

REVIEW

Ophthalmic Adverse Events of Systemic Immunotherapy and Targeted Cancer Therapy: A Review

Michael R. Dong¹  | Zelia K. Chiu¹  | Lyndell L. Lim^{1,2,3,4}  | Ming Lee Lin^{1,5}

¹Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia | ²Centre for Eye Research Australia, East Melbourne, Victoria, Australia | ³Ophthalmology, Department of Surgery, The University of Melbourne, East Melbourne, Victoria, Australia | ⁴The Royal Melbourne Hospital, Melbourne, Victoria, Australia | ⁵Alfred Health, Melbourne, Victoria, Australia

Correspondence: Ming Lee Lin (mllin4@gmail.com)

Received: 16 September 2025 | **Revised:** 14 December 2025 | **Accepted:** 27 December 2025

ABSTRACT

Systemic anti-cancer treatment has evolved rapidly with the introduction of immunotherapy and targeted therapies, substantially improving survival across a broad spectrum of malignancies. However, as their use expands, ophthalmic toxicities are increasingly recognised as clinically significant adverse effects. This review outlines the pathophysiology, clinical spectrum and management strategies for ophthalmic adverse events linked to immune checkpoint inhibitors, MEK, BRAF, FGFR, ERK, EGFR, HER2, BTK, FLT-3, Bcr-Abl, ALK inhibitors and antibody-drug conjugates.

1 | Introduction

While traditional chemotherapy was the mainstay of treatment for many malignancies, advances in molecular profiling, epigenetics and gene expression have led to more targeted approaches in treating cancer. This has transformed the treatment landscape for many malignancies by improving survival and providing options for cancers resistant to conventional chemotherapy. These biologic agents harness the body's own immune system to interfere with tumour growth by acting selectively on molecular pathways critical to tumour survival, thereby reducing the systemic toxicities traditionally associated with conventional chemotherapy.

Ophthalmic toxicities have been increasingly recognised as a clinical concern. With the growing number of systemic anti-neoplastic agents, understanding the mechanism, clinical spectrum and management of these toxicities is crucial for both oncologists and ophthalmologists.

This narrative review summarises the current evidence on ophthalmic adverse effects (OAEs) of systemic targeted and immune-based cancer therapies. It is beyond the scope of this review to encompass conventional and hormonal chemotherapeutic agents, which have been extensively reported elsewhere [1–3].

2 | Common Terminology Criteria for Adverse Events (CTCAE) Grading

Grading the severity of OAEs related to cancer treatment is standardised according to the Common Terminology Criteria for Adverse Events (CTCAE v6.0) [4]. Briefly, the definition of Grade 1 is asymptomatic or mild disease without need for intervention. Grade 2 is defined as moderate symptomatic disease with moderate decrease in visual acuity (best-corrected visual acuity (BCVA) $\geq 6/12$ or a 3 line decrease from baseline). Grade 3 is defined as severe disease with marked reduction in visual acuity (BCVA $< 6/12$ and $> 6/60$ or more than 3 line decrease from baseline). Grade 4 is the most severe with BCVA $\leq 6/60$ in the affected eye and/or threat of irreversible visual loss.

3 | Immune Checkpoint Inhibitors (ICIs)

3.1 | Mechanism of Action

Immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment, particularly the treatment of metastatic melanoma and non-small cell lung cancer (NSCLC) [5, 6]. Over time, the indications for ICIs have expanded, including advanced urological,

gynaecological, gastrointestinal, haematologic, head and neck, triple-negative breast and non-melanoma skin cancers (Table 1).

Immune checkpoints are innate regulators of the immune system, which mediate self-tolerance and prevent auto-immunity through downregulating T-lymphocyte responses [7–9]. Some

tumour cells are able to interact with the immune checkpoints on T-lymphocytes, downregulating immune responses against them, allowing these tumour cells to avoid immune recognition and proliferate unchecked. ICIs inhibit the interaction of neoplastic cells with immune checkpoints, thus activating the immune system to target these cells.

TABLE 1 | Summary of immune checkpoint inhibitors and their TGA-approved indications.

Drug class	Drug	Indication
CTLA-4 inhibitor	Ipilimumab	Malignant melanoma Renal cell carcinoma Non-small cell lung cancer Malignant mesothelioma
	Tremelimumab ^a	Hepatocellular carcinoma
PD-1 inhibitor	Nivolumab	Malignant melanoma Non-small cell lung cancer Laryngeal and oropharyngeal squamous cell carcinoma Malignant mesothelioma Gastro-oesophageal cancers Renal cell carcinoma Urothelial cancers
	Pembrolizumab	Malignant melanoma Hodgkin lymphoma Non-small cell lung cancer Urothelial cancer Mediastinal B-cell lymphoma Colorectal cancer Laryngeal and oropharyngeal squamous cell carcinoma Renal cell carcinoma Endometrial carcinoma Breast cancer Cervical carcinoma
	Cemiplimab	Squamous cell carcinoma Non-small cell lung cancer
	Tislelizumab	Gastro-oesophageal cancer
	Dostarlimab	Endometrial carcinoma
PD-L1 inhibitor	Atezolizumab	Non-small cell lung cancer Small cell lung cancer Hepatocellular carcinoma
	Durvalumab	Non-small cell lung cancer Small cell lung cancer Biliary tract cancer
	Avelumab	Metastatic Merkel cell carcinoma Urothelial carcinoma Renal cell carcinoma

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; TGA, Therapeutic Goods Administration of Australia.

^aApproved or provisionally approved by the Therapeutic Goods Administration of Australia but not subsidised by the Pharmaceutical Benefits Scheme of Australia.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a transmembrane protein found on CD4⁺ and CD8⁺ T-lymphocytes. It binds to co-stimulatory molecules CD80 and CD86 on antigen-presenting cells [5, 7]. This interaction inhibits both CD4⁺ and CD8⁺ T-cell activation, thereby suppressing immune responses. Programmed death-1/programmed death ligand-1 (PD-1/PD-L1) are inhibitory proteins found on T- and B-lymphocytes, natural killer and dendritic cells. Ligand binding results in suppression of T-cell proliferation and maturation. Tumour cells expressing CD80 (binding to CTLA-4 proteins) and PD-L1 (binding to PD-1 proteins) are thus able to downregulate T-cell responses against them and continue their malignant proliferation unhindered (Figure 1).

Widely used ICIs include CTLA-4 inhibitors (ipilimumab, tremelimumab), PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab, tislelizumab, dostarlimab), and PD-L1 inhibitors (atezolizumab, durvalumab, avelumab) (Table 1). While these treatments are potent enhancers of the immune system, the same mechanism by which they kill tumour cells can also trigger immune-related adverse events (irAEs). Systemic irAEs are frequent (70%–90%) [10, 11]. Common systemic irAEs include fatigue (15.0%–28.0%), diarrhoea (9.7%–29.2%) and rash (10.3%–19.2%), whereas the most frequent high-grade toxicities are colitis (0.6%–6.1%) and neutropenia (0.4%–3.3%) [12]. Ocular and orbital irAEs are uncommon (0.8%–8%) arising from the same autoimmune dysregulation which causes systemic irAEs and, when occurring concomitantly, may provide valuable diagnostic clues (Figure 2). There is an increased incidence of OAEs in anti-CTLA-4 mono- or combination therapy compared to anti-PD-1/anti-PD-L1 monotherapy [8, 13–15]. This is also true for systemic irAEs; 38.6%–57.9% of patients on CTLA-4 inhibitors have been reported to have high-grade toxicities compared to 10%–15% of those on PD-1/PD-L1 inhibitors [16]. It is postulated that anti-CTLA-4 activates T-cells throughout the body, while anti-PD-1/PD-L1 enhances antitumour immune cell activity more specifically [17, 18]. irAEs are thought to be an indirect indicator of immune activation and therefore linked to tumour response and increased survival [19].

Whilst the molecular pathways triggering irAEs are largely unknown, ICIs are believed to cause immune-mediated events through three main mechanisms. Firstly, ICIs can result in cross-reactivity between tumour-specific T-cells and ocular tissues (Type 1a) or clonal expansion of autoreactive ocular-specific T-cells in susceptible individuals (Type 1b), leading to T-cell mediated destruction of healthy tissue by suppressing the downregulating effect of immune checkpoints [20]. As part of the immune tolerance of the eye, the cornea, uvea and retinal pigment epithelium (RPE) express PD-L1 molecules, which aid in preventing inflammation. Thus, ICI blockade of PD-1/PD-L1 interactions reduces regulatory T-cell differentiation in the anterior segment and disrupts immune tolerance

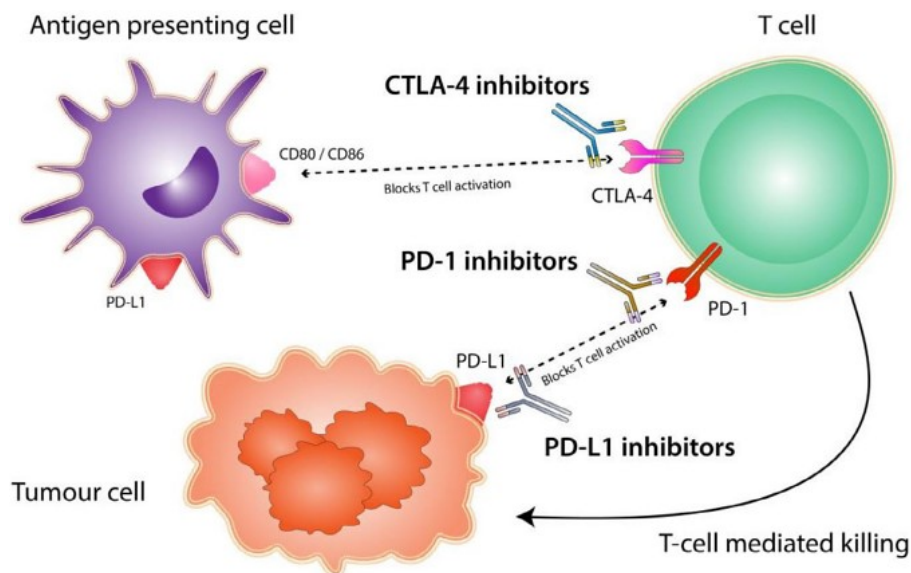


FIGURE 1 | Immune checkpoint inhibitor mechanism of action. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) binds to cluster of differentiation (CD) 80/86 proteins to inhibit T-cell activation (in central lymphoid compartment). CTLA-4 inhibitors are antibodies that block this interaction to allow T-cell activation to attack tumour cells. Binding of programmed death-1 (PD-1) protein to programmed death ligand-1 (PD-L1) on T cells (mainly in peripheral tissues) inhibits T-cell function. PD-1 and PD-L1 inhibitors prevent T-cell inhibition and promote T-cell mediated killing of tumour cells [5].

in the posterior segment by releasing effector T-cell inhibition by PD-L1 on RPE cells, which can result in granulomatous uveitis including multifocal choroiditis and Vogt-Koyanagi-Harada (VKH)-like panuveitis [7, 21–24]. The second postulated mechanism relates to non-specific bystander inflammation resulting in perivascular T-cell proliferation and ultimately vascular occlusion (e.g., occlusive retinal vasculitis, acute macular neuroretinopathy [AMN], paracentral acute middle maculopathy and giant cell arteritis [GCA]) [20]. Thirdly, ICI blockade of inhibitory T-cell signals can drive B-cell production of autoantibodies, exacerbating paraneoplastic syndromes such as melanoma-associated retinopathy and autoimmune retinopathy [7, 25, 26].

3.2 | Ophthalmic Adverse Events

OAEs have been identified within 12 months of ICI initiation in approximately 4% of a cohort of 41 020 patients receiving ICI therapy in the real world [13]. While they have been reported to occur up to 3 years following ICI initiation and up to 2 years following ICI cessation [27–29], most OAEs occur within the first 3–6 months of initiation [30, 31], with a median onset of 5 weeks [27]. The ocular surface, uveal tract, orbit and neuro-ophthalmic tract are common sites of inflammatory adverse events.

Dry eye disease is the most commonly reported OAE, with an incidence ranging from 1.2% to 24.2% [5, 32]. Associated keratitis can range from mild to severe, in some cases causing peripheral ulcerative keratitis, corneal melt and perforation, as well as corneal graft rejection [33–35]. Other ocular surface irAEs include conjunctivitis, episcleritis, scleritis, conjunctival cicatrization and Stevens–Johnsons syndrome (SJS) [3, 36].

Uveitis is the second commonest OAE, with an incidence of 0.3%–0.6% [32]. Given its frequency and potential severity, all patients on ICIs with visual symptoms must be carefully examined for signs of uveitis; severe uveitis could present with hypotony and minimal inflammatory changes (Figure 2). Non-granulomatous bilateral anterior uveitis accounts for the majority of cases but any type of uveitis (intermediate, posterior or panuveitis) can occur, with a reported time of onset between 2 weeks and 14 months [28, 37, 38]. Despite accounting for only 5%–20% of all OAE, posterior segment inflammation such as VKH-like multifocal exudative retinal detachments, ciliochoroidal effusions, multifocal choroiditis resembling Birdshot chorioretinopathy, AMN and occlusive retinal vasculitis may be severe, potentially leading to permanent visual loss if unrecognised and untreated [20, 39, 40]. Exudative retinal detachments, whether single or multifocal, can be associated with choroidopathy, immune retinopathy and ciliochoroidal effusion [28, 41, 42]. One retrospective cohort study of 4695 995 patients found that those receiving ICI for metastatic melanoma were 6.45 times more likely to develop ICI-uveitis compared to non-melanoma cancer, suggesting release of melanin-associated proteins during tumour lysis may play a role in immune dysregulation [28, 41–43].

Myasthenia gravis (MG) has been associated with ICIs, with an incidence of approximately 0.47% [3, 5]. This is more significantly associated with PD-1 and PD-L1 inhibitors used for lung cancer treatment [17]. It usually presents with diplopia and ptosis, but can lead to respiratory compromise. The signs of MG may overlap with orbital myositis, which can co-exist with MG or occur in isolation [5, 44]. Orbital myositis presents as an inflammatory orbitopathy with muscle enlargement and tendon involvement. Up to 30% of ICI-induced MG cases are associated with systemic myositis and myocarditis. ICI-associated MG has a 20%–40% mortality rate which is higher

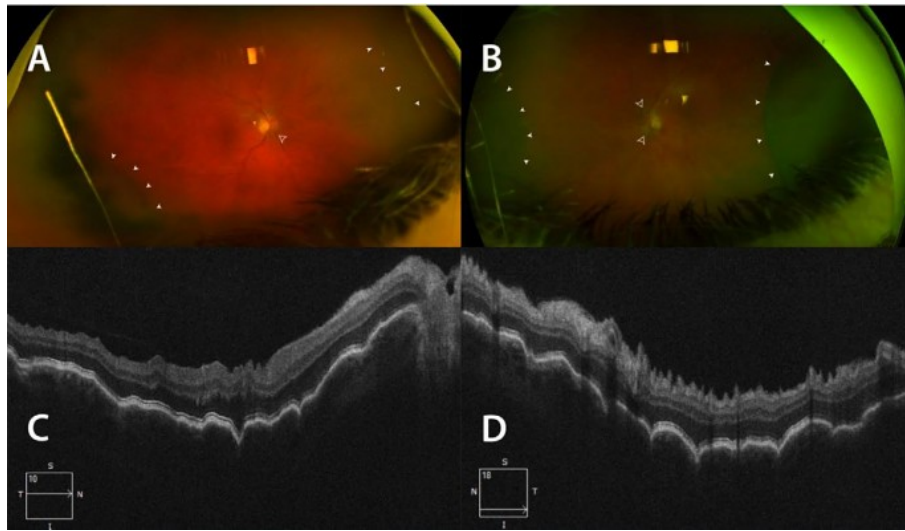


FIGURE 2 | Bilateral panuveitis and hypotony maculopathy following combined CTLA-4/PD-1 checkpoint inhibitor blockade. A 55-year-old Caucasian woman with metastatic melanoma commenced ipilimumab and nivolumab and developed severe immune-related adverse events, including inflammatory bowel disease and new-onset Type 1 diabetes, leading to cessation of therapy after three cycles. Shortly after the onset of autoimmune diabetes, she experienced bilateral painless blurred vision. On presentation, vision was markedly reduced (RE 6/60, LE 1/60) with bilateral hypotony (IOP 2 mmHg). Examination showed 1+ anterior chamber cells, 3+ flare, 360° posterior synechiae without iris bombe, bilateral choroidal effusions (solid arrows 2A and 2B) with bilateral disc swelling (open arrows A and B) and extensive macular subretinal fluid. OCT horizontal raster scans of the macula exhibiting chorioretinal folds secondary to hypotony maculopathy in the right (C) and left eye (D). Treatment consisted of high-dose oral prednisolone with taper, bilateral peripheral iridotomies, intensive topical corticosteroids and subsequent periocular/intraocular triamcinolone. Five years later, she remains in systemic remission without further immunotherapy. Despite persistent hypotony (IOP 4–6 mmHg OU) and interval cataract surgery, she maintains good visual acuities (RE 6/6, LE 6/7.5) with ongoing topical steroids and intermittent intravitreal triamcinolone for recurrent cystoid macular oedema. CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; PD-1, programmed death-1; OCT, optical coherence tomography.

(50%) with myocarditis. Referral for cardiorespiratory evaluation is therefore imperative [7]. Graves' disease and thyroid-like orbitopathy is more commonly associated with CTLA-4 treatment [5].

Other neuro-ophthalmic manifestations include optic neuritis (ON) with a reported incidence of 0.5% [5], cranial neuropathies and rarely GCA [13]. Unlike other inflammatory forms of ON, ICI-associated ON typically presents with bilateral painless visual decline but preservation of colour vision; vision impairment and field loss can range from mild to severe [3, 5]. One study of 11 patients reported the onset of ON is mostly within 4 cycles of ICI therapy [29] but may occur later with prolonged monotherapy, with a propensity for retrobulbar and proximal optic nerve sparing on MRI imaging [29].

3.3 | Management

In general, most OAE can be managed with local or systemic corticosteroids without discontinuing ICI treatment [18]. Severe cases should be managed in consultation with the treating oncologist, as they may require suspension of therapy for several months or even permanent cessation, particularly as OAE often occur together with other systemic side effects. The American Society of Clinical Oncology recommends continuing ICI therapy for Grade 1 toxicity and withholding ICIs for Grade 2 or worse toxicity. When symptoms revert to grade 1 or less, ICI rechallenge may be considered, except in grade

4 toxicities [45]. ICIs are administered on fixed dosing schedules with prolonged receptor occupancy. As such, iAEs are generally managed with temporary treatment cessation rather than dose reduction [46].

Importantly, irAEs are often a good prognostic marker of response to immunotherapy. The overall efficacy of the drug may be reduced through administrations of systemic immunosuppressive therapy; thus, local corticosteroids may be preferable to systemic steroids where possible, to avoid disrupting survival-enhancing anti-cancer therapy.

While there are limited reports on the associations between ocular and systemic irAEs, they often occur concurrently. One case series of ocular irAEs demonstrated that OAEs were the primary reason for ceasing treatment in 2 out of 7 cases, with a median of three irAEs contributing to treatment cessation per patient [27]. Thus, ocular irAEs can represent significant morbidity and the decision to modify treatment warrants multidisciplinary discussion.

Prior history of uveitis is an important risk factor for ICI-related uveitis. In an IRIS Registry analysis, patients with a prior diagnosis had recurrence rates up to 51.1% for uveitis and 36.4% for papillitis within the first year of ICI therapy [15]. Similarly, another study reported a 28.6% ($n=2/7$) rate of uveitis recurrence within 1 year of ICI therapy if there was prior uveitis [43]. Despite the risk of recurrence, there are currently no clear recommendations for prophylactic treatment.

Mild to moderate ocular surface disease and cases of isolated mild anterior uveitis can be treated locally without ICI cessation, where the risk: benefit balance tips in favour of continued ICI therapy. However, more severe disease, such as corneal melt, perforation, SJS and graft rejection usually require drug cessation [28, 34]. Some cases of posterior uveitis, panuveitis, retinal vasculitis and other posterior segment adverse events can be treated with aggressive local corticosteroid treatment (e.g., periocular, intraocular injections) and/or systemic corticosteroids, with subsequent immunomodulatory therapy as required. However, these conditions can also have potentially devastating visual consequences and close communication with the treating oncologist is needed should drug cessation be required [47].

Neuro-ophthalmological complications such as MG, ON and orbital inflammatory disease respond to systemic corticosteroids with discontinuation of therapy; intravenous immunoglobulin (IVIG) and plasma exchange therapy may be required, especially for severe cases [3, 28].

4 | Fibroblast Growth Factor Receptor (FGFR)—Mitogen Activated Protein Kinase (MAPK) Signalling

The fibroblast growth factor receptor (FGFR) pathway plays a critical role in cell growth, survival and differentiation through activation of several downstream signalling cascades, in particular the mitogen-activated protein kinase (MAPK) pathway [48]. Upon binding of fibroblast growth factors to FGFRs, receptor dimerisation and autophosphorylation trigger adaptor proteins such as fibroblast growth factor receptor substrate-2 (FRS2) and growth factor receptor-bound protein-2 (GRB2), leading to activation of rat sarcoma protein (RAS)—rapidly accelerated fibrosarcoma (RAF)—MEK—ERK signalling cascade (Figure 3).

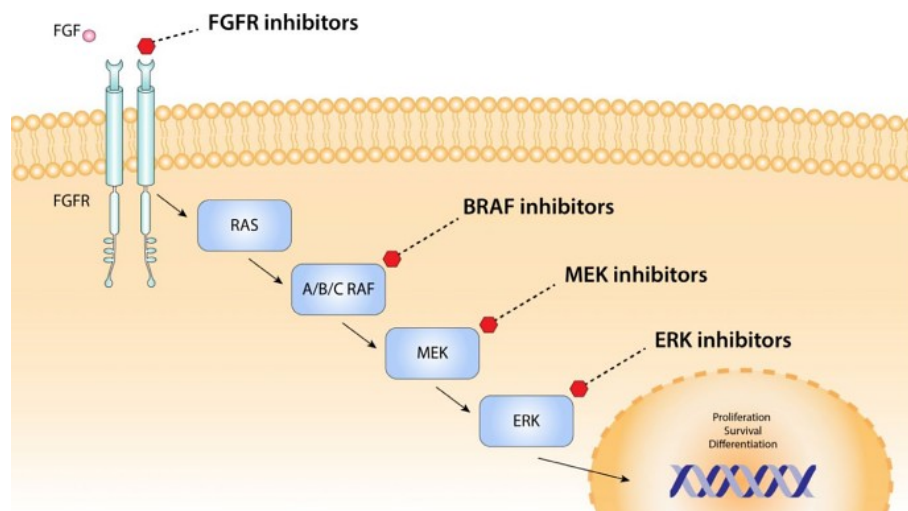


FIGURE 3 | The MAPK pathway. FGF binds to FGFR on the cell surface to activate RAS proteins. RAS protein recruits and activates A, B, or C-type RAF kinases, which phosphorylate and activate MEK. MEK phosphorylates ERK. Once activated, ERK enters the nucleus and phosphorylates transcription factors that regulate cell proliferation, survival and differentiation. FGFR, BRAF and MEK inhibitors block this pathway at different steps to prevent uncontrolled tumour growth. ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma.

This MAPK pathway transmits signals from the cell surface to the nucleus, ultimately regulating gene expression involved in cellular proliferation and homeostasis [49]. Dysregulation at any point can contribute to oncogenesis and is therefore a therapeutic target. Disruption of this pathway by targeted therapies, including MEK, BRAF, FGFR and ERK inhibitors, has been implicated in a range of ocular toxicities, particularly affecting the retina and RPE, underscoring the shared mechanistic basis of these effects [50].

5 | Mitogen-Activated Protein Kinase (MEK) and B Rapidly Accelerated Fibrosarcoma (BRAF) Inhibitors

5.1 | Mechanism of Action

The MAPK/ERK signalling pathway regulates normal cell growth, differentiation and survival. Mutations in BRAF, most commonly V600E, lead to constitutive activation of BRAF kinase, resulting in persistent downstream phosphorylation of MEK/ERK and uncontrolled tumour proliferation [49]. Dysregulation of the MAPK pathway is implicated in the pathogenesis of over 40% of human cancers, including melanoma, NSCLC, colorectal, thyroid, pancreatic, breast and endometrial cancers (Table 2) [48]. MEK inhibitors have gained significant clinical attention as agents targeting a key component of the MAPK pathway, with inhibitors selective for MEK1 and MEK2 most efficacious [51].

Approximately 50% of cutaneous melanomas carry a mutation on the signal transduction molecule BRAF^{V600E} kinase [49], a key mediator of the MAPK pathway, upstream of MEK, which leads to constitutive activation of RAS-RAF-MEK-ERK signalling. This confers resistance to apoptosis in neoplastic cells and thus promotes tumour proliferation. Although signal

TABLE 2 | Summary of MEK, BRAF, FGFR, EGFR, BCR-ABL, HER2, BTK, FLT-3 and ALK inhibitors and their TGA-approved indications.

Drug class	Drug	Indication
MEK inhibitor	Trametinib	Malignant melanoma Paediatric glioma
	Cobimetinib	Malignant melanoma
	Binimetinib	
	Selumetinib	Neurofibromatosis type 1
BRAF inhibitor	Vemurafenib	Malignant melanoma
	Dabrafenib	Malignant melanoma Paediatric glioma
	Encorafenib	Malignant melanoma Metastatic colorectal cancer
FGFR inhibitor	Pemigatinib ^a	Cholangiocarcinoma
	Infigratinib ^a	
	Erdafitinib ^a	
	Futibatinib ^a	
	Derazantinib ^a	
EGFR inhibitor	Erlotinib	Non-small cell lung cancer
	Gefitinib	
	Osimertinib ^a	
	Lazertinib ^a	
	Amivantamab	
	Sunvozertinib ^a	
	Mobocertinib ^a	
	Cetuximab	Metastatic colorectal cancer Squamous cell cancer of the larynx, oropharynx or hypopharynx
BCR-ABL inhibitors	Imatinib	Chronic myeloid leukaemia Acute lymphoblastic leukaemia Myelodysplastic or myeloproliferative disorder Aggressive systemic mastocytosis with eosinophilia Chronic eosinophilic leukaemia Hypereosinophilic syndrome Dermatofibrosarcoma protuberans Gastrointestinal stromal tumour
	Nilotinib	Chronic myeloid leukaemia
	Bosutinib ^a	
	Asciminib	
	Dasatinib	Chronic myeloid leukaemia
	Ponatinib ^b	Acute lymphoblastic leukaemia
HER2 inhibitor	Trastuzumab	HER2-positive breast cancer
	Pertuzumab	
	Lapatinib	
	Tucatinib ^a	

(Continues)

TABLE 2 | (Continued)

Drug class	Drug	Indication
BTK inhibitor	Ibrutinib	Chronic lymphocytic leukaemia Small lymphocytic lymphoma
	Acalabrutinib	Mantle cell lymphoma Chronic lymphocytic leukaemia Small lymphocytic lymphoma
	Zanubrutinib	Chronic lymphocytic leukaemia Small lymphocytic lymphoma Mantle cell lymphoma Waldenstrom macroglobulinaemia
FLT3 inhibitor	Midostaurin	Acute myeloid leukaemia Systemic mastocytosis Mast cell leukaemia
	Sorafenib	Renal cell carcinoma Hepatocellular carcinoma
	Sunitinib ^b	Gastrointestinal stromal tumour
	Gilteritinib	Acute myeloid leukaemia
	Regorafenib ^a	Hepatocellular carcinoma
ALK inhibitor	Crizotinib	Non-small cell lung cancer
	Ceritinib	
	Alectinib	
	Lorlatinib	
	Brigatinib	
	Entrectinib	

Abbreviations: ALK, anaplastic lymphoma kinase; Bcr-abl, breakpoint cluster region-abelson; BRAF, B-type rapidly accelerating fibrosarcoma protein; BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MEK, mitogen-activated protein kinase kinase; TGA, Therapeutic Goods Administration of Australia; TKI, tyrosine kinase inhibitor.

^aApproved or provisionally approved by the Therapeutic Goods Administration of Australia but not subsidised by the Pharmaceutical Benefits Scheme of Australia.

^bPonatinib and Sunitinib are both BCR-ABL and FLT3 inhibitors.

transduction pathway inhibitors are not strictly immune activators, they induce tumour cell and bystander cell death and can therefore generate autoimmune responses [49].

MEK inhibitors are often used in conjunction with BRAF inhibitors which target upstream mediators of the MAPK pathway. Combined therapy aims to prevent or delay resistance which is common with monotherapy [52]. However, combination therapy also results in increased ocular toxicity [53].

5.2 | Ophthalmic Adverse Events

5.2.1 | MEK Inhibitors

MEK inhibitor ophthalmic toxicity predominantly affects the retina. MEK-associated retinopathy (MEKAR) causes self-limiting bilateral neurosensory retinal detachment [54]. Clinical trial data suggests the risk of MEKAR to be up to 90%–100% [55, 56]. The proposed mechanism involves an increased permeability of the RPE and accumulation of subretinal fluid (SRF) through upregulation of aquaporin-1 [57].

Activation of the MAPK pathway is critical for the maintenance, survival and repair of the RPE; thus MEKAR can be considered an on-target toxicity. The incidence of MEKAR depends on the specific agent, though most cases are asymptomatic and spontaneously resolve without treatment modification. In a cohort of 50 eyes of 25 patients with MEKAR, all cases resolved without intervention at a median of 32 days (range 5–182) [54, 58]. One clinical trial demonstrated 90% (46/51) of patients on binimetinib developed MEKAR, with only 20% (9/51) experiencing symptoms [55]. MEKAR onset is most common within the first 3 months of treatment (median 14 days) [54, 58].

Examination may reveal subfoveal and/or multifocal SRF and, less commonly, pigmented deposits. Almost all patients have bilateral lesions, and the majority (76%) are multifocal, averaging six lesions per eye [58]. OCT most commonly shows dome-shaped SRF (Figure 4) but other morphologies of outer retinal oedema that displace the interdigitation zone have also been described. Distinguishing factors from central serous chorioretinopathy (CSCR) include the lack of gravitational fluid tracking, multifocality, lack of RPE detachment and clearly

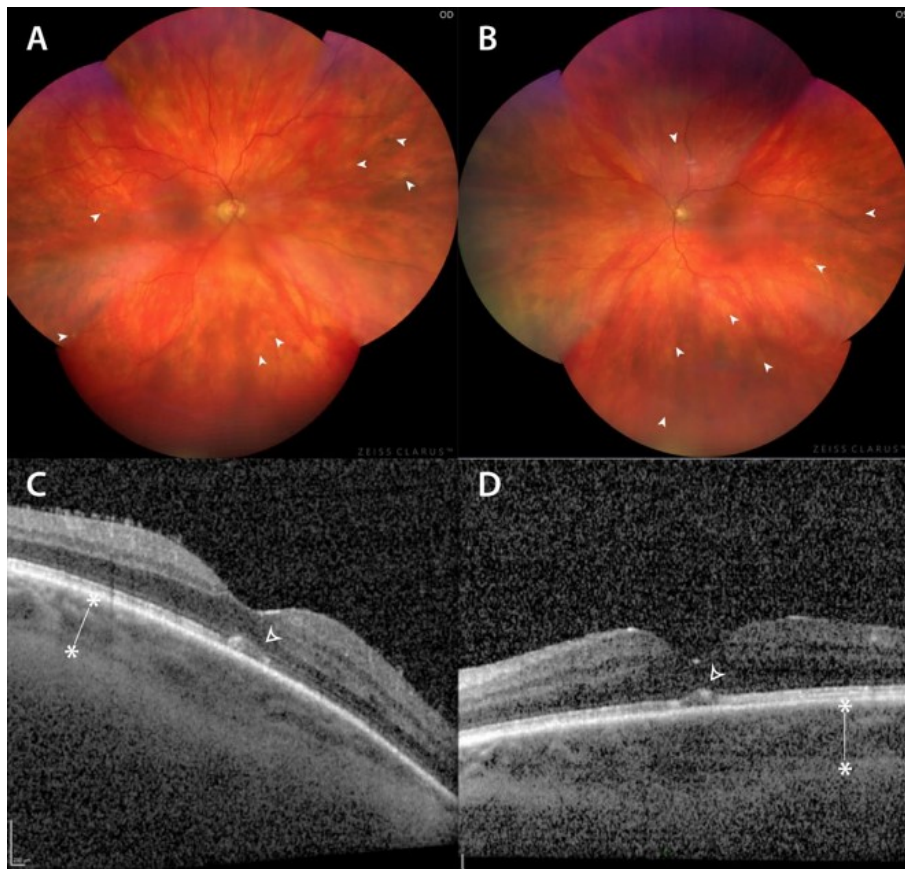


FIGURE 4 | Bilateral panuveitis and MEKAR with combined BRAF/MEK inhibitor therapy for metastatic melanoma. A 61-year-old man with metastatic BRAF V600E mutant melanoma was treated with combination therapy using encorafenib and binimetinib. He developed severe bilateral anterior uveitis, vitritis and ill-defined multifocal choroiditis lesions (solid arrows A and B) with cystoid macular oedema (not shown). Visual acuity at presentation was RE 6/9.6 LE 6/15. OCT (C and D) demonstrated subfoveal MEKAR lesions (open arrows) and choroidal thickening (asterisks). He was treated with topical corticosteroid drops, topical non-steroidal anti-inflammatory drops and a right orbital floor steroid injection for persistent CMO with good response and quiescence of intraocular inflammation. BRAF, B rapidly accelerating fibrosarcoma; CMO, cystoid macular oedema; MEK, mitogen-activated protein kinase kinase; MEKAR, mitogen-activated protein kinase kinase associated retinopathy; OCT, optical coherence tomography. Images courtesy of Dr Christine Tan and Sophie Gutknecht, Royal Melbourne Hospital.

distinguishable RPE, interdigitation zone and ellipsoid zone on OCT, generally without choroidal thickening [58] although choroidal thickness may be secondarily increased in the presence of concurrent uveitis. Fluorescein angiography typically does not show leakage or vascular abnormalities [59]. Autofluorescence may reveal mild central hypoautofluorescence corresponding to areas of SRF [59].

Retinal vein occlusion is a rare adverse effect of MEK inhibitors. The incidence is estimated to be 0.5%, compared to the population risk of 0.1% [60]. This may serve as an indicator of systemic vasculopathic risk or hyperviscosity in the setting of malignancy, so appropriate systemic evaluation is recommended. Due to its potential sight threatening nature, multidisciplinary decision-making regarding treatment cessation should be considered in conjunction with the patient's oncologist [60].

MEK inhibitors are also associated with dry eye symptoms and may infrequently cause intraocular inflammation, with reports of anterior, intermediate, posterior and panuveitis [3, 54]. Severe uveitis is extremely rare and limited to individual case reports [61]. However, in clinical practice, MEK inhibitors are

frequently used in conjunction with BRAF inhibitors, with the latter more likely to be responsible for uveitis in patients on dual therapy (discussed below).

5.2.2 | BRAF Inhibitors

The incidence of OAEs associated with BRAF inhibitors range from 22% to 45% [62]. Uveitis occurs in approximately 4%–5% [63]. In the first year of treatment, one study reported an incidence of 2.27%, with 77.8% of uveitis and 100% of severe uveitis cases occurring within the first 160 days of treatment [64]. Higher rates of uveitis have been reported from clinical trials (4.0% [95% CI 2.6–6.0]), where mild to moderate uveitis was diagnosed at a median of 117 days after treatment initiation (range 7–550 days) [62]. Anterior uveitis is the commonest form of uveitis encountered [65, 66]. However, cases of intermediate uveitis, panuveitis, papillitis with multifocal neurosensory detachments, VKH-like syndrome, ischaemic retinal vasculitis, central retinal vein occlusion, outer retinal lesions and multifocal choroiditis with secondary choroidal neovascularisation have also been reported [62, 67–71]. Other less common OAEs secondary to BRAF inhibition include conjunctivitis, dry eyes and episcleritis [62].

Combination MEK/BRAF inhibitor therapy is associated with a higher rate of all types of uveitis, retinal, choroidal, vitreous, iris and ciliary body abnormalities [53]. Similar to ICI toxicity, treatment for melanoma has been associated with higher rates of OAEs. This is postulated to either be due to epitope sharing between melanoma antigens and melanocytes in the RPE and uvea, or direct activation of downstream ERK, hence the overlapping toxicity profile with MEK inhibitors [1].

5.3 | Management

Patients should be informed of the possibility of developing OAEs prior to commencing treatment, which would allow early identification of symptoms and prompt ophthalmologic assessment. No guidelines currently exist outside clinical trials regarding baseline ophthalmic screening. However, in patients with known ocular disease, in particular a history of retinal pathology, baseline assessment is recommended to detect any pre-existing macular disease which can help determine if subsequent development of MEKAR is visually significant. CTCAE Grade 1 and 2 toxicities can be managed with close observation by an ophthalmologist without cessation of therapy, as most cases resolve within weeks despite continued treatment. For Grade 3 toxicities that are associated with more significant symptoms, MEK inhibitor treatment interruption is recommended with recommencement at the same dose once symptoms and OCT findings have resolved. For Grade 4 toxicities, MEK inhibitor treatment should be discontinued but may be reinstituted at a lower dose upon resolution of symptoms and OCT changes [72].

For management of BRAF inhibitor-associated anterior uveitis, proposed management guidelines recommend temporary interruption of therapy, prompt ophthalmological assessment and treatment with topical corticosteroids, with dose reduction required in most cases [73]. Severe inflammation involving the posterior segment or occlusive vasculopathy may require permanent discontinuation.

In combined BRAF/MEK inhibitor therapy, the anatomic location of inflammation can guide the clinician to decide which drug needs to be discontinued to preserve vision. Mettler et al. proposed management guidelines which suggest permanent discontinuation of both therapies for diffuse abnormalities including panuveitis and intermediate uveitis. Anterior uveitis is more likely to be secondary to BRAF inhibitors, which should be ceased first in this setting. Retinal and choroidal inflammation should prompt preferential cessation of MEK inhibitors. In both scenarios, once the ocular reaction has resolved, monotherapy may be continued, but if there are persistent abnormalities, the remaining agent should also be ceased [53].

6 | Fibroblast Growth Factor Receptor (FGFR) Inhibitors

6.1 | Mechanism of Action

FGFR inhibitors are a class of tyrosine kinase inhibitors. There are four isoforms of FGFR1-4 that are critical to cell development. FGFR pathway alterations are seen in a

variety of solid tumours including breast, ovarian, lung, urological and head and neck cancers (Table 2). The FGFR-MAPK signalling pathway is essential for RPE homeostasis and repair [74].

6.2 | Ophthalmic Adverse Events

FGFR inhibitor OAEs are common, affecting up to a quarter of clinical trial participants [75]. FGFR1-4 are differentially expressed in ocular structures [75], including eyelash follicles, cornea, iris, lens, optic nerve and retina. Adverse events such as trichiasis and trichomegaly have been reported to result in keratopathies [75]. These changes are usually reversible within weeks of treatment discontinuation [76].

6.2.1 | FGFR Inhibitor-Associated Retinopathy (FGFRAR)

FGFRAR has been reported in almost every FGFR inhibitor investigated [75]. The RPE expresses FGFR1 and disruption of RPE homeostasis increases choroidal permeability and SRF accumulation [50]. Due to the overlap between FGFR and MEK pathways, FGFRAR is similar to MEKAR. FGFRAR is characterised by SRF accumulation. Like MEKAR described above, FGFRAR has been labelled pseudo-CSCR due to the presence of SRF on OCT. Like MEKAR, it is distinct from CSCR due to its reversibility and intact photoreceptor and RPE layers. The frequency of FGFRAR varies significantly in the literature from 1% to 50% [75]. Over half (56%) of reported cases are asymptomatic. Median time to detection of SRF is approximately 21 days [77]. Similar to MEKAR, presentations are generally bilateral and multifocal in nature with similar OCT findings [77].

6.2.2 | Other FGFR Inhibitor Toxicities

Ocular surface toxicities have been reported in all FGFR inhibitors, with dry eye being the most common symptom, in addition to blepharitis, conjunctivitis, corneal deposits, keratitis and limbal stem cell deficiency. The prevalence of ocular surface toxicity is approximately 25% [75]. Severe corneal toxicity is rare; however, there have been a number of case reports of corneal thinning and melt. These may be bilateral and generally require treatment discontinuation [78]. A recent small retrospective cohort study of 41 patients treated with erdafitinib reported corneal thinning appearing between 3 and 6 months after treatment initiation in 7.3% ($n=3$) of patients treated with erdafitinib, which was reversible with treatment discontinuation [79]. One patient suffered loss of corneal transparency after resolution of the corneal ulcer and one patient was able to recommence therapy at a lower dose without recurrence [79]. The proposed mechanism of FGFR corneal toxicity is through corneal epithelial dysregulation and impaired wound healing from affected corneal FGFRs. FGFR inhibition can dysregulate TGF- β and platelet-derived growth factors in corneal wound healing. Although rare, there are reports of accelerated cataractogenesis and anterior capsular opacification following FGFR inhibition [79, 80].

6.3 | Management

The natural history and therefore management of FGFRAR is similar to MEKAR [50]. Clinical trial data indicates 62%–70% of FGFRAR resolves with monitoring, dose interruption or dose reduction. Of patients with residual FGFRAR, the majority (67%–71%) were asymptomatic [81–83]. Whilst the manufacturer-recommended approach to managing retinopathy varies between specific agents, a general approach involves observation for grades 1 to 2 FGFRAR and dose-interruption for grade 3 until symptom resolution. For grade 4 FGFRAR, treatment should be discontinued until resolution of symptoms and OCT findings; recommencement at a lower dose can be considered [75]. In reported cases of therapy discontinuation, the retinopathy demonstrates complete or near-complete reversal [84, 85]. In cases of dose disruption, recommencement resulted in recurrence of SRF, albeit at lower severity following dose reduction. This suggests a dose-dependent on-target effect [86].

Ocular surface toxicity is usually reversible with intensive lubricants; however, severe toxicity such as corneal melt requires permanent discontinuation [78].

7 | Extracellular Signal-Regulated Kinase (ERK) Inhibitors

ERK works downstream of FGFR, RAF and MEK. Thus, ERK inhibitors target the final effector kinase of the FGFR–MAPK pathway (Figure 3). Although spontaneous ERK mutations are rare, ERK inhibition may be useful in overcoming resistance that affects upstream mechanisms [87].

Francis et al. reported 33% (20/61) of patients developed retinopathy while receiving Ulixertinib for treatment of metastatic cancer [87]. All cases presented bilaterally, with 80% (16/20) during the first cycle of treatment. As part of the same pathway, ERK retinopathy appears similar to MEK retinopathy. Both drugs cause bilateral multifocal SRF involving the fovea with other foci near the arcades. With limited data, ERK inhibitor retinopathy appears to have a potential for greater impact on visual acuity (up to 6 Snellen lines) compared to MEK inhibitor retinopathy. However, it mirrors the pattern of symptomatic and anatomical resolution without intervention or dose adjustment within a median of 28 days (range 6–132) [87]. Unique features of ERK retinopathy may include intraretinal oedema in the outer nuclear layer and a multifoil or scalloped appearance of SRF. However, these features do not appear to be clinically significant [87].

8 | Epidermal Growth Factor Receptor (EGFR) Inhibitors

8.1 | Mechanism of Action

The EGFR tyrosine kinase family of receptors, which includes EGFR, eukaryotic ribosome biogenesis 1 (ErbB1), HER1, HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4), plays a critical role in regulating cell proliferation, differentiation, angiogenesis and

apoptosis [88]. EGFR activation triggers several downstream signalling cascades which play key roles in tumour development and progression, including the RAS/RAF/MEK/STAT and PI3K/AKT/mTOR pathways. Aberrant EGFR overexpression has been identified in a wide range of solid tumours, including head and neck, brain, breast, lung, colon, prostate, kidney, pancreas and ovary (Table 2) [88].

8.2 | Ophthalmic Adverse Events

EGFR receptors are widely expressed in ocular and periocular structures, including the skin, hair follicles, meibomian and lacrimal glands, conjunctiva and cornea. Consequently, they frequently cause adverse effects on the ocular surface. For example, conjunctivitis has been described in 8% of patients on gefitinib [89].

As EGFR is a key receptor in corneal epithelial wound repair, its inhibition can lead to persistent epithelial defects and recurrent corneal erosions [18]. Superficial punctate keratopathy (SPK) is common, with an incidence that varies between agents. As an example, the incidence of SPK in patients on gefitinib is 2.0%–2.7%, with corneal erosions affecting up to 1.8% [89].

EGFR blockade disrupts normal hair follicle cycling, resulting in hypertrichosis, trichomegaly and trichiasis [90]. A prospective study of 30 patients treated with cetuximab or erlotinib reported trichomegaly in 10% ($n=3$) [91]. Periocular skin toxicity is common, with patients experiencing eyelid swelling, erythema, blepharitis, hyperpigmentation, and in some cases, scarring or cicatricial changes [91]. Additional reports have described erlotinib-induced keratitis, keratouveitis and corneal oedema, leading to treatment discontinuation and reversal of inflammatory changes within 1 week [92].

8.3 | Management

Mild EGFR inhibitor-induced ocular surface disease can be managed conservatively with preservative-free lubricants, warm compresses and lid hygiene. Topical corticosteroids or antibiotic–steroid combinations may be used for persistent blepharitis or conjunctivitis. Trichomegaly and trichiasis causing ocular surface irritation can be addressed with epilation or, in recurrent cases, electrolysis or laser ablation [93].

Persistent epithelial defects or recurrent corneal erosions can be managed with bandage contact lenses, prophylactic antibiotic drops and treatment interruption until resolution [89]. Corneal ulceration, keratitis and keratouveitis warrant urgent ophthalmic assessment, intensive topical antibiotic and/or corticosteroid therapy with drug cessation in refractory or sight-threatening cases. Periocular skin toxicity is managed with emollients, mild topical corticosteroids or oral tetracyclines if secondary meibomian gland dysfunction is present. Close monitoring is advised in patients with pre-existing ocular surface disease or those developing severe corneal changes. Permanent discontinuation of EGFR therapy is rarely required but may be necessary for corneal melt or perforation [94].

9 | Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors

9.1 | Mechanism of Action

Human epidermal growth factor receptor-2 (HER2) is a transmembrane tyrosine kinase receptor which is over-expressed in breast, gastric and oesophageal cancers [95]. HER2 inhibitors such as trastuzumab, pertuzumab and lapatinib directly target these receptors and are the mainstay of HER2-positive breast cancers.

9.2 | Ophthalmic Adverse Effects

Ocular surface toxicities such as epiphora, conjunctivitis, keratitis and dry eyes are the most common OAE with HER2 inhibitors. Epiphora is associated with trastuzumab and pertuzumab, with an incidence of 5%–15% [96]. While trastuzumab and antibody-drug conjugate (ADC) combination therapies have a higher rate of OAEs (up to 31.3% reported in trastuzumab emtansine), most are mild dry eye and conjunctivitis without requiring amendments to treatment [97]. This is likely secondary to inhibition of HER2 receptors in the corneal epithelium which regulate cellular proliferation and epithelial repair [98]. A study of 445 patients reported toxicities in 2.5% of patients on trastuzumab, all of which were conjunctivitis [99]. Trastuzumab rarely leads to corneal melt and perforation requiring corneal transplantation; this may occur at any time during treatment [100–102].

OAEs mostly occur within 4 weeks of starting anti-HER2 therapy; however, they have been reported up to 266 days from initiation [103]. Trastuzumab-ADC combinations have a longer time to onset, approximately 1–3 months from initiation [104].

9.3 | Management

Mild ocular surface toxicities can be treated with lubricants and topical steroids as required without chemotherapy cessation. However, in cases of corneal thinning/melt, HER2 therapy should be withheld until documented healing due to the risk of corneal perforation. It is possible to successfully re-institute anti-HER2 therapy with low-dose topical steroids and lubricants and close monitoring, although case reports do not describe whether dose reduction on recommencement is required [101, 102].

10 | Bruton Tyrosine Kinase (BTK) Inhibitors

10.1 | Mechanism of Action

Bruton tyrosine kinase (BTK) molecules play a pivotal role in the regulation of B-cell development, activation, proliferation and survival [105]. BTK inhibitors, such as ibrutinib, acalabrutinib and zanubrutinib, are commonly used for B-cell neoplasms. Preliminary reports also show promise for zanubrutinib in the treatment of vitreoretinal lymphoma due to its ability to cross the blood–brain/blood-retinal barrier [106, 107].

10.2 | Ocular Adverse Events

Ocular surface toxicity such as dry eye and conjunctivitis are the most common adverse effects [108]. The next commonest OAE is uveitis. Anterior, intermediate, posterior and panuveitis, with or without cystoid macular oedema (CMO) or optic nerve swelling, have been reported, mainly in association with ibrutinib [109–112]. The majority of these occur within 8–24 months of starting treatment [111]. Isolated CMO also occurs mostly within a month or up to 2 years after treatment initiation [113, 114]. The mechanism of uveitis is unclear; however, a proposed mechanism is the blockade of interleukin-2-inducible T-cell kinase resulting in skewed T-cell signalling toward a Th1-dominant profile, promoting autoimmune and pro-inflammatory phenomena [115].

BTK inhibitors also carry an increased risk of bleeding in up to 50% of patients due to inhibition of platelet aggregation or thrombocytopaenia [116, 117]. There have been reports of spontaneous hyphaema with ibrutinib and acalabrutinib a year after treatment initiation [112, 118]. Furthermore, there has been one report of bilateral hyphaema and vitreous haemorrhage following intravitreal methotrexate and anterior chamber paracentesis while on zanubrutinib [119].

10.3 | Management

All ocular surface toxicity can be satisfactorily treated with frequent lubricants without treatment cessation [108]. Similarly, anterior and mild intermediate uveitis may be treated with topical steroids without drug interruption, but if ceased, treatment can be successfully re-introduced, although it is unclear whether dose reduction is required [110, 112]. Posterior or panuveitis and refractory CMO often require permanent treatment discontinuation and local steroid injections [109, 110, 112].

11 | FMS-Like Tyrosine Kinase 3 (FLT3) Inhibitors

11.1 | Mechanism of Action

FMS-like tyrosine kinase 3 (FLT3) is a Class 3 tyrosine kinase receptor found on haematopoietic progenitor cells. FLT3-ligand binding triggers activation of downstream signalling pathways which regulate cell survival, proliferation and differentiation [120]. FLT3 mutations are commonly found in acute myeloid leukaemia. First-generation FLT3 inhibitors (e.g., midostaurin, sorafenib, sunitinib) have broad-spectrum activity against many targets including FLT3, vascular endothelial growth factors, platelet-derived growth factors and stem cell factors, whereas second-generation FLT3 inhibitors (e.g., regorafenib, gilteritinib) have greater specificity and thus, lower toxicity [120].

11.2 | Ophthalmic Adverse Effects

A study from the National Registry of Drug-Induced Ocular Side Effects between 2008 and 2017 found that the most

common OAEs are mild, including periocular or eyelid oedema and dry eye and keratitis [121]. Extraocular motility disorders, with or without ptosis, were also reported with sorafenib and sunitinib.

Posterior segment AEs such as retinal arterial or venous occlusions, CMO and optic neuropathy, as well as uveitis have been reported secondary to sorafenib, sunitinib and regorafenib [122–125]. These mostly occur within 1–2 years of treatment initiation; however, cases have been described up to 4 years from commencement. Sunitinib has been associated with bilateral SRF and VKH-like disease, with or without inflammation [126, 127]. The reported timeframe for SRF was 3 weeks following initiation. Gilteritinib, a second-generation FLT3 inhibitor, has a lower systemic and ocular side effect profile [120].

11.3 | Management

Retinal vascular events in the context of FLT3 inhibition generally require permanent treatment discontinuation with intravitreal anti-VEGF, steroids and panretinal photocoagulation as required [122, 124, 125]. In leukaemia patients, it can be difficult to dissociate the effect of the drug from the prothrombotic state induced by malignancy itself. Similarly, optic neuropathy is sight-threatening and treatment should be withheld, with or without high-dose systemic steroids [128, 129]. While visual outcomes were good, there are no data on treatment re-challenge.

In cases of SRF, only treatment interruption resulted in fluid resolution; dose reduction alone was ineffective. Interestingly, an intermittent chemotherapy schedule resulted in a “yo-yo effect” of SRF, resolving during treatment interruptions [126]. Withholding or ceasing treatment should be discussed with oncologists and tailored to each individual patient's fluid location, visual acuity and systemic needs.

12 | Breakpoint Cluster Region-Abelson Oncogene (BCR-ABL) Inhibitors

12.1 | Mechanism of Action

BCR-ABL tyrosine kinase is the fusion protein formed by the Philadelphia chromosome translocation in chronic myeloid leukaemia. The kinase drives uncontrolled cell proliferation and survival via multiple signalling pathways (RAS–MAPK, PI3K–AKT, JAK–STAT) [130]. BCR-ABL inhibitors bind to the ATP-binding site of the BCR-ABL protein, preventing phosphorylation [130].

12.2 | Ophthalmic Adverse Events

BCR-ABL inhibitors can cause fluid retention that manifests as periorbital, pulmonary, pericardial and pleural effusion [131]. Imatinib is associated with the highest rate of fluid retention; periorbital oedema has been reported in 10.5%–80% of patients with an average onset of 68 $\pm$ 48 days [131–134]. Reports indicate approximately 29% have concurrent peripheral oedema

[134]. Female patients are at significantly higher risk of periorbital oedema secondary to imatinib compared to other BCR-ABL inhibitors [131].

Several reports describe optic nerve head swelling and ON with imatinib, sunitinib and dasatinib [128, 135–138]. There are also cases of periorbital phototoxic rash, vitreous haemorrhage, blepharospasm, CMO, serous retinal detachment and ischaemic maculopathy [3, 62, 139–143].

12.3 | Management

Typically, patients with periorbital oedema can be managed conservatively with observation or short courses of mild diuretics where symptomatic [134]. Rarely, surgical debulking is required [132, 144]. Other rare side effects reported in case reports are managed with local therapies such as botulinum toxin for blepharospasm [140]. Optic nerve swelling typically resolves with drug discontinuation; successful recommencement without recurrence was reported in one case [137]. ON requires discontinuation and oral corticosteroids and may be associated with central nervous system demyelinating disease [135, 145, 146].

13 | Anaplastic Lymphoma Kinase (ALK) Inhibitors

13.1 | Mechanism of Action

ALK is a transmembrane receptor tyrosine kinase that becomes oncogenic in the setting of mutations/transforming rearrangements in NSCLC. ALK inhibitors competitively bind to the ATP-binding site to prevent autophosphorylation of ALK and downstream signalling molecules [147].

13.2 | Ophthalmic Adverse Events

Amongst all ALK inhibitors, crizotinib (first generation) is most commonly responsible for visual disturbances (41%–73% of patients) [148]. In next generation agents, OAEs are less frequent (1%–21%) (Table 2) [3, 149, 150]. Visual disturbances are described as blurred vision, halos, flashes, floaters, light trails, field defects or transient image persistence or loss, with no abnormal findings on ophthalmological exam [151]. These visual disturbances usually last less than 60 s and are most prominent when changing from scotopic to photopic conditions and improve with time as treatment continues [151].

OAEs with structural changes have been reported in isolated case reports. One case of posterior uveitis with preserved vision occurred 2 years after starting crizotinib and resolved 2 months after switching to alectinib [152]. Another case described chronic conjunctival chemosis, resolving 1 week after crizotinib cessation [153].

Severe vision loss is rare; however, bilateral optic neuropathy with enhancement on MRI has been reported in crizotinib and lorlatinib with onset from 2 to 9 months after treatment initiation [154–156].

TABLE 3 | Antibody-drug conjugates with known ocular toxicities and their TGA-approved indications.

Drug	Indication	Antibody/tumour target (ocular surface expression)	Payload (mechanism)	Ocular surface side effects (rate of occurrence where data is available)
Belantamab mafodotin ^b	Relapsed or refractory multiple myeloma	BCMA (not expressed)	MMAF (microtubule disruption)	Corneal microcyst-like epithelial changes (70%–75%) [159] Keratopathy (76%) Dry eye (19%) [160]
Mirvetuximab soravtansine ^a	Epithelial ovarian, fallopian tube or primary peritoneal cancer	FR α (conjunctiva)	DM4 (microtubule disruption)	Corneal microcyst-like epithelial changes (41%–100%) Keratopathy (29%) Dry eye (25%) [160]
Trastuzumab emtansine	Metastatic HER2 positive breast cancer or as adjuvant in early disease	HER2 (cornea and conjunctiva)	DM1 (microtubule disruption)	Corneal microcyst-like epithelial changes (100%) Dry eye (10%) Conjunctivitis (4%) [160]
Trastuzumab deruxtecan	Unresectable and/or metastatic HER2-low breast cancer	HER2 (cornea and conjunctiva)	Camptothecin (DNA damage)	Dry eye (11%) [160]
Enfortumab vedotin	Urothelial carcinoma	Nectin4 (cornea and conjunctiva)	MMAE (microtubule disruption)	Dry eye (13%–36%) [160, 161]
Brentuximab vedotin	CD30 positive systemic anaplastic large cell lymphoma Relapsed or refractory Hodgkins lymphoma CD30 positive T-cell lymphoma	CD30 (not expressed)	MMAE (microtubule disruption)	Transient blurred vision (rare) Optic disc oedema (rare) Dry eye [162]
Inotuzumab ozogamicin	Acute lymphoblastic leukaemia	CD22 (conjunctiva)	Calicheamicin (DNA damage)	Conjunctival haemorrhage Eyelid oedema [162]
Sacituzumab govitecan	Unresectable, locally advanced or metastatic triple-negative breast cancer	TROP-2 (cornea and conjunctiva)	Camptothecin (DNA damage)	Eyelid ptosis Dry eye [162]
Tisotumab vedotin ^c	Recurrent or metastatic cervical cancer	Tissue factor (cornea and conjunctiva)	MMAE (microtubule disruption)	Conjunctivitis (43%) Conjunctival adverse events (40%) Dry eye (23%) Corneal adverse events (21%) Keratitis (11%) [160]
Polatuzumab vedotin ^a	B-cell lymphoma	CD79b (not expressed)	MMAE (microtubule disruption)	Blurred vision Dry eye [162]

Abbreviations: BCMA, B-cell maturation antigen; CD, cluster differentiation; DM1, DM4, drug maytansinoid 1.4; FR- α , folate receptor alpha; HER2, human epidermal growth factor receptor 2; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; TGA, Therapeutic Goods Administration of Australia; TROP-2, trophoblast cell surface antigen 2.

^aApproved or provisionally approved by the Therapeutic Goods Administration (TGA) of Australia but not subsidised by the Pharmaceutical Benefits Scheme of Australia.

^bNot widely available in Australia outside clinical trials.

^cNot TGA registered or approved.

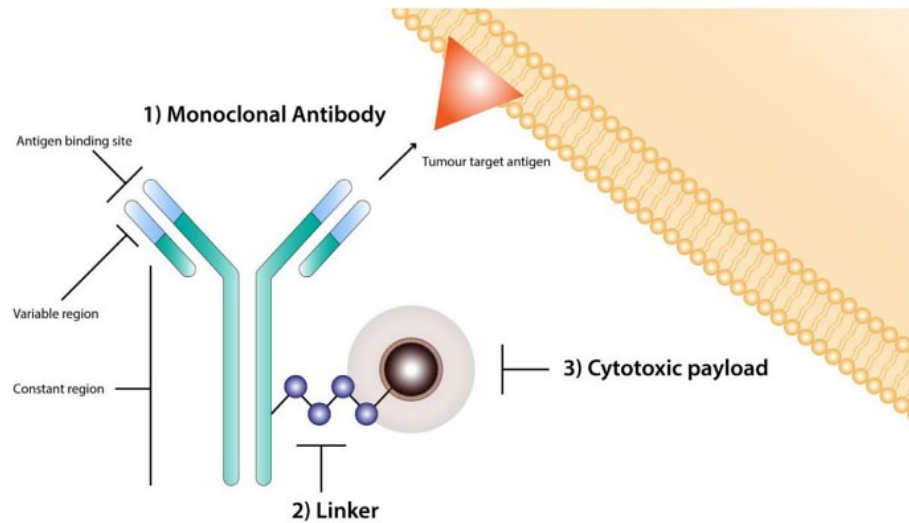


FIGURE 5 | Molecular structure of ADCs. Antibody-drug conjugates (ADCs) consist of three parts: (1) a monoclonal antibody targeting an antigen expressed on the surface of a cancer cell, (2) a chemical linker connecting the antibody to the cytotoxic payload and (3) a cytotoxic payload that releases potent doses of chemotherapy at target tissue, leading to apoptosis of tumour cells.

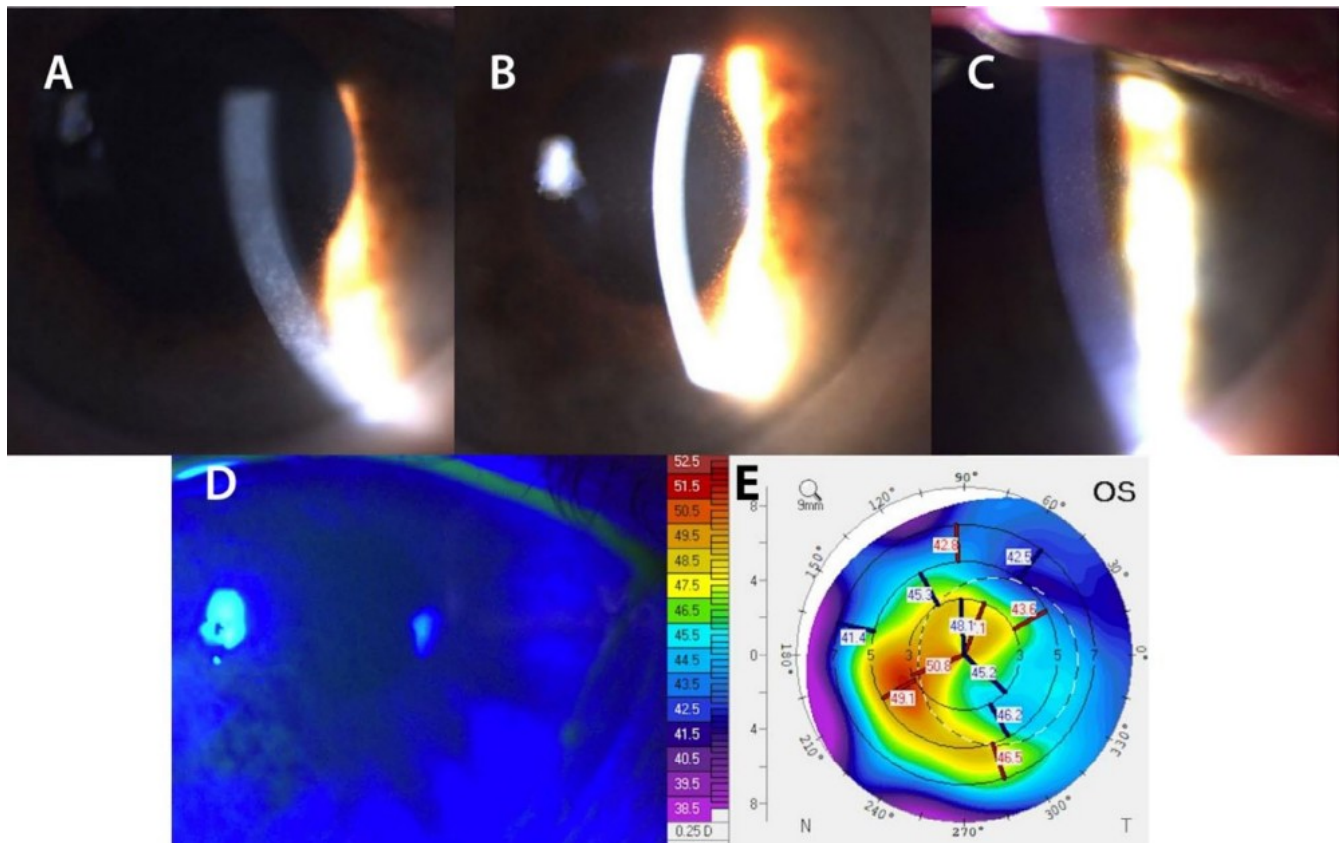


FIGURE 6 | Corneal toxicity associated with antibody-drug conjugates (ADCs). (A) High magnification sclerotic scatter demonstrating peripheral corneal microcyst-like epithelial changes initially; followed by (B) central corneal microcyst-like changes; (C) at high magnification; (D) with fluorescein staining; (E) corneal topography demonstrates ring-like steepening predominantly of the peripheral cornea corresponding to peripheral microcyst-like changes.

Whilst the exact mechanism of these visual disturbances is unclear, the heterogeneity amongst different ALK agents suggests that downstream tyrosine kinases are responsible, rather than direct ALK inhibition [157].

13.3 | Management

The majority of OAEs with ALK inhibitors are of low-grade severity accompanied by a normal ophthalmic examination

TABLE 4 | Summary of systemic immunotherapy/targeted cancer therapies and their proposed mechanisms for ophthalmic toxicity.

Drug class	Ocular tissues typically affected	Relevant receptor/pathway expression	Mechanisms of ophthalmic toxicity
Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)	Cornea, uvea, choroid, RPE, retina, optic nerve	PD-L1 expression in cornea, iris, ciliary body and RPE supports anterior and posterior immune privilege (ACAID, BRB) [21–24]	Loss of ocular immune tolerance via checkpoint blockade; T-cell cross-reactivity with melanocyte antigens; bystander perivascular inflammation; autoantibody-mediated retinopathies [7, 20, 26, 53]
MEK inhibitors	Retina, RPE	MAPK pathway activity essential for RPE homeostasis and fluid transport [48, 75]	On-target RPE dysfunction; aquaporin-1 upregulation leading to subretinal fluid accumulation (MEKAR); reversible outer retinal oedema [53–57]
BRAF inhibitors	Uvea, retina, RPE, choroid	BRAF/MAPK activation in melanocyte-rich tissues; shared melanoma antigens in RPE/uvea [1, 61–65]	Immune cross-reactivity; downstream MEK/ERK dysregulation; choroidal permeability changes; inflammatory uveitis and VKH-like presentations [62–70]
FGFR inhibitors	Cornea, retina, RPE	FGFR1–4 expressed in corneal epithelium, iris, lens, optic nerve, retina; FGFR signalling crucial for RPE repair [74, 75]	On-target corneal epithelial toxicity (blepharitis, keratopathy, melt); RPE dysfunction giving rise to FGFRAR with subretinal fluid; impaired corneal wound healing [74–78]
ERK inhibitors	Retina, RPE	ERK is final effector of RAF–MEK–ERK cascade in RPE [48, 87]	MEKAR-like subretinal fluid; possible greater reduction in visual acuity; outer nuclear layer oedema; reversible RPE pump dysfunction [86]
EGFR inhibitors	Corneal epithelium, conjunctiva, eyelid margin	EGFR expressed in conjunctiva, corneal epithelium, meibomian/lacrimal glands, hair follicles [87–90]	Impaired epithelial repair leading to conjunctival and corneal erosions; trichiasis/trichomegaly; meibomian gland dysfunction; rare keratouveitis [87–92]
HER2 inhibitors	Cornea, conjunctiva	HER2 expression in corneal epithelium and conjunctiva [97]	On-target epithelial inhibition causing dry eye, keratitis; rare corneal melt from impaired epithelial regeneration [95–103]
BTK inhibitors	Ocular surface, uvea, retina	BTK signalling in B-cell regulation, shift to pro-inflammatory T-cell signalling; platelet aggregation effects [104–115]	Immune dysregulation giving rise to uveitis +/- CMO. Platelet dysfunction leading to increased bleeding risk with hyphaema/vitreous haemorrhage [108–117]
FLT3 inhibitors	Eyelids/periorbital, ocular surface, optic nerve, choroid	Off-target VEGF/PDGF inhibition (first-generation agents) [119–124]	Dry eyes, periocular oedema. Extraocular motility disorders. Retinal vascular occlusions; optic neuropathy, subretinal fluid [121–128]
BCR-ABL inhibitors	Eyelids/periorbital, retina, optic nerve	RAS–MAPK, PI3K–AKT signalling; fluid-retention pathways [130–133]	Periorbital oedema; optic neuritis/neuropathy; CMO or serous detachment from vascular dysregulation [128, 134–142]
ALK inhibitors	Neural visual pathways; retina (functional)	ALK inhibition leading to downstream tyrosine kinase activity [157]	Transient visual disturbances via altered phototransduction; rare uveitis or optic neuropathy [148–155]

and do not require treatment modification [158]. Visual disturbances decrease with time without requiring treatment, dose adjustment or cessation [149]. Optic neuropathy requires drug discontinuation; rechallenging can result in further visual field loss [154–156].

14 | Antibody-Drug Conjugates (ADCs)

ADCs are a novel class of immunoconjugates that combine the potent killing effect of chemotherapy with the specificity of monoclonal antibodies to exclusively target tumour cells.

Conceptually, they work like ‘smart bombs’, honing to a target expressed more selectively by tumour cells and dropping-off potent doses of chemotherapy that would otherwise not be tolerated systemically. This review will focus on ADCs currently available or under investigation in Australia with significant or unique ocular toxicity (Table 3).

14.1 | Mechanism of Action

Each ADC consists of (1) a monoclonal antibody (mAb), (2) a cytotoxic payload and (3) a linker molecule that connects the two (Figure 5) [163]. The mAb is directed to malignant cells by preferential binding to a cell-surface antigen expressed more selectively in tumour cells. Once the conjugate is internalised, lysosomal degradation occurs and the cytotoxic payload is released intracellularly, causing apoptosis of tumour cells [104].

14.2 | Ocular Adverse Events

The design selectivity of ADCs is not absolute, and ocular tissues express some similar receptors to mAb targets on tumour cells, giving rise to on-target toxicity [164]. For example, tisotumab vedotin, used in the treatment of metastatic or recurrent cervical cancer, targets tissue factor (TF) highly expressed on cervical cancer cells. However, TF is also expressed in conjunctival cells, leading to on-target delivery of the cytotoxic payload here, causing conjunctival inflammation [165].

The ocular adverse events of ADCs predominantly affect the ocular surface, including corneal microcyst-like epithelial changes (MECs), keratitis, non-staining epithelial keratopathy with subepithelial inclusion cysts, SPK with dry eye, conjunctivitis and blepharitis (Table 3). Symptoms include epiphora, photophobia and blurred vision. Rarely, Grade 3 or worse toxicity such as ulcerative keratitis has been reported, leading to discontinuation of the ADC [164]. The cytotoxic payload of an ADC, particularly microtubule inhibitors (such as ravtansine [DM4]), may damage rapidly renewing corneal epithelial cells through both on-target, antigen-independent off-target mechanisms and bystander killing, where the cytotoxic payload diffuses to neighbouring host cells to cause apoptosis [166, 167]. Ocular toxicities are common and represent a significant cause of morbidity, with up to half of treated patients reporting one or more treatment-related side effects [168, 169]. Belantamab mafodotin (used in refractory myeloma), trastuzumab emtansine (for breast cancer) and mirvetuximab soravtansine (for advanced gynaecological malignancies), whose payloads contain microtubule disruptors, were the most susceptible to causing ocular toxicity [104]. The median time to onset of OAE in clinical trials was between 22.5 and 37 days for belantamab, 21 days for sacituzumab and as long as 223 days for trastuzumab deruxtecan [104, 159].

MECs, which are a unique feature of ADCs, appear histologically as intracytoplasmic inclusions within apoptotic corneal epithelial cells [170]. MECs start bilaterally around the limbus in an annular distribution, migrating centrally with subsequent drug cycles (Figure 6) [171–174]. On anterior segment optical

coherence tomography (AS-OCT), they appear hyper-reflective. When located in the periphery, MECs induce peripheral corneal steepening and therefore relative central flattening with a hyperopic shift, but when the central cornea eventually becomes affected, this induces a myopic shift with corresponding central corneal steepening [175].

14.3 | Management

Treatment of ADC-related OAEs is generally supportive with many centres utilising frequent preservative-free lubricants and/or topical steroids during severe episodes of keratopathy. Corneal epithelium turns over every 7–14 days; therefore, microcystic changes and their secondary refractive effects are generally reversible after completion or cessation of therapy [175, 176]. Corneal MECs improve 2–32 weeks after drug discontinuation but can take up to 9 months for full resolution [160]. Dose delays or reduction may be required depending on the severity of epitheliopathy [177].

Given the reversibility of these OAEs, there is no consistent evidence for any significant benefit from prophylactic treatment. Conflicting evidence exists regarding preventative topical vasoconstrictors (e.g., brimonidine), corticosteroids and cold compresses [160].

The exception to this is tisotumab vedotin, where the severity of OAEs such as keratitis and corneal melt has led to recommendations for increased pre-treatment surveillance with prophylactic corticosteroids and vasoconstrictors [164, 178].

15 | Conclusion

Targeted therapies and immunotherapies have significantly improved outcomes across a broad range of malignancies but are increasingly associated with ocular adverse events (Mechanisms summarised in Table 4). While many toxicities are mild and self-limiting, a subset can be vision-threatening or indicate systemic immune dysregulation, necessitating early recognition and multidisciplinary management.

Close collaboration between oncologists and ophthalmologists is essential to balance ocular safety with the oncological benefits of therapy. Early ophthalmic assessment, patient education and standardised monitoring protocols are key to minimising morbidity while allowing continuation of life-prolonging treatment whenever possible.

Funding

The authors have nothing to report.

Conflicts of Interest

L.L.L. receives grant funding from Bayer and Roche paid to her institution and is a paid consultant for Roche and Novotech. She has also received speaker fees from Roche, Bayer, Abbvie, Kodiak Science, Novartis and Allergan. The other authors (M.R.D., Z.K.C., M.L.L.) declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1. S. Arora, T. Surakiatchanukul, T. Arora, et al., "Retinal Toxicities of Systemic Anticancer Drugs," *Survey of Ophthalmology* 67, no. 1 (2022): 97–148.
2. R. Boucher, O. Haigh, E. Barreau, et al., "Ocular Surface Toxicities Associated With Modern Anticancer Therapies," *Survey of Ophthalmology* 69, no. 2 (2024): 198–210.
3. B. H. Fortes, P. D. Taylor, and L. A. Dalvin, "Ocular Toxicity of Targeted Anticancer Agents," *Drugs* 81, no. 7 (2021): 771–823.
4. "Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (MedDRA 28.0)," Cancer Therapy Evaluation Program, Division of Cancer Therapy and Diagnosis, National Cancer Institute National Institutes of Health, U.S. Department of Health and Human Services, 2025.
5. A. Martens, P. P. Schauwvlieghe, A. Madoe, I. Casteels, and S. Aspeslagh, "Ocular Adverse Events Associated With Immune Checkpoint Inhibitors, a Scoping Review," *Journal of Ophthalmic Inflammation and Infection* 13, no. 1 (2023): 5.
6. F. S. Hodi, S. J. O'Day, D. F. McDermott, et al., "Improved Survival With Ipilimumab in Patients With Metastatic Melanoma," *New England Journal of Medicine* 363, no. 8 (2010): 711–723.
7. K. Y. Wu, Y. Yakobi, D. D. Gueorguieva, and É. Mazerolle, "Emerging Ocular Side Effects of Immune Checkpoint Inhibitors: A Comprehensive Review," *Biomedicine* 12, no. 11 (2024): 2547.
8. Q. Yin, L. Wu, L. Han, et al., "Immune-Related Adverse Events of Immune Checkpoint Inhibitors: A Review," *Frontiers in Immunology* 14 (2023): 1167975.
9. P. Iranzo, A. Callejo, J. D. Assaf, et al., "Overview of Checkpoint Inhibitors Mechanism of Action: Role of Immune-Related Adverse Events and Their Treatment on Progression of Underlying Cancer," *Frontiers in Medicine (Lausanne)* 9 (2022): 875974.
10. L. Spain, S. Diem, and J. Larkin, "Management of Toxicities of Immune Checkpoint Inhibitors," *Cancer Treatment Reviews* 44 (2016): 51–60.
11. J. M. Michot, C. Bigenwald, S. Champiat, et al., "Immune-Related Adverse Events With Immune Checkpoint Blockade: A Comprehensive Review," *European Journal of Cancer* 54 (2016): 139–148.
12. S. Kanji, S. Morin, K. Agtarap, et al., "Adverse Events Associated With Immune Checkpoint Inhibitors: Overview of Systematic Reviews," *Drugs* 82, no. 7 (2022): 793–809.
13. L. Quiruz, N. Yavari, B. Kikani, et al., "Ophthalmic Immune-Related Adverse Events and Association With Survival: Results From a Real-World Database," *American Journal of Ophthalmology* 268 (2024): 348–359.
14. K. Bitton, J. M. Michot, E. Barreau, et al., "Prevalence and Clinical Patterns of Ocular Complications Associated With Anti-PD-1/PD-L1 Anticancer Immunotherapy," *American Journal of Ophthalmology* 202 (2019): 109–117.
15. M. M. Sun, S. P. Kelly, B. S. A. L. Mylavarapu, et al., "Ophthalmic Immune-Related Adverse Events After Anti-CTLA-4 or PD-1 Therapy Recorded in the American Academy of Ophthalmology Intelligent Research in Sight Registry," *Ophthalmology* 128, no. 6 (2021): 910–919.
16. D. B. Johnson, C. A. Nebhan, J. J. Moslehi, and J. M. Balko, "Immune-Checkpoint Inhibitors: Long-Term Implications of Toxicity," *Nature Reviews. Clinical Oncology* 19, no. 4 (2022): 254–267.
17. L. Gan, H. Chen, X. Liu, and L. Zhang, "Ophthalmic Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors," *Frontiers in Immunology* 14 (2023): 1130238.
18. B. H. Fortes, H. Liou, and L. A. Dalvin, "Ophthalmic Adverse Effects of Immune Checkpoint Inhibitors: The Mayo Clinic Experience," *British Journal of Ophthalmology* 105, no. 9 (2021): 1263–1271.
19. A. M. M. Eggermont, M. Kicinski, C. U. Blank, et al., "Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial," *JAMA Oncology* 6, no. 4 (2020): 519–527.
20. R. Haliyur, S. G. Elner, T. Sassalos, S. Kodati, and M. W. Johnson, "Pathogenic Mechanisms of Immune Checkpoint Inhibitor (ICI)-Associated Retinal and Choroidal Adverse Reactions," *American Journal of Ophthalmology* 272 (2025): 8–18.
21. J. Hori, T. Yamaguchi, H. Keino, P. Hamrah, and K. Maruyama, "Immune Privilege in Corneal Transplantation," *Progress in Retinal and Eye Research* 72 (2019): 100758.
22. R. Caspi, "Autoimmunity in the Immune Privileged Eye: Pathogenic and Regulatory T Cells," *Immunologic Research* 42, no. 1–3 (2008): 41–50.
23. A. Inno, G. Metro, P. Bironzo, et al., "Pathogenesis, Clinical Manifestations and Management of Immune Checkpoint Inhibitors Toxicity," *Tumori* 103, no. 5 (2017): 405–421.
24. W. Yang, H. Li, P. W. Chen, et al., "PD-L1 Expression on Human Ocular Cells and Its Possible Role in Regulating Immune-Mediated Ocular Inflammation," *Investigative Ophthalmology & Visual Science* 50, no. 1 (2009): 273–280.
25. F. Graus and J. Dalmau, "Paraneoplastic Neurological Syndromes in the Era of Immune-Checkpoint Inhibitors," *Nature Reviews. Clinical Oncology* 16, no. 9 (2019): 535–548.
26. P. Sarkar, A. Mehtani, H. C. Gandhi, J. S. Bhalla, and S. Tapariya, "Paraneoplastic Ocular Syndrome: A Pandora's Box of Underlying Malignancies," *Eye (London, England)* 36, no. 7 (2022): 1355–1367.
27. O. Shahzad, N. Thompson, G. Clare, S. Welsh, E. Damato, and P. Corrie, "Ocular Adverse Events Associated With Immune Checkpoint Inhibitors: A Novel Multidisciplinary Management Algorithm," *Therapeutic Advances in Medical Oncology* 13 (2021): 1758835921992989.
28. Y. W. Zhou, Q. Xu, Y. Wang, R. L. Xia, J. Y. Liu, and X. L. Ma, "Immune Checkpoint Inhibitor-Associated Ophthalmic Adverse Events: Current Understanding of Its Mechanisms, Diagnosis, and Management," *International Journal of Ophthalmology* 15, no. 4 (2022): 646–656.
29. J. H. Francis, K. Jaben, B. D. Santomasso, et al., "Immune Checkpoint Inhibitor-Associated Optic Neuritis," *Ophthalmology* 127, no. 11 (2020): 1585–1589.
30. E. L. Chang, R. Liu, K. Keyhanian, et al., "Consensus Disease Definitions for Ophthalmic Immune-Related Adverse Events of Immune Checkpoint Inhibitors," *Journal for Immunotherapy of Cancer* 13, no. 4 (2025): e011049.
31. D. B. Johnson, S. Chandra, and J. A. Sosman, "Immune Checkpoint Inhibitor Toxicity in 2018," *Journal of the American Medical Association* 320, no. 16 (2018): 1702–1703.
32. O. Abdel-Rahman, H. Oweira, U. Petrusch, et al., "Immune-Related Ocular Toxicities in Solid Tumor Patients Treated With Immune Checkpoint Inhibitors: A Systematic Review," *Expert Review of Anticancer Therapy* 17, no. 4 (2017): 387–394.
33. J. Weber, G. Gibney, R. Kudchadkar, et al., "Phase I/II Study of Metastatic Melanoma Patients Treated With Nivolumab Who Had Progressed After Ipilimumab," *Cancer Immunology Research* 4, no. 4 (2016): 345–353.

34. A. T. Nguyen, M. Elia, M. A. Materin, M. Sznol, and J. Chow, "Cyclosporine for Dry Eye Associated With Nivolumab: A Case Progressing to Corneal Perforation," *Cornea* 35, no. 3 (2016): 399–401.
35. J. M. Kim, M. A. Materin, M. Sznol, et al., "Ophthalmic Immune-Related Adverse Events of Immunotherapy: A Single-Site Case Series," *Ophthalmology* 126, no. 7 (2019): 1058–1062.
36. N. J. Maloney, V. Ravi, K. Cheng, D. Q. Bach, and S. Worswick, "Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis-Like Reactions to Checkpoint Inhibitors: A Systematic Review," *International Journal of Dermatology* 59, no. 6 (2020): e183–e188.
37. L. Zimmer, S. M. Goldinger, L. Hofmann, et al., "Neurological, Respiratory, Musculoskeletal, Cardiac and Ocular Side-Effects of Anti-PD-1 Therapy," *European Journal of Cancer* 60 (2016): 210–225.
38. R. S. Moorthy, M. S. Moorthy, and E. T. Cunningham, Jr., "Drug-Induced Uveitis," *Current Opinion in Ophthalmology* 29, no. 6 (2018): 588–603.
39. P. Ramtohul and K. B. Freund, "Clinical and Morphological Characteristics of Anti-Programmed Death Ligand 1-Associated Retinopathy: Expanding the Spectrum of Acute Macular Neuroretinopathy," *Ophthalmology Retina* 4, no. 4 (2020): 446–450.
40. L. A. Emens, S. L. Davis, S. C. N. Oliver, et al., "Association of Cancer Immunotherapy With Acute Macular Neuroretinopathy and Diffuse Retinal Venulitis," *JAMA Ophthalmology* 137, no. 1 (2019): 96–100.
41. J. Crews, A. Agarwal, L. Jack, D. Xu, D. V. Do, and Q. D. Nguyen, "Ipilimumab-Associated Retinopathy," *Ophthalmic Surgery, Lasers & Imaging Retina* 46, no. 6 (2015): 658–660.
42. E. Tsui, A. Madu, I. Belinsky, L. A. Yannuzzi, K. B. Freund, and Y. S. Modi, "Combination Ipilimumab and Nivolumab for Metastatic Melanoma Associated With Ciliochoroidal Effusion and Exudative Retinal Detachment," *JAMA Ophthalmology* 135, no. 12 (2017): 1455–1457.
43. D. Braun, D. Getahun, V. Y. Chiu, et al., "Population-Based Frequency of Ophthalmic Adverse Events in Melanoma, Other Cancers, and After Immune Checkpoint Inhibitor Treatment," *American Journal of Ophthalmology* 224 (2021): 282–291.
44. M. Garibaldi, F. Calabrò, G. Merlonghi, et al., "Immune Checkpoint Inhibitors (ICIs)-Related Ocular Myositis," *Neuromuscular Disorders* 30, no. 5 (2020): 420–423.
45. J. R. Brahmer, C. Lacchetti, B. J. Schneider, et al., "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline," *Journal of Clinical Oncology* 36, no. 17 (2018): 1714–1768.
46. M. Jiang, Y. Hu, G. Lin, and C. Chen, "Dosing Regimens of Immune Checkpoint Inhibitors: Attempts at Lower Dose, Less Frequency, Shorter Course," *Frontiers in Oncology* 12 (2022): 906251.
47. E. R. Dow, M. Yung, and E. Tsui, "Immune Checkpoint Inhibitor-Associated Uveitis: Review of Treatments and Outcomes," *Ocular Immunology and Inflammation* 29, no. 1 (2021): 203–211.
48. J. Yuan, X. Dong, J. Yap, and J. Hu, "The MAPK and AMPK Signalings: Interplay and Implication in Targeted Cancer Therapy," *Journal of Hematology & Oncology* 13, no. 1 (2020): 113.
49. Y.-J. Guo, W.-W. Pan, S.-B. Liu, Z.-F. Shen, Y. Xu, and L.-L. Hu, "ERK/MAPK Signalling Pathway and Tumorigenesis," *Experimental and Therapeutic Medicine* 19, no. 3 (2020): 1997–2007.
50. R. van der Noll, S. Leijen, G. H. Neuteboom, J. H. Beijnen, and J. H. Schellens, "Effect of Inhibition of the FGFR-MAPK Signaling Pathway on the Development of Ocular Toxicities," *Cancer Treatment Reviews* 39, no. 6 (2013): 664–672.
51. A. Akinleye, M. Furqan, N. Mukhi, P. Ravella, and D. Liu, "MEK and the Inhibitors: From Bench to Bedside," *Journal of Hematology & Oncology* 6, no. 1 (2013): 27.
52. V. Subbiah, C. Baik, and J. M. Kirkwood, "Clinical Development of BRAF Plus MEK Inhibitor Combinations," *Trends Cancer* 6, no. 9 (2020): 797–810.
53. C. Mettler, D. Monnet, N. Kramkimel, et al., "Ocular Safety Profile of BRAF and MEK Inhibitors: Data From the World Health Organization Pharmacovigilance Database," *Ophthalmology* 128, no. 12 (2021): 1748–1755.
54. S. Méndez-Martínez, P. Calvo, O. Ruiz-Moreno, et al., "Ocular Adverse Events Associated With MEK Inhibitors," *Retina* 39, no. 8 (2019): 1435–1450.
55. M. L. Weber, M. C. Liang, K. T. Flaherty, and J. S. Heier, "Subretinal Fluid Associated With MEK Inhibitor Use in the Treatment of Systemic Cancer," *JAMA Ophthalmology* 134, no. 8 (2016): 855–862.
56. U. Urner-Bloch, M. Urner, N. Jaberg-Bentele, A. Frauchiger, R. Dummer, and S. Goldinger, "MEK Inhibitor-Associated Retinopathy (MEKAR) in Metastatic Melanoma: Long-Term Ophthalmic Effects," *European Journal of Cancer* 65 (2016): 130–138.
57. Q. Jiang, C. Cao, S. Lu, et al., "MEK/ERK Pathway Mediates UVB-Induced AQP1 Downregulation and Water Permeability Impairment in Human Retinal Pigment Epithelial Cells," *International Journal of Molecular Medicine* 23, no. 6 (2009): 771–777.
58. J. H. Francis, L. A. Habib, D. H. Abramson, et al., "Clinical and Morphologic Characteristics of MEK Inhibitor-Associated Retinopathy: Differences From Central Serous Chorioretinopathy," *Ophthalmology* 124, no. 12 (2017): 1788–1798.
59. J. R. Chancellor, D. A. Kilgore, A. B. Sallam, R. C. Allen, and S. H. Uwaydat, "A Case of Non-Resolving MEK Inhibitor-Associated Retinopathy," *Case Reports in Ophthalmology* 10, no. 3 (2019): 334–338.
60. K. W. Jeng-Miller, M. A. Miller, and J. S. Heier, "Ocular Effects of MEK Inhibitor Therapy: Literature Review, Clinical Presentation, and Best Practices for Mitigation," *Oncologist* 29, no. 5 (2024): e616–e21.
61. T. Fujimura, Y. Kambayashi, K. Tanita, et al., "HLA-DRB1*04:05 in Two Cases of Vogt-Koyanagi-Harada Disease-Like Uveitis Developing From an Advanced Melanoma Patient Treated by Sequential Administration of Nivolumab and Dabrafenib/Trametinib Therapy," *Journal of Dermatology* 45, no. 6 (2018): 735–737.
62. C. H. Choe, G. A. McArthur, I. Caro, J. H. Kempen, and R. K. Amaravadi, "Ocular Toxicity in BRAF Mutant Cutaneous Melanoma Patients Treated With Vemurafenib," *American Journal of Ophthalmology* 158, no. 4 (2014): 831–837.e2.
63. J. H. Francis, J. Canestraro, and D. H. Abramson, "Re: Thibault Et al.: Drug-Induced Uveitis Related to Checkpoint Inhibitors and MAP-Kinase Inhibitors (Ophthalmology. 2024; 131: 249–251)," *Ophthalmology* 131, no. 7 (2024): e31–e2.
64. H. Jung, S. Kim, C. S. Lee, et al., "Real-World Incidence of Incident Noninfectious Uveitis in Patients Treated With BRAF Inhibitors: A Nationwide Clinical Cohort Study," *American Journal of Ophthalmology* 267 (2024): 142–152.
65. E. Whist, R. J. Symes, J. H. Chang, et al., "Uveitis Caused by Treatment for Malignant Melanoma: A Case Series," *Retinal Cases and Brief Reports* 15, no. 6 (2021): 718–723.
66. S. Thureau, H. Engelke, P. McCluskey, et al., "Uveitis in Tumor Patients Treated With Immunological Checkpoint- and Signal Transduction Pathway-Inhibitors," *Ocular Immunology and Inflammation* 30, no. 7–8 (2022): 1588–1594.
67. D. Draganova, J. Kerger, L. Caspers, and F. Willermain, "Severe Bilateral Panuveitis During Melanoma Treatment by Dabrafenib and Trametinib," *Journal of Ophthalmic Inflammation and Infection* 5, no. 1 (2015): 17.
68. G. C. Albertini, E. Corbelli, M. Battaglia Parodi, and F. Bandello, "Choroidal Neovascularization in Multifocal Choroiditis After

- Dabrafenib and Trametinib,” *European Journal of Ophthalmology* 27, no. 6 (2017): e184-e6.
69. M. Brambati, C. Giuffrè, A. Marchese, F. Bandello, G. M. Modorati, and E. Miserocchi, “A Case of Vogt-Koyanagi-Harada-Like Uveitis Secondary to Dabrafenib/Trametinib Therapy for Advanced Melanoma,” *European Journal of Ophthalmology* 32, no. 1 (2022): NP109–NP113.
70. A. Niro, N. Recchimurzo, A. Sborgia, M. Guida, and G. Alessio, “Bilateral Ischemic Retinal Vasculitis in Metastatic Cutaneous Melanoma Patient Treated With Dabrafenib and Trametinib: A Case Report,” *Ocular Immunology and Inflammation* 26, no. 5 (2018): 783–785.
71. C. Robert, B. Karaszewska, J. Schachter, et al., “Improved Overall Survival in Melanoma With Combined Dabrafenib and Trametinib,” *New England Journal of Medicine* 372, no. 1 (2015): 30–39.
72. N. Stjepanovic, J. Velazquez-Martin, and P. Bedard, “Ocular Toxicities of MEK Inhibitors and Other Targeted Therapies,” *Annals of Oncology* 27, no. 6 (2016): 998–1005.
73. S. J. Welsh and P. G. Corrie, “Management of BRAF and MEK Inhibitor Toxicities in Patients With Metastatic Melanoma,” *Therapeutic Advances in Medical Oncology* 7, no. 2 (2015): 122–136.
74. A. Weaver and J. B. Bossaer, “Fibroblast Growth Factor Receptor (FGFR) Inhibitors: A Review of a Novel Therapeutic Class,” *Journal of Oncology Pharmacy Practice* 27, no. 3 (2021): 702–710.
75. J. Hsu, J. H. Francis, and S. Ahmad, “Ocular Toxicities of Fibroblast Growth Factor Receptor Inhibitors: A Review,” *Survey of Ophthalmology* 69, no. 1 (2024): 34–41.
76. A. Deutsch and B. N. McLellan, “Severe Onycholysis and Eyelash Trichomegaly in a Patient Treated With Erdafitinib,” *JAAD Case Reports* 6, no. 6 (2020): 569–571.
77. J. H. Francis, J. J. Harding, A. M. Schram, et al., “Clinical and Morphologic Characteristics of Fibroblast Growth Factor Receptor Inhibitor-Associated Retinopathy,” *JAMA Ophthalmology* 139, no. 10 (2021): 1126–1130.
78. J. Hsu, L. Dixit, V. Jhanji, and S. Ahmad, “Corneal Melt Associated With Cancer Immunotherapy,” *Cornea Open* 2, no. 1 (2023): e0005.
79. G. Bauters, M. Paques, V. Borderie, and N. Bouheraoua, “Reversible Corneal Stromal Thinning, Acute-Onset White Cataract and Angle-Closure Glaucoma due to Erdafitinib, a Fibroblast Growth Factor Receptor Inhibitor: Report of Three Cases,” *Journal Français d’Ophtalmologie* 44, no. 1 (2021): 67–75.
80. Z. A. Wainberg, P. C. Enzinger, Y.-K. Kang, et al., “Bemarituzumab in Patients With FGFR2b-Selected Gastric or Gastro-Oesophageal Junction Adenocarcinoma (FIGHT): A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Study,” *Lancet Oncology* 23, no. 11 (2022): 1430–1440.
81. J. W. F. Catto, B. Tran, M. Rouprêt, et al., “Erdafitinib in BCG-Treated High-Risk Non-Muscle-Invasive Bladder Cancer,” *Annals of Oncology* 35, no. 1 (2024): 98–106.
82. Y. Lorient, N. Matsubara, S. H. Park, et al., “Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma,” *New England Journal of Medicine* 389, no. 21 (2023): 1961–1971.
83. A. O. Siefker-Radtke, N. Matsubara, S. H. Park, et al., “Erdafitinib Versus Pembrolizumab in Pretreated Patients With Advanced or Metastatic Urothelial Cancer With Select FGFR Alterations: Cohort 2 of the Randomized Phase III THOR Trial☆,” *Annals of Oncology* 35, no. 1 (2024): 107–117.
84. O. Alekseev, E. Ojuok, and S. Cousins, “Multifocal Serous Retinopathy With Pemigatinib Therapy for Metastatic Colon Adenocarcinoma,” *International Journal of Retina and Vitreous* 7, no. 1 (2021): 34.
85. M. T. Magone, I. R. Hartley, E. Fitzgibbon, et al., “Ocular Adverse Effects of Infigratinib, a New Fibroblast Growth Factor Receptor Tyrosine Kinase Inhibitor,” *Ophthalmology* 128, no. 4 (2020): 624.
86. C. Prenskey, E. Marlow, M. Gupta, C. Sales, S. Kiss, and D. J. D’Amico, “Reversible Macular Lesions in the Setting of Oral Pan-Fibroblast Growth Factor Inhibitor for the Treatment of Bladder Cancer,” *Journal of VitreoRetinal Diseases* 2, no. 2 (2018): 111–114.
87. J. H. Francis, J. Canestraro, D. Haggag-Lindgren, et al., “Clinical and Morphologic Characteristics of Extracellular Signal-Regulated Kinase Inhibitor-Associated Retinopathy,” *Ophthalmology Retina* 5, no. 12 (2021): 1187–1195.
88. A. Ayati, S. Moghimi, S. Salarinejad, M. Safavi, B. Pouramiri, and A. Foroumadi, “A Review on Progression of Epidermal Growth Factor Receptor (EGFR) Inhibitors as an Efficient Approach in Cancer Targeted Therapy,” *Bioorganic Chemistry* 99 (2020): 103811.
89. A. B. Tullo, B. Esmaeli, P. Murray, E. Bristow, B. Forsythe, and K. Faulkner, “Ocular Findings in Patients With Solid Tumours Treated With the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Gefitinib (Iressa, ZD1839) in Phase I and II Clinical Trials,” *Eye* 19, no. 7 (2005): 729–738.
90. P. R. Cohen, S. M. Escudier, and R. Kurzrock, “Cetuximab-Associated Elongation of the Eyelashes: Case Report and Review of Eyelash Trichomegaly Secondary to Epidermal Growth Factor Receptor Inhibitors,” *American Journal of Clinical Dermatology* 12, no. 1 (2011): 63–67.
91. E. Roé, M. P. G. Muret, E. Marcuello, J. Capdevila, C. Pallarés, and A. Alomar, “Description and Management of Cutaneous Side Effects During Cetuximab or Erlotinib Treatments: A Prospective Study of 30 Patients,” *Journal of the American Academy of Dermatology* 55, no. 3 (2006): 429–437.
92. M. Tamura, Y. Takai, S. Nakamura, and A. Ohira, “A Case Report of Pseudo-Exfoliation Syndrome With Prolonged Corneal Epithelial Regeneration Because of Erlotinib-Induced Unilateral Corneal Ulcer and Anterior Uveitis,” *Acta Ophthalmologica* 98, no. 8 (2020): e1055–e1056.
93. T. Celik and M. Kosker, “Ocular Side Effects and Trichomegaly of Eyelashes Induced by Erlotinib: A Case Report and Review of the Literature,” *Contact Lens & Anterior Eye* 38, no. 1 (2015): 59–60.
94. A. Saint-Jean, M. S. de la Maza, M. Morral, et al., “Ocular Adverse Events of Systemic Inhibitors of the Epidermal Growth Factor Receptor: Report of 5 Cases,” *Ophthalmology* 119, no. 9 (2012): 1798–1802.
95. N. L. Spector and K. L. Blackwell, “Understanding the Mechanisms Behind Trastuzumab Therapy for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer,” *Journal of Clinical Oncology* 27, no. 34 (2009): 5838–5847.
96. M. Marty, F. Cognetti, D. Maraninchi, et al., “Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered as First-Line Treatment: The M77001 Study Group,” *Journal of Clinical Oncology* 23, no. 19 (2005): 4265–4274.
97. H. A. Burris, 3rd, H. S. Rugo, S. J. Vukelja, et al., “Phase II Study of the Antibody Drug Conjugate Trastuzumab-DM1 for the Treatment of Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer After Prior HER2-Directed Therapy,” *Journal of Clinical Oncology* 29, no. 4 (2011): 398–405.
98. K. P. Xu, A. Riggs, Y. Ding, and F. S. Yu, “Role of ErbB2 in Corneal Epithelial Wound Healing,” *Investigative Ophthalmology & Visual Science* 45, no. 12 (2004): 4277–4283.
99. M. Untch, M. Rezai, S. Loibl, et al., “Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer: Results From the GeparQuattro Study,” *Journal of Clinical Oncology* 28, no. 12 (2010): 2024–2031.

100. A. Orlandi, R. Fasciani, A. Cassano, et al., "Trastuzumab-Induced Corneal Ulceration: Successful No-Drug Treatment of a "Blind" Side Effect in a Case Report," *BMC Cancer* 15, no. 1 (2015): 973.
101. D. Peeters, M. Vereecken, H. Denys, and D. Roels, "A Case of Corneal Melting in a Patient With HER2-Positive Breast Cancer," *Case Reports in Ophthalmology* 13, no. 3 (2022): 1036–1041.
102. D. Barmas-Alamdari, H. Chaudhary, E. Baghdasaryan, P. Dua, and I. Cheela, "Trastuzumab-Induced Early Corneal Melt in HER2-Positive Breast Cancer: A Case Report and Review," *American Journal of Case Reports* 25 (2024): e945488.
103. H. Chen, G. Yang, and J. Ma, "Ocular Toxicity Associated With Anti-HER2 Agents in Breast Cancer: A Pharmacovigilance Analysis Using the FAERS Database," *International Journal of Cancer* 154, no. 9 (2024): 1616–1625.
104. K. Mao, P. Chen, H. Sun, S. Zhong, H. Zheng, and L. Xu, "Ocular Adverse Events Associated With Antibody-Drug Conjugates in Oncology: A Pharmacovigilance Study Based on FDA Adverse Event Reporting System (FAERS)," *Frontiers in Pharmacology* 15 (2024): 1425617.
105. T. Wen, J. Wang, Y. Shi, H. Qian, and P. Liu, "Inhibitors Targeting Bruton's Tyrosine Kinase in Cancers: Drug Development Advances," *Leukemia* 35, no. 2 (2021): 312–332.
106. A. L. Chaudhry, P. Chévez-Barrios, and P. Strati, "Zanubrutinib Is Active for the Treatment of Relapsed Primary Vitreoretinal Lymphoma," *Leukemia & Lymphoma* 66 (2025): 2316–2319.
107. L. Wang, W. Guan, and X. Peng, "Targeting Bruton Tyrosine Kinase With Zanubrutinib for Treatment of Vitreoretinal Lymphoma: Report of 3 Cases," *Frontiers in Oncology* 11 (2021): 676792.
108. A. L. Kunkler, E. M. Binkley, D. Mantopoulos, et al., "Known and Novel Ocular Toxicities of Biologics, Targeted Agents, and Traditional Chemotherapeutics," *Graefes' Archive for Clinical and Experimental Ophthalmology* 257, no. 8 (2019): 1771–1781.
109. S. P. Mirgh, R. Ahmed, N. Agrawal, et al., "Knowing the Flip Side of the Coin: Ibrutinib Associated Cystoid Macular Edema," *Indian Journal of Hematology and Blood Transfusion* 36, no. 1 (2020): 208–210.
110. Z. K. Chiu, J. K. Goh, C. Ling, M. L. Lin, and A. J. Hall, "Ibrutinib-Related Uveitis: A Case Series," *American Journal of Ophthalmology Case Reports* 25 (2022): 101300.
111. M. Bohn, L. Bravo-Ljubetic, R. W. J. Lee, and H. Petrushkin, "Ibrutinib-Related Uveitis: A Report of Two Severe Cases," *European Journal of Ophthalmology* 32, no. 4 (2022): Np94–Np97.
112. H. Ibrahim, C. S. Chean, A. J. M. Kalakonda, et al., "Ibrutinib-Related Uveitis: A Case Series From Two Tertiary Centres in the United Kingdom," *Ocular Immunology and Inflammation* 32, no. 10 (2024): 2583–2588.
113. R. Ben-Avi, D. Dori, and I. Chowers, "Cystoid Macular Edema Secondary to Ibrutinib," *American Journal of Ophthalmology Case Reports* 26 (2022): 101436.
114. M. Saenz-de-Viteri and T. Cudrnak, "Bilateral Cystoid Macular Edema in a Patient With Chronic Lymphocytic Leukemia Treated With Ibrutinib," *Leukemia & Lymphoma* 60, no. 3 (2019): 842–844.
115. J. A. Dubovsky, K. A. Beckwith, G. Natarajan, et al., "Ibrutinib Is an Irreversible Molecular Inhibitor of ITK Driving a Th1-Selective Pressure in T Lymphocytes," *Blood* 122, no. 15 (2013): 2539–2549.
116. J. Series, C. Garcia, M. Levade, et al., "Differences and Similarities in the Effects of Ibrutinib and Acalabrutinib on Platelet Functions," *Haematologica* 104, no. 11 (2019): 2292–2299.
117. M. L. Wang, K. A. Blum, P. Martin, et al., "Long-Term Follow-Up of MCL Patients Treated With Single-Agent Ibrutinib: Updated Safety and Efficacy Results," *Blood* 126, no. 6 (2015): 739–745.
118. W. K. Alsarhani, S. AlShaker, M. Lichter, and C. C. Chan, "Spontaneous Hyphema in a Patient Receiving Acalabrutinib," *Canadian Journal of Ophthalmology* 58, no. 5 (2023): e211–e213.
119. X. Zhang, R. Dai, C. Zhao, and M. Zhang, "Case Report: Intraocular Hemorrhage in a Primary Vitreoretinal Lymphoma Patient Treated With Zanubrutinib," *Frontiers in Medicine* 9 (2022): 833565.
120. C. Negotei, A. Colita, I. Mitu, et al., "A Review of FLT3 Kinase Inhibitors in AML," *Journal of Clinical Medicine* 12, no. 20 (2023): 6429.
121. F. T. Fraunfelder and F. W. Fraunfelder, "Oral Anti-Vascular Endothelial Growth Factor Drugs and Ocular Adverse Events," *Journal of Ocular Pharmacology and Therapeutics* 34, no. 6 (2018): 432–435.
122. S. Szczepanik and D. Kecik, "Bilateral Central Retinal Vein Occlusion in A Patient With Disseminated Metastatic Renal Cell Carcinoma Treated With SORAFENIB," *Retinal Cases and Brief Reports* 6, no. 2 (2012): 148–150.
123. Z. Y. Li, X. X. Fan, Y. J. Wang, et al., "Metastatic Renal Cell Carcinoma: The First Report of Unilateral Fundus Hemorrhage Induced by Sorafenib," *Oncotarget* 7, no. 23 (2016): 35181–35187.
124. M. Luo, L. Sun, R. Dai, Y. Chen, and C. Wu, "Central Retinal Vein Occlusion in Patients With Metastatic Solid Tumors on Tyrosine Kinase Inhibitors: A Report of Case Series and Literature Review," *Frontiers in Medicine* 11 (2024): 1362108.
125. G. Schwartzman, M. J. Wagner, C. M. Zobniw, V. A. Trinh, S. Patel, and N. Somaiah, "An Unusual Case of Central Retinal Vein Occlusion and Review of the Toxicity Profile of Regorafenib in GIST Patients," *Current Oncology Reports* 18, no. 8 (2016): 49.
126. A. Wegner and R. Khoramnia, "Neurosensory Retinal Detachment due to Sunitinib Treatment," *Eye (London, England)* 25, no. 11 (2011): 1517–1518.
127. M. C. S. van Olden, Y. de Jong-Hesse, T. Vollebregt, S. de Groot, S. A. C. Luelmo, and M. Marinkovic, "Vogt-Koyanagi-Harada-Like Disease With Loss of Visual Acuity due to Sunitinib Treatment Restored After Switch in Therapy: A Case Report," *Case Reports in Ophthalmology* 15, no. 1 (2024): 184–188.
128. S. Na and T. Kim, "Optic Neuritis Associated With Sunitinib," *Neurological Sciences* 42, no. 3 (2021): 1165–1167.
129. J. Yoong, G. Chong, and K. Hamilton, "Bilateral Papilledema on Sunitinib Therapy for Advanced Renal Cell Carcinoma," *Medical Oncology (Northwood, London, England)* 28, no. Suppl 1 (2011): S395–S397.
130. T. Shammass, M. N. Peiris, A. N. Meyer, and D. J. Donoghue, "BCR-ABL: The Molecular Mastermind Behind Chronic Myeloid Leukemia," *Cytokine & Growth Factor Reviews* 83 (2025): 45–58.
131. J. Huang, J. Cai, Q. Ye, Q. Jiang, H. Lin, and L. Wu, "Fluid Retention-Associated Adverse Events in Patients Treated With BCR::ABL1 Inhibitors Based on FDA Adverse Event Reporting System (FAERS): A Retrospective Pharmacovigilance Study," *BMJ Open* 13, no. 8 (2023): e071456.
132. M. Breccia, F. Gentilini, L. Cannella, et al., "Ocular Side Effects in Chronic Myeloid Leukemia Patients Treated With Imatinib," *Leukemia Research* 32, no. 7 (2008): 1022–1025.
133. M. Gemelli, E. M. Elli, C. Elena, et al., "Use of Generic Imatinib as First-Line Treatment in Patients With Chronic Myeloid Leukemia (CML): The GIMS (Glivec to Imatinib Switch) Study," *Blood Research* 55, no. 3 (2020): 139–145.
134. F. W. Fraunfelder, J. Solomon, B. J. Druker, B. Esmaeli, and J. Kuyl, "Ocular Side-Effects Associated With Imatinib Mesylate (Gleevec)," *Journal of Ocular Pharmacology and Therapeutics* 19, no. 4 (2003): 371–375.
135. K. Govind Babu, V. S. S. Attili, P. Bapsy, and G. Anupama, "Imatinib-Induced Optic Neuritis in a Patient of Chronic Myeloid Leukemia," *International Ophthalmology* 27, no. 1 (2007): 43–44.

136. M. Napolitano, M. Santoro, S. Mancuso, et al., "Late Onset of Unilateral Optic Disk Edema Secondary to Treatment With Imatinib Mesylate," *Clinical Case Reports* 5, no. 10 (2017): 1573.
137. S.-I. Kwon, D.-H. Lee, and Y.-J. Kim, "Optic Disc Edema as a Possible Complication of Imatinib Mesylate (Gleevec)," *Japanese Journal of Ophthalmology* 52, no. 4 (2008): 331–333.
138. K. S. Monge, A. Gálvez-Ruiz, A. Álvarez-Carrón, C. Quijada, and A. Matheu, "Optic Neuropathy Secondary to Dasatinib in the Treatment of a Chronic Myeloid Leukemia Case," *Saudi Journal of Ophthalmology* 29, no. 3 (2015): 227.
139. F. Yilmaz, M. Albayrak, P. Tığlıoğlu, et al., "Vitreous Hemorrhage: A Rare Ophthalmic Adverse Effect due to Imatinib Treatment," *Journal of Oncology Pharmacy Practice* 28, no. 3 (2022): 725–728.
140. H. A. Teive, F. M. Germiniani, R. P. Munhoz, and C. H. F. Camargo, "Blepharospasm and Periorbital Edema After Imatinib Mesylate: Improvement With Botulinum Toxin," *Arquivos de Neuro-Psiquiatria* 78, no. 1 (2020): 58–59.
141. B. O. Ugurlu and U. Y. Malkan, "Periorbital Edema and Phototoxic Rash Associated With Dasatinib: A Case Report," *SAGE Open Medical Case Reports* 13 (2025): 2050313X251330969.
142. D. B. Roth, S. Akbari, and A. Rothstein, "Macular Ischemia Associated With Imatinib Mesylate Therapy for Chronic Myeloid Leukemia," *Retinal Cases and Brief Reports* 3, no. 2 (2009): 161–164.
143. D. C. Moore, A. Muslimani, and P. Sinclair, "Nilotinib-Induced Ocular Toxicity: A Case Report," *American Journal of Therapeutics* 25, no. 5 (2018): e570-e1.
144. B. Esmaeli, V. G. Prieto, C. E. Butler, et al., "Severe Periorbital Edema Secondary to STI571 (Gleevec)," *Cancer* 95, no. 4 (2002): 881–887.
145. H. Rafei, E. J. Jabbour, H. Kantarjian, et al., "Neurotoxic Events Associated With BCR-ABL1 Tyrosine Kinase Inhibitors: A Case Series," *Leukemia & Lymphoma* 60, no. 13 (2019): 3292–3295.
146. D. L. Rotstein, K. Sawicka, A. Bharatha, X. Montalban, and J. H. Lipton, "CNS Demyelination After Initiating the Tyrosine Kinase Inhibitor Imatinib: A Report of Two Cases," *Multiple Sclerosis Journal* 26, no. 9 (2020): 1121–1124.
147. C. Gridelli, S. Peters, A. Sgambato, F. Casaluce, A. A. Adjei, and F. Ciardiello, "ALK Inhibitors in the Treatment of Advanced NSCLC," *Cancer Treatment Reviews* 40, no. 2 (2014): 300–306.
148. H. Zhang, Y. Song, F. Xia, et al., "Adverse Event Profile of Crizotinib in Real-World From the FAERS Database: A 12-Year Pharmacovigilance Study," *BMC Pharmacology and Toxicology* 26, no. 1 (2025): 61.
149. D. R. Camidge, Y.-J. Bang, E. L. Kwak, et al., "Activity and Safety of Crizotinib in Patients With ALK-Positive Non-Small-Cell Lung Cancer: Updated Results From a Phase 1 Study," *Lancet Oncology* 13, no. 10 (2012): 1011–1019.
150. S. Peters, D. R. Camidge, A. T. Shaw, et al., "Alectinib Versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 377, no. 9 (2017): 829–838.
151. E. L. Kwak, Y.-J. Bang, D. R. Camidge, et al., "Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 363, no. 18 (2010): 1693–1703.
152. M. Iseki, T. Kaburaki, M. Aihara, and H. Sawamura, "Late-Onset Ocular Toxicity Presenting as Uveitis Caused by Crizotinib," *Neuro-Ophthalmology* 46, no. 1 (2022): 44–49.
153. J. Das and N. Das, "Chronic Conjunctival Chemosis—A New Ocular Side Effect of Crizotinib," *Ophthalmic Plastic and Reconstructive Surgery* 37, no. 1 (2021): e18-e21.
154. N. Dincer, O. Can, G. Demir, and E. Ozyar, "Lorlatinib-Induced Blindness: A Rare Entity," *Practical Radiation Oncology* 15, no. 2 (2025): 120–123.
155. A. W. Kong, A. R. Engelmann, M. Hosseini, and L. Bonelli, "Bilateral Optic Neuropathy Associated With Lorlatinib Monotherapy for ALK-Positive Metastatic Lung Adenocarcinoma," *American Journal of Ophthalmology Case Reports* 34 (2024): 102063.
156. S. G. Chun, P. Iyengar, D. E. Gerber, R. N. Hogan, and R. D. Timmerman, "Optic Neuropathy and Blindness Associated With Crizotinib for Non-Small-Cell Lung Cancer With EML4-ALK Translocation," *Journal of Clinical Oncology* 33, no. 5 (2015): e25-e6.
157. T. Ishii, S. Iwasawa, R. Kurimoto, A. Maeda, Y. Takiguchi, and M. Kaneda, "Crizotinib-Induced Abnormal Signal Processing in the Retina," *PLoS One* 10, no. 8 (2015): e0135521.
158. B. J. Solomon, E. E. Kim, M. Winter, et al., "Ophthalmological Assessment of Crizotinib in Advanced Non-Small-Cell Lung Cancer," *Lung Cancer* 145 (2020): 167–172.
159. S. Lonial, H. C. Lee, A. Badros, et al., "Belantamab Mafodotin for Relapsed or Refractory Multiple Myeloma (DREAMM-2): A Two-Arm, Randomised, Open-Label, Phase 2 Study," *Lancet Oncology* 21, no. 2 (2020): 207–221.
160. E. S. Lindgren, R. Yan, O. Cil, et al., "Incidence and Mitigation of Corneal Pseudomicrocysts Induced by Antibody–Drug Conjugates (ADCs)," *Current Ophthalmology Reports* 12, no. 2 (2024): 13–22.
161. "Australian Product Information - Padcev™ (Enfortumab Vedotin) [Internet]," 2025, Astellas Pharma Australia, <https://www.tga.gov.au/sites/default/files/2023-03/auspar-padcev-230227-pi.pdf>.
162. H. Chen, G. He, J. Huang, L. Hu, and J. Ma, "Ocular Adverse Events Associated With Antibody-Drug Conjugates: A Comprehensive Pharmacovigilance Analysis," *Frontiers in Immunology* 15 (2024): 1495137.
163. C. Peters and S. Brown, "Antibody–Drug Conjugates as Novel Anti-Cancer Chemotherapeutics," *Bioscience Reports* 35, no. 4 (2015): e00225.
164. R. F. Marshall, H. Xu, and M. Berkenstock, "Ocular Toxicities Associated With Antibody Drug Conjugates," *Current Opinion in Ophthalmology* 35, no. 6 (2024): 494–498.
165. K. Yonemori, Y. Kuboki, K. Hasegawa, et al., "Tisotumab Vedotin in Japanese Patients With Recurrent/Metastatic Cervical Cancer: Results From the innovaTV 206 Study," *Cancer Science* 113, no. 8 (2022): 2788–2797.
166. H. Donaghy, ed., "Effects of Antibody, Drug and Linker on the Preclinical and Clinical Toxicities of Antibody-Drug Conjugates," in *MAbs* (Taylor & Francis, 2016).
167. J. C. Masters, D. J. Nickens, D. Xuan, R. L. Shazer, and M. Amantea, "Clinical Toxicity of Antibody Drug Conjugates: A Meta-Analysis of Payloads," *Investigational New Drugs* 36, no. 1 (2018): 121–135.
168. R. L. Coleman, D. Lorusso, C. Gennigens, et al., "Efficacy and Safety of Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer (innovaTV 204/GOG-3023/ENGOT-cx6): A Multicentre, Open-Label, Single-Arm, Phase 2 Study," *Lancet Oncology* 22, no. 5 (2021): 609–619.
169. L. P. Martin, J. Konner, K. N. Moore, et al., "Characterization of Folate Receptor Alpha (FR α) Expression in Archival Tumor and Biopsy Samples in a Phase I Study of Mirvetuximab Soravtansine, a FR α -Targeting Antibody-Drug Conjugate (ADC), in Relapsed Epithelial Ovarian Cancer Patients," *Gynecologic Oncology* 145 (2017): 34.
170. B. A. Lee, M. S. Lee, A. C. Maltry, and J. H. Hou, "Clinical and Histological Characterization of Toxic Keratopathy From Depatuxizumab Mafodotin (ABT-414), an Antibody-Drug Conjugate," *Cornea* 40, no. 9 (2021): 1197–1200.
171. J. S. Eaton, P. E. Miller, M. J. Mannis, and C. J. Murphy, "Ocular Adverse Events Associated With Antibody–Drug Conjugates in Human Clinical Trials," *Journal of Ocular Pharmacology and Therapeutics* 31, no. 10 (2015): 589–604.

172. A. V. Farooq, S. Degli Esposti, R. Popat, et al., “Corneal Epithelial Findings in Patients With Multiple Myeloma Treated With Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study,” *Ophthalmology and therapy* 9, no. 4 (2020): 889–911.
173. R. B. Bausell, A. Soleimani, A. Vinnett, et al., “Corneal Changes After Belantamab Mafodotin in Multiple Myeloma Patients,” *Eye & Contact Lens* 47, no. 6 (2021): 362–365.
174. T. Mickevicius, A. E. Pink, M. Bhogal, D. O’Brart, and S. J. Robbie, “Dupilumab-Induced, Tralokinumab-Induced, and Belantamab Mafodotin-Induced Adverse Ocular Events—Incidence, Etiology, and Management,” *Cornea* 42, no. 4 (2023): 507–519.
175. J. Canestraro, M. Hultcrantz, S. Modi, et al., “Refractive Shifts and Changes in Corneal Curvature Associated With Antibody–Drug Conjugates,” *Cornea* 41, no. 6 (2022): 792–801.
176. J. Martin, E. Zacholski, R. O’Cearbhaill, U. Matulonis, and L. Chen, “Society of Gynecologic Oncology Journal Club: Controversial Conversations in Gynecologic Cancer—the ABCs of ADCs (Antibody Drug Conjugates),” *Gynecologic Oncology Reports* 45 (2023): 101141.
177. M. Offidani, L. Corvatta, S. Morè, and A. Olivieri, “Belantamab Mafodotin for the Treatment of Multiple Myeloma: An Overview of the Clinical Efficacy and Safety,” *Drug Design, Development and Therapy* 15 (2021): 2401–2415.
178. S. K. Kim, P. Ursell, R. L. Coleman, B. J. Monk, and I. Vergote, “Mitigation and Management Strategies for Ocular Events Associated With Tisotumab Vedotin,” *Gynecologic Oncology* 165, no. 2 (2022): 385–392.