Clinical Cancer Research

Evaluation of Prophylactic Corticosteroid Eye Drop Use in the Management of Corneal Abnormalities Induced by the Antibody–Drug Conjugate Mirvetuximab Soravtansine

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Abstract

Purpose: Reversible, low-grade ocular adverse events (AE) are associated with administration of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeted antibody–drug conjugate undergoing phase III clinical evaluation in platinum-resistant ovarian cancer. This study investigated the underlying mechanisms of ocular toxicity and evaluated primary prophylactic use of corticosteroid eye drops in patients receiving mirvetuximab soravtansine.

Patients and Methods: Target expression in the human eye was determined by IHC. The ocular toxicity profile of mirvetuximab soravtansine was assessed preclinically using Dutch-Belted rabbits. In a phase I clinical study, patients with ovarian cancer were treated with 6 mg/kg mirvetuximab soravtansine intravenously once every 3 weeks, including one expansion cohort with corticosteroid eye drops administered daily for the first 10 days of each treatment cycle.

Results: FRα expression was absent from human corneal tissues. Ocular abnormalities in the rabbit eye appeared phenotypically consistent with off-target effects on the cornea. Forty patients were enrolled in the expansion cohort. Reversible grade 1 or 2 blurred vision and keratopathy occurred in 16 (40%) and 12 (30%) patients, respectively; no grade 3/4 ocular events were observed. Compared with those patients who did not receive primary prophylaxis, corticosteroid eye drop use resulted in fewer dose reductions (5% vs. 15%) and none discontinued due to ocular AEs.

Conclusions: Preclinical modeling was predictive of the corneal-related symptoms seen in some patients dosed with mirvetuximab soravtansine. Primary prophylactic use of topical corticosteroid eye drops resulted in a trend toward symptomatic improvement and a reduction in ocular AE-related dose modifications in patients treated with mirvetuximab soravtansine.

Introduction

It is well established that the eye is susceptible to toxic insults that arise in response to systemic chemotherapy, resulting in a variety of ophthalmic complications that range in severity from mild irritation to visual loss, including conjunctivitis, blurred vision, photophobia, keratitis, retinopathy, and optic neuropathy (1, 2). This broad spectrum of ocular toxicities reflects the unique anatomic, physiologic, and biochemical features of the eye (1) and varies with the class of cytotoxic drug used (e.g., alkylating agents, antimetabolites, taxanes, or platinum agents). Ocular side effects have also emerged as an important clinical concern for molecularly targeted therapies entering standard oncology practice, despite these being more tumor selective than traditional cytotoxic chemotherapy (3, 4). In some cases they can be attributed to on-target effects due to target antigen expression in the eye, as exemplified by the class effect visual disturbances seen during the early development of MEK and HSP90 inhibitors (5). Alternatively, toxicities may occur via off-target mechanisms and the etiology of such events is less clearly defined.

Antibody–drug conjugates (ADC) are designed for targeted delivery of potent cytotoxic compounds through conjugation to mABs that recognize tumor-associated antigens (6). Currently four ADCs are approved for use in a variety of solid and hematological malignancies, and more than 60 others are under active clinical evaluation (7). Importantly, this unique method of site-selective drug delivery affords a means to reduce off-target toxicities in patients by limiting the exposure of normal tissues to the payload (8). In this regard, the safety and tolerability profiles for this rapidly growing class of anticancer therapeutics were expected to correlate with the levels of target antigen found in normal tissues. However, for most ADCs, the clinical experience has revealed that toxicities

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Translational Relevance

Ocular toxicities associated with antibody–drug conjugate (ADC) administration have been observed clinically but underlying mechanisms and strategies for symptomatic mitigation in patients remain to be elucidated. Mirvetuximab soravtansine is a folate-receptor alpha (FRα)-targeting ADC in late-stage clinical development showing promise for the treatment of recurrent ovarian cancer. The primary ocular abnormalities with mirvetuximab soravtansine include low-grade, reversible blurred vision, and keratopathy. This study describes nonreceptor-mediated effects on the corneal epithelium that account for this ocular toxicity profile, evidenced by a lack of FRα expression in human corneal tissues and preclinical modeling studies in rabbits. The addition of primary prophylaxis with corticosteroid eye drops as a means to alleviate ocular adverse events as part of a phase I study in patients receiving mirvetuximab soravtansine is summarized. These results may have broad implications for the application of this and other ADCs for which ocular side effects are an important clinical consideration.

(including ocular) are driven by the payload present and not antigen expression (9). Indeed, there appears to be a clear payload association with ocular side effects, which have been most commonly reported for ADCs that bear either the maytansinoid DM4 (derivative of maytansine-4) or the auristatin metabolite MMAF (monomethyl auristatin-F) as their cytotoxic effector molecules (10). In most cases, these toxicities are consistent with corneal changes (causing symptoms of blurred vision due to keratopathy, microcystic epithelial changes etc.) and appear irrespective of the cellular targets of the individual ADC, which are typically absent or only minimally expressed in the eye (9, 10).

Mirvetuximab soravtansine is a folate receptor alpha (FRα)-targeting ADC, comprised of a humanized anti-FRα mAB linked to DM4 (11), currently undergoing pivotal phase III evaluation in patients with platinum-resistant ovarian cancer (12). In the first-in-human study of mirvetuximab soravtansine, ocular abnormalities emerged as adverse events (AE) of interest during the escalation stage, prompting dose modifications (13). These primarily manifested as blurred vision and/or keratopathy, which were generally mild ($\leq$ grade 2), reversible, and similar in nature to those reported for other maytansinoid-conjugated antibodies (8). Early recognition of dose- and exposure-dependent correlations with these ocular events resulted in modification of mirvetuximab soravtansine dosing from total to adjusted ideal body weight, to decrease the range of variance in interpatient drug exposures (13). Moreover, implementation of daily lubricating eye drop use and other proactive measures (e.g., avoidance of contact lenses, application of compresses over the eyes etc.) subsequently decreased both the incidence and grade of visual disturbances in patients while on treatment (14). In addition to these mitigating strategies, steroid eye drops were used as treatment or in the secondary prophylaxis setting to help manage ocular symptoms.

To examine the pathogenesis of the ocular side effects observed in patients treated with mirvetuximab soravtansine, the distribution pattern of FRα expression in the human eye was determined, followed by preclinical assessment of the ocular toxicity profile of mirvetuximab soravtansine in rabbits, a commonly used species for modeling potential drug-mediated ocular toxicities (15). We further report on the clinical findings of a dedicated expansion cohort, opened as part of the initial phase I study, in individuals with relapsed ovarian cancer to investigate the potential benefits of primary prophylactic corticosteroid eye drop use with mirvetuximab soravtansine monotherapy.

Patients and Methods

IHC

IHC staining for FRα expression in formalin-fixed, paraffin-embedded (FFPE) normal human eye whole-section samples (Cooperative Human Tissue Network) was performed by automated IHC assay using the anti-human FRα mouse monoclonal FOLR1-2.1 and OptiView detection kit. The FOLR1-2.1 antibody was developed at ImmunoGen and recognizes FRα in FFPE tissues and the assay was optimized and validated with a broad dynamic range to detect FRα staining in FFPE tissue samples with weak receptor expression. Non–small cell lung cancer FFPE samples with confirmed FRα expression levels were used as positive controls. Staining was evaluated by a board-certified pathologist. For positive samples, staining intensity (weak, moderate, or strong) and localization (membranous, cytoplasmic) were recorded.

Rabbit ocular toxicity model

Rabbit studies were performed by Covance Laboratories, an organization fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). All procedures were in compliance with applicable animal welfare acts and approved by the local Institutional Animal Care and Use Committee (IACUC). Male Dutch-Belted rabbits ($n = 5$/group) were administered mirvetuximab soravtansine once every 3 weeks for four consecutive doses (i.e., on days 1, 22, 43, and 64) by intravenous infusion via a marginal ear vein over approximately 15 minutes. Two dose levels were tested, 4 and 12 mg/kg, and animals were monitored until study day 107 (end of 3-week recovery phase). A control group was administered the formulation buffer following the same dosing schedule. The antibody component of mirvetuximab soravtansine is not cross-reactive with rabbit FRα, therefore no unconjugated antibody arm was included in the study. Assessment of toxicity was based on mortality, clinical observations, qualitative food consumption, body weights, ophthalmic examinations, and anatomic pathology (day 85 terminal sacrifice; day 107 recovery sacrifice). Ocular toxicity was assessed by external examination via slit lamp biomicroscopy as well as microscopic analysis. The adnexa and anterior portion of both eyes were examined using a slit-lamp biomicroscope and ocular fundus of both eyes examined using an indirect ophthalmoscope. Prior to examination with the indirect ophthalmoscope, pupils were dilated with a mydriatic agent (1% tropicamide). In addition, corneal fluorescein staining was performed at each interval. Animals were euthanized on days 85 (end of dosing phase) and 107 (end of 3-week recovery phase) of the study and selected tissues placed in fixative according to established procedures for IHC microscopic analysis by a Board-certified pathologist.

Patient selection and eligibility criteria

An expansion cohort was opened as part of the first-in-human, phase I study of mirvetuximab soravtansine monotherapy in

adults with FRα-positive ovarian tumors to evaluate primary prophylaxis with corticosteroid eye drops. Adults with histologically confirmed advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer who had received either three or four prior lines of systemic therapy were eligible to enroll. Patients had to have met the minimum requirement of FRα positivity on archival tumor samples by IHC (≥25% of tumor staining at ≥2+ intensity). Tumor tissues were analyzed for FRα expression at Ventana Medical Systems, Inc. using a validated assay for sensitivity, specificity, and reproducibility. Patients had measurable or nonmeasureable disease according to RECIST version 1.1 (16). Patients were also required to be ≥18 years of age; have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; have adequate hematologic, renal, and hepatic function; and be willing and able to self-administer low-dose corticosteroid eye drops for the first 10 days of each cycle during active study treatment. Key exclusion criteria included neuropathy > grade 1; as well as any active or chronic corneal disorder such as Sjögren syndrome, Fuchs corneal dystrophy, history of corneal transplantation, active herpetic keratitis, active ocular conditions requiring ongoing treatment/monitoring like wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, or acquired monocular vision. All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

Study design and treatment administration

The primary objective of the expansion cohort was to evaluate the impact of primary prophylactic use of corticosteroid eye drops on the incidence and/or severity of ocular AEs observed in patients dosed with mirvetuximab soravtansine. Patients were administered mirvetuximab soravtansine intravenous once every 3 weeks at 6 mg/kg (adjusted ideal body weight), established as the recommended phase II dose during dose-finding (13). In addition to daily use of lubricating eye drops, patients self-administered corticosteroid eye drops (1% prednisolone acetate) 4–6 times daily for the first 10 days of each treatment cycle. Patients continued on mirvetuximab soravtansine until intolerable toxicity or AEs, disease progression, or investigator/patient decision. The trial was conducted in accordance with the FDA regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study was compliant with all relevant Institutional Review Board and Independent Ethics Committee requirements and is registered at ClinicalTrials.gov (NCT01609556).

Clinical assessments

Baseline assessments included medical history and physical examination, ECOG performance status, blood chemistry and hematology, and electrocardiogram. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 and monitored continuously throughout the study from the time of first dose until 28 days after treatment cessation. For the purposes of this study, keratopathy was used as a grouped term to capture the specific corneal pathologies of the observed AEs, including occurrences of keratopathy, keratitis, and corneal epithelial microcysts. Baseline ophthalmic exams were performed by a board-certified ophthalmologist and included slit-lamp examination under dilatation, intraocular pressure measurement, corneal photography, and dilated funduscopic examination. A Schirmer test was performed at baseline for all patients and, for those who experienced ocular symptoms, was repeated at the first on-study ophthalmic examination (and subsequently, if clinically indicated). Ocular symptom assessment was performed prior to the start of each cycle by the treating physician.

Patients who experienced ocular symptoms had a complete ophthalmologic exam performed every other cycle from the point where the ocular AE was first reported, including patients with blurred vision symptoms without any obvious clinical findings. Dose modification guidelines were as follows. For patients who experienced a grade 1 ocular AE, mirvetuximab soravtansine dosing continued and the individual monitored for worsening symptoms. For grade 2 events, mirvetuximab soravtansine dosing was held and patients subjected to weekly symptomatic ocular assessments until symptoms resolved to grade 1 or baseline. Patients were permitted to resume therapy at the same dose level unless the dosing delay was >14 days, in which case treatment resumed at a reduced dose level. All patients received a complete ophthalmologic exam at the end of treatment or 28-day follow-up visit.

Statistical analysis

The eye drop expansion cohort enrolled 40 patients. Given this sample size, the power to detect a difference of 20% against benchmark values is 68% using one-sided alpha of 20% and χ^2 test statistics. For comparative purposes in this article, an analysis of the ocular AE profiles from a pooled population of patients with ovarian cancer enrolled as part of the overall phase I trial was performed. For both groups, descriptive statistics were used to summarize demographic and baseline characteristics and additional analyses were performed using SAS statistical software (version 9.4). For the safety evaluations, baseline was defined as the last available assessment prior to day 1, cycle 1 and any AE with the same onset date as the start of study treatment or later was reported as treatment-emergent. The safety population included all patients who received at least one dose of mirvetuximab soravtansine.

Results

FRα expression in human ocular tissues

FRα has previously been reported to be expressed in the mammalian retina, particularly in the retinal pigmented epithelium (17, 18). Representative images from IHC assessment of FRα expression in human ocular tissues are shown in Fig. 1. No FRα staining was observed in the major nonretinal structures in the human eye, including the optic nerve, sclera, and choroid (Fig. 1A). Importantly, FRα expression was also notably absent throughout the entire cornea, including the corneal epithelium, stroma, and endothelium, as well as the adjacent conjunctiva and limbal region ($n = 7$ samples; Fig. 1B). Positive receptor staining was only seen in ciliary body epithelia (strong membranous and cytoplasmic staining in 4/4 samples; Fig. 1C), a result consistent with recent gene expression profiling in this tissue (19).

Preclinical modeling in rabbits predicts for potential corneal abnormalities

Mirvetuximab soravtansine was administered to Dutch-Belted rabbits at either 4 or 12 mg/kg (5/group) and animals monitored until study day 107 to assess the reversibility, persistence, and/or

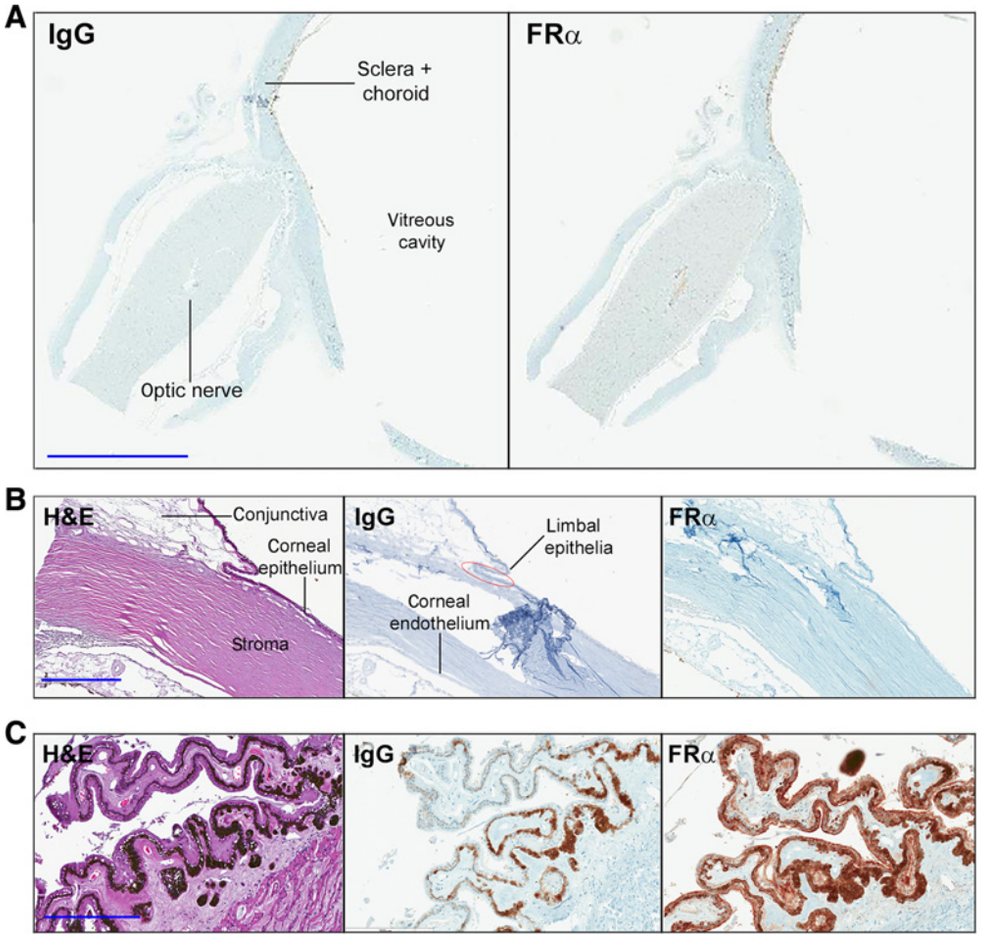
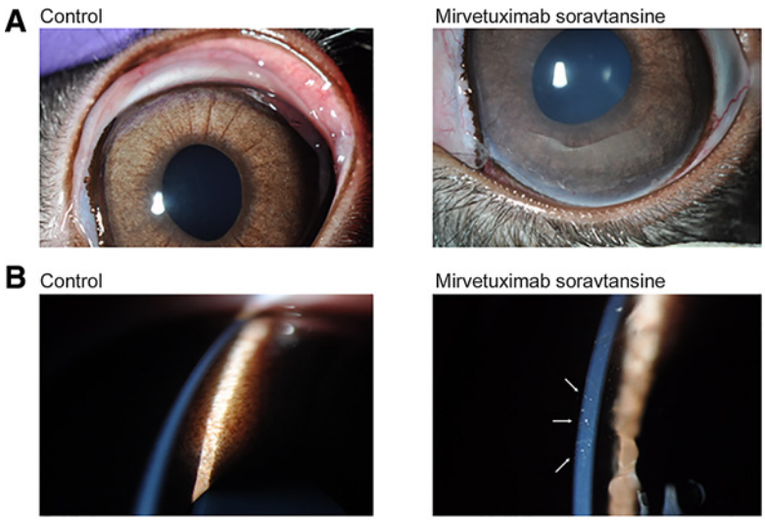


Figure 1.

FRα expression in human ocular tissues. **A,** Low magnification images from the rear sagittal section of a normal human eye incubated with control IgG or anti-FRα antibodies, respectively. Scale bar, 5 mm. **B,** Hematoxylin and eosin (H&E), IgG, and anti-FRα IHC staining of the cornea, limbus, and conjunctiva regions. Scale bar, 500 μm. **C,** Representative images showing FRα immunoreactivity in the ciliary body (nonspecific pigmentation seen in IgG control). Scale bar, 300 μm.

delayed occurrence of any ocular effects. Gross examination of the eyes revealed the development of corneal haze (Fig. 2A) in 1 animal administered the high-dose of mirvetuximab soravtansine, on days 71 and 85. The key observation to arise from ophthalmic evaluations was the appearance of punctate microcystic lesions within the corneal epithelium (associated with multifocal fluorescein stain uptake on slit-lamp microscopy) in response to mirvetuximab soravtansine exposure (Fig. 2B). This development of corneal microcystic lesions in the rabbit was similar to that seen in patients receiving mirvetuximab soravtansine monotherapy. The microcystic lesions were largely restricted to the perilimbal region of the cornea and tended to be less frequent, later in onset, and faster to resolve in animals given the lower dose of mirvetuximab soravtansine. Figure 2C summarizes the temporal incidence of corneal microcystic epitheliopathy observed during the study period for both dose levels. For animals treated at 4 mg/kg/dose, the maximal incidence of corneal lesions was 20% (i.e., 2/10 eyes affected) which occurred on day 15, 2 weeks following the initial mirvetuximab soravtansine dose. Symptomatic onset was more rapid in rabbits treated at 12 mg/kg/dose, with 20% of eyes affected within 1 week of initial dosing (day 8) and peaking at 80% on day 71, 1 week after the last dose. Despite the higher prevalence in rabbits dosed at 12 mg/kg/dose, the effects showed signs of reversibility as evidenced by a marked reduction in numbers seen during the recovery phase (80% to 10% between days 71 and 85), although complete resolution was observed only in animals treated with 4 mg/kg/dose.

At terminal sacrifice on day 85, histologic examination of the eyes revealed a clear attenuation of the corneal epithelium that persisted in animals dosed at the 12 mg/kg/dose level (5/6 eyes examined; Fig. 2D), characterized by clear cellular disorganization (including fewer and larger epithelial cells, discontinuous basal layer). These microscopic findings showed signs of recovery with a lower incidence (1/4 eyes) noted at the recovery sacrifice (day 107). Of note, no retinal effects were observed in any of the ophthalmic or histologic examinations. Together with the absence of FRα expression in the cornea, the development of



C

Dose	Dosing phase day						
	8	15	29	50	64	71	85
4 mg/kg	0	2	0	0	0	0	0
12 mg/kg	2	2	2	4	3	8	1

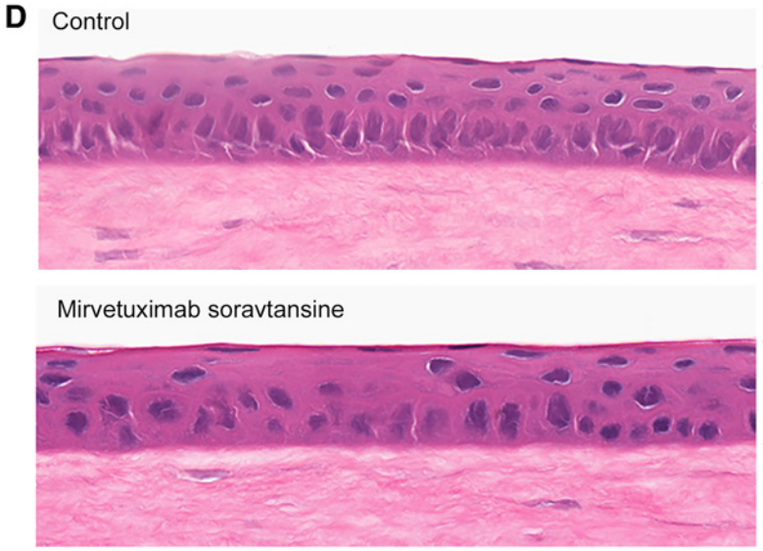


Figure 2.
Mirvetuximab soravtansine exposure induces corneal abnormalities in rabbits. **A,** Images of rabbit eyes from control (left) or mirvetuximab soravtansine–treated (12 mg/kg/dose; right) animals that developed corneal haze. **B,** Slit-lamp images showing the appearance of diffuse, perilimbal microcysts within the corneal epithelium of mirvetuximab soravtansine–treated rabbits. Arrows depict multifocal punctate perilimbal corneal microcysts in affected animals. **C,** Incidence of corneal microcysts identified during ophthalmic examinations. Values represent numbers of eyes affected. **D,** Hematoxylin and eosin staining of corneal tissue sections taken from control (top) or mirvetuximab soravtansine–treated animals (12 mg/kg/dose; bottom) following terminal sacrifice on day 85. Attenuation of the epithelium (E) in response to mirvetuximab soravtansine exposure is characterized by fewer and larger epithelial cells and disorganization of the basal epithelial layer. Original magnification, 40×.

corneal abnormalities in response to mirvetuximab soravtansine exposure appeared to be nontarget-related.

Patient characteristics

Forty patients were enrolled in the expansion cohort evaluating primary prophylactic use of corticosteroids, starting from cycle 1. Patients were required to record eye drop administration in a diary format. Of those who provided diaries (87.5%), the median compliance with self-administration was 90% (range, 45%–100%). Patient demographics and baseline characteristics are summarized in Table 1. The median age was 60 years (range, 49–83). The distribution of tumor types was epithelial ovarian carcinoma (85%), fallopian tube cancer (7.5%), and primary peritoneal cancer (7.5%), with a majority of patients (90%) presenting with serous histology. All individuals were heavily pretreated, with 100% having prior platinum and taxane exposure. Twenty-four patients (60%) received three previous systemic therapies and 15 (37.5%) had undergone four prior lines.

Safety

All 40 patients were included in the safety analyses. Treatment-emergent adverse events (TEAE) occurring in $\geq$ 15% of patients are presented in Fig. 3. The most frequently reported TEAEs were diarrhea, fatigue (each 58%), and nausea (48%), the majority of which were either grade 1 or 2. No grade 4 events were observed and no deaths occurred in patients while on study. Related AEs led

Table 1. Patient demographics and baseline characteristics

Characteristic	Corticosteroid prophylaxis ($n = 40$)	No corticosteroid prophylaxis ($n = 73$)
Age in years, median (range)	60 (49–83)	62 (38–81)
Race, *n* (%)		
White	34 (85.0)	66 (90.4)
Black or African American	1 (2.5)	2 (2.7)
Asian	3 (7.5)	2 (2.7)
American Indian or Alaskan native	0 (0.0)	2 (2.7)
Not reported	2 (5.0)	1 (1.4)
Primary cancer diagnosis, *n* (%)		
Epithelial ovarian cancer	34 (85.0)	67 (91.8)
Fallopian tube cancer	3 (7.5)	5 (6.8)
Primary peritoneal cancer	3 (7.5)	1 (1.4)
Histology, *n* (%)		
Serous	36 (90.0)	67 (91.8)
Endometrioid	2 (5.0)	1 (1.4)
Mixed	2 (5.0)	2 (2.7)
Carcinosarcoma	0 (0.0)	2 (2.7)
Mullerian carcinoma	0 (0.0)	1 (1.4)
ECOG PS, *n* (%)		
0	20 (50.0)	32 (43.8)
1	20 (50.0)	41 (56.2)
Platinum resistance, *n* (%)		
Yes	31 (77.5)	65 (89.0)
No	9 (22.5)	8 (11.0)
Number of prior systemic therapies, *n* (%)		
1–2	1[a] (2.5)	16 (22)
3–4	39 (97.5)	30 (41)
5+	0 (0)	27 (37)
Prior compound exposure, *n* (%)		
Platinum	40 (100.0)	73 (100.0)
Taxane	40 (100.0)	73 (100.0)
Bevacizumab	24 (60.0)	53 (72.6)
PARP inhibitor	8 (20.0)	15 (20.5)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]One patient enrolled with two prior lines of therapy, although three or four prior lines were defined in the protocol.

to study discontinuation for 4 individuals (10%), involving 3 cases of pneumonitis (grade 1/2) and 1 case of grade 2 thrombocytopenia.

Ocular AEs

The two major ocular AEs of interest, blurred vision and keratopathy, were seen in 16 (40%) and 12 (30%) patients, respectively, with no grade 3 or 4 events observed. A comparator pooled population of patients from the same phase I trial ($n = 73$, Table 1) received the same dosing regimen of mirvetuximab soravtansine, underwent identical ocular management procedures, but did not receive primary prophylactic corticosteroid eye drops. Although no significant differences in the frequency or median time to onset of the two toxicities were observed between groups, there was a trend toward a lower incidence, particularly of keratopathy, in those patients who received corticosteroid prophylaxis (Table 2). Furthermore, the percentage of patients in each group requiring a dose delay due to ocular toxicity was similar, however the number of dose reductions was lower (2 patients, 5%) and no discontinuations in response to ocular events were seen in the corticosteroid cohort (Table 3). Consistent with the lower frequency of dose modifications associated with primary prophylactic steroid eye drop use, the median relative dose intensity (RDI) in the eye drop cohort was 98.6% versus 95.6% in the comparator group. With respect to other ocular AEs, dry eye and cataracts were reported in 9 (23%) and 6 patients (15%), respectively (Fig. 3) in the eye drop cohort. Importantly, no retinal-related toxicities were observed in patients who received mirvetuximab soravtansine.

Discussion

Mirvetuximab soravtansine is a FRα-targeting ADC currently undergoing late-stage clinical development in ovarian cancer, and was granted Fast Track designation in June 2018 by the FDA following complete enrollment of a pivotal phase III study (FORWARD I; NCT02631876; ref. 20). The reversible, low-grade ocular abnormalities seen with mirvetuximab soravtansine are similar to those reported for a variety of other ADCs that bear tubulin-disrupting payloads (10, 21). The exact mechanisms of such ocular toxicities are still poorly defined. Beyond the apparent payload association, the type of linker employed for drug attachment has also been suggested as a potential contributory factor, with prolonged retention in the circulation conferred by stable linkers (such as that present in mirvetuximab soravtansine) proposed to enhance overall exposure in normal tissues, including the eye (22). Understanding the etiology of the ocular disturbances of mirvetuximab soravtansine and developing mitigation strategies remain important clinical considerations for the optimal application of this promising investigational agent.

To better understand the pathophysiology of mirvetuximab soravtansine–induced ocular AEs, the distribution pattern of FRα in the human eye was evaluated using IHC. FRα has previously been reported to be expressed in retinal tissues, primarily localized to the basolateral surface of the retinal pigmented epithelium, where it is believed to be involved in vectorial transfer of folate from the choroidal blood supply into the retina (17, 18). In this study, we show that FRα protein is also expressed in the ciliary body, a multifunctional tissue whose principal roles include production of aqueous humor and accommodation of the lens by the ciliary muscle (23). The ciliary body, along with the iris and choroid, form the uvea, the pigmented middle layer of the eye that is structurally and functionally distinct from the cornea. Of note, this anatomic differentiation suggests that there is little likelihood of any potential on-target effects of mirvetuximab soravtansine on the ciliary body manifesting as corneal damage. The ciliary body has been linked to a number of pathologies, the most important of which are glaucoma and anterior uveitis/iritis (24). Furthermore, there are few reports of specific drug-induced effects on this tissue, with the exception of certain sulfamate-derived drugs such as the antiepileptic topiramate, which can cause swelling and lead to the development of angle-closure glaucoma (25). However, none of these toxicities, nor any retinal abnormalities, were observed in the preclinical modeling or in human subjects treated with mirvetuximab soravtansine. Together with the absence of FRα expression in corneal tissues, the ocular adverse event profile of mirvetuximab soravtansine thus appears to be target independent.

Studies of ocular drug toxicities are best performed in species for which the information can be applied to the clinical setting. Dutch-Belted rabbits, a strain with pigmented eyes and noncross reactivity to the mirvetuximab soravtansine antibody moiety, were used to assess the preclinical ocular toxicity profile of mirvetuximab soravtansine. The major ophthalmic observation to emerge from this animal model was the development of

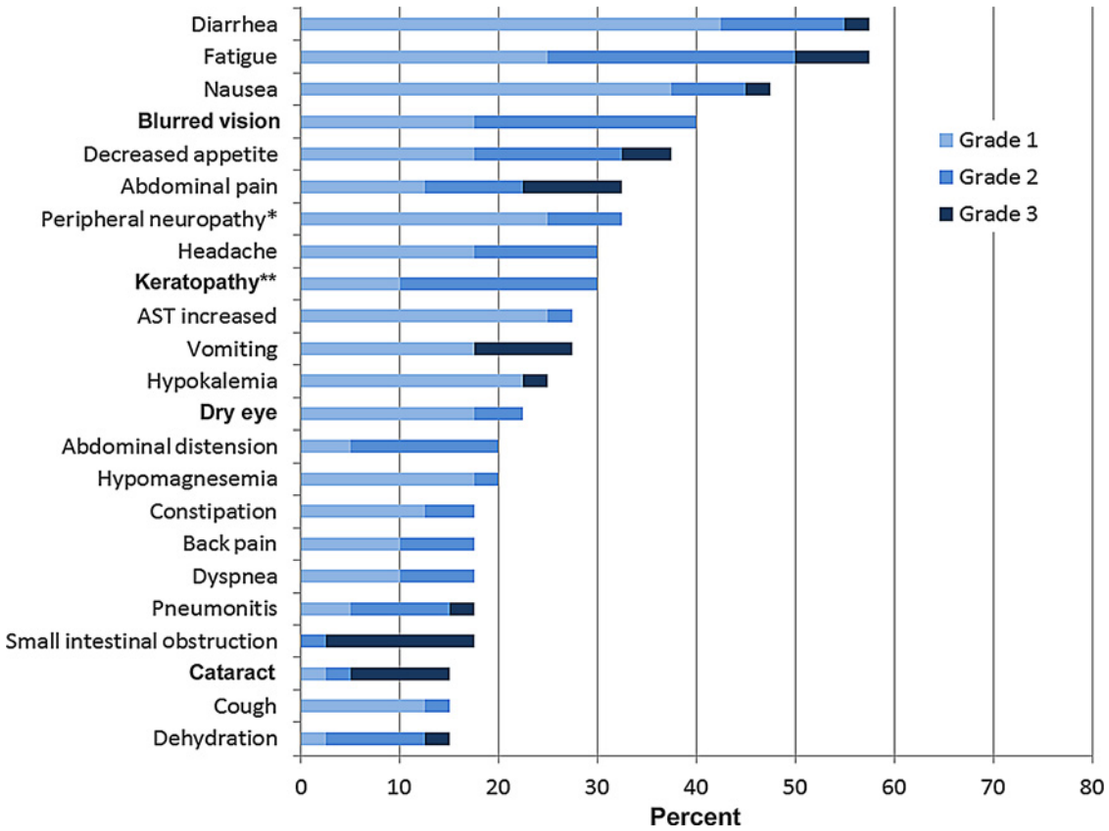


Figure 3.
TEAEs reported in ≥15% of patients. All 40 patients enrolled in the corticosteroid expansion cohort were included in the safety analysis. Ocular events are highlighted in bold text. *, Peripheral neuropathy is a grouped term that included occurrences of neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia; **, keratopathy is a grouped term that included occurrences of keratopathy, keratitis, and corneal epithelial microcysts.

punctate microcystic lesions in the cornea suggesting a close phenotypic match to the keratopathy observed in human trial subjects. Histopathologic evaluation of the keratopathy at terminal sacrifice showed marked attenuation and disorganization of the corneal epithelium in mirvetuximab soravtansine–treated animals. These corneal effects occurred in a dose-dependent manner with respect to onset, duration, and severity. Importantly, the abnormalities also showed evidence of reversibility, with the degree of resolution also correlating with the dose of mirvetuximab soravtansine. Taken together, these results are consistent with damage occurring within the proliferative compartment of the corneal epithelium, mediated by the antimitotic activity of the DM4 payload. The mechanism of action underlying these off-target yet selective effects on the corneal epithelium was not determined in this assay. However, a recent report by Zhao and colleagues (26) revealed that macropinocytosis-mediated uptake by corneal epithelial and other primary cells was responsible for ocular toxicity of AGS-16C3F, an ENPP3-targeting ADC containing a MMAF payload. Furthermore, they showed that the

Table 2. Summary of ocular TEAEs

Ocular AE	Corticosteroid prophylaxis ($n = 40$)	No corticosteroid Prophylaxis ($n = 73$)
Blurred vision		
Total, *n* (%)	16 (40.0)	34 (46.6)
Grade 1	7 (17.5)	16 (21.9)
Grade 2	9 (22.5)	18 (24.7)
Time to onset (days)		
Median	33	36
Keratopathy[a]		
Total, *n* (%)	12 (30.0)	30 (41.1)
Grade 1	4 (10.0)	18 (24.7)
Grade 2	8 (20.0)	11 (15.1)
Grade 3	0	1 (1.4)
Time to onset (days)		
Median	42	43

[a]Grouped term that includes keratopathy, keratitis, and corneal epithelial microcysts.

Table 3. Action taken due to ocular AEs

	Corticosteroid prophylaxis ($n = 40$)	No corticosteroid Prophylaxis ($n = 73$)
No. of patients with ocular TEAEs	$n = 18$	$n = 38$
Action taken due to ocular events, *n* (%)		
Dose interruption	0 (0)	0 (0)
Dose delay	9 (22.5)	17 (23.3)
Dose reduction	2 (5.0)	11 (15.1)
Dose discontinuation	0 (0)	1 (1.4)

biophysical properties of the ADC itself (overall hydrophobicity and/or presence of positive charges on the antibody) were important determinants for this nonreceptor-mediated process and could affect the ocular toxicity profile in animal models. The ophthalmic observations of our clinical study are also in agreement with the current model proposed to explain the observed changes in the ocular surface, in which corneal damage begins peripherally after ADCs reach the cornea via the vascularized limbal region, followed by internalization and consequent accumulation of the cytotoxic payload into transient amplifying cells. These damaged progenitor cells then migrate centripetally, sufficient to account for the development of microcystic deposits seen in patients (26, 27). Overall, the findings validate the use of this rabbit model to assess the pathogenesis of ocular abnormalities, as well as the risks of visual disturbances, induced by mirvetuximab soravtansine exposure in human subjects.

An important consideration related to ocular toxicity relates to prior treatment history. While a cumulative effect of chemotherapy on the corneal epithelium cannot be ruled out, it is unlikely that this represents a major contributing factor to the corneal damage seen in patients in this study. Systemic chemotherapy can induce ocular side effects, affecting multiple sites within the eye including the optic nerve, retina, and anterior chamber (1). All patients in this study had received prior platinum compound and taxane exposure; however, these agents are not associated with corneal abnormalities but instead can induce optic neuropathy and retinopathy (2), neither of which were reported as AEs. Keratitis/keratopathy is more commonly seen with chemotherapeutics such as 5-fluorouracil, tamoxifen, and cytarabine (1, 2), but none of these drugs are used in ovarian cancer therapy and no patients in this study were exposed to them as part of their treatment history.

A number of mitigation strategies have been implemented clinically to help reduce the incidence and severity of the corneal and visual disorders induced by mirvetuximab soravtansine exposure. During early dose escalation, in which doses were determined using total body weight, pharmacokinetic analysis suggested an association between the degree of reversible ocular toxicity and high early exposure levels of the ADC (13). A change in the weight-based dosing strategy to adjusted ideal body weight was therefore undertaken to reduce peak plasma concentrations to levels below the threshold for ocular toxicity. This approach is now standard in all clinical evaluations of mirvetuximab soravtansine. Furthermore, daily use of lubricating eye drops in conjunction with other proactive ocular management procedures reduced the incidence of blurred vision and corneal keratopathy to levels seen in the pooled population of patients with ovarian cancer used for comparative purposes in this study. Prophylactic use of steroid eye drops is another approach that has been reported to be successful in reducing the frequency and severity of ocular events in trials of other ADCs, such as ABT-414 and SGN-CD19A (both of which utilize MMAF as their cytotoxic payload; refs. 28–30). The actual mechanism(s) by which steroids can reduce ADC-induced keratopathy remain poorly defined and, as supported by our preclinical modeling, there appears to be no inflammatory component underlying the etiology of the corneal toxicity observed with mirvetuximab soravtansine. However, it has been hypothesized that ocular steroids can slow down the proliferation of limbal stem cells, potentially leading to a lower sensitivity to the damaging effects of chemotherapeutics, including cell-cycle–dependent agents like the DM4 payload present in mirvetuximab soravtansine. Furthermore, ocular steroids may contribute to a thinning of the corneal epithelium, thereby facilitating shedding of corneal microcysts induced by exposure to the ADC.

In the clinical expansion cohort, primary prophylaxis with corticosteroid eye drops starting with the first cycle of mirvetuximab soravtansine infusion resulted in a reduced, albeit not significant, incidence of keratopathy that is suggestive of potential clinical benefit. The more modest effects on blurred vision suggest that additional mechanisms, less influenced by steroid prophylaxis, are likely contributing to this symptom in patients. Of interest, in the ADC studies where steroid prophylaxis has been shown to be effective, the ocular AEs were more severe at onset (grades 3 or 4) and were subsequently reduced to grade 1/2 events (27–30), comparable with the baseline levels seen with mirvetuximab soravtansine. Prophylactic steroid eye drop use as a mitigation strategy has not eliminated ADC-induced keratopathy, and it is reasonable to suggest that there is a role for additional strategies to further optimize ADC-related ocular AE profiles. Also, any potential side effects of topical ophthalmic steroid use (e.g., rise in intraocular pressure, accelerated cataract formation) are both easily treatable and outweighed by the prospective therapeutic benefit for a patient staying on treatment longer with an effective ADC. There was no apparent influence on the development of cataracts in patients who received corticosteroids in this study because the observed incidence was 15%, and the prevalence of cataracts in women of this age group (median, 60 years) in the general population is approximately 17%–20% and increases sharply with age (31). In this regard, the most significant observation of the clinical study was the requirement for fewer dose reductions and lack of discontinuations due to ocular AEs in patients receiving primary steroid prophylaxis compared with those individuals on study without it. This has important therapeutic implications, because better compliance with the treatment schedule would be expected to maintain mirvetuximab soravtansine dose intensity. Indeed, the improved median RDI seen in the eye drop cohort is consistent with this premise.

In summary, the principal ocular AEs associated with mirvetuximab soravtansine can be attributed to off-target effects on the cornea, characterized by primary involvement of the corneal epithelium and manifesting with blurred vision that is often associated with microcystic keratopathy. Primary corticosteroid eye drop prophylaxis provides clinical benefit to patients while on study and, based on these findings, prophylactic steroid eye drop use is now mandated along with lubricating eye drops in ongoing trials of this agent in patients with advanced ovarian cancer. Given that the ocular AEs are not eliminated by prophylactic topical steroid measures, explorations of additional mitigating strategies are ongoing. The findings of this study underscore the need for patients to continue to be appropriately screened for ocular AEs and highlight the importance of close collaboration between treating physicians and ophthalmologists to tailor treatment options for patients experiencing ocular AEs from ADC-directed therapy.

Disclosure of Potential Conflicts of Interest

U.A. Matulonis is a consultant/advisory board member for Immunogen, Fujifilm, Geneos, 2X Oncology, Mersana, and Merck. D.M. O'Malley reports receiving other commercial research support from Agenus Inc., Ajinomoto Co, Inc, Array BioPharma Inc., Astrazeneca Lp, Bristol-Myers Squibb Co, Clovis Oncology, Gynecologic Oncology Group, ImmunoGen, Inc, INC

Research, Inc, inVentiv Health Clinical, Iovance Biotherapeutics, Inc, Janssen Research and Development, LLC, Ludwig Institute for Cancer Research Ltd, NRG Oncology, PRA Intl, Regeneron Pharmaceuticals, Inc, Serono Inc, Stemcentrx, Inc., TESARO, and TRACON Pharmaceuticals, is a consultant/advisory board member for Agenus, Roche/Genentech, AstraZeneca, Immunogen, OncoQuest, Tesaro, Ambry, Clovis, Janssen, Abbvie, Regeneron, Myriad, and Novocure. K.N. Moore is an employee of NRG Oncology, reports receiving other commercial research support from PTC THerapeutics, Clovis, and Lilly, speakers bureau honoraria from Astra Zeneca, and is a consultant/advisory board member for Astra Zeneca, Immunogen, Tesaro, Genentech/Roche, Clovis, VBL Therapeutics, Aravive, Merck, Janssen, and OncoMed. J. Konner is a consultant/advisory board member for AstraZeneca, Clovis, and Immunogen. L.P. Martin is a consultant/advisory board member for Immunogen and Tesaro. T.M. Bauer is a consultant/advisory board member for LOXO, Pfizer, and Guardant Health. No potential conflicts of interest were disclosed by the other authors.

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