disease and monotherapy may have been used more for adjuvant therapy, accounting for the lower overall survival in the combination treatment arm. Our cohort's 1, 2, and 5-year overall survival rates were found to be higher than previously reported clinical trials among all treatment arms (Table 3) [14–18]. Overall 5-year survival has been previously reported at 34% with

pembrolizumab, 52% with ipilimumab-plus-nivolumab, and 44% with nivolumab therapies in clinical trials. OS within our cohort was at 87%, 56.8% and 79.7% for the same respective categories of therapy [15, 18].

Although direct comparison between real-world and clinical trials patients cannot be made, the increased OS rates and TTNT in our study may represent associated clinical benefit in the setting of ICI-induced vitiligo. Further study into the mechanism may aid in our understanding of the effect of ICI-associated vitiligo on TTNT and overall survival outcomes in melanoma patients. At this time, we are only discussing an association, which may have confounders such as patients having good enough response and low enough toxicity profile to remain on ICI therapy long enough to develop vitiligo. Mechanistic causation has yet to be established.

One limitation we noted in our chart review is that reporting of vitiligo was often inconsistent with skipped notes in documentation and non-specific descriptions of the disease. In combination with the single cohort nature of this study, this inconsistency complicates the calculation of incidence numbers as well as time to onset due to potential delays in reporting. With time to onset being dependent on patient or physician observation of vitiligo, a lower number of cases may also have been reported. The distribution of the patients' disease may also affect the likelihood of diagnosis or documentation. This is supported in our cohort by vitiligo distribution, 95 (62.9%) patients had face/neck involvement and 104 (68.9%) had upper extremities involvement, areas that are easily noticed by the patient and clinicians. In contrast, only 53 (35.1%) had trunk and 51 (33.8%) had lower extremities involvement. Incidence was not calculated in this study due to the above recognized limitations.

Another limitation is that of the 151 patients reviewed, 39 had ICI treatments prior to the ICI they were on when vitiligo was noted in their electronic medical record. This represents a confounding variable in the treatment that definitively caused the vitiligo. Since time to onset can be delayed, it is possible that the prior ICI is the treatment that caused the vitiligo rather than the ICI the patient was currently being treated with when the vitiligo started. Though the exact vitiligo-inducing ICI may be unknown in these patients, it remains reasonable to assume that they had ICI induced vitiligo and should remain as part of the cohort.

In conclusion, ICI-induced vitiligo can be seen with virtually any cancer type and there are multiple reasons for delayed and under reporting. As the cancer types treated with ICIs expands, it is important for patient care teams to recognize the quality-of-life impact on an increasingly diverse patient population and to treat their skin disease accordingly.

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### **Conflicts of Interest/Competing Interests:**

The authors have no relevant financial or non-financial interests to disclose.

### **Availability of data and material:**

Data is available upon request to the corresponding author.

### **Code availability:**

N/A

### **Author Contributions:**

Anisha Patel conceived the project. Jonathan Lo conducted the chart review, wrote initial drafts, and continued to edit and revise the manuscript until submission. Hannah Hanania and Monika Keiser assisted in the chart review, manuscript writing and editing process. Anisha Patel directly supervised the first three authors and worked closely with them on this manuscript in multiple aspects, including verification of chart review data and editing the manuscript.

### **Ethics Approval:**

This study was conducted under protocol PA15-0959, approved by our institutional IRB.

### **Consent to participate:**

A waiver of consent was granted by the institutional IRB for this retrospective chart review.

### **Consent to publication:**

N/A

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