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# Uveitis in Patients Treated with CTLA-4 and PD-1 Checkpoint Blockade Inhibition

**Michel M. Sun, M.D., Ph.D.**[1], **Ralph D. Levinson, M.D.**[1], **Artur Filipowicz, D.O.**[2], **Stephen Anesi, M.D.**[2], **Henry J. Kaplan, M.D.**[3], **Wei Wang, M.D., Ph.D.**[3], **Debra A. Goldstein, M.D.**[4], **Sapna Gangaputra, M.D.**[5], **Robert T. Swan, M.D.**[6], **H. Nida Sen, M.D.**[7], **Lynn K. Gordon, M.D., Ph.D.**[1]

[1]Department of Ophthalmology, Jules Stein Eye Institute, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA

[2]Massachusetts Eye Research and Surgical Institution, Waltham, MA

[3]University of Louisville, Louisville, KY

[4]Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL

[5]Vanderbilt Eye Institute, Nashville, TN

[6]SUNY Upstate Medical University, Syracuse, NY

[7]National Eye Institute, NIH, Bethesda, MD

## Abstract

**Purpose:** To investigate the link between treatment with CTLA-4 and PD-1 checkpoint blockade inhibitors and development of noninfectious uveitis.

**Methods:** A survey was distributed to uveitis specialists to identify patients who developed uveitis while receiving either PD-1 inhibitors pembrolizumab and nivolumab; PD-L1 inhibitors atezolizumab, avelumab, and durvalumab; or the CTLA-4 inhibitor ipilimumab.

**Results:** Fifteen patients from seven institutions were identified. The most common cancer diagnosis (13/15) was malignant melanoma. Fourteen patients had a new uveitis diagnosis following checkpoint blockade administration (6 anterior uveitis, 6 panuveitis, 1 posterior uveitis, 1 anterior/intermediate combined); one patient developed optic neuritis. Uveitis was diagnosed within 6 months after drug initiation for 11/12 patients (median 63 days). Corticosteroid treatment was effective for most patients, although 2 patients had permanent loss of vision.

**Conclusions:** Patients on checkpoint inhibitor therapy should be educated to seek care if they develop ocular symptoms, and prompt referral to specialists should be incorporated into oncology protocols.

Corresponding author: Lynn Gordon, LGordon@mednet.ucla.edu, 100 Stein Plaza, Los Angeles, CA 90095-7000.

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**Keywords**

uveitis; PD-1; CTLA-4; checkpoint inhibitor; ocular inflammation; immunotherapy

## Introduction

This past decade has seen a rapid and dramatic shift in cancer management with the increasingly widespread use of cancer immunotherapy drugs. Immunotherapy is based on the concept of cancer immunosurveillance [1], the idea that a natural function of the immune system includes detection and elimination of transformed host cells, and that by extension, enhancing immune function can amplify antitumor response and aid in eradication of existing cancers and metastases. This study focuses on the class of immune checkpoint inhibitors, specifically CTLA-4 and PD-1 monoclonal antibody blockade [2], which act by releasing inhibitory “brakes” on immune cells to promote antitumor response [3,4]. Use of these immunotherapeutic drugs whose actions work in the spectrum between anti-tumor and anti-self, disrupts the balance of self-tolerance and the well-established roles of the PD-1 and CTLA-4 pathways in autoimmunity [5]. The subsequent immune related adverse events (irAEs) and their management is a critical area of immunotherapeutic research, as autoimmune related toxicity often limits the use of these otherwise effective cancer therapeutics.

Autoimmune side effects are extremely common in patients on cancer immunotherapy, with up to 80-90% of patients on CTLA-4 checkpoint blockade (ipilimumab) [6,7] and up to 70% of patients on PD-1 (pembrolizumab & nivolumab) or PD-L1 (atezolizumab, avelumab, & durvalumab) therapy [8-10] experiencing irAEs, most of which are mild, transient, and self-limited, but which can occasionally be severe and can affect almost any organ or system. Ophthalmologic autoimmune complications were reported in 10.3% of patients on ipilimumab treatment in a systematic review of 234 ipilimumab patients, with 4.3% classified as uveitis [11]. Studies with pembrolizumab have determined a lower rate of approximately 1% - 1.5% rate of uveitis [12-15]. Immune related ocular complications in cancer patients treated with immune checkpoint inhibitors (ipilimumab, tremelimumab, nivolumab, or pembrolizumab) occur with an odds ratio of about 3.4 times higher frequency as compared to patients on conventional cancer regimens [16]. Combination ipilimumab-nivolumab has been shown to have stronger anti-tumor effect, but also a higher uveitis toxicity (6%) than either agent alone [17,18].

However, the cases with ophthalmic complications that have been referenced in the literature have not been completely described. Here we detail the clinical course of 14 patients who developed uveitis after administration of CTLA-4 or PD-1 cancer immunotherapeutics to aid in the understanding and management of patients who develop immune related ocular complications in this setting.

## Methods

Patient cases were collected through a survey containing 18 primary questions that was distributed to uveitis specialists who were members of the American Uveitis Society (AUS)

listserv (Supplemental Figure 1). AUS is a 276 member society with all members having access to the listserv. Physicians were asked to identify patients with uveitis who were previously treated with one of the two commercially available PD-1 inhibitors (pembrolizumab and nivolumab), three available PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab), or the CTLA-4 inhibitor (ipilimumab). Participating physicians submitted HIPAA compliant, deidentified information including patient demographics, uveitis severity, treatment, clinical response, checkpoint inhibitor drug used, and cancer diagnosis for each patient. Physicians were asked to report diagnosis and scoring consistent with Standardization of Uveitis Nomenclature (SUN) working group criteria [19]. This research was conducted under IRB approval through the University of California, Los Angeles (IRB #17-001861) for multicenter collection of deidentified patient data from uveitis specialists in the American Uveitis Society.

The online survey was designed and distributed through the secure electronic data collection tool REDCap and responses saved in HIPAA compliant data backup in house. Numeric data was exported and basic statistical analyses performed. Text responses were aggregated and edited for consistency, style, and removal of potentially identifiable information.

### Literature Search:

A literature search of published manuscripts in the PubMed database was performed using the search terms “pembrolizumab,” “nivolumab,” “atezolizumab,” “avelumab,” and “durvalumab” with the term “uveitis,” to identify published cases of uveitis found in association with these drugs. The PubMed database was searched for available publications up to August 2018.

## Results

A total of 15 patients from 7 institutions were submitted to the study. Of the submitted patients, four had been treated with ipilimumab monotherapy, six on combination ipilimumab-nivolumab, two on single agent nivolumab, and three on single agent pembrolizumab. Of note, none of the patients submitted for inclusion in this report were treated with any of the more recently approved PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab).

The mean patient age at the time of uveitis diagnosis was 54 years (SD 10.2, range 37-71 years, Table 1). The patients reported were 53.3% male and 86.7% Caucasian. The majority of patients (13/15 patients, 86.7%) had a concurrent cancer diagnosis of malignant melanoma (Table 1). The physician reported type of uveitis included 6 cases of anterior uveitis, 6 cases of panuveitis, and 1 case each involving posterior uveitis, anterior and intermediate uveitis combined, and optic neuritis. One patient (patient #15) had a diagnosis of optic neuritis in the absence of uveitis, and for the purposes of this paper was not included in further uveitis specific analysis. All other patients had documented diagnosis of their first episode of uveitis following checkpoint blockade inhibitor administration. The interval between initiation of the checkpoint inhibitor regimen and diagnosis of clinical uveitis ranged from 4 to 380 days, with a relatively short median time of 63 days (Table 2).

All cases of uveitis where laterality was documented were bilateral. Most (10/14) patients had mild (trace cell) to moderate (1-2+ cell) uveitis severity. However two patients (patient #4 and patient #8) had more severe anterior chamber involvement (3-4+ AC cell) with no documented vitreous cell, while two other patients (patient #10 and patient #13) had more severe vitreous involvement (2-4+ vitreous cell) with moderate anterior chamber inflammation (Table 2). Most patients were initially started on corticosteroids, including topical difluprednate, oral prednisone, or local steroid injection. Only two patients were treated with less potent topical prednisolone acetate alone.

The checkpoint inhibitor associated uveitis episodes were typically short in duration (median 20 days, range 5-67 days) with excellent response to treatment and generally favorable clinical outcome even in more severe cases, however there were a few exceptions (Table 3). Recurrence of uveitis occurred only in one case that had continuation of checkpoint inhibitor therapy (patient #8). Patient #10 did not achieve complete control of inflammation by 3 months of treatment, and patient #14 was unresponsive to topical difluprednate and local steroid injection, resulting in hypotony and HM vision OS after 2 years. Additionally, complications of treatment can develop, as in patient #1 who had visual function impacted from glaucoma secondary to fluocinolone acetonide implant (Retisert - Bausch & Lomb, Bridgewater, NJ).

## Discussion:

This report adds a cohort of 14 patients who developed uveitis following CTLA-4 and/or PD-1 checkpoint blockade immunotherapy to the existing literature. The patients presented here are limited to patients who were treated with anti-CTLA-4 and/or anti-PD-1 immunotherapeutics only. Although physicians were requested to query for anti-PD-L1 therapeutics as well, no patients treated with the anti-PD-L1 drugs atezolizumab, avelumab, or durvalumab have been reported to have developed uveitis complications here or in the literature, although pharmaceutical company studies report a 1% or <1% risk of uveitis in their prescribing information. The observation that no reports of uveitis related side effects have been published in patients receiving PD-L1 therapeutics may reflect the smaller number of patients on these more recently approved PD-L1 therapeutics with few currently approved indications. Alternatively, this may hint at an underlying difference in mechanism of action between the PD-1 and PD-L1 pathways. Another possibility is that this disparity may be the result of differing uveitis susceptibility in the distinct groups of malignancies that these drug regimens are currently approved for. Of note, while CTLA-4 and both PD-1 inhibitors were initially approved for malignant melanoma and widely used for the treatment of that disease, none of the PD-L1 inhibitors are currently approved for the treatment of melanoma.

We propose that there may be an underlying difference in uveitis risk in patients with melanoma vs non-melanoma cancers. Consistent with this proposal, 12 of 14 patients with uveitis in this case series and 19 of 22 patients in the literature (Table 4) had an underlying cancer diagnosis of malignant melanoma or choroidal/uveal melanoma. There is a known relationship between melanoma and uveitis in the setting of VKH, and there are multiple reports of VKH-like disease in patients on checkpoint inhibitor therapy [20-23] (Table 4).

Development of VKH-like disease in melanoma patients is thought to be due to cross reactivity of malignant melanoma cells and normal choroidal melanocytes [24,25], in patients with a possible HLA related genetic predisposition [25,26]. VKH may be a consequence of autoimmune response in melanoma patients with good cancer immunosurveillance, and VKH-like disease has been associated with long recurrence-free intervals in patients with cutaneous malignant melanoma [27]. Congruent with these observations, development of VKH has been associated with strong anti-tumor response with PD-1 immunotherapy in melanoma patients, and has been proposed as a clinical sign to suggest treatment efficacy, similar to vitiligo [28-30]. Vitiligo is also a common skin manifestation of immunotherapy, more frequently reported with nivolumab and pembrolizumab compared to ipilimumab [31-33], suggesting melanocyte antigens may be more immunogenic than other self-antigens. Vitiligo and VKH-like uveitis have been described in other forms of cancer immunotherapy, including adoptive transfer of autologous tumor reactive tumor infiltrating lymphocytes for metastatic melanoma [34]. Additionally, a highly significant correlation between the efficacy of tumor immunotherapy (using adoptively transferred melanocyte specific CD8+ T cells) and severity of ocular autoimmunity has been well documented in mice [35].

Another notable observation was the unexpectedly high frequency of optic nerve involvement that was reported in these patients. One patient (patient #15) had optic neuritis as the main ocular finding. Other patients here and in the literature had bilateral papillitis [36] (patients #1, 14), optic disc edema [37,38] (patient #11) and optic nerve leakage (patient #12) in addition to anterior inflammatory findings. The significance of these optic nerve complications in the setting of checkpoint inhibitor related uveitis is yet unclear, but deserves further follow up.

None of the patients in our cohort had a prior history of uveitis, and most patients experienced first time uveitis diagnosis within several months after initiation of checkpoint blockade immunotherapy. Of note, 11 of 12 patients (where both inhibitor start date and uveitis diagnosis date were known) had uveitis manifest within the first 6 months after initiating therapy (median 63 days, range 4-161 days), with only one patient with Hodgkin's lymphoma developing uveitis symptoms 380 days after initiation of immunotherapy. This is consistent with published cases reporting 18/20 patients with onset of uveitis within the first 6 months (Table 4). The highest risk period for development of ocular inflammatory manifestations therefore appears to be within the first 6 months of checkpoint blockade initiation. This is concordant with observations for non-ocular immune-related adverse events with these immunotherapeutic drugs, which generally occur by 3-6 months of starting therapy [8,39-41].

The majority (10/14) of patients reported here exhibited uveitis with relatively mild to moderate severity with 2+ AC and vitreous cell or less. The patients reported in this paper were all referred to uveitis trained specialists, where the majority had an excellent, rapid response to treatment with generally favorable clinical outcome, including those with more severe disease. Development of uveitis may not be a contraindication to continuing checkpoint blockade immunotherapy, as most cases of uveitis are readily treated with conventional therapy, but this must be evaluated on a case by case basis. Most patients had resolution of disease relatively quickly, with median duration of disease of 20 days (range

5-67 days, 95% CI 10.4-35). Recurrence of uveitis was rare, and when present, was associated with long-term continuation of checkpoint blockade therapy for cancer treatment. Notably, one published case describes a 75 y/o M with a uveitis diagnosis prior to starting pembrolizumab therapy, who had a total of 3 uveitis relapses before pembrolizumab treatment was completed [28]. This may suggest that patients with known autoimmune uveitis or other autoimmune disease may have a higher propensity for recurrences, and may need closer monitoring. Additionally, some patients had a poor clinical course both in the literature [37,42] and presented here in a case of uncontrolled uveitis leading to severe hypotony and end stage phthisical eye (patient #14), and from complications of steroid treatment resulting in glaucomatous damage (patient #1), emphasizing the need for prompt specialist referral for appropriate treatment and follow up.

A literature review for cases of uveitis following PD-1 or PD-L1 immunotherapy was also performed. The literature for the CTLA-4 inhibitor ipilimumab induced uveitis has been well cited [43], and was not repeated here. Uveitis has been reported after PD-1 therapy (pembrolizumab or nivolumab) in published cases totaling 22 patients (Table 4). Ten patients were treated with single agent pembrolizumab, eleven with single agent nivolumab, and one with combination ipilimumab/nivolumab therapy. The mean age was 65 years old, with range from 35 to 92 years old. The cases in the literature were 50% male; the majority of published cases did not include race or ethnicity with the exception of 8 cases (6 Caucasian and 2 Japanese). Similar to our cohort, most patients had a cancer diagnosis of malignant melanoma, with 17/22 (77%) cutaneous melanoma, 2/22 (9%) uveal or choroidal melanoma, 2/22 (9%) clear cell renal cell carcinoma, and 1/22 (4.5%) non-small cell lung cancer. All patients had bilateral disease, with the exception of one who had unilateral disease where the other eye was enucleated prior to treatment [44]. The published reports include 12 cases of anterior uveitis, 5 posterior uveitis, and 4 panuveitis, which demonstrates a higher predominance of anterior uveitis than the cohort presented in this report. However congruent with our observations, 18/20 of the previously published cases reported onset of uveitis less than 6 months after initiation of checkpoint inhibitor treatment, with the remaining outliers manifesting at 14 months and 16 months after treatment. Although treatment regimens were varied, most reported good response to corticosteroid treatment, with 11/15 cases reporting uveitis control within one month or less of steroid treatment. However some cases reported continued inflammation for up to 3-5 months, and some patients experienced a poor overall visual outcome [42].

A major limitation to this study is inconsistent reporting and missing data inherent to the questionnaire format that was used to collect these cases. Although valuable in facilitating aggregation of cases from multiple physicians at multiple centers, this format relies exclusively on the accuracy and amount of information that participating physicians are willing to contribute. Although consistency with SUN criteria was encouraged [19,45], variability in diagnosis and scoring between different physicians may be present. Treatment regimens were also not standardized, and may vary between medical centers. No independent chart review was conducted. Although the survey was distributed through the American Uveitis Society listserv, an overall low response rate (7 out of 276 members) resulted in a limited number of cases in which select institutions are overrepresented. Further, we are unable to determine absolute risk of uveitis in this patient subset with this

study design. The majority of patients presented (13 of 15) are Caucasian, perhaps limiting applicability in other ethnicities. However, the Caucasian predominance is likely a reflection of the large number of melanoma patients in the cohort, as skin neoplasms are disproportionately high in this population. An additional confounder is that patients with malignant melanoma are regularly offered CTLA-4 and PD-1 immunotherapy, as these drugs have been used the longest in the melanoma population with good results. This confounder makes it difficult to define actual risk of uveitis in this population. Despite these limitations, we believe this report provides additional needed insights into the presentation, treatment, and clinical course of patients on checkpoint immunotherapy who develop these rare but sight threatening conditions.

Uveitis presentations of cases in this study and in the literature appear to be similar, however there is not enough resolution to clearly identify differences across individual drug regimens, including monotherapy vs combination therapy. The main findings from this report show that most cases were observed in patients with malignant melanoma, suggesting the possibility of a higher risk of developing uveitis or VKH-like disease in malignant melanoma patients in particular over other cancer patients. All cases were bilateral, and most involved anterior uveitis or panuveitis. Uveitis diagnosis appeared to occur soon after drug therapy, with highest risk within the first six months, and most resolved completely on steroid therapy, with select exceptions.

Given the close temporal association of uveitis with checkpoint immunotherapy initiation and the generally favorable and rapid response to steroid treatment, we propose that at minimum, patients beginning checkpoint inhibitor immunotherapy should be routinely queried for possible ocular side effects, including ocular pain, redness, photophobia, and decreased vision, and prompt referral to specialists should be included in the oncology protocols for these patients. Routine screening of patients on checkpoint inhibitor therapy can be considered, however all patients reported here were symptomatic on presentation. The management of cancer patients on complex immunotherapeutic drugs will require a multidisciplinary approach involving oncologists, ophthalmologists, and other specialties, and guidelines for side effect monitoring and prompt referral and management should be reviewed and clarified.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1:**

Patient Demographics, Drug Regimen, Cancer and Uveitis Diagnosis

| Patient ID | Age | Gender | Race/Ethnicity | Checkpoint Inhibitor Regimen | Cancer Diagnosis | Type of Uveitis | Unilateral vs Bilateral |
|---|---|---|---|---|---|---|---|
| 1 | 56 | Female | White | Ipilimumab [a] | Malignant melanoma | Anterior uveitis | Bilateral |
| 2 | 43 | Female | White | Ipilimumab [b] | Malignant melanoma | Posterior uveitis | Bilateral |
| 3 | 61 | Female | N/A | Ipilimumab | Malignant melanoma | Panuveitis | Bilateral |
| 4 | 66 | Male | White | Ipilimumab [b] | Malignant melanoma | Panuveitis | Bilateral |
| 5 | 47 | Male | White | Ipi-Nivo | Malignant melanoma | Anterior uveitis | N/A |
| 6 | 71 | Male | White | Ipi-Nivo [c] | Malignant melanoma | Anterior uveitis | Bilateral |
| 7 | 53 | Female | White | Ipi-Nivo [d] | Malignant melanoma | Anterior uveitis | Bilateral |
| 8 | 52 | Male | White | Ipi-Nivo | Malignant melanoma | Panuveitis | Bilateral |
| 9 | 60 | Male | White | Ipi-Nivo [d] | Malignant melanoma | Anterior uveitis | Bilateral |
| 10 | 60 | Female | African American / Black | Ipi-Nivo [e] | Endometrial cancer | Anterior & Intermediate uveitis | Bilateral |
| 11 | 47 | Male | White | Nivolumab | Malignant melanoma | Panuveitis | Bilateral |
| 12 | 37 | Female | White | Nivolumab | Hodgkin's lymphoma | Anterior uveitis | Bilateral |
| 13 | 45 | Male | White | Pembrolizumab | Malignant melanoma | Panuveitis | N/A |
| 14 | 68 | Female | White | Pembrolizumab [f] | Malignant melanoma | Panuveitis | Bilateral |
| 15 | 43 | Male | White | Pembrolizumab | Malignant melanoma | Optic Neuritis | N/A |

[a] with anti-KIR;

[b] with IV Avastin;

[c] with prednisone;

[d] with GM-CSF;

[e] first infusion ipilimumab & nivolumab, second infusion nivolumab only;

[f] with PEGylated IL-10 (AM0010), previously on dabrafenib and trametinib

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**Table 2:**

Uveitis Presentation at Onset

| Patient ID | Cancer Diagnosis | Checkpoint Inhibitor Regimen | Time from checkpoint inhibitor start to uveitis diagnosis (days) | Anterior chamber cell | Anterior chamber flare | Vitreous cell | Vitreous haze | Complications |
|---|---|---|---|---|---|---|---|---|
| 1 | Malignant melanoma | Ipilimumab | 52 | 2+ | - | 0.5+ | - | Macular edema, Papillitis OU |
| 2 | Malignant melanoma | Ipilimumab | 63 | - | - | - | - | None |
| 3 | Malignant melanoma | Ipilimumab | 41 | 0.5+ | - | 0.5+ | - | None |
| 4 | Malignant melanoma | Ipilimumab | 85 | 4+ | - | - | - | Macular edema |
| 5 | Malignant melanoma | Ipi-Nivo | 114 | 2+ | 2+ | - | - | None |
| 6 | Malignant melanoma | Ipi-Nivo | 63 | 2+ | - | 0.5+ | - | None |
| 7 | Malignant melanoma | Ipi-Nivo | 126 | 1+ | 1+ | 0.5+ | 0.5+ | None |
| 8 | Malignant melanoma | Ipi-Nivo | 4 | 3+ | - | - | - | Subretinal fluid |
| 9 | Malignant melanoma | Ipi-Nivo | 161 | 2+ | - | - | - | Posterior synechiae OU |
| 10 | Endometrial cancer | Ipi-Nivo | 22 | 2+ | 2+ | 2+ | 1+ | None |
| 11 | Malignant melanoma | Nivolumab | - | 1+ | 0.5+ | 0.5+ | 0.5+ | Optic disc edema, ocular hypertension |
| 12 | Hodgkin's lymphoma | Nivolumab | 380 | 2+ | - | 0.5+ | - | Subretinal fluid, Macular edema, Optic nerve leakage on FA |
| 13 | Malignant melanoma | Pembrolizumab | - | 2+ | 0.5+ | 4+ | 1+ | Vitreous hemorrhage, Neovascular glaucoma |
| 14 | Malignant melanoma | Pembrolizumab | 43 | 1+ | - | - | - | KP OU, Hypotony OU, Papillitis OU |

**Table 3:**

Uveitis Treatment and Clinical Course

| Patient ID | Checkpoint Inhibitor Regimen | Initial uveitis treatment | Time to uveitis control | VA initial | VA after treatment | Clinical course | Duration of ophthalmology follow up |
|---|---|---|---|---|---|---|---|
| 1 | Ipilimumab | triamcinolone OU, trans-septal followed by retrobulbar | 2 months - complete resolution of AC inflammation OU, CME OU and papillitis OU | 20/60 OD 20/50 OS | 2 months: 20/20 OU | 2 additional retrobulbar triamcinolone injections OU, followed by Retisert OU. Recurrent inflammation controlled, no additional uveitis episodes since initial flare. Developed glaucoma requiring Ahmed valve OU, visual decline secondary to significant glaucomatous damage. | 5 years |
| 2 | Ipilimumab | prednisone 70mg PO qD | 6 weeks - improvement of vasculitis and choroiditis OU by angiography | cc 20/20 OU | 4 months: cc 20/20 OD 20/30 OS | On angiography, several retinal 'hot spots' in the macula and mid-periphery area; also impressive choroidal leaking on ICG indicative of choroiditis. Ipilimumab discontinued. | 4 months |
| 3 | Ipilimumab | difluprednate QID OU | 2 weeks – resolution of AC inflammation | PH 20/25 OD PH 20/30 OS | 2 weeks: PH 20/25 OU | No mention of recurrent uveitis or visual symptoms in oncology follow up notes up to 9 months later. | 2 weeks |
| 4 | Ipilimumab | prednisone 60mg PO qD, difluprednate q1H OU, and fluorometholone ointment qHS OU | 2 weeks - resolution of panuveitis and improvement of vision | cc: 20/40 OD 20/100 OS | 6 months: cc: 20/20 OD 20/25 OS | Initial FA showed “fleck like retinopathy with multiple early hypoflourescent and late hyperflourescent lesions with an irregular choroidal filling.” Ipilimumab discontinued after 3 months. | 6 months |
| 5 | Ipi-Nivo | prednisolone acetate | 1 week – excellent response | | | Quiet 4 months | 4 months |
| 6 | Ipi-Nivo | difluprednate QID OU | 2 weeks - resolution of uveitis OU | PH 20/20 OU | 2 months: PH 20/20 OU | Initial FA revealed no vasculitis, papillitis, staining, or leakage OU. Received two doses of immunotherapy 3 weeks apart and then lost to follow-up. No cell/flare on exam OU at 2 months | 2 months |
| 7 | Ipi-Nivo | difluprednate QID OU | 3 weeks - resolution of AC inflammation and symptoms | PH 20/20 OU | 1 month: sc 20/20 OU | Patient switched to nivolumab monotherapy | 1 month |
| 8 | Ipi-Nivo | difluprednate q2H OU with cyclopentolate 1% TID OU | 1 week - 1.5+ AC cell 3 weeks - complete resolution of AC inflammation | PH 20/20 OU | 18 months: PH 20/20 OU | 2 recurrences of AC inflammation (trace cell OU) and new disc leakage OU by angiography, both episodes resolved within 2 months on difluprednate QID OU +/− cyclopentolate. Pt continuing ipilimumab immunotherapy at 18 months | 18 months |
| 9 | Ipi-Nivo | atropine & difluprednate q1-2H, already on oral steroid for hypophysitis | 9 days - Synechiae OS broke, synechiae OD remained unchanged | PH 20/25 OD cc 20/20 OS | 9 days: PH 20/20 OD cc 20/15 OS 2 months: cc 20/15 OU | Ipi-Nivo immunotherapy completed | |

| Patient ID | Checkpoint Inhibitor Regimen | Initial uveitis treatment | Time to uveitis control | VA initial | VA after treatment | Clinical course | Duration of ophthalmology follow up |
|---|---|---|---|---|---|---|---|
| 10 | Ipi-Nivo | topical corticosteroids | Decrease in inflammation, not complete resolution | | | Ongoing inflammation after 3 months follow up | 3 months |
| 11 | Nivolumab | prednisolone acetate QID OU, prednisone 60 mg PO qD | 1 month – no inflammation | | | Vision stable and no intraocular inflammation after 1 month | 1 month |
| 12 | Nivolumab | prednisolone acetate 6x/day OU, prednisone 40mg PO qD | 3 weeks - AC inflammation improved | | | Vision stable off medication after 2 months | 2 months |
| 13 | Pembrolizumab | prednisolone acetate QID | 1 month - no active intraocular inflammation | | | VA stable. Continued elevated IOP due to neovascular glaucoma | |
| 14 | Pembrolizumab | Difluprednate QID OU, subtenons triamcinolone acetonide OS | 2 weeks & 2 months – continued 1+ AC inflammation, KPs, severe hypotony | 20/70 OD<br>CF at 2’ OS | 2 weeks:<br>PH 20/400 OD<br>PH 20/600 OS<br>2 months:<br>PH 20/400 OD<br>PH 20/800 OS<br>2 years:<br>CF at 4’OD<br>HM OS | Unresponsive to difluprednate and subtenons triamcinolone acetonide. Continued hypotony (unmeasurable), choroidal folds. Silicone oil placed OS for hypotony. Phthisical or pre-phthisical OS at 2 years | 2 years |

**Table 4:**

Previously Published Uveitis Cases with Nivolumab and Pembrolizumab Therapy

| Age | Sex | Race/ Ethnicity | Checkpoint Inhibitor Therapy | Cancer Diagnosis | Type of Uveitis | Unilateral v Bilateral | Time to uveitis diagnosis | Initial Uveitis Treatment | Time to Uveitis Control | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| 74 | M | N/A | Ipilimumab & Nivolumab | Metastatic uveal melanoma | Anterior uveitis | Bilateral | 4 months | Topical steroid gtt OU, anticholinergic gtt OU, prednisone 1mg/kg PO | N/A | Chan[46] |
| 54 | F | N/A | Nivolumab | Metastatic melanoma | Anterior uveitis | Bilateral | 2 months | 0.1% betamethasone OU | 4.5 months | Kanno[47] |
| 60 | F | N/A | Nivolumab | Metastatic melanoma | Posterior uveitis | Bilateral | 6 weeks | 0.1% betamethasone QID OU, prednisolone PO | 2 weeks | Matsuo[20] |
| 55 | M | N/A | Nivolumab | Metastatic melanoma | Anterior uveitis | Bilateral | 2 weeks | Topical steroid gtt OU, cycloplegic gtt OU | N/A | Arai[22] |
| 66 | M | N/A | Nivolumab | Non-small cell lung carcinoma | Anterior uveitis | Bilateral | 3 months | Topical prednisolone acetate OU, cyclopentolate OU | 3 months | Karlin[48] |
| 60 | M | N/A | Nivolumab | Metastatic clear cell renal cell carcinoma | N/A | N/A | 14 months | Intravitreal steroid treatment | N/A | De Velasco[49] |
| 74 | F | N/A | Nivolumab | Metastatic melanoma | Anterior uveitis | Bilateral | 5 months | Prednisolone acetate q2hr OU, cyclosporine BID OU, prednisolone 50mg/day PO | 3 weeks | Richardson[38] |
| 92 | F | N/A | Nivolumab | Metastatic melanoma | Anterior uveitis | Bilateral | 3 months | Topical prednisolone acetate OU, cyclopentolate OU, tobramycin/ dexamethasone ointment OU | 2 weeks | Baughman[50] |
| 55 | M | white | Nivolumab | Metastatic melanoma | Anterior uveitis | Bilateral | 6 weeks | Topical dexamethasone 0.1% OU, prednisone 1mg/kg PO | 1 month | Theillac[51] |
| 66 | M | white | Nivolumab | Metastatic clear cell renal cell carcinoma | Anterior uveitis | Bilateral | 2 months | Prednisolone acetate 1% QID OU, prednisone 60mg PO daily | 1 week | Gonzales[52] |
| 73 | M | Japanese | Nivolumab | Metastatic melanoma | Posterior uveitis | Bilateral | 6 months | Methylprednisolone 500mg/day IV x3 days, prednisolone 40mg/day PO | 1 week | Fujimura[29] |
| 35 | F | Japanese | Nivolumab | Metastatic melanoma | Posterior uveitis | Bilateral | 5 months | Methylprednisolone 500mg/day IV x3days | 1 week | Fujimura[29] |
| 68 | F | N/A | Pembrolizumab | Metastatic melanoma | Panuveitis | Bilateral | 6 months | Observation | N/A | Lise[53] |
| 78 | F | white | Pembrolizumab [a] | Metastatic melanoma | Panuveitis | Bilateral | 9 weeks | Methylprednisolone IV 1g/day × 3 days, Prednisone 60mg/day x2 weeks, sub-Tenons triamcinolone OU | 2 weeks | Hanna[54] |
| 82 | M | N/A | Pembrolizumab [a] | Metastatic melanoma | Anterior uveitis | Bilateral | 2 months | Hydrocortisone 25mg/day, difluprednate q2hr OU | 2 weeks | Abu Samra[36] |

| Age | Sex | Race/ Ethnicity | Checkpoint Inhibitor Therapy | Cancer Diagnosis | Type of Uveitis | Unilateral v Bilateral | Time to uveitis diagnosis | Initial Uveitis Treatment | Time to Uveitis Control | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| 61 | F | white | Pembrolizumab | Metastatic melanoma | Panuveitis | Bilateral | 3 days | Prednisolone acetate OU, Prednisone 40mg/day PO | 4 months | Taylor[55] |
| 54 | F | N/A | Pembrolizumab [a] | Metastatic choroidal melanoma | Posterior uveitis | Unilateral (other eye enucleated) | 12 weeks | Dexamethasone sustained release (Ozurdex) implant | 4 months | Aaberg[44] |
| 63 | F | N/A | Pembrolizumab | Metastatic melanoma | Anterior uveitis | Bilateral | N/A | Prednisolone acetate q1hr OU, homoatropine daily OU, dexamethasone qHS OU | N/A | Basilious[42] |
| 60 | N/A | N/A | Pembrolizumab [a] | Metastatic melanoma | Posterior uveitis | Bilateral | 1 week | Topical steroids, abx, oral steroids | N/A | Diem[28] |
| 75 | M | N/A | Pembrolizumab [a] | Metastatic melanoma | Anterior uveitis | Bilateral | 8, 24, 32 weeks | Prednisolone acetate OU, nepafenac OU | 2-3 weeks | Diem[28] |
| 59 | M | white | Pembrolizumab [a] | Metastatic melanoma | Anterior uveitis | Bilateral | 16 months | Methylprednisolone 1mg/kg IV, prednisone 1mg/kg PO, topical dexamethasone q1hr, subconjunctival betamethasone 4mg/ml | 3 weeks | Bricout[21] |
| 73 | M | white | Pembrolizumab | Metastatic melanoma | Panuveitis | Bilateral | N/A | Prednisolone 75mg PO, acetazolamide PO | N/A | Reid[37] |

[a] previously received ipilimumab