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# Cancer Immunotherapy and Uveitis: Balancing Anti-Tumor Immunity and Ocular Autoimmunity

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## Abstract

Immune checkpoint inhibitors and targeted therapies are two classes of pharmacologic therapies used to treat metastatic malignancy by amplifying the immune system activity against cancerous cells. However, these drugs can consequently cause immune-related adverse events (irAEs). Albeit rare, cases of ocular IRAEs occurring among patients taking these drugs have been documented in literature, including a spectrum of uveitis findings. The classes of immune checkpoint inhibitors explored here include anti-CTLA4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab) and anti-PDL-1 (atezolizumab, avelumab, durvalumab). Targeted therapies include the MEK inhibitors (trametinib) and BRAF enzyme inhibitors (dabrafenib, vemurafenib), both of which are involved in the MAPK/ERK signaling pathway responsible for cell proliferation. Reported cases of ocular irAEs caused by these drugs include anterior uveitis, posterior uveitis, panuveitis, and Vogt-Koyanagi-Harada (VKH)-like syndrome. Treatment can be determined on a case-by-case basis and depending on the severity of the irAE, may include temporary cessation of the offending drug, local corticosteroids, or systemic corticosteroids. Although the mechanism by which these ocular toxicities occur is not clearly elucidated, it is hypothesized that they are secondary to increased activity of auto-reactive T-cells. Further investigation into mechanisms underlying these inflammatory findings are relevant for cancer targeting, as well as insights into ocular autoimmune diseases.

### Keywords

checkpoint inhibitor; targeted therapy; immune-related adverse events; VKH-like syndrome; uveitis

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## Introduction

Immune checkpoint inhibitors and targeted therapies are increasingly used for treatment of metastatic malignancies.[1, 2] These novel therapies have shown remarkable benefit in a range of malignancies including melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and numerous others. In general, these therapies work by increasing the activity of the immune system against tumor cells. Increasing the activity of immune system, however, can have unwanted inflammatory side effects, termed immune-related adverse events (IRAEs). IRAEs can include ophthalmic manifestations including uveitis, which can very between anterior uveitis (i.e. iris, ciliary body inflammation), intermediate uveitis (i.e. ciliary body inflammation leading to vitreous cellular infiltrates), posterior uveitis (i.e. retina and choroidal inflammatory findings), and panuveitis. We review the ophthalmic manifestations, mechanisms for immune checkpoint inhibitors and targeted therapies including BRAF and MEK inhibitors, and their associations with secondary uveitis. We also discuss potential mechanisms from which IRAEs may emerge, which may allow us to tailor future therapies to reduce their undesired effects.

## Mechanism of Action: Immune Checkpoint Inhibitors

### Anti-CTLA4

T-cell activation is a complex pathway with multiple positive and negative feedback mechanisms modulating activity within the pathway. CTLA-4 plays an important role in this signaling cascade, making it a suitable target for cancer therapies. Binding of B7-1 (CD80) or B7-2 (CD86) molecules on antigen-presenting cells (APC) with CD28 molecules on the effector T cell acts as a stimulatory signal for increased T cell proliferation, survival, and differentiation.[3] CTLA-4 is a CD28 homolog with one key difference: binding of CTLA-4 to B7 produces an inhibitory effect on T-cell activation.[4-8] CTLA-4 is also constitutively expressed by regulatory T cell (Tregs) and is vital for its suppressive functions.[9]

Given the inhibitory function of CTLA-4 both directly on effector T-cells and indirectly through increased T-regulatory activity, CTLA-4 blockade leads to increased effector T-cell activity (Figure 1). Indeed, research suggests that this blockade affects the immune priming phase by increasing activity and proliferation of a larger number and diversity of effector T-cells, and by decreasing Treg-mediated suppression of T-cell activity.[10] Monoclonal antibodies (ipilimumab) acting via this mechanism consequently induce an anti-tumor response.

### Anti-PD-1 and Anti-PDL-1

While CTLA-4 acts on the early stages of T-cell activation in the lymph nodes, PD-1 regulates previously activated T-cells at later stages in the peripheral tissues.[11] When PD-1 binds to its ligands – programmed death ligand 1 (PDL-1) and programmed death ligand 2 (PDL-2) – decreased effector T-cell activity and survival are observed. Whereas CTLA-4 is localized to T-cells, PD-1 can be found on a diverse range of immune cell types including T cells, B cells, and myeloid cells.[10, 12-15] PDL-1 and PDL-2 are similarly broadly expressed on the cell surface of multiple tumor types.[16, 17] Because PD-1 binding PDL-1/2

is considered a more downstream regulatory mechanism, its major effect is to downregulate already ongoing effector T-cell response. Anti-PD1 (pembrolizumab and nivolumab) and anti-PDL1 (atezolizumab, avelumab, durvalumab) allow for a sustained and more robust T-cell response, leading to its anti-tumor effect (Figure 1).[18]

## Mechanism of Action: Targeted Therapies

### BRAF and MEK inhibitors

The current targeted therapies of interest in cancer therapeutics are mitogen-activated protein kinase-kinase (MEK) inhibitors and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) enzyme inhibitors. Both MEK and BRAF are enzymes in the mitogen activated protein kinase pathway (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway.[19] This is a complex multi-tiered signaling pathway that includes activation of multiple substrates that eventually lead to cell proliferation. In healthy non-tumor cells, the MAPK/ERK pathway is highly regulated, but this regulation is disrupted in cancer cells. The first, most upstream, level includes the BRAF enzyme. BRAF is the most-commonly mutated proto-oncogene at this level and therefore a logical therapy target.[19] One level below includes MEK1 and MEK2. The final—most downstream—level includes ERK1 and ERK2. By counter-acting the effect of BRAF and MEK1/MEK2, targeted therapies such as vemurafenib or dabrafenib (BRAF inhibitors) and trametinib (MEK1/MEK2 inhibitor) disrupt the MAPK/ERK signaling cascade, thereby aiming to inhibit cancer cell survival and proliferation (Figure 2). In addition to their direct effects, BRAF inhibitors and MEK inhibitors have also been shown *in vitro* to promote an immune-stimulating tumor microenvironment; this facilitates better immune cell penetration into tumors and increased functionality of effector T cells.[20] BRAF and MEK inhibitors are often used as combination therapy for treatment of metastatic melanoma, as the combination treatment is more efficacious as compared to BRAFi or MEKi alone.[21]

## Proposed Mechanism of Ocular IRAEs

### Immune Checkpoint Inhibitors: Anti CTLA-4 and anti PD-1/PDL-1 and Tumor-infiltrating Lymphocyte Therapy

While immune checkpoint inhibitors can lead to anti-tumor effect, they can also have numerous side effects (irAEs) that range in severity and can affect numerous organ systems. While the exact mechanism has not been elucidated, it is thought to be due to disruption of the balance between immunity and self-tolerance. The immune checkpoint inhibitors upregulate overall T-cell proliferation and activity, but some of these T-cells, which would typically be suppressed, are auto-reactive.[22]

One postulated mechanism regarding the pathogenesis of uveitis, a well-described ocular IRAE associated with immune checkpoint inhibition has been drawn from parallels in the clinical phenotype observed in the Vogt-Koyanagi-Harada (VKH) syndrome. VKH syndrome features ocular, cutaneous, and central nervous system autoimmune features resulting from T-cell targeting of melanocytic antigens. A VKH-like syndrome in patients receiving immune checkpoint inhibitor (ICPi) therapy may involve T-cell recognition of

antigens of melanoma cells and non-cancerous melanocytes. While this is the basis by which ICPi therapy achieve enhanced destruction of cancer cells, this can also lead to the destruction of melanocytes in organ systems including the eye, hair, and skin. This theory explains the constellation of symptoms seen in patients who develop VKH-like syndrome while receiving ICPi treatment. Although not fully understood, the pathogenesis of VKH syndrome is believed to involve CD4+ and CD8+ T cells that target melanocyte antigens.

One prior report of a patient who received adoptive T-cell transfer of tumor-infiltrating lymphocytes targeting melanoma tumor antigen led to a durable tumor remission, while also leading to VKH-like features associated with melanoma tumor antigen-reactive lymphocytes within the patient's aqueous humor.[23] Furthermore, similar consequences have been observed in experiments in which MART-1 peptide-specific CD8+ T-cell clones obtained from a VKH patient were able to lyse melanocytes and melanoma cells.[24] These findings may suggest a possible similarity in target epitope between malignant melanoma cells and choroidal melanocytes.

### Targeted Therapies: BRAF inhibitors and MEK inhibitors

The mechanisms by which BRAF inhibitors and MEK inhibitors cause irAEs are not fully known. VKH-like symptoms have been reported and it is plausible that mechanisms related to anti-tumor immunity may lead to ocular autoimmunity. Further research related to BRAF and MEK inhibiton and uveitis, as well as pathways that may parallel those seen with checkpoint inhibition and ocular autoimmunity, is needed.

## Uveitis with Cancer Therapeutics

While the precise mechanism of ocular side effects has not been determined, the checkpoint inhibitors and targeted therapies can result in a variety of ocular and orbital manifestations.[1, 25] Ocular side effects have been reported in roughly 1% of patients, with a fraction of those being affected by uveitis.[1, 25] Here we will focus on uveitis and uveitis-related irAEs. Even within this focused spectrum of inflammatory findings, prior case reports outline a wide range of manifestations from isolated anterior uveitis to systemic Vogt-Koyanagi-Harada (VKH) like syndrome.

### *Ipilimumab or Yervoy® (anti-CTLA4)*

Anterior uveitis is a frequently reported side effect associated with ipilimumab therapy. Treatment of isolated anterior uveitis with topical steroids often sufficient to reduce inflammation and maintain visual acuity.[26-28] Recalcitrant cases, such as a case of a patient who developed pituitary inflammation and uveitis, reported by Nallapaneni et al., have been treated effectively with oral prednisone.[29]

Other reports describe involvement of posterior segment structures including intermediate uveitis, panuveitis and optic nerve inflammation. Robinson et. al. treated a case of anterior/intermediate uveitis, disc and macular edema with topical and periocular steroids.[30] They also successfully treated a similar case but without macular edema with only topical steroids.[30] Fierz et. al. reported a case of panuveitis treated with topical and oral prednisone.[31] Two case reports also report bilateral neuroretinitis, one treated with only

topical steroids and the other with the addition of oral corticosteroid.[32, 33] Meanwhile, a case of retinal vasculitis and macular edema requiring oral and intravitreal steroids has also been reported.[34] Severe ocular and systemic manifestations in a VKH-like syndrome have been described and often necessitate treatment with more intensive oral or intravenous steroids.[35-37] In many of these cases, especially with isolated anterior or intermediate uveitis findings, ipilimumab therapy was continued while still effectively managing the uveitis.

### *Pembrolizumab or Keytruda® (anti-PD1)*

A variety of uveitic side effects have been reported with pembrolizumab including anterior uveitis, posterior uveitis, panuveitis and VKH-like syndrome (Figure 1). Zimmer et. al. reported a case of isolated anterior uveitis, which improved with topical steroids, and did not necessitate discontinuation of pembrolizumab.[38] A few case reports also highlight cases of posterior uveitis treated with topical and oral steroids, along with pembrolizumab discontinuation.[39-41] Numerous case reports show more involved cases of panuveitis. DeVries et al. describe a case of bilateral panuveitis, papillitis and serous retinal detachments after five pembrolizumab injections. Treatment with topical steroids, oral steroids and cessation of pembrolizumab therapy led to resolution.[42] Most other cases of panuveitis also required oral and topical steroids along with Pembrolizumab cessation.[43-46] Meanwhile, Aaberg and Aaberg report a case where they successfully manage panuveitis and retinal vasculitis in a monocular patient with serial sustained-release dexamethasone implants while continuing pembrolizumab therapy.[47] Enomoto et. al. report a case of bilateral VKH-like syndrome treated with oral and topical steroids, along with pembrolizumab cessation.[48] While isolated anterior uveitis may warrant a trial of topical steroids while continuing pembrolizumab, other cases of posterior or panuveitis may necessitate therapy cessation.

### *Nivolumab or Opdivo® (anti-PD1)*

When examining the Food and Drug Administration (FDA) Adverse Events Reporting System database between 2003 and 2018, out of all checkpoint inhibitors, nivolumab had the highest number of ocular adverse events overall, most commonly associated with ocular myasthenia.[49] Anterior uveitis has also been reported with numerous case reports showing improvement with topical steroids, while still continuing nivolumab therapy.[50-53] Baughman et. al. report an interesting case of simultaneous bilateral keratitis and anterior uveitis after nivolumab infusions that was managed effectively by using high frequency topical steroids prior to nivolumab infusions such that the patient was able to continue nivolumab for another three months. Continuation of nivolumab resulted in decreased disease burden from metastatic melanoma and stable ocular function.[54] Multiple case reports also describe further involvement with posterior uveitis, panuveitis or VKH-like syndrome; nivolumamb had to be discontinued in these instances and commencing oral, intravitreal or sub-tenons steroids was required.[55-58]

### *Atezolizumab or Tecentriq® (anti-PDL1)*

Per the FDA prescriber information, uveitis occurred at an incidence of <1%.[59] Case reports highlight a diverse range of presentations. Suwa et. al. describe a case of bilateral VKH-like uveitis with multiple bilateral serous detachments, wavy retinal pigment epithelium

(RPE) and thickened choroid along with systemic signs such as hair loss, vitiligo, and sensorineural hearing loss.[60] Discontinuation of atezolizumab and systemic steroids led to resolution within two months. In a case report, atezolizumab use also led to symptomatic exacerbation of pre-existing sarcoidosis, resulting in uveitis.[61] Additionally, Emens et al. also describe two instances of acute macular neuroretinopathy.[62] A case of uveal effusion, retinal detachment, and retinal hemorrhage has also been documented.[63]

Treatment typically consists of discontinuation of atezolizumab and occasionally systemic steroids.[60, 61] Episodes of ocular adverse events usually resolved within a few months.[61, 63]

### *Avelumab or Bavencio® (anti-PDL1)*

Less than 1% of patients receiving avelumab developed uveitis according to the FDA prescriber information. A Medline search revealed no case reports, perhaps in part due to the fact that Avelumab is new—approved for use in 2017—with current indications that include Merkel cell carcinoma, urothelial carcinoma and renal cell carcinoma.[64]

### *Durvalumab or Imfinzi® (anti-PDL1)*

Per the FDA fact sheet, <1% of patients receiving durvalumab developed uveitis.[65] Ahmad et al. report a case of a patient with a history of bilateral panuveitis who developed recurrent bilateral anterior uveitis six months after the initial episode and two months after starting durvulumab.[66] This patient was treated with topical steroids with quiescence within 1 month of therapy and did not require discontinuation of durvalumab.

### *Trametinib or Mekinist® (MEK pathway) and Dabrafenib or Tafinlar® (BRAF inhibitor)*

Trametinib and dabrafenib are often used in combination and the case reports highlighting adverse events are with patients on combination therapy. Reported side effects include chorioretinopathy with a 2% incidence in patients with combination treatment.[67] Numerous case reports also highlight VKH-like syndrome; Brambati et. al. report a case of bilateral VKH-like syndrome with granulomatous anterior uveitis and multiple serous detachments that resolved after discontinuation of dabrafenib/trametinib and aggressive topical and systemic corticosteroids.[68] Lim et. al. describe another case of VKH-like syndrome with bilateral panuveitis with serous retinal detachments and papillitis that improved with IV steroids followed by oral steroid taper, and when the IMTs were re-introduced at a lower dose, the patient tolerated therapy.[69] Meanwhile, Campos et. al. report a case of VKH-like syndrome with bilateral anterior uveitis, vitritis, serous retinal detachments, vasculitis and disc edema that showed improvement with IMT cessation in conjunction with commencing intravitreal steroid implants.[70] Two cases also highlight the incidence of multifocal chroiditis (MFC) on trametinib/dabrafenib therapy. In one instance, there was re-activation of prior MFC.[71] Another patient had new-onset MFC that improved with discontinuation of the combination therapy and topical steroids but recurred when the therapy was re-initiated.[72] Overall, uveitis-related adverse events with trametinib/dabrafenib can have severe presentations that require cessation of therapy along with topical, oral and/or IV steroids.

### *Vemurafenib or Zelboraf® (BRAF)*

The incidence of uveitis is reported to be 2.1% in patients taking vemurafenib.[73] Case reports range from isolated anterior uveitis to VKH-like syndrome. Deitch-Harel et. al. report a case of bilateral anterior uveitis that resolved in 10 weeks with cessation of vemurafenib and topical steroids.[50] Gedj et. al. report a case series where uveitic adverse effects in four out of the seven patients was limited to mild anterior uveitis.[74] Out of those patients with anterior uveitis, two were continued on vemurafenib while two discontinued the medication; all were treated with topical corticosteroid therapy with resolution of signs and symptoms, regardless of vemurafenib status. Sizmaz et. al. report a case of bilateral panuveitis that resolved with cessation of vemurafenib, oral and topical steroids.[75] Wolf et. al. report a similar case of a patient who developed severe bilateral panuveitis with improvement in symptoms after vemurafenib cessation, oral and topical steroids.[76] VKH-like syndrome has also been reported requiring vemurafenib cessation along with intensive oral and/or intravenous steroids.[77, 78]

## Visual Acuity Outcomes Following Treatment

In an extensive review of the literature by Dow et. al., patients' visual acuities at the time of diagnosis approximated 20/40. Patients with anterior uveitis had better visual acuities (20/30) than those with posterior uveitis (20/40) or panuveitis (20/40-20/50). Overall, presenting visual acuities were good with over half of patients having visual acuities of 20/30 or better. Topical corticosteroids were used in 72% of the patients in the review. In over two-thirds of the cases included, final visual acuities improved to be better than 20/30.[79]

In a case series of 54 patients, a statistically significant improvement in visual acuity was found in the ICPi and MEK/BRAFi groups before and after steroid treatment. Interestingly, patients receiving combination therapy of an ICPi with a MEK/BRAFi had better visual acuities than other groups at presentation and therefore did not improve following treatment. The majority of patients exhibited a full or partial recovery, and only 18% of the patients in the series developed chronic uveitis requiring ongoing followup.[80]

## Directions for Future Research

While substantial progress has been made related to the clinical phenotypes associated with checkpoint inhibitor associated uveitis, including the impact on vision in large case series and empirical observations, areas of future research involve both immune mechanistic studies and best practices for clinical management. Given the parallels of checkpoint inhibition with VKH syndrome, studies in adaptive immune pathways targeting melanocyte-specific antigen may improve our basic understanding of disease. Unresolved questions include identification of patient risk factors for uveitis and recurrent disease as well as the role of prophylactic corticosteroids at ICPi initiation or when patients may restart immunotherapy.

## Conclusions

Immune checkpoint inhibitors and targeted therapies are increasingly used with strong efficacy signals for multiple malignancies.[81] As increasing numbers of patients receive these medications, our understanding of the true prevalence of IRAEs, including uveitis and other ophthalmic manifestations, will be increasingly important for long-term cancer survivor care.

The American Society of Clinical Oncology (ASCO) provides guidelines on the management of uveitis based on their severity grading scale (Table 1).[82] The majority of uveitis, based on our review, falls within G2 or G3 on their scale. Per ASCO, G2 (anterior uveitis) necessitates temporary ICPi cessation and treatment with topical corticosteroids, cycloplegic agents and/or systemic corticosteroids; the ICPi may be reduced once off systemic corticosteroids and topical/ocular corticosteroids may be continued while ICPi therapy is resumed. Meanwhile, G3 (posterior or panuveitis) requires permanent discontinuation of ICPi and systemic and intravitreal/periocular/topical corticosteroids. These recommendations, especially as they pertain to Grade 3 and 4 uveitis, may be more stringent than desirable depending on the patient's tumor response and alternatives to medications that target the immune system.

Specifically, we found that in multiple cases of posterior or panuveitis, re-introduction of ICPi therapy, often at a lower dose, did not necessarily lead to a re-occurrence of the uveitis. Combined with the important role ICPi therapy plays in management of malignancy, discontinuation may not be the best choice in each case. The ASCO guidelines may serve as a framework for ophthalmologists to manage these complications in conjunction with the oncology and medical care team, while bearing in mind that each case may be unique and re-exposure to ICPi could be considered even in Grade 3 and 4 uveitis.

Optimal management guidelines, in particular for ocular IRAEs, requires ongoing research. The management of ocular IRAEs undoubtedly requires a multidisciplinary approach between the ophthalmologist, oncologist and rheumatologist in certain cases to determine the best course of action and whether temporary or permanent ICPi cessation is warranted.

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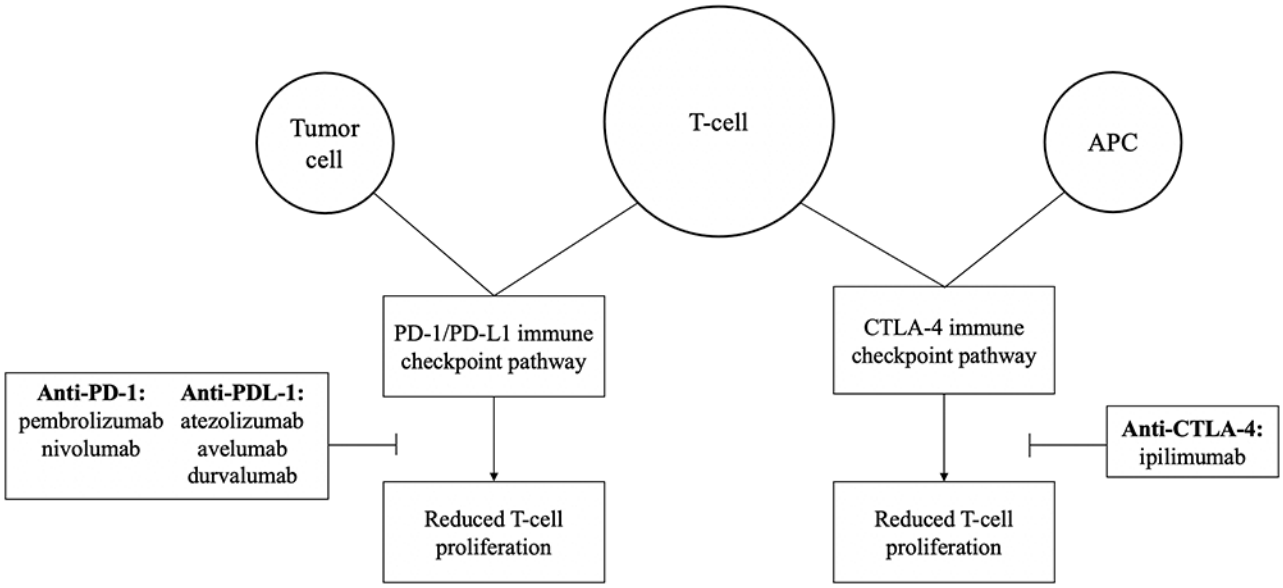


**Figure 1.**

Binding of PD-1 receptor of the T-cell to PD-L1 on tumor cell results in a suppressed T-cell response and promotion of tumor growth. The anti-PD-1/PD-L1 drugs inhibit this interaction, thereby enhancing anti-tumor immune activity. Similarly, the CTLA-4 receptor of the T-cell is inhibitory and prevents T-cell activation. By blocking this receptor, ipilimumab allows for the B7 co-stimulatory ligand of the antigen-presenting cell (APC) to activate the CD28 receptor of the T-cell, leading to T-cell stimulation and enhanced anti-tumor immune activation.

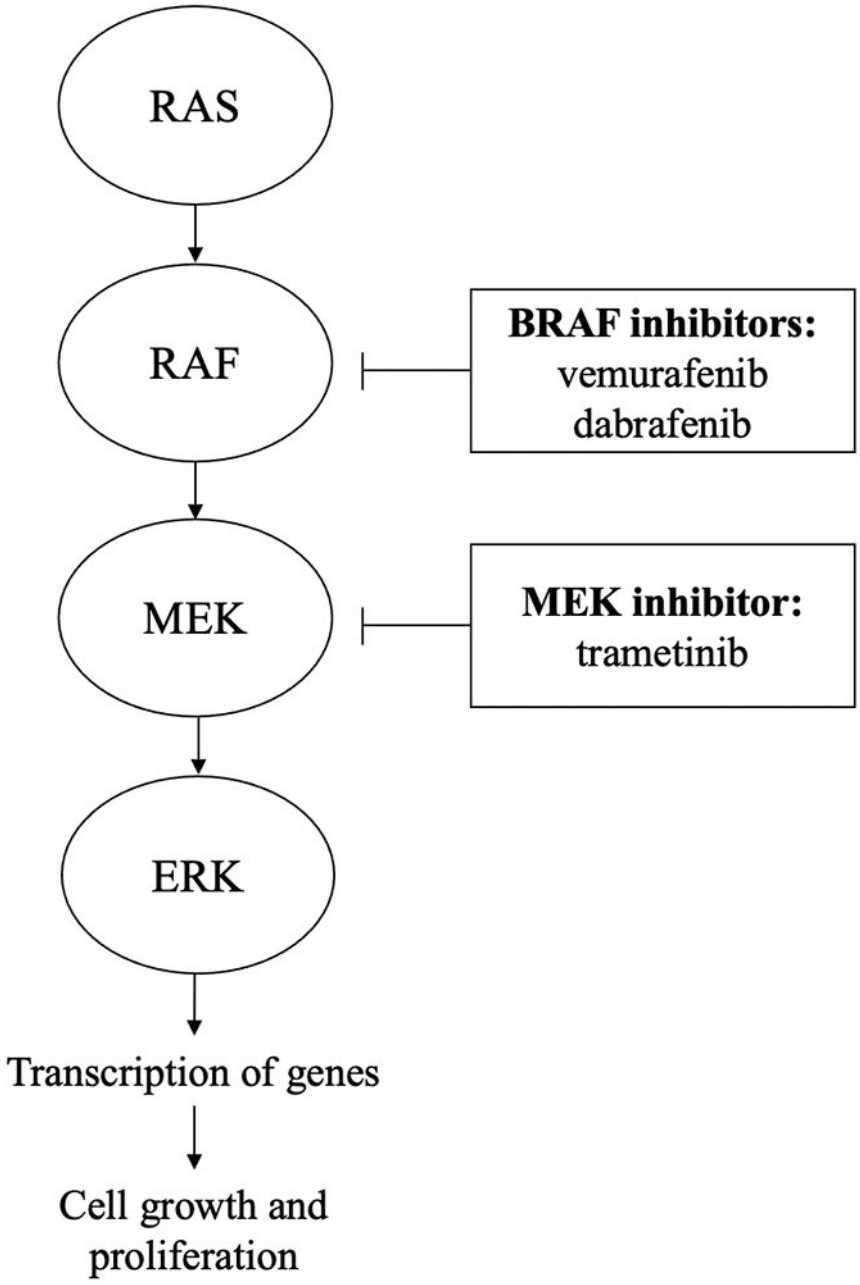


**Figure 2.**

Binding of BRAF inhibitors and MEK inhibitors creates blockade points in the MAPK pathway, inhibiting oncogenic signaling (i.e., reduced gene transcription, reduced cell growth and proliferation).

**Table 1.**

Uveitis/Iritis Grading and Management Guidelines per American Society of Clinical Oncology[82] *

| **10.1 Uveitis/iritis** | |
|---|---|
| Definition: Inflammation of the middle layer of the eye | |
| Diagnostic work-up: as per above | |
| Grading | Management |
| G1: Asymptomatic | Continue ICPi<br>Refer to ophthalmology within 1 week<br>Artificial tears |
| G2: Medical intervention required, anterior uveitis | Hold ICPi temporarily until after ophthalmology consult<br>Urgent ophthalmology referral<br>Topical corticosteroids, cycloplegic agents, systemic corticosteroids<br>May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity<br>Re-treat after return to G1 or less |
| G3: Posterior or panuveitis | Permanently discontinue ICPi<br>Urgent ophthalmology referral.<br>Systemic corticosteroids and intravitreal/periocular/topical corticosteroids |
| G4: 20/200 or worse | Permanently discontinue ICPi<br>Emergent ophthalmology referral<br>Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion |
| Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment [121,122] | |