Population-Based Frequency of Ophthalmic Adverse Events in Melanoma, Other Cancers, and After Immune Checkpoint Inhibitor Treatment

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• PURPOSE: To examine the frequency of ophthalmic immune-related adverse events (OirAEs) in melanoma, other cancers, and after immune checkpoint inhibitor (ICI) treatment.

• DESIGN: Retrospective clinical cohort study.

• METHODS: This study identified patients diagnosed with OirAEs between January 1, 2011, and December 31, 2018, in the Kaiser Permanente Southern California electronic health records. The primary exposures of interest were prior initiation of ICIs and underlying cancer diagnosis. Risk-adjusted prevalence of OirAEs was evaluated in patients with melanoma, with nonmelanoma cancer, and without cancer. The 1-year incidence of OirAEs and recurrence of prior ophthalmic disease were identified in ICI-receiving patients with melanoma and nonmelanoma.

• RESULTS: Among 4,695,669 unique patients identified, 9.9% had a cancer diagnosis, of whom 2.8% had a diagnosis of melanoma. Overall prevalence for uveitis and selected neuro-ophthalmic diagnoses was 341.8/100,000 patient-years in patients with melanoma and 369.6/100,000 patient-years in patients with nonmelanoma cancer regardless of ICI treatment, compared with 142.2/100,000 patient-years in patients without cancer. A total of 2,911 unique patients received ICI therapy. Compared with patients with nonmelanoma cancer, patients with melanoma on any ICI had elevated 1-year incidence rates of uveitis (1.2% vs 0.2%; risk-adjusted odds ratio, 6.45). High 1-year recurrence rates for uveitis in ICI patients with a prior uveitis history were also observed.

• CONCLUSIONS: The prevalence of all OirAEs was substantially higher in patients with cancer, with ICI-related uveitis risk specifically increased in patients with melanoma compared with patients with nonmelanoma cancer. Evidence-based guidelines for ophthalmic monitoring of patients undergoing ICI treatment may require different risk stratifications based on underlying cancer diagnosis, specific ICI used, and prior history of uveitis. (Am J Ophthalmol 2021;224:282–291. © 2020 Elsevier Inc. All rights reserved.)

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OPHTHALMOLOGIC COMPLICATIONS OF IMMUNE origin are relatively uncommon but can arise from idiopathic etiologies, secondary to infections, or secondary to enhanced autoimmunity; these complications can be devastating.[1,2]

The goal of cancer immunotherapy is to harness the body's natural immune mechanisms to eliminate transformed cancer cells. Antitumor efficacy of these new classes of drugs, including the immune checkpoint inhibitors (ICIs), has been extremely favorable but may be limited by a wide range of induced immune-related adverse events (irAEs).[2–4] A detailed understanding of ophthalmic immune-related adverse events (OirAEs) is of increasing importance in the evolving field of cancer immunotherapy because use of ICI therapy is rapidly expanding, with as many as 43% of patients with cancer now eligible for ICI treatment.[5]

Autoimmune adverse events are reported in up to 80%-90% of patients on the ICI cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; ipilimumab) and up to 70% of patients on inhibitors of the ICI programmed cell death protein 1 (PD-1; pembrolizumab and nivolumab) or programmed death-ligand 1 (PD-L1; atezolizumab, avelumab, and durvalumab). Most of these side effects are mild, transient, and self-limited, but they can occasionally be severe and can affect almost any organ or system.[3,6] Autoimmune effects associated with PD-1 or PD-L1 therapy are generally less severe when compared with CTLA-4 therapy.[4,7,8]

Autoimmune ophthalmic complications such as uveitis,[9–12] as well as neuro-ophthalmic complications

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TABLE 1. Demographic Characteristics of Study Population Between January 1, 2011, and December 31, 2018

Demographic	Total KPSC Members N = 4,695,669 (%)	Patients Without Cancer N = 4,231,654 (%)	Patients With Cancer	
			Melanoma N = 12,838 (%)	Nonmelanoma N = 451,177 (%)
Sex				
Male	2,289,010 (48.8)	2,071,184 (49.0)	7,479 (58.3)	210,347 (46.6)
Female	2,406,659 (51.3)	2,160,470 (51.1)	5,359 (41.7)	240,830 (53.4)
Age (y)				
18-24	411,460 (8.8)	407,861 (9.6)	100 (0.8)	9,681 (2.2)
25-44	1,845,609 (39.3)	1,790,138 (42.3)	1,292 (10.1)	65,779 (14.6)
45-64	1,523,301 (32.4)	1,373,632 (32.5)	5,107 (39.8)	177,860 (39.4)
≥65	915,299 (19.5)	660,023 (15.6)	6,339 (49.4)	197,857 (43.9)
Race/ethnicity				
Non-Hispanic white	1,628,962 (34.7)	1,341,473 (31.7)	11,493 (89.5)	275,996 (61.2)
Non-Hispanic black	373,195 (8.0)	340,164 (8.0)	80 (0.6)	32,951 (7.3)
Hispanic	1,750,665 (37.3)	1,650,828 (39.0)	995 (7.8)	98,842 (21.9)
American Indian/Alaskan Native	10,989 (0.2)	9,898 (0.2)	20 (0.2)	1,071 (0.2)
Asian	466,658 (9.9)	435,245 (10.3)	96 (0.7)	31,317 (6.9)
Native Hawaiian/other Pacific Islander	35,469 (0.8)	33,282 (0.8)	11 (0.1)	2,176 (0.5)
Many/other	83,304 (1.8)	79,533 (1.9)	58 (0.5)	3,713 (0.8)
Unknown	346,427 (7.4)	341,231 (8.1)	85 (0.7)	5,111 (1.1)

KPSC = Kaiser Permanente Southern California.

including optic neuropathy,[13,14] orbital inflammation,[15,16] thyroid-like ophthalmopathy,[17] myasthenia gravis–like ophthalmopathy,[11] orbital apex syndrome,[18] hypophysitis,[19] and acute visual loss,[20] are also observed after ICI use. A systematic review including 234 ipilimumab patients reported ophthalmic autoimmune complications in 10.3% of patients on ipilimumab treatment, with 4.3% classified as uveitis.[12] Patients on pembrolizumab are reported to have 1%-2% incidence of uveitis,[21–24] whereas combination ipilimumab-nivolumab has been associated with uveitis at a higher incidence (6%) than either agent alone.[25] It is becoming critically important to understand the frequency, severity, and clinical course of treatment-associated OirAEs with increasing numbers of patients on ICIs and the potentially vision-threatening nature of these diseases.

Quantification of the incidence and prevalence of OirAEs in patients with cancer treated with ICIs has been limited by the relatively low prevalence and incidence of these diseases and the limited availability of health systems databases that track all of the care delivered to individual patients. The Kaiser Permanente Southern California (KPSC) health care system electronic health record (EHR) consisting of a large racially and socioeconomically diverse population gave us the opportunity to investigate diseases like OirAEs in patients with cancer, while still providing sufficient power to identify important relationships that could aid in the development of evidence-based management recommendations in the future.

METHODS

• **STUDY DESIGN:** In this retrospective cohort study, we analyzed clinical data on member patients managed at the KPSC from January 1, 2011, through December 31, 2018. The KPSC health care system provides integrated health care for a large, racially/ethnically, and socioeconomically diverse member population in 15 hospitals and 234 medical offices located throughout Southern California. KPSC member population is broadly representative of the Southern California population.[26] January 1, 2011, was chosen as the beginning of the cohort because this was the first year for which complete data on prescription medications were uniformly recorded in the KPSC-EHR system. Data extracted from EHRs include demographic characteristics, medical history, clinical diagnostic and procedural codes, and pharmacy records. The data were linked longitudinally using the medical record number that is unique to each patient. The study was approved by the institutional review board of the KPSC, met their expectations for Health Insurance Portability and Accountability Act (HIPAA) compliance, and was granted a waiver for informed consent.

• **STUDY POPULATION:** Patients 18 years of age or older who sought care from a KPSC provider between January 1, 2011, and December 31, 2018, were included (N = 5,944,193). A priori demographic data were obtained from the EHRs (Table 1), including gender (male vs female), age (categorized as 18-24, 25-44, 45-64, ≥65 years),

and race/ethnicity (categorized as non-Hispanic white [white], non-Hispanic black [black], Hispanic, Asian/Pacific Islander, and other/mixed racial ethnic groups). In this study, age was defined as either age at the time of diagnosis for those with a documented cancer diagnosis or age at the study end date of December 31, 2018, for patients with no cancer diagnosis.

Ophthalmic complication diagnoses (including anterior uveitis, intermediate, posterior, or panuveitis, scleritis, papilledema, optic neuritis, optic atrophy, cranial nerve 3, 4, or 6 mononeuropathy, internuclear ophthalmoplegia, and myasthenia gravis) and cancer diagnoses (grouped into melanoma vs nonmelanoma cancers) were identified using International Classification of Diseases, 9th/10th revision, Clinical Modification (ICD-9/10-CM) codes (Supplemental Tables 1 and 2). Although some have considered dry eye to be a potential complication of ICI therapy, dry eye was not studied in this patient population. For the current analysis, records of patients who had a melanoma diagnosis with a secondary nonmelanoma cancer diagnosis were combined with records of patients who had only a melanoma cancer diagnosis. Nonmelanoma skin cancers were excluded from this analysis. Patients with less than 1-year membership during the study period (N = 1,248,524) were excluded from analysis. The justification for the latter exclusion was to have complete personal diagnostic medical and treatment information during the study period. After these exclusions, records on 4,695,669 patients remained for analysis.

The ICI medications and timing of initiation were identified through medication administration tables of the EHRs. ICIs of interest in this study included anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapy, which included the following ICIs: the CTLA-4 inhibitor ipilimumab (on or after the Food and Drug Administration [FDA] approval date of March 25, 2011), the PD-1 inhibitor nivolumab (on or after the FDA approval date of December 22, 2014), the PD-1 inhibitor pembrolizumab (on or after the FDA approval date of September 4, 2014), the PD-L1 inhibitor durvalumab (FDA approval May 1, 2017), the PD-L1 inhibitor avelumab (FDA approval March 23, 2017), and the PD-L1 inhibitor atezolizumab (FDA approval May 18, 2016). We also examined combined same-day usage of ipilimumab and nivolumab (on or after the latter's FDA approval date of December 22, 2014). Detailed drug codes are listed in Supplemental Table 3. Where patients received more than 1 permutation of same-day medications over the study period, we analyzed medication permutations separated by more than 1 year as separate therapeutic episodes. A total of 2,911 unique patients with 3,146 therapeutic episodes were identified to have had use of any CTLA-4 or PD-1/PD-L1 inhibitor by drug prescription documentation with at least 12 months of follow-up after the ICI was initiated. The effect on therapeutic episodes was performed by checkpoint inhibitor categories: anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab or pembrolizumab), anti-PD-L1 (durvalumab, avelumab, or atezolizumab), or combination anti-CTLA-4 and anti-PD-1 (ipilimumab with nivolumab). Combination drug therapy was defined as administration dates within the same day. A search for patients on the PD-L1 inhibitors (durvalumab, avelumab, and atezolizumab) was also conducted; however, patients on these checkpoint inhibitors were omitted from subsequent detailed analysis because of low numbers.

• **OUTCOMES:** In this study, autoimmune ophthalmic complications including ICI-related uveitis and neuro-ophthalmic complications (optic neuropathy, orbital inflammation, thyroid-like ophthalmopathy, myasthenia gravis–like ophthalmopathy, orbital apex syndrome, hypophysitis, and acute visual loss) were the outcomes of interest.

• **STATISTICAL ANALYSIS:** Between-group comparisons of patient characteristics and rates of OirAEs between groups were assessed by the χ^2 test. For this study prevalence was defined as the presence of a relevant diagnosis code in the EHR whose onset occurred during the study period divided by the years of the study and the number of patients in the group. The prevalence of OirAEs was calculated among patients without cancer, patients with nonmelanoma cancer, and patients with melanoma adjusted for demographic characteristics including age, gender, and race/ethnicity of patients and analyzed both regardless of cancer treatment and in the setting of ICI treatment. The incidence of OirAEs within 1 year after initiation of ICI was calculated stratified by the patient's underlying cancer diagnosis (melanoma vs nonmelanoma) and type of ICI. The recurrence risk of OirAEs in patients with any prior history of ocular inflammation within 1 year after initiation of ICI was also estimated stratified by the patient's underlying cancer diagnosis (melanoma vs nonmelanoma) and type of ICI. Risk-adjusted odds ratios (adj.OR) and their 95% confidence intervals (CI) were derived from logistic regression models. The potential confounders that were included in the analysis were the patient's age at diagnosis, race/ethnicity, and gender. To assess the relative influences of ICI treatment modalities on the observed uveitis risk relationships, the following sensitivity analyses were performed after fitting ICI drug type along with demographic covariates (age, race/ethnicity, and gender) in the model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A TOTAL OF 4,695,669 UNIQUE PATIENTS IN THE KPSC MEMbership were queried. A cancer diagnosis was present in 9.9% of all patients (Table 1). Of those patients with any cancer recorded in the EHR, 2.8% had a diagnosis of

TABLE 2. Prevalence of Uveitis and Selected Neuro-Ophthalmic Diagnoses

Complication	Patients Without Cancer	Patients With Cancer					
		Melanoma			Nonmelanoma		
	N = 4,231,654 (Rate)[a]	N = 12,838 (Rate)[a]	Adjusted OR[b] (95% CI)	*P* Value[c]	N = 451,177 (Rate)[a]	Adjusted OR[b] (95% CI)	*P* Value[c]
Anterior uveitis	24,014 (70.9)	142 (138.3)	1.44 (1.22, 1.70)	<.001	5,946 (164.7)	1.53 (1.48, 1.57)	<.001
Intermediate/posterior/panuveitis	1,460 (4.3)	15 (14.6)	2.80 (1.68, 4.68)	<.001	401 (11.1)	1.99 (1.77, 2.24)	<.001
Any uveitis OirAEs (anterior/intermediate/posterior/panuveitis)	24,811 (73.3)	151 (147)	1.48 (1.26, 1.74)	<.001	6,167 (170.9)	1.54 (1.49, 1.59)	<.001
Scleritis	6,561 (19.4)	30 (29.2)	1.27 (0.89, 1.82)	.191	1,354 (37.5)	1.49 (1.40, 1.59)	<.001
Papilledema	2,409 (7.1)	13 (12.7)	2.05 (1.19, 3.55)	.010	498 (13.8)	2.05 (1.85, 2.27)	<.001
Optic neuritis	3,775 (11.2)	32 (31.2)	1.75 (1.23, 2.48)	.002	1,275 (35.3)	2.04 (1.91, 2.19)	<.001
Optic atrophy	5,150 (15.2)	56 (54.5)	1.84 (1.41, 2.40)	<.001	2,054 (56.9)	1.97 (1.87, 2.08)	<.001
CN3,4,6 palsy or INO	6,211 (18.3)	82 (79.8)	2.24 (1.80, 2.80)	<.001	2,479 (68.7)	2.07 (1.97, 2.18)	<.001
Myasthenia gravis	1,707 (5)	15 (14.6)	1.36 (0.82, 2.27)	.238	743 (20.6)	2.14 (1.96, 2.35)	<.001
Any selected neuro-ophthalmic diagnosis (scleritis, papilledema, optic neuritis, optic atrophy, CN3,4,6, INO, or myasthenia gravis)	23,890 (70.6)	214 (208.4)	1.86 (1.62, 2.13)	<.001	7,618 (211.1)	1.90 (1.85, 1.96)	<.001
Any uveitis OirAE or selected neuro-ophthalmic diagnosis	48,146 (142.2)	351 (341.8)	1.66 (1.49, 1.85)	<.001	13,339 (369.6)	1.72 (1.69, 1.76)	<.001

CI = confidence intervals, INO = internuclear ophthalmoplegia, OirAE = ophthalmic immune-related adverse event, OR = odds ratio.
[a]All rates are shown per 100,000 patients/y.
[b]Adjustments were made for age, gender, and race/ethnicity.
[c]*P* value comparisons against patients without cancer.

melanoma or melanoma in conjunction with another cancer diagnosis. There was a slight male predominance in patients with melanoma (58.3%). Patients with cancer were on average older than patients without cancer and total KPSC membership as would be expected, with most melanoma-affected individuals in the 45-64 and ≥65 age categories. White individuals appeared to have a disproportionately higher cancer rate in general, accounting for 62.0% of all patients with cancer, while making up only 34.7% of total membership. Patients with melanoma were also mostly white, making up 89.5% of those with melanoma diagnosis.

The overall uveitis prevalence in patients without cancer was 73.3/100,000 patient-years (Table 2). The overall uveitis prevalence in patients with melanoma and nonmelanoma cancer diagnoses were both increased relative to the population without cancer at 147/100,000 patient-years and 170.9/100,000 patient-years, respectively, corresponding to an overall uveitis adj.OR (95% CI) of 1.48 (1.26, 1.74) and 1.54 (1.49, 1.59). Specific diagnoses such as intermediate, posterior, or panuveitis appear to have an elevated prevalence in patients with melanoma (adj.OR, 2.80; 95% CI: 1.68, 4.68) compared with patients with nonmelanoma cancer (adj.OR, 1.99; 95% CI: 1.77, 2.24). The prevalence of selected neuro-ophthalmic conditions in patients without cancer was 70.6/100,000 patient-years (Table 2). The prevalence in patients with melanoma and nonmelanoma cancer diagnoses were 208.4/100,000 patient-years and 211.1/100,000 patient-years, respectively, corresponding to adj.OR (95% CI) of 1.86 (1.62, 2.13) and 1.90 (1.85, 1.96). All adj.OR were statistically significantly higher compared with patients without cancer.

ICIs were administered to 0.63% of all patients with cancer. A total of 694 unique patients with melanoma and 2,217 unique patients with nonmelanoma cancer received any ICI (Tables 3 and 4). PD-1 was the most commonly used ICI in both the patients with melanoma and nonmelanoma. For specific therapeutic events, a total of 2,434 patients received a PD-1 inhibitor, 261 patients received a PD-L1 inhibitor, 241 patients received the CTLA-4 inhibitor, and 210 patients received the CTLA-4/PD-1 combination therapy (Tables 3 and 4). Patients with melanoma were analyzed separately from patients with nonmelanoma cancer. Most patients with melanoma treated with ICIs were male (70.2%) and disproportionately white (82.0%, Table 3). In contrast, patients with nonmelanoma treated with ICIs were 55.3% male and 51.9% white (Table 4). Patients with cancer treated with ICIs also tended to be older in age than patients with cancer on other treatment protocols (Table 4).

TABLE 3. Demographics of Patients With Melanoma on Checkpoint Inhibitor Medications (ICI)

	Checkpoint Inhibitor (Total Events)[a]				Checkpoint Inhibitor (Unique Patients)		
Demographics	CTLA-4 N = 229 (%)	CTLA-4/PD-1 N = 126 (%)	PD-1 N = 501 (%)	PD-L1 N = 6 (%)	All ICI N = 694 (%)	No ICI N = 12,144 (%)	*P* Value
Sex							<.001
Male	160 (69.9)	81 (64.3)	354 (70.7)	6 (100.0)	487 (70.2)	6,992 (57.6)	
Female	69 (30.1)	45 (35.7)	147 (29.3)	0 (0.0)	207 (29.8)	5,152 (42.4)	
Age (y)							.476
18-24	1 (0.4)	1 (0.8)	4 (0.8)	0 (0.0)	5 (0.7)	95 (0.8)	
25-44	18 (7.9)	20 (15.9)	39 (7.8)	0 (0.0)	58 (8.4)	1,234 (10.2)	
45-64	98 (42.8)	67 (53.2)	202 (40.3)	1 (16.7)	285 (41.1)	4,822 (39.7)	
≥65	112 (48.9)	38 (30.2)	256 (51.1)	5 (83.3)	346 (49.9)	5,993 (49.3)	
Race/ethnicity							<.001
Non-Hispanic white	191 (83.4)	92 (73.0)	416 (83.0)	4 (66.7)	569 (82.0)	10,924 (90.0)	
Non-Hispanic black	4 (1.7)	4 (3.2)	11 (2.2)	0 (0.0)	14 (2.0)	66 (0.5)	
Hispanic	30 (13.1)	25 (19.8)	60 (12.0)	2 (33.3)	93 (13.4)	902 (7.4)	
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	19 (0.2)	
Asian	4 (1.7)	3 (2.4)	10 (2.0)	0 (0.0)	13 (1.9)	83 (0.7)	
Native Hawaiian/other PI	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	10 (0.1)	
Many/other	0 (0.0)	2 (1.6)	2 (0.4)	0 (0.0)	3 (0.4)	55 (0.5)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	85 (0.7)	

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, CTLA-4/PD-1 = combinatorial use on the same day of the 2 medications, ICI = immune checkpoint inhibitor, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1, PI = Pacific Islander.

[a]Use of each specific ICI was deemed as an event; some patients sequentially received more than 1 ICI over the course of their therapeutic treatment; therefore, the total events are greater than the total number of unique patients.

TABLE 4. Demographics of Patients With Nonmelanoma Cancer on Checkpoint Inhibitor Medications (ICI)

	Checkpoint Inhibitor (Total Events)[a]				Checkpoint Inhibitor (Unique Patients)		
Demographics	CTLA-4 N = 12 (%)	CTLA-4/PD-1 N = 84 (%)	PD-1 N = 1,933 (%)	PD-L1 N = 255 (%)	All ICI N = 2,217 (%)	No ICI N = 448,960 (%)	*P* Value
Sex							<.001
Male	11 (91.7)	53 (63.1)	1,059 (54.8)	143 (56.1)	1,226 (55.3)	209,121 (46.6)	
Female	1 (8.3)	31 (36.9)	874 (45.2)	112 (43.9)	991 (44.7)	239,839 (53.4)	
Age (y)							<.001
18-24	0 (0.0)	0 (0.0)	8 (0.4)	0 (0.0)	8 (0.4)	9,673 (2.2)	
25-44	0 (0.0)	10 (11.9)	103 (5.3)	10 (3.9)	114 (5.1)	65,665 (14.6)	
45-64	5 (41.7)	43 (51.2)	759 (39.3)	93 (36.5)	867 (39.1)	176,993 (39.4)	
≥65	7 (58.3)	31 (36.9)	1,063 (55.0)	152 (59.6)	1,228 (55.4)	196,629 (43.8)	
Race/ethnicity							<.001
Non-Hispanic white	6 (50.0)	42 (50.0)	1,005 (52.0)	125 (49.0)	1,150 (51.9)	274,846 (61.2)	
Non-Hispanic black	2 (16.7)	3 (3.6)	220 (11.4)	34 (13.3)	255 (11.5)	32,696 (7.3)	
Hispanic	3 (25.0)	32 (38.1)	469 (24.3)	63 (24.7)	540 (24.4)	98,302 (21.9)	
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)	5 (0.2)	1,066 (0.2)	
Asian	1 (8.3)	7 (8.3)	213 (11.0)	31 (12.2)	244 (11.0)	31,073 (6.9)	
Native Hawaiian/other PI	0 (0.0)	0 (0.0)	6 (0.3)	0 (0.0)	6 (0.3)	2,170 (0.5)	
Many/other	0 (0.0)	0 (0.0)	12 (0.6)	2 (0.8)	14 (0.6)	3,699 (0.8)	
Unknown	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	3 (0.1)	5,108 (1.1)	

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, CTLA-4/PD-1 = combinatorial use on the same day of the 2 medications, ICI = immune checkpoint inhibitor, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1, PI = Pacific Islander.

[a]Use of each specific ICI was deemed as an event; some patients sequentially received more than 1 ICI over the course of their therapeutic treatment; therefore, the total events are greater than the total number of unique patients.

TABLE 5. One-Year Incidence and Recurrence Rates of Uveitis OirAE in Patients With Melanoma vs Nonmelanoma Cancers

	One-Year Incidence and OR				Recurrence Rate and OR			
	Melanoma, n/N (%)	Nonmelanoma Cancer, n/N (%)	Adjusted OR [a] (95% CI)	*P* Value	Melanoma, n/N (%)	Nonmelanoma Cancer, n/N (%)	Adjusted OR [a] (95% CI)	*P* Value
CTLA-4	6/229 (2.6)	0/12 (0.0)	N/A	N/A	0/1 (0.0)	0/0 (0.0)	N/A	N/A
CTLA-4/PD-1 combo	1/126 (0.8)	0/84 (0.0)	N/A	N/A	1/1 (100.0)	0/2 (0.0)	N/A	N/A
PD-1	3/501 (0.6)	4/1,933 (0.2)	2.79 (0.37, 18.64)	.389	2/6 (33.3)	4/24 (16.7)	1.51 (0.07, 37.86)	1.000
PD-L1	0/6 (0.0)	0/255 (0.0)	N/A	N/A	0/0 (0.0)	0/7 (0.0)	N/A	N/A
All checkpoint inhibitors	8/694 (1.2)	4/2,217 (0.2)	5.87 (1.45, 28.57)	.010	2/7 (28.6)	4/31 (12.9)	1.17 (0.06, 23.28)	1.000

CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, ICI = immune checkpoint inhibitor, N/A = not available, OirAE = ophthalmic immune-related adverse event, OR = odds ratio, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1.

The incidence of OirAEs within 1 year after initiation of ICI was calculated according to cancer (melanoma vs nonmelanoma) and ICI. The recurrence risk of OirAEs evaluated patients with a prior history of ocular inflammation who developed recurrent ocular inflammation within 1 year after initiation of ICI, also stratified by cancer (melanoma vs nonmelanoma) and ICI.

[a]Adjustments were made for age, gender, and race/ethnicity. Adjusted OR and *P* values were derived from exact logistic regression analysis.

The 1-year incidence rates for uveitis were found to be higher in patients treated for melanoma for all ICIs used, with the highest rate of 2.6% associated with the use of the CTLA-4 inhibitor (Table 5). A rate of 0.6% was found for use with PD-1 inhibitors, whereas an intermediate rate of 0.8% was determined for combination CTLA-4/PD-1 use in patients with melanoma (Table 5). In comparison, a lower incidence rate of 0.2% was determined for PD-1 use in patients with nonmelanoma cancers. When taken collectively, patients with melanoma had a 1.2% incidence rate (8 of 694) of developing uveitis on any ICI, largely driven by the patients on CTLA-4, compared with a 0.2% incidence rate (4 of 2,217) in patients with nonmelanoma cancers (adj.OR, 6.45; 95% CI: 1.94, 21.50). The ICI treatment duration between the first and last ICI infusion during the study period had a mean of 245.6 days for those with uveitis and a mean of 156.2 days for those without uveitis, $P = .1207$. A sensitivity analysis to determine the ICI treatment effect on the observed uveitis diagnosis was attempted; however, numerator in several of ICI-specific uveitis was too small to obtain meaningful adjusted estimates. Concurrent or sequential use of BRAF/MEK and ICI therapy was identified in 4% of unique patients in our cohort, the majority of whom had an underlying diagnosis of melanoma. The addition of the BRAF/MEK therapy did not increase the uveitis risk over the use of ICI alone by a Fisher exact test (data not shown).

The overall 1-year recurrence rate for uveitis in the first year after ICI initiation in patients with melanoma who had a prior uveitis diagnosis was 28.6% (Table 5, right). Patients with nonmelanoma cancers and a history of prior uveitis, by comparison, also had a high recurrence rate of 12.9% (4 of 31) when they were started on ICIs. In contrast, the recurrence rate of uveitis on ICI therapy was higher in patients treated for melanoma (adj.OR, 2.70; 95% CI: 0.39, 18.93), but this difference failed to achieve statistical significance, likely due to the small sample size (Table 5). Among those patients with uveitis recurrence on ICI, the interval between the previous uveitis and initiation of ICI treatment was significantly shorter, mean 307.4 days, compared with those who had a prior history of uveitis with no recurrence, mean 1,407.4 days, $P = .0003$.

The overall 1-year incidence rate for non-uveitis OirAEs (including scleritis, papilledema, optic neuritis, optic atrophy, cranial nerve 3, 4, or 6 mononeuropathy, internuclear ophthalmoplegia, and myasthenia gravis) was not significantly different between patients treated for melanoma (1.3%) or nonmelanoma cancers (1.4%) (Table 6); however, 2.2% of patients with melanoma treated with either CTLA-4 or the CTLA-4/PD-1 combination therapy experienced a non-uveitis OirAE on comparison to none of the patients with nonmelanoma cancer on these therapies. For patients treated with PD-1 therapy, 0.8% of patients with melanoma and 1.6% of patients with nonmelanoma developed a non-uveitis OirAE within 1 year of therapy, but this difference was not statistically significant. Recurrence rates for the non-uveitis OirAEs were high for the combination of all ICIs and were 25% for patients with melanoma and 34.6% for patients with nonmelanoma, without a statistically significant difference between the 2 cancer groups.

DISCUSSION

IN THIS STUDY, THERE WAS A HIGHER PREVALENCE OF UVEitis and selected neuro-ophthalmic diagnoses in patients with cancer than patients without cancer. Furthermore, the ICI-related incidence of uveitis-OirAEs was much

TABLE 6. One-Year Incidence and Recurrence Rates of Selected Neuro-ophthalmic Diagnoses in Patients With Melanoma vs Nonmelanoma Cancers

	One-Year Incidence and OR				One-Year Recurrence Rate and OR			
	Melanoma, n/N (%)	Nonmelanoma Cancer, n/N (%)	Adjusted OR [a] (95% CI)	*P* Value	Melanoma, n/N (%)	Nonmelanoma Cancer, n/N (%)	Adjusted OR [a] (95% CI)	*P* Value
CTLA-4	4/229 (1.8)	0/12 (0.0)	N/A	N/A	2/5 (40.0)	0/0 (0.0)	N/A	N/A
CTLA-4/PD-1 combo	4/126 (3.2)	0/84 (0.0)	N/A	N/A	0/1 (0.0)	0/3 (0.0)	N/A	N/A
PD-1	4/501 (0.8)	30/1,933 (1.6)	0.41 (0.10, 1.24)	.138	3/14 (21.4)	15/44 (34.1)	0.58 (0.07, 3.61)	.790
PD-L1	0/6 (0.0)	2/255 (0.8)	N/A	N/A	0/0 (0.0)	3/7 (42.9)	N/A	N/A
All checkpoint inhibitors	9/694 (1.3)	32/2,217 (1.4)	0.70 (0.28, 1.58)	.477	4/16 (25.0)	18/52 (34.6)	0.48 (0.07, 2.62)	.546

CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, ICI = immune checkpoint inhibitor, N/A = not available, OirAE = ophthalmic immune-related adverse event, OR = odds ratio, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1.

The incidence of OirAEs within 1 year after initiation of ICI was calculated according to cancer (melanoma vs nonmelanoma) and ICI. The recurrence risk of OirAEs evaluated patients with a prior history of neuro-ophthalmic diagnosis who developed recurrent neuro-ophthalmic diagnosis within 1 year after initiation of ICI, also stratified by cancer (melanoma vs nonmelanoma) and ICI.

[a]Adjustments were made for age, gender, and race/ethnicity. Adjusted OR and *P* values were derived from exact logistic regression analysis.

higher in patients with melanoma than patients with nonmelanoma cancer, largely driven by CTLA-4 use. Moreover, the recurrence risk of uveitis was greatly increased by initiating ICI therapy in both patients with melanoma and nonmelanoma cancer.

• **CANCER VS NONCANCER PREVALENCE OF UVEITIS AND SELECTED NEURO-OPHTHALMIC DIAGNOSES:** The overall prevalence of uveitis in patients without cancer in our study was similar to previously published values.[1,27,28] The prevalence of uveitis among patients with any cancer diagnosis was higher compared with noncancer controls. We also observed that the rate of all of the selected neuro-ophthalmic diagnoses was higher in patients with cancer. This difference cannot be explained by the small number of ICI-induced uveitis cases among the larger population of patients with cancer. We could find no previous reports looking at the overall rate of uveitis in patients with cancer on a computerized search of the literature, but this finding is consistent with a prior association of other immune disorders with cancer risk.[29] Another possible contributor for the higher prevalence is a surveillance bias in patients with cancer with an increased evaluation of any new symptom.[30] These observations are worth additional future investigations.

• **ICI EFFECTS ON UVEITIS AND SELECTED NEURO-OPHTHALMIC DIAGNOSES, AND MELANOMA:** The present study quantified the risk of ophthalmic OirAEs in patients with cancer treated with ICIs. The greater frequency of CTLA-4 inhibitor use in the melanoma population may partially account for the higher rates of uveitis seen in this population, as CTLA-4 inhibitors have been well documented to have higher rates of irAEs than the newer PD-1 and PD-L1 inhibitors.[10,23,31–33] Nevertheless, when controlling for drug regimen differences by exclusively comparing the rates of uveitis associated with PD-1 inhibitors, the increased risk in patients with malignant melanoma (0.6%, 3 of 501) compared with those with other cancers (0.2%, 4 of 1,933) persists, suggesting that the pathology of the melanoma diagnosis itself may play a role in uveitis susceptibility in these patients (Table 5). Notably, despite the higher adjusted odds ratio, this did not reach statistical significance. We previously proposed that there may be an underlying difference in uveitis risk in patients with melanoma vs nonmelanoma cancers who are on ICIs.[9]

Melanoma is known to be a highly immunogenic tumor with high tumor mutational burden,[34] and melanomas have the greatest number of irAEs reported to the US Food and Drug Administration Adverse Event Reporting System.[35] There is also a well-described relationship between melanoma and a particular type of uveitis, Vogt-Koyanagi-Harada (VKH) disease.[36–38] Development of vitiligo and VKH in patients with melanoma on ICIs is associated with strong antitumor responses and may be indicative of antitumor treatment efficacy.[39–41] Melanocyte antigens may be intrinsically more immunogenic than other self-antigens; vitiligo is a common manifestation of immunotherapy.[42–44] T-cell responses against many antigens common to metastatic non-small cell lung cancer (NSCLC) and skin suggest overlapping T-cell antigens as the mechanism for irAEs and skin toxic effects with anti PD-1 therapy.[45] Cross-reactivity between melanoma and retinal antigens, as have been proposed in melanoma-associated retinopathy and VKH disease, may similarly contribute to the etiology of ICI-associated uveitis. The findings reported here can also be analyzed in contrast to the published data available

on the ocular complication frequencies of other immune-related cancer therapies including the widely used BRAF and MEK inhibitors.[46] In the present study, the addition of BRAF/MEK inhibitors to ICI did not result in a significant increase in uveitis; however, additional studies in larger patient populations are required to specifically address a potential additive or synergistic effect of these agents.

Patients with a history of uveitis diagnosis at any time before the initiation of an ICI were found to have high rates of uveitis recurrence. This observation is consistent with the mechanism of action of ICIs, which may lower the threshold for autoimmune disorders overall. Interestingly, we observed that individuals who were diagnosed with melanoma had higher uveitis recurrence rates (28.6%, 2/7) than those treated for other cancers (12.1%, 4/31). Although the sample sizes in this study are small, these trends are consistent with that reported in an independent analysis of the American Academy of Ophthalmology IRIS Registry (Intelligent Research in Sight).[47] These new findings suggest that individuals who have had previous diagnoses of uveitis or other immune-related ophthalmic conditions may require early coordination with ophthalmologic subspecialty care, possibly even before immune ICIs are initiated, as recurrence rates in this population may be especially high.

The strengths of this study include the analysis of a large integrated health care system population with an opportunity to obtain data from the EHR including detailed medication records, diagnosis codes, and procedure codes from close to 4.7 million patients from a socioeconomically diverse population. This health care system has a good retention rate, allowing the opportunity for extremely comprehensive, longitudinal analysis needed to quantify relationships between low-frequency diseases and low-frequency treatments. No previously published reports assessing the relationship between cancer and OirAEs were found on a computerized search of the literature. To our knowledge, this is the first study to report this finding and is also the largest epidemiological evaluation to date of ICI-associated OirAEs in patients with cancer.

There are numerous limitations of this study. In spite of the large study population, some permutations of diseases and treatments were still too small to assess. Also, we did not calculate non-ICI OirAE incidence because we thought we could not identify acceptable criteria to choose non-ICI start dates for 1-year incidence that would be comparable to the ICI initiation start point. We hope that future investigations will allow these and other observations. Furthermore, a sensitivity analysis to determine the ICI treatment effect on uveitis diagnosis was attempted; however, numerator in several of ICI-specific uveitis was too small to obtain meaningful adjusted estimates. Therefore, further research is required to provide evidence whether the observed difference in uveitis risk, in our study, is driven by ICI drug type.

These results taken together suggest that the prevalence of uveitis and selected neuro-ophthalmic complications is high in patients with cancer. The use of ICIs increased the risk of many OirAEs, with particularly elevated risk for specific OirAEs in patients undergoing ICI treatment for malignant melanoma. Patients who had any previous history of uveitis appeared to be at special risk of recurrence after ICI initiation, which was also further increased in the setting of melanoma. Evidence-based recommendations for optimal management and monitoring in this population of patients have not yet been determined. It is likely that guidelines will need to be set based on underlying cancer diagnosis (melanoma vs nonmelanoma) and history of prior uveitis or other autoimmune disease to reflect differing risk stratifications in these populations.

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