Ocular Adverse Events Following Treatment of Advanced Cutaneous Melanoma

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Introduction

Over the past ten years, the treatment of various malignancies and in particular cutaneous melanoma has changed dramatically. Two therapies are profoundly effective:

1) immunotherapy, indicated in all genetic types of melanomas,
2) «targeted» BRAF and MEK inhibitor therapy, suitable for cases with BRAF mutation, which is proven in 45 % of melanoma cases.[1–4]

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target receptors on T-lymphocytes which prevent antitumor activity of the T-cell. The inhibition of these receptors (immunotherapy), such as CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) or PD-1 (programmed cell death protein-1), enhances the host immune response against cancer cells: T-lymphocytes are enabled to bypass the defenses of tumor cells and to eliminate them (Fig. 1).[5,6] Tasaku Honjo and James Allison received the Nobel Prize in 2018 for their pioneering work in the development of the immune checkpoint inhibitors anti-PD1 and anti-CTLA-4.

Targeted BRAF and MEK inhibitor therapy. Metabolic processes between the cell membrane and the nucleus depend on complex enzymatic chains. In melanoma, the MAPK pathway is important (Fig. 1).[7] This cascade of protein kinases finally activates gene transcription factors in the nucleus encoding cellular processes such as growth, differentiation, migration, inflammation, angiogenesis, and apoptosis. Malfunctioning of transcription factors leads to the formation of cancerous cells.[66] In BRAF mutation, these processes are amplified and escape their regulation: the cell reproduces itself.

The most recent targeted agents in oncology are drugs that target the MAPK signaling pathway.

BRAF- and MEK-inhibitors (BRAFi, MEKi) can block this self-feeding cascade and the tumor cell's mitotic processes.

Anti-CTLA-4 was approved in 2011,[8] followed by the BRAF-inhibitors vemurafenib,[9] and dabrafenib. However, with BRAFi-monotherapy the neoplasm was able to activate intrinsic resistance by reactivation of the MAPK pathway. The combination of BRAFi with the subsequently introduced MEK inhibitors[11,12] proved to be more effective, while reducing the severity and the spectrum of side effects. Interestingly, this is no true for ocular adverse events.[13–16]

Of ophthalmologic interest is the fact that *conjunctival melanomas* – unlike uveal melanomas – often carry a BRAF mutation. Therefore, treatment with BRAF/MEK or immune checkpoint inhibitors is an adequate treatment, as for cutaneous melanomas.[17]

For *metastatic uveal melanoma*, which has been mostly refractory to treatment, encouraging results have been reported in a phase-3 clinical trial with tebentafusp (Kimmtrak®), a bispecific protein (antibody) with an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T-cells to target glycoprotein 100-positive melanoma cells.[18]

The Standard of care is immunotherapy (ICI) as first-line treatment for most patients with advanced melanoma; it includes PD-1 blockade (nivolumab or ➜

Abbreviations

AJCC:	American Joint Committee on Cancer staging system
BRAF:	a human gene that encodes a protein called B-RAF, a proto-oncogene
BRAFi:	BRAF Inhibitor: vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), encorafenib (BRAFTOVI®)
CAR:	cancer-associated retinopathy
CD3:	a cluster of differentiation 3; an antigen involved in activating cytotoxic T cells and T helper cells
CSC(R):	central serous chorioretinopathy
CTCAE:	standard terminology criteria for adverse events
CTLA-4:	T-Lymphocyte- associated Antigen 4; anti-CTLA-4: Ipilimumab (Yervoy®)
ICI or ICB:	immune-checkpoint-inhibitor or immune-checkpoint-blocker
LAG-3:	Lymphocyte-activation gene 3 anti-LAG-3: relatlimab; combined with nivolumab (Opdualag®)
MAPK:	mitogen-activated protein kinase
MAR:	melanoma-associated retinopathy
MEK:	mitogen-activated protein kinase
MEKi:	MEK inhibitor: cobimetinib (Cotellic®), trametinib (Mekinist®), binimetinib (Mektovi®)
MEKAR:	MEK inhibitor-associated retinopathy
OS:	overall survival (%)
PD-1:	programmed cell death-1; anti-PD-1: nivolumab (Optivo®), pembrolizumab (Keytruda®), cemiplimab (Libtayo®)
PD-L1:	programmed death-ligand 1; anti-PD-L1: atezolizumab (Tecentriq®), avelumab (Bavencio®); durvalumab (Imfinzi®)
RPE:	retinal pigment epithelium

pembrolizumab), or the combination of PD-1 blockade (nivolumab) and CTLA-4 blockade (ipilimumab).

Even though the onset of action is delayed, effective and durable responses are documented and may persist after treatment discontinuation. However, only about 50 % of patients achieve this therapeutic success, at the cost of potentially lifelong adverse side effects, such as endocrine side effects.

In proven BRAF mutations, a systemic treatment with targeted therapy (combined BRAF- and MEK-inhibitors) can be offered, especially when symptomatic metastases require rapid disease control. However, acquired resistance after initial response is frequent. Treatment-related side effects gradually diminish during therapy and mostly disappear after treatment discontinuation.[19] Evidence about overlapping toxicities in sequential treatment (immunotherapy and targeted therapy) in BRAF mutated patients is still lacking.

Apart from the metastatic setting, anti- PD1 ICIs (nivolumab or pembrolizumab) and dabrafenib/trametinib for BRAF mutant melanoma are currently also recommended as **adjuvant treatment** after resection of high-risk stage III, IV melanoma,[2,20,21] and recent data also support the use of anti-PD1 in resected stage IIB/IIC.[4,6,22]

- **Since more patients will become candidates for systemic treatment, toxicity will gain importance.**

Adverse events of targeted therapy

The combinations differ in their adverse event (AE) profile. The most frequent systemic AE

1) vemurafenib/cobimetinib: diarrhea in 61 %; discontinuation in 27 % of patients
2) dabrafenib/trametinib: pyrexia in 58 % / 69 %, leading to discontinuation in 18 % / 16 %, respectively (Robert 2019, Long 2018)
3) encorafenib/binimetinib: with decreasing frequency nausea, and diarrhea in 43.8–38.5 %, leading to discontinuation in 16 % (Ascierto 2020).[19,23,24]
4) On MEKi treatment: a peculiar retinopathy is reported in 8–100 %. Rare ocular events from MEK-inhibition such as retinal vein occlusion and elevation of intraocular pressure have been described. On BRAFi treatment uveitis may be observed.

Here we report three challenging cases. Challenging, because we had to balance ocular safety against the potentially life-saving oncologic therapy. All patients gave their informed consent to publish their clinical cases.

Case report 1 (MEK-inhibitor-associated retinopathy, MEKAR)

A 76-year-old man presented with bilateral visual impairment for two weeks, most notable when reading. Medical history revealed a cutaneous melanoma (stage IIIA) on adjuvant month-long therapy with the combination dabrafenib/trametinib (Tafinlar®/Mekinist®).

Best-corrected distance visual acuity was 0.63 (Snellen) bilaterally. Dilated ophthalmological examination was unremarkable. Optical coherence tomography (OCT) scans of the macula showed bilateral serous neuroretinal detachments and serous exudate (Fig. 2), characteristic of MEK inhibitor-associated retinopathy (MEKAR). Because of the deterioration of the visual acuity and the retinal changes, the patient decided to discontinue the combination therapy and switch to immunosuppressive treatment.

After discontinuation of the BRAF and MEK inhibition, the central pathology regressed gradually. Fourteen months later, the visual acuity recovered to 0.9 (RE) and 0.8 (LE); some subretinal fluid remained, but without evidence of neovascularization in OCT angiography.

Ophthalmic aspects

The akronym **MEKAR** (MEK inhibitor-associated retinopathy, proposed by R. Dummer) describes retinal morphological changes during the treatment with MEK inhibitors in analogy to melanoma-associated and cancer associated-retinopathy (MAR and CAR).[25, (26–28)]

Visual disturbances including blurry vision, metamorphopsia and dyschromatopsia, usually mild and transient, are most pronounced during the first 4 treatment weeks.

Biomicroscopy shows yellowish lesions similar to that of acute central serous chorioretinopathy (CSCR). Unlike CSCR, the foci are bilateral, multifocal, typically subfoveal, and along the vascular arcades.

On OCT, the fluid is subretinal, localized between the RPE and the interdigital zone, with no gravitational effects and no leakage in fluorescein-angiography. There are neither RPE detachments, hyperreflective foci, nor increased choroidal thickness as in CSCR.[25] These findings relate in particular to binimetinib monotherapy, which is only rarely indicated, but it supports the understanding of this retinopathy. On combined treatment with ➜

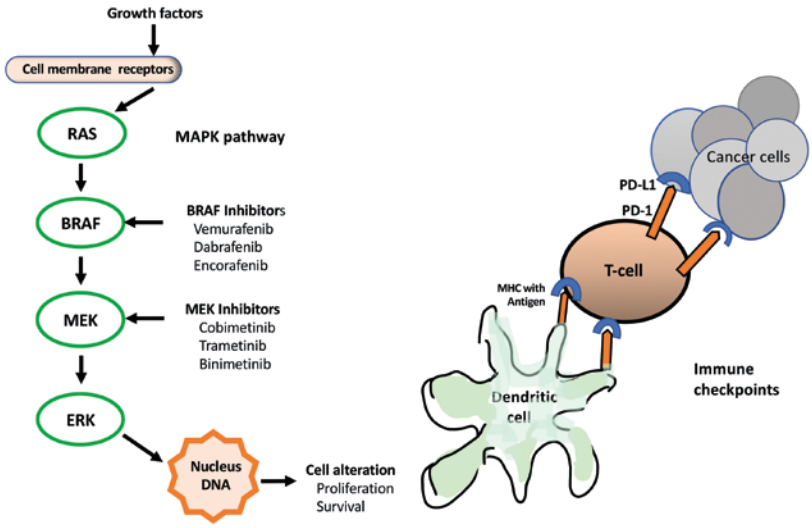

Fig. 1 The MAPK (mitogen-activated protein kinase) pathway: BRAFi and MEKi block this self-feeding cascade. By this mechanism, the tumour cell's mitotic processes such as proliferation, angiogenesis, metastasis, and resistance to apoptosis are inhibited. **Immune checkpoints:** The immune balance is granted by driving and weakening factors. Blocking the immune checkpoints (IC) on T-cells with anti-CTLA-4, or anti PD-1 or blocking IC on tumour cells with anti PD-L1 upregulate T-cell activity and enhance tumour defense. The prerequisite is the recognition of tumour antigens that are perceived as foreign on antigen-presenting dendritic cells. An excessive overreaction of the immune system, which spreads to the patient's own tissues, triggers autoimmune diseases or immune-related adverse events (irAE).

Fig. 2, Case 1 Optical coherence tomography (OCT) upper line right eye, lower line left eye: neuroretinal detachments with fluid accumulation between the RPE and the interdigital zone, and bilateral accumulation of hyperreflective material, isolated small drusen. No detachment of the RPE. **a** and **d)** at admission; **b** and **e**) gradual regression of the pathology, left with some residual subretinal fluid at 3 ½ mts; **c** and **f**) 14 mts after treatment stop.

MEKi and BRAFi (the standard treatment today), the exudations are more isolated and subfoveal. In encorafenib/binimetinib therapy, the typical OCT finding is a flat neuroretinal detachment expanding over a large part of the posterior pole. This is often not visible on fundoscopy.[14,26]

The incidence of these findings depends strongly on the interval of eye examinations, OCT imaging, pharmacokinetics, and dosage of the drugs.[29]

The T_{max} of binimetinib is 1.18 h and its plasma half-life is 8h. For cobimetinib and trametinib, the corresponding values are around 2 d (49h) and 4.5 d (108h).[30]

Findings and incidence of eye AE

- **on cobimetinib / vemurafenib in 8–12 % (2014[15]), in 2021 as retinal detachment or central serous chorioretinopathy in 27 %**
- **on encorafenib / binimetinib a serous retinopathy in 15.3 % during the first 6 months, and in 5.1 % after 18–24 months[19]**
- **on trametinib in 9 %, reported as blurred vision or reversible chorioretinopathy[12]**
- **on trametinib / dabrafenib in 1 %[31]**
- **On binimetinib monotherapy and in combination with encorafenib a retinopathy defined also by OCT 90 to 100 %[14]**

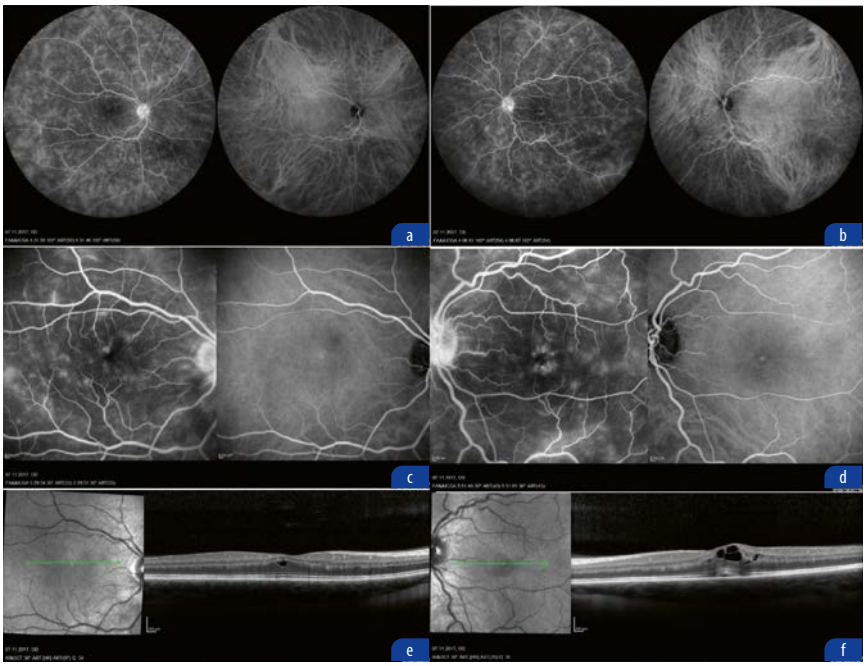

Figure 3, Case 2: a,b: wide angle Fluorescein- and ICG angiography; **c, d:** central recordings, **e,f:** OCT, **a,c,e:** right eye; **b,d,f:** left eye. At the second flare up of uveitis Fluorescein- and ICG-Angiography reveal a peripheral vasculitis and cystoid macular oedema, more pronounced left. The macular oedema with cysts in the inner layers is confirmed by a foveal linear cross-scan on OCT.

As MEKAR is observed on various MEKi, it is considered **a class effect**. With continued treatment, retinal volume and thickness gradually decrease, without leaving functional deficits or changes in structural integrity.

Dysfunction of the outer blood-retinal barrier represented by the RPE was supposed for this drug-induced retinopathy based on morphological findings with OCT, as well as abnormalities in the electro-oculography of patients.[32] This was supported by laboratory studies of cell line models of the RPE and primary neuroretina.[33]

Checkpoint inhibitors: Systemic and ocular adverse events

Immune checkpoint inhibitors (ICI) are effective in advanced melanoma and many other tumors. The onset of action is delayed, but with substantial long-term benefit in a subset of patients.[5,20,34-36] All checkpoint inhibitors, mainly when used in combination, are associated with a wide spectrum of systemic autoimmune or inflammatory side-effects.[37-41] Endocrinologic, cardiac or neurological events may lead to severe organ damage or life-threatening complications.[42]

Ocular adverse events have been reported in 1–4 % of patients. Most of them are reversible such as the dry eye or minor inflammations. However, treatment-related uveitis as published in clinical studies, reviews[43-49] and case reports,[50-53] may lead to persistent loss of visual function.

A broad spectrum of clinical patterns including extraocular manifestations resembling the Vogt-Koyanagi-Harada dis- ➜

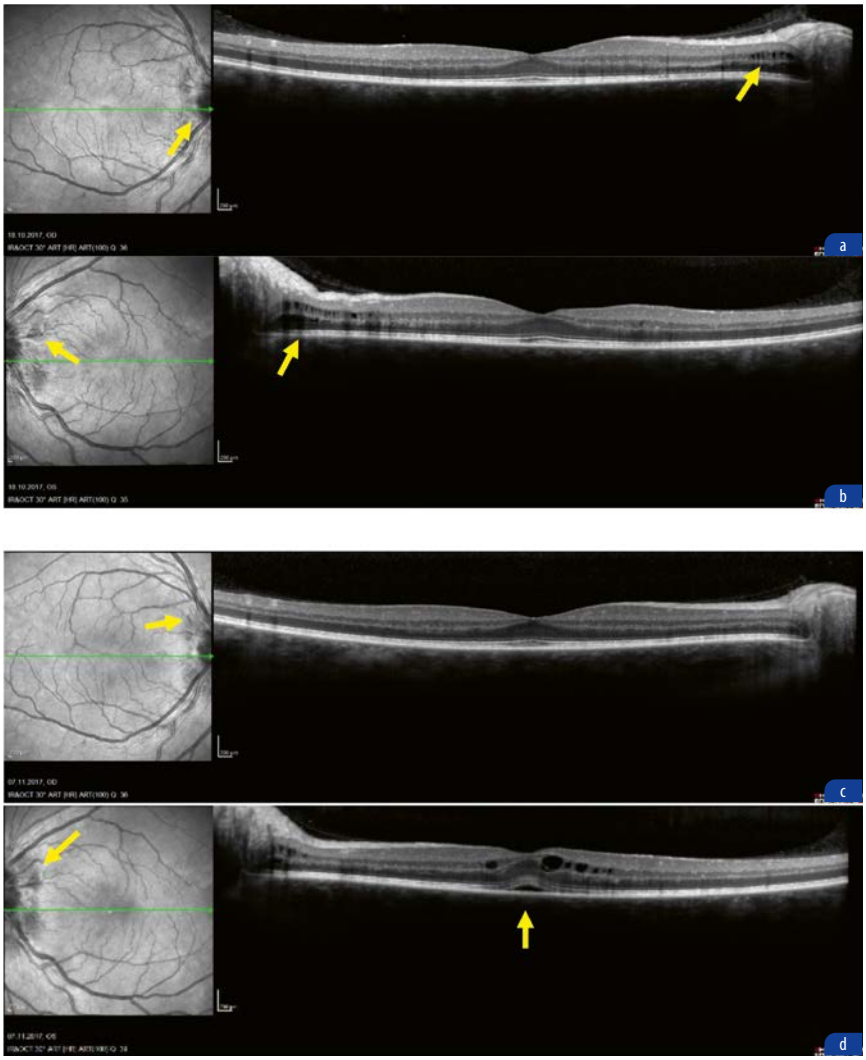

Fig. 4, Case 3: First visit for mild visual disturbances and floaters: **a**: right, **b**: left eye: Scanning laser ophthalmoscopy (SLO) shows optic disk edema with fuzzy margins; on optical coherence tomography (OCT): linear scan through fovea and optic disk reveals cysts within the inner retinal layers near the optic nerve as a sign of disrupted fluid barriers. Three weeks later, with pronounced visual disturbances: **c**: right eye: Scanning laser ophthalmoscopy (SLO) still shows optic disk edema; the cysts on the linear scan with OCT have disappeared. **d**: left eye: disk oedema persists, on OCT, the linear scan reveals large central cysts in the inner retinal layers and a subfoveal neuroretinal detachment, a possible additional sign of MEKAR.

ease has been reported. First-line therapies with checkpoint- and particularly BRAF-monotherapy or combined BRAF/MEK-inhibitors have been associated with a mean relative risk increase for uveitis by factor 80 to 120. The absolute risk remains relatively low; the mean probability of developing uveitis during 1 year of treatment is 3 % to 5 %.[54] Uveitis is considered **a class effect of BRAF inhibition** since it has not been observed in MEKi monotherapy.[55]

Case report 2

A 34-year-old female with resected melanoma Stage IIIB was treated with ipilimumab in 2017 in an adjuvant setting for 4 months (4 infusions). Two months after treatment cessation, she reported blurred vision. Bilateral anterior uveitis with left eye posterior synechiae was diagnosed, on the left side with a distorted pupil and incomplete dilation. Concomitant amblyopia explained a symptom delay in the more severely affected left eye. Treatment with local steroids and mydriatics achieved full resolution.

Six months later, a recurrence of the uveitis was diagnosed, involving not only the anterior segment, but also complicated by retinal vasculitis and macular edema, more severely in the left than right eye. Systemic immunosuppressive therapy with corticosteroids led to complete resolution. No recurrence was observed under tapering local steroids and NSAID (Fig. 3).

Case report 3

A 38-year-old man with metastatic melanoma stage IV M1b was enrolled in a clinical trial with a triple-treatment of MEK/BRAF-Inhibitors (Tafinlar/Mekinist) in combination with anti-PD-1 (spartalizumab) (NCT02967692). Two weeks after treatment initiation, he developed severe systemic adverse events with high fever, rash, and elevated liver enzymes, a so-called Cytokine-Release Syndrome,[56] and was treated with steroid infusions. The anti-PD-1 treatment was interrupted. Two weeks later, at the regular ophthalmic visit, peripheral retinal oedema without inflammatory signs on biomicroscopy, and without visual deterioration was noted.

Subsequently, when full oncological therapy was resumed, febrile episodes recurred and forced conversion to intermittent treatment of the MEK/BRAF-inhibitors at a reduced dose, due to treatment intolerance with recurrent pyrexia.

Three months after newly introduced intermittent oncologic therapy and with stable visual function we found bilaterally slightly blurred disk margins. OCT revealed a bilateral papilloedema (Fig. 4).

Three weeks later, the patient reported for the first-time visual disturbances and floaters. Slit lamp examination revealed an anterior uveitis with cell spillover to the vitreous, OCT showed a bilateral cystoid macular oedema and a flat neuroretinal detachment in the left eye.

Thus, both: an uveitis induced by BRAF or Checkpoint-inhibition and a potential additional MEKAR had to be assumed. The laboratory work-up was not indicative for other uveitis causes. Again, an oral steroid treatment was initiated together with intensive local treatment (steroids, mydriatics and NSAID) followed by tapering over months. Central retinal thickness and volumes were elevated compared to baseline over many months, but the inflammatory signs disappeared slowly. Due to unacceptably elevated liver and pancreatic enzymes and complete remission of the disease the investigational treatment was discontinued.

The experience from this study and two others with triplet combinations indicated

that only a small therapeutic gain has to be balanced with an increase in unacceptable toxicity.[57]

New strategies are urgently needed to improve treatment efficacy for melanoma and for many other cancer types with combined or sequenced modalities.[58] This might result in an increase of treatment-related adverse events including retinopathies or uveitis with late complications as glaucoma, cataract, and epiretinal membranes.[54]

Uveitis-triggering drugs or other causatives in the patients' history have to be ruled out. An initial episode of uveitis may have passed unnoticed or manifest as a late complication, even after cessation (as in our Case 2) or change of therapy. Uveitis forms that need a specific treatment or include risks for the general health have to be identified.[59] In severe cases with involvement of the posterior segment (CTCAE Grade 2–3) an interdisciplinary discussion is needed about which investigations and measures are appropriate, and if the oncologic treatment has to be interrupted during a systemic steroid cure. After restarting the vital cancer treatments, a long-term prevention with local anti-inflammatory drugs is highly recommended. An adapted management of uveitis is proposed with regard to the widely applied CTCAE gradings for adverse events[67] during oncologic treatments in table 1.

Take-Home Message for Ophthalmologists

- **In melanoma treatment with BRAFi/MEKi, an accumulation of subretinal fluid may be drug related (often cited as MEKAR, MEK-inhibitor-associated retinopathy)**
- **OCT is indispensable for diagnosis and quantitative follow-up of retinal changes.**
- **The retinopathy is clearly dose dependent (representing a toxic effect) and related to the pharmacokinetics of the respective drug.** ➜

Ocular toxicity – uveitis CTCAE grading

Definition: A disorder characterized by inflammation of the uvea
Symptoms: Anterior uveitis: pain, photophobia; redness; sometimes without symptoms
Intermediate and posterior uveitis: visual impairment, blurring, floaters

Symptom grade	Management escalation pathway	Assessment and investigations
Grade 1 Asymptomatic; clinical or diagnostic observation only	Continue ICI/TT Local treatment with corticosteroids	• Immediate confirmation of diagnosis by an ophthalmologist • A first episode with unremarkable history may be treated without additional measures • Closely monitor for any symptoms (=Grade 2) or persistence
Grade 2 Symptomatic: moderate decrease in visual acuity (20/40 or better) Anterior and intermediate uveitis; medical intervention indicated	**Withhold ICI/TT** • Treat initially with local application (drops) then tapering or pulsed low-dosage • followed by systemic therapy in a step-wise approach • consider steroid-sparing NSAID drops (preventive long-term therapy) • mydriatics and cycloplegics, pressure lowering drops ICI/TT rechallenge after return to Grade 1 or less	• As for Grade 1 • If relapse and in cases which may need a specific treatment or involve other organs: complete history and a tailored workup* • Slit lamp examination and biomicroscopy • Multimodal imaging
Grade 3 Posterior or pan-uveitis marked decrease of visual acuity (< 20/40, > 20/200)	**Withhold or permanently discontinue ICI/TT (upon interdisciplinary discussion)**** • Systemic corticosteroids, eg. prednisolone 1mg/kg OD for limited time with tapering, particularly in macular involvement • Consider the risk of peri- or intraocular corticosteroid injection in bilateral inflammations	• As for Grade 2 • Interdisciplinary discussion is highly recommended
Grade 4 Blindness (20/200 or worse in the more affected eye)	**Permanently discontinue ICI/ TT**	• As for Grade 3, intensified workup, vitreous biopsy in treatment resistant cases

Tab. 1 Management of uveitis proposed by the authors (FD/UUB) regarding the widely applied CTCAE version 5.0 grading for adverse events during oncologic treatments.[67]
AE: adverse event, OD: once daily, ICI: immune-checkpoint inhibitor, TT: targeted treatment; NSAID: non-steroidal anti-inflammatory drug, VKH disease: Vogt- Koyanagi-Harada disease
* Screening for active infections or inflammations (viral, tuberculosis, syphilis, Borrelia, Bartonella), exclusion of rheumatic diseases (HLA-B27 associated uveitis; juvenile idiopathic arthritis, psoriasis-arthritis), M. Behçet, sarcoidosis, MS, VKH disease, injuries, masquerade syndromes
• CRP or blood sedimentation rate; inflammation parameters; creatinine, electrolyte, ASAT, ALAT, HLA B27, ACE, IL-2, VDR-L
• chest x-ray; CT imaging, anterior chamber tap, polymerase chain reaction, vitreous biopsy, and others)
** Permanently discontinue ICI/TT in treatment resistance, chronic or recurrent visual threats

- **A concomitant wet AMD in an elderly person may need further investigations and follow-up with fluorescein- or OCT-angiography. A rare paraneoplastic retinopathy, with unfavorable prognosis, has to be considered.**
- **Despite of the importance of retinal changes, there is usually no need to suspend oncological treatment as morphological integrity is restored and functional recovery to be expected in the majority of cases.**
- **However, ocular toxicities may lead to permanent visual impairment or are potentially blinding, such as severe cases of uveitis or VKH-like disease associated with BRAF inhibitors or immunotherapy. Vascular occlusion and ischaemic optic neuropathy from MEK inhibitors require discontinuation of the causative drug.**
- **Familiarity with the wide range of potential ocular events and their management is essential.**

In many cases of mild to moderate uveitis and cystoid macular oedema discontinuation of the drug does not need to be permanent, and the patient can be reallocated to the same or a lower dose depending on the situation.

Take-Home Message for Oncologists

- **Side effects of these treatments are frequent with a wide spectrum of new clinical patterns including late onsets. It is not always easy to trace symptoms back to the causative drugs. Interdisciplinary evaluation is essential to promptly diagnose complications and modify the therapy if necessary.**

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Related to the topic: Please read page 352, SSO Best Poster Prizes

Dr. Safia Hsin, Hôpital Jules-Gonin, Lausanne was awarded the «Best Case Report 2022» SSO Award for her work about bilateral severe panuveitis occurring during checkpoint inhibitor therapy with Dabrafenib and Trametinib due to ocular toxoplasmosis. *(Red.)*

Immuncheckpoint-Inhibitoren (ICI): Vielfältige Einsatzgebiete in der Onkologie

Die ICI werden bei Vorliegen bestimmter Rezeptoren in immer breiteren onkologischen Indikationsgebieten eingesetzt, in bestimmten Situationen auch als First-line-Therapie. Damit werden auch die insgesamt seltenen Nebenwirkungen am Auge häufiger anzutreffen sein. *(Red.)*

Indikationen von ICI
• Nichtkleinzelliges Lungenkarzinom
• Hodgkin-Lymphom
• Urothel-Karzinom
• Hepatozelluläres Karzinom
• Merkelzell-Karzinom
• Zervixkarzinom
• Mammakarzinom
• Karzinome im Kopf- und Halsbereich einschliesslich Ösophaguskarzinom