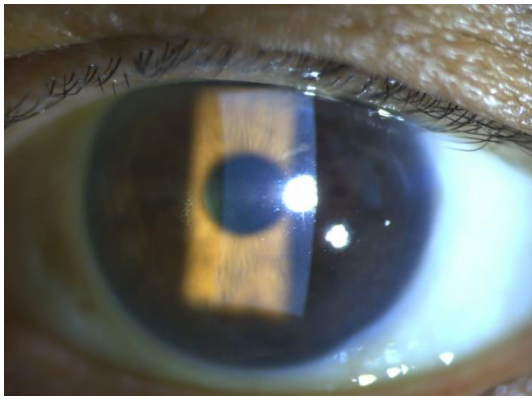
The ABC's of ADCs

A Guide for Eye Care Professionals



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Disclosure

Saba Al-Hashimi, M.D.

- Consultant (ad hoc)
  - GlaxoSmithKline (GSK)
- Research Funding
  - Research to Prevent Blindness

Antibody-Drug Conjugates (ADCs) Overview

- What are ADCs?
- Ocular adverse events with ADCs
- Management of ocular adverse events
- Discussion

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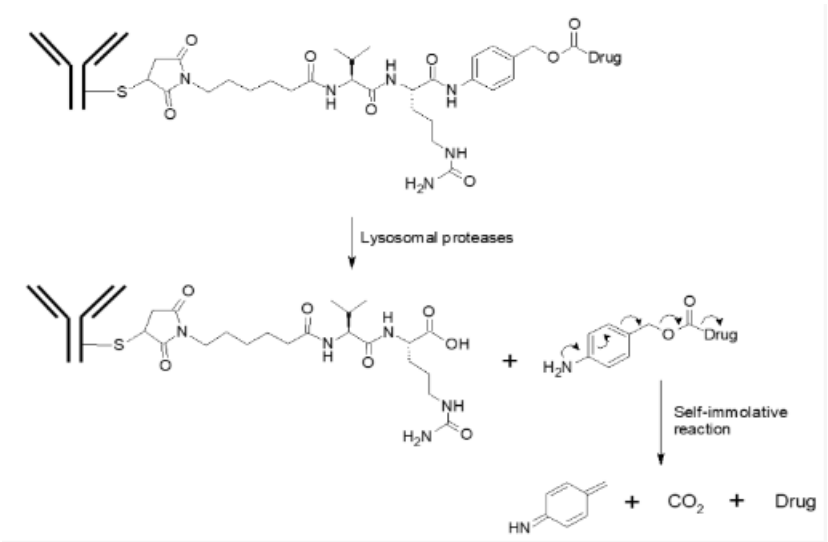
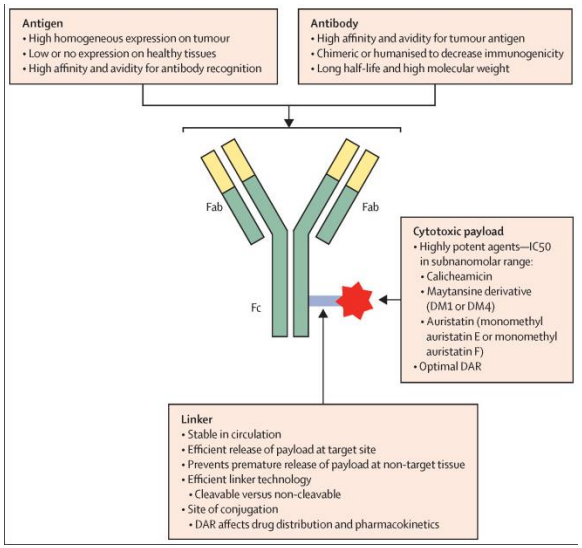
ADCs Represent a Newer Class of Antigen-Targeting Therapies

Highly potent antibody-based therapeutic consisting of 3 parts

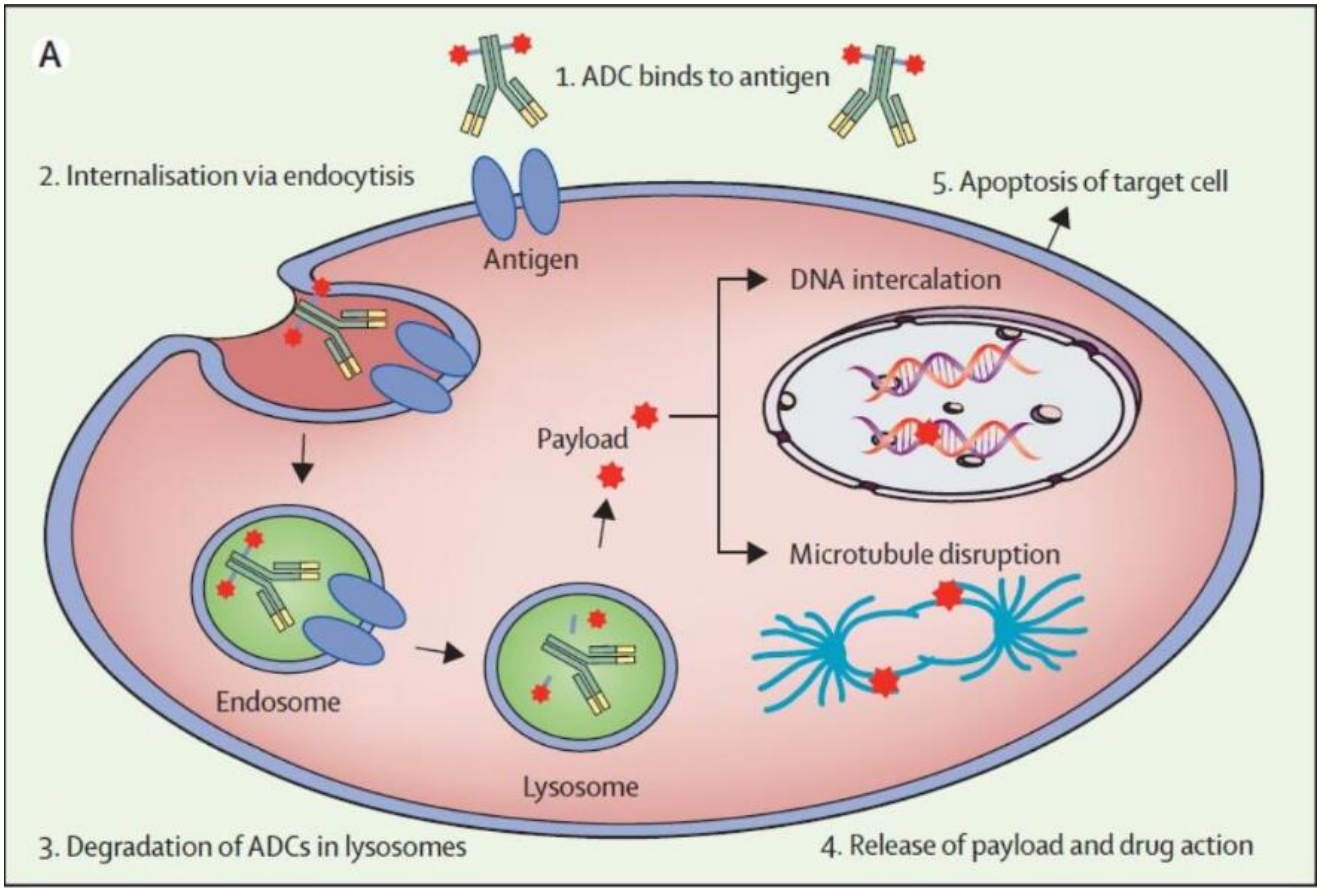
1. A Monoclonal Antibody targeting cancer cell-specific antigen
2. A cytotoxic payload
3. A chemical linker that connects the drug and the antibody





Shim H. Bispecific Antibodies and Antibody–Drug Conjugates for Cancer Therapy: Technological Considerations. *Biomolecules*. 2020; 10(3):360. https://doi.org/10.3390/biom10030360
Chau, C. Antibody-drug conjugates for cancer. *Therapeutics.* 2019; 394(10200):793-804

Mechanism of Action of ADCs



Chau, C. Antibody-drug conjugates for cancer. *Therapeutics.* 2019; 394(10200):793-804

Currently there are 12 FDA Approved ADCs

Drug	Trade name	Maker	Condition	Target	Approval Year
Gemtuzumab ozogamicin	Mylotarg	Pfizer/Wyeth	relapsed acute myelogenous leukemia (AML)	CD33	2017;2000
Brentuximab vedotin	Adcetris	Seagen Genetics, Millennium/Takeda	relapsed HL and relapsed sALCL	CD30	2011
Trastuzumab emtansine	Kadcyla	Genentech, Roche	HER2-positive metastatic breast cancer (mBC) following treatment with trastuzumab and a maytansinoid	HER2	2013
Inotuzumab ozogamicin	Besponsa	Pfizer/Wyeth	relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia	CD22	2017
Moxetumomab pasudotox	Lumoxiti	Astrazeneca	adults with relapsed or refractory hairy cell leukemia (HCL)	CD22	2018
Polatuzumab vedotin-piiq	Polivy	Genentech, Roche	relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)	CD79	2019
Enfortumab vedotin	Padcev	Astellas/Seagen Genetics	adult patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor, and a Pt-containing therapy	Nectin-4	2019
Trastuzumab deruxtecan	Enhertu	AstraZeneca/Daiichi Sankyo	adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens	HER2	2019
Sacituzumab govitecan	Trodelvy	Immunomedics	adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for patients with relapsed or refractory metastatic disease	Trop-2	2020
Belantamab mafodotin-blmf	Blenrep	GlaxoSmithKline (GSK)	adult patients with relapsed or refractory multiple myeloma	BCMA	2020, withdrawn on 22 Nov. 2022
Loncastuximab tesirine-lpyl	Zynlonta	ADC Therapeutics	Large B-cell lymphoma	CD19	2021
Tisotumab vedotin-tftv	Tivdak	Seagen Inc	Recurrent or metastatic cervical cancer	Tissue factor	2021
Mirvetuximab soravtansine	ELAHERE	ImmunoGen	Platinum-Resistant Ovarian Cancer	FRα	2022

Antibody-Drug Conjugates (ADCs)

- What are ADCs?
- Ocular adverse events with ADCs
- Management of ocular adverse events
- Case Reports

Ocular Toxicities

- Have been reported with increased frequency in ADCs
  - Specifically those that utilize a tubulin-inhibiting cytotoxin

- Most common ocular toxicities observed (over 22 citations):
  - Blurred vision (10/22)
  - Dry Eye/Keratitis (8/22)
  - Corneal Abnormalities (5/22)
    - Range from mild to vision threatening
    - ***Characterized by Microcyst-Like Epithelial changes***

Eaton JS, Miller PE, Mannis MJ, et al. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther. 2015;31:589–604

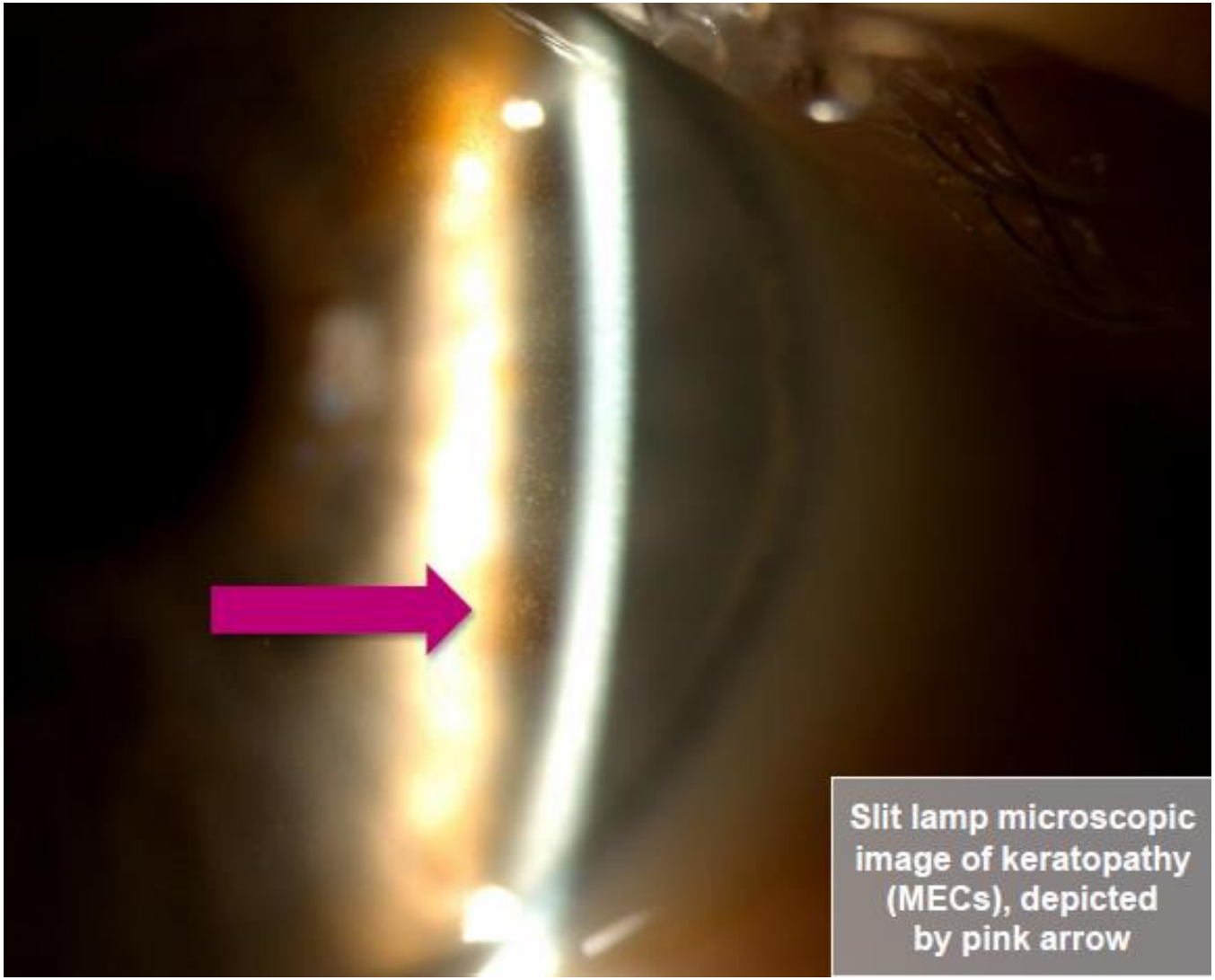
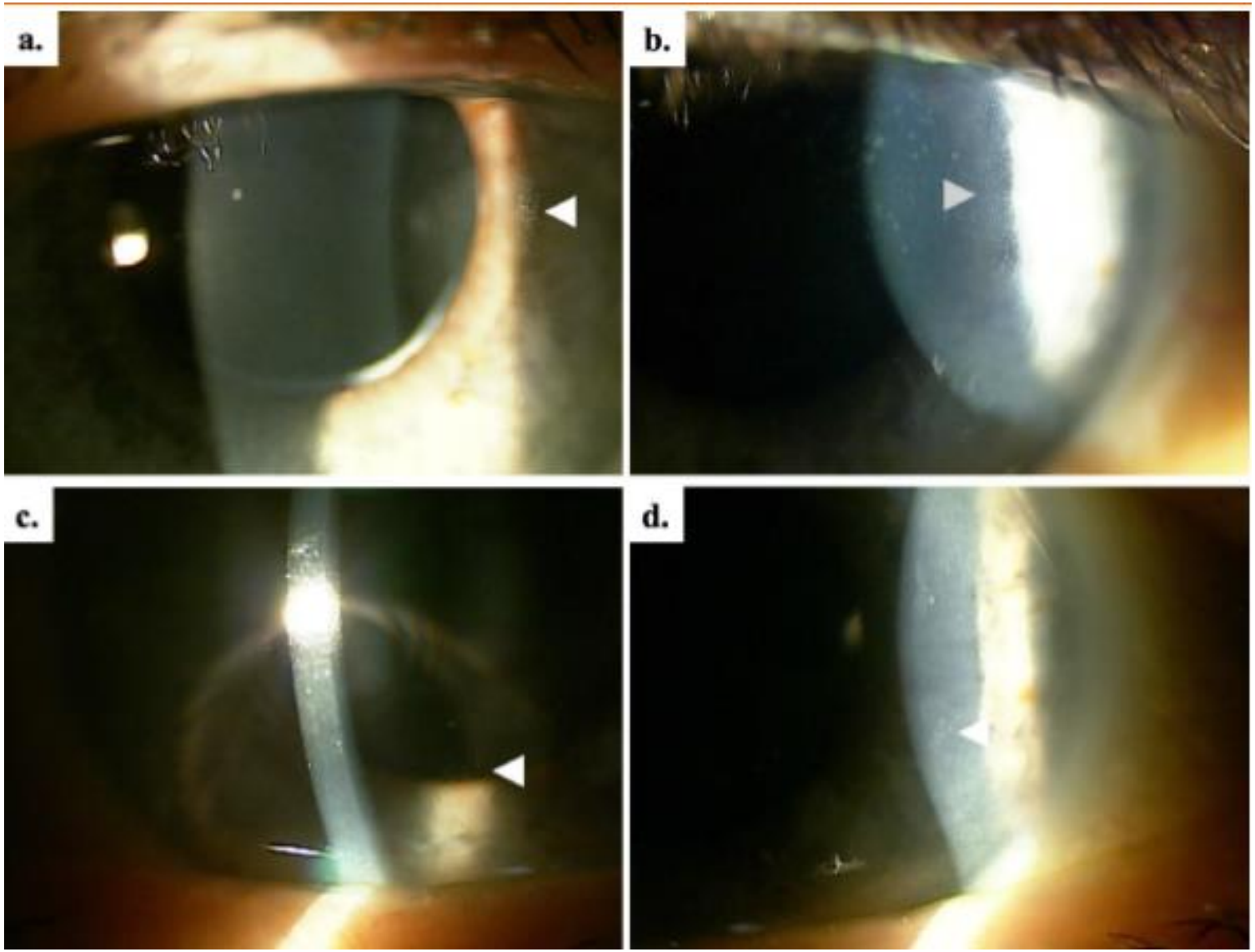


Image courtesy of Dr. Shaohui Liu, Assistant Professor of Clinical Ophthalmology, Indiana University School of Medicine



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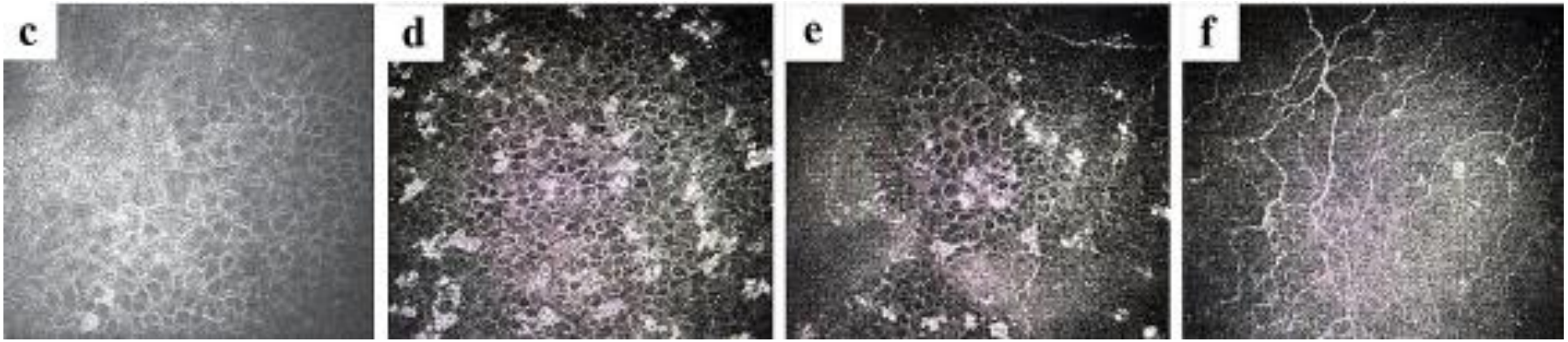
MEC, microcyst-like epithelial change. Farooq A, et al. *Ophthalmol Ther* 2020 Jul 25. doi: 10.1007/s40123-020-00280-8.



Farooq, A.V., Degli Esposti, S., Popat, R. *et al.* Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study. *Ophthalmol Ther* **9**, 889–911 (2020). https://doi.org/10.1007/s40123-020-00280-8

Antibody Drug Conjugates with Boxed Warnings for Ocular Toxicity, per US Prescribing Information

ADC Accelerated Approval Date	Most Common Ocular Adverse Reactions (Pooled Safety Populations)	Ophthalmic Exam Guidance (Visual Acuity & Slit Lamp Exam)	Ophthalmic Premedication Guidance	Risk Evaluation and Mitigation Strategy (REMS) Requirement
BLENREP®[1] belantamab mafodotin-blmf 2020 (withdrawn 2022)	Keratopathy (76%), Visual acuity reduced (55%), Blurred vision (27%), Dry Eye (19%)	Perform baseline examinations within 3 weeks prior to the first dose. Perform follow-up examination prior to each dose, at least 1 week after the previous dose and within 2 weeks prior to the next dose.	Preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment.	Yes. Prescribers must counsel patients about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose. Patients must be enrolled in REMS program and comply with monitoring.
TIVDAK®[2] tisotumab vedotin-tftv 2021	Conjunctival adverse reactions (40%), Dry eye (29%), Corneal adverse reactions (21%), Blepharitis (8%)	At baseline, prior to each dose, and as clinically indicated.	Administer topical corticosteroid eye drops prior to each infusion, instruct patients to administer as prescribed for 72 hours after each infusion. Administer topical ocular vasoconstrictor drops immediately prior to each infusion. Use cooling eye pads during the infusion. Instruct patients to administer lubricating eye drops for the duration of therapy and for 30 days after the last dose.	No
ELAHERE™[3] mirvetuximab soravtansine-gynx 2022	Visual impairment (49%), Keratopathy (36%), Dry eye (26%), Cataract (15%), Photophobia (13%), and Eye pain (12%)	Prior to treatment initiation, every other cycle for the first 8 cycles, and as clinically indicated.	Administer one drop of ophthalmic topical steroids in each eye 6 times daily starting the day prior to each infusion until day 4; administer one drop in each eye 4 times daily for days 5-8 of each cycle. The use of lubricating eye drops at least four times daily and as needed is recommended during treatment.	No

1. BLENREP®. Prescribing Information. GSK, 2022 2. TIVDAK®. Prescribing Information. Seagen Inc. and Genmab US, Inc., 2021 3. ELAHERE™ . Prescribing Information. ImmunoGen, 2022

DREAMM-2 Study Grading

(DRiving Excellence in Approaches to Multiple Myeloma)

- Grade 1
  - Mild superficial keratopathy
  - Decline from baseline of 1 line on Snellen VA
- Grade 2
  - Moderate superficial keratopathy
  - Decline from baseline of 2 or 3 lines (not worse than 20/200)
- Grade 3
  - Severe superficial keratopathy
  - Decline by more than 3 lines (not worse than 20/200)
- Grade 4
  - Corneal epithelial defect
  - Visual acuity worse than 20/200

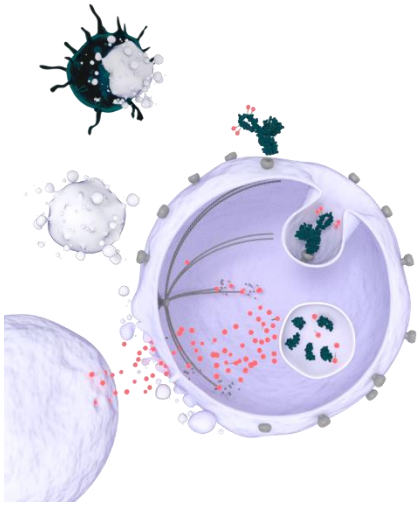
DREAMM-2 Study

Table 2 Incidence, duration, and resolution of MECs, BCVA change, and corneal symptoms in patients receiving belamaf (2.5 mg/kg) in DREAMM-2

	Eye examination findings per KVA scale			CTCAE scale	
	MECs (n = 95)	**BCVA change (n = 95)**	**MECs + BCVA change (n = 95)**	**Blurred vision (n = 95)**	**Subjective dry eye (n = 95)**
Any grade, n (%)[a]	68 (72)	51 (54)	68 (72)	24 (25)	14 (15)
Maximum grade					
Grade 1	8 (8)	7 (7)	7 (7)	11 (12)	9 (9)
Grade 2	16 (17)	15 (16)	14 (15)	9 (9)	4 (4)
Grade 3	43 (45)	28 (29)	45 (47)	4 (4)	1 (1)
Grade 4	1 (1)	1 (1)	2 (2)	0	0
Median time to onset of first occurrence (range), days	37.0 (19–143)[b]	64.0 (20–213)	36.0 (19–143)	51.5 (6–339)	42.0 (12–151)
Median duration of first event (range), days	86.5 (8–358)[b]	33.0 (8–127)[b]	96.0 (8–358)[b]	42.5 (6–441)	39.0 (12–316)
First event outcomes,[c] n/N (%)					
Recovered	46/60 (77)[b]	34/44 (77)[b]	45/61 (74)[b]	16/24 (67)	12/14 (86)
Not recovered	14/60 (23)[b]	10/44 (23)[b]	16/61 (26)[b]	8/24 (33)	2/14 (14)
Event outcomes as of last follow-up,[c] n/N (%)					
Recovered	29/60 (48)[b]	26/44 (59)[b]	30/61 (49)[b]	15/24 (63)	11/14 (79)
Not recovered	31/60 (52)[b]	18/44 (41)[b]	31/61 (51)[b]	9/24 (38)	3/14 (21)
Dose delays due to event, n (%)	–	–	45 (47)[d]	7 (7)[e]	3 (3)
Dose reductions due to event, n (%)	–	–	24 (25)[d]	2 (2)[e]	0

Mirvetuximab Soravtansine

Mirvetuximab soravtansine (MIRV) is the first biomarker-directed agent showing antitumor activity in patients with FRα-positive[a] platinum-resistant ovarian cancer (PROC)[1]



- MIRV is an antibody-drug conjugate (ADC) comprising an FRα-binding antibody, cleavable linker, and maytansinoid DM4 payload[1]
- A phase 3 clinical study, SORAYA, evaluated MIRV in patients with FRα-high PROC who had received 1 to 3 prior therapies, including required bevacizumab[1-3]

AEs, adverse events; DM4, N2′-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2′-deacetylmaytansine; FRα, folate receptor alpha.
[a]Antitumor activity with MIRV has been demonstrated with single-agent MIRV in FRα-high PROC (≥75% tumor cells FRα-positive by PS2+)[1] and in combination with other agents in FRα low-to-high PROC (≥25% tumor cells FRα-positive by PS2+).[4]

1. Matulonis UA, et al. Presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL. Poster 391. **2.** Matulonis UA, et al. *Clin Cancer Res*. 2019;25(6):1727-1736.
3. ClinicalTrials.gov identifier: NCT04296890. Updated April 21, 2022. Accessed August 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04296890. **4.** Matulonis UA, et al. Presented at: 2018 European Society for Medical Oncology Congress; October 19-23, 2018; Munich, Germany. Abstract 949P.

SORAYA: Study Design (Ocular Management)

SORAYA is a global single-arm phase 3 study evaluating MIRV in adult patients with FRα-high platinum-resistant ovarian cancer[1,2]

- Patients received MIRV 6 mg/kg, based on AIBW[a], IV once every 3 weeks[1]
- A baseline ophthalmic examination was performed for all patients[1]
- Ocular symptoms were assessed by the investigator at each visit (approximately every 3 weeks) and patients with any symptoms were referred to an eye care specialist for evaluation[1,2]
- For patients who experienced ocular adverse events, ophthalmic examinations were conducted with every other cycle until resolution, stabilization, or return to baseline[3]
- Proactive supportive care included[3]:
  - Required use of corticosteroid eye drops (6 times daily on days 1 to 4 and 4 times daily on days 5-8 of each cycle)
  - Preservative-free lubricating artificial tears daily as needed

AIBW, adjusted ideal body weight; FRα, folate receptor alpha; IBW, ideal body weight; IV, intravenously; MIRV, mirvetuximab soravtansine.
[a]AIBW is calculated as IBW (kg) + 0.4 (actual weight – IBW). IBW for females is calculated as 0.9*height (cm)-92.[4]
1. Matulonis UA, et al. Presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Poster 391. **2.** Moore K, et al. Presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Poster 450. **3.** Data on file. ImmunoGen, Inc. **4.** Moore K, et al. Presented at: 2014 American Society of Clinical Oncology Annual Meeting; May 30-June 3, 2014; Chicago, Illinois. Abstract 5571.

SORAYA: Ocular Events

- 58 of 106 patients (55%) reported an ocular event[1]
  - 46 patients (43%) experienced ocular events that were grade ≤2
  - 12 patients (11%) experienced ocular events that were grade ≥3
- Onset of ocular events typically occurred during cycle 2
  - Blurred vision median time to onset was 1.3 months (range, 0.0-9.9)
  - Keratopathy median time to onset was 1.5 months (range, 1.1-8.6)

Ocular TRAEs Reported in ≥10% of Patients (N=106)[1,2,a]

Patients with any TRAE	91 (86)	30 (29)	1 (1)
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy	31 (29)	8 (8)	1 (1)[b]
Dry eye	26 (25)	2 (2)	0 (0)
Photophobia	14 (13)	0 (0)	0 (0)
Eye pain	8 (8)	0 (0)	0 (0)
Visual acuity reduced	3 (3)	0 (0)	0 (0)

AE, adverse event; eCRF, electronic case report form; TRAEs, treatment-related adverse events.
[a]When counting events, each record was counted once for each AE entered in the eCRF. For the remaining frequencies, each patient was counted once, with the worst grade for each patient.[3]
[b]One patient had a grade 4 keratopathy, based upon the visual acuity evaluation of one eye (20/200). This patient had with nonconfluent corneal deposits treated as dry eye syndrome. Visual acuity and corneal changes both resolved completely (grade 0) in 15 days, prior to next dosing cycle.[1]

1. Matulonis UA, et al. Poster presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Poster 391. **2.** Moore K, et al. Presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Poster 450. **3.** Data on file. ImmunoGen, Inc.

CTCAE v.5: Ocular AEs and Grading

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity; limiting instrumental ADL[a]	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[b]	Best corrected visual acuity of **20/200 or worse** in the affected eye
Keratitis[c]	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; corneal ulcer; limiting self-care ADL[b]	Perforation; best corrected visual acuity of **20/200 or worse** in the affected eye
Dry eye[d]	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[b]	NA
Photophobia[e]	Symptomatic but not limiting ADL	Limiting instrumental ADL[a]	Limiting self-care ADL[b]	NA

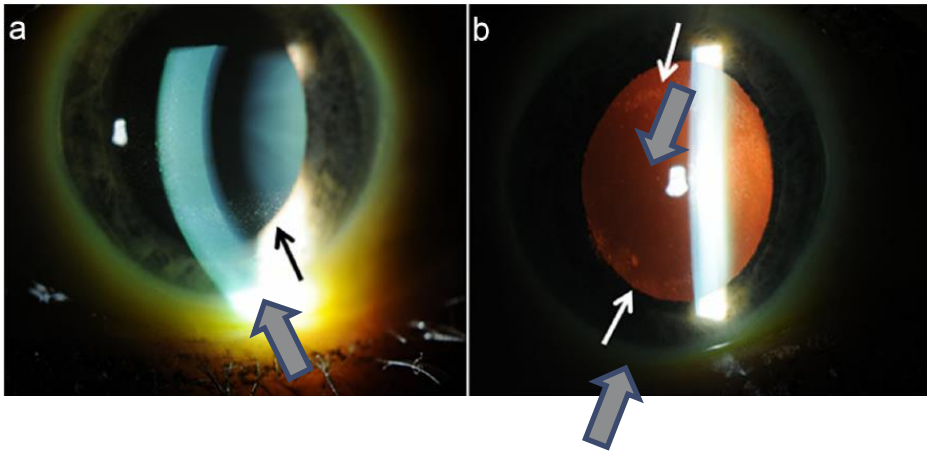
ADL, activities of daily living; AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; NA, not available.
[a]*Instrumental ADL* refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [b]*Self-care ADL* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. [c]Disorder characterized by inflammation to the cornea of the eye. [d]Disorder characterized by dryness of the cornea and conjunctiva. [e]Disorder characterized by fear and avoidance of light.
National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE).* Version 5. US Department of Health and Human Services; 2017. Published November 27, 2017. Accessed July 30, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Patient Case Example

- A 56-year-old woman with ovarian cancer was treated with MIRV
- Results of her baseline ocular examination were normal
- 5 weeks into therapy (cycle 2), she presented with complaints of vision changes
- Upon evaluation, she was found to have developed corneal microcysts

Slit Lamp Images of Corneal Microcysts

(5 Weeks Into MIRV Therapy)



Arrows depict areas of subepithelial microcysts

MIRV, mirvetuximab soravtansine. Kunkler AL, et al. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(8):1771-1781.

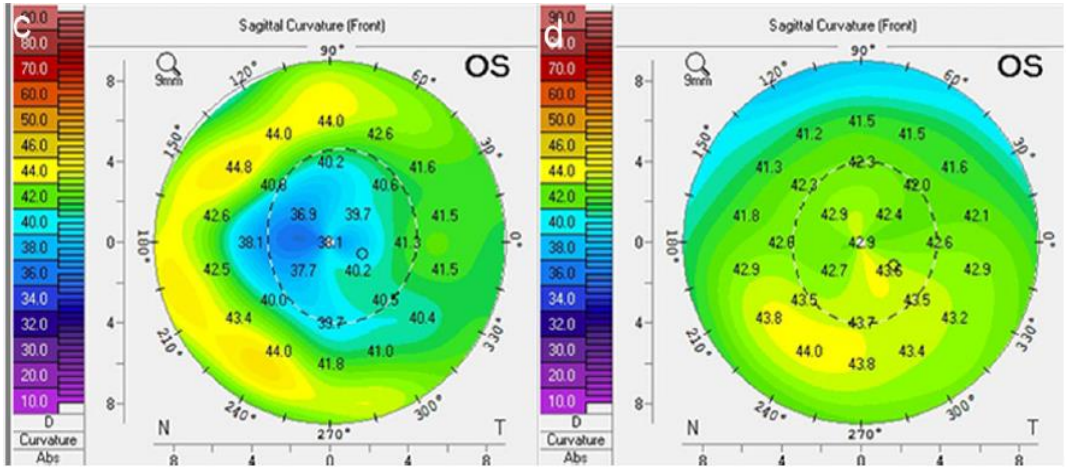
Patient Case Example (continued)

- This patient also exhibited central corneal flattening on topography, with an associated hyperopic refractive shift of +1.5 diopters
- While remaining on MIRV, she used tobramycin/dexamethasone drops and noticed improvement in symptoms in 1 week
- Within 1 month, her ocular examination returned to baseline

Corneal Topography

Corneal flattening on MIRV
(5 Weeks Into MIRV Therapy)

Improvement Following 1 Month Of Tobramycin/Dexamethasone Drops While Remaining On MIRV



Abs, absolute scale; D, diopter; MIRV, mirvetuximab soravtansine; OS, oculus sinister (left eye). Kunkler AL, et al. *Graefes Arch Clin Exp Ophthalmol.* 019;257(8):1771-1781.

Antibody-Drug Conjugates (ADCs)

- What are ADCs?
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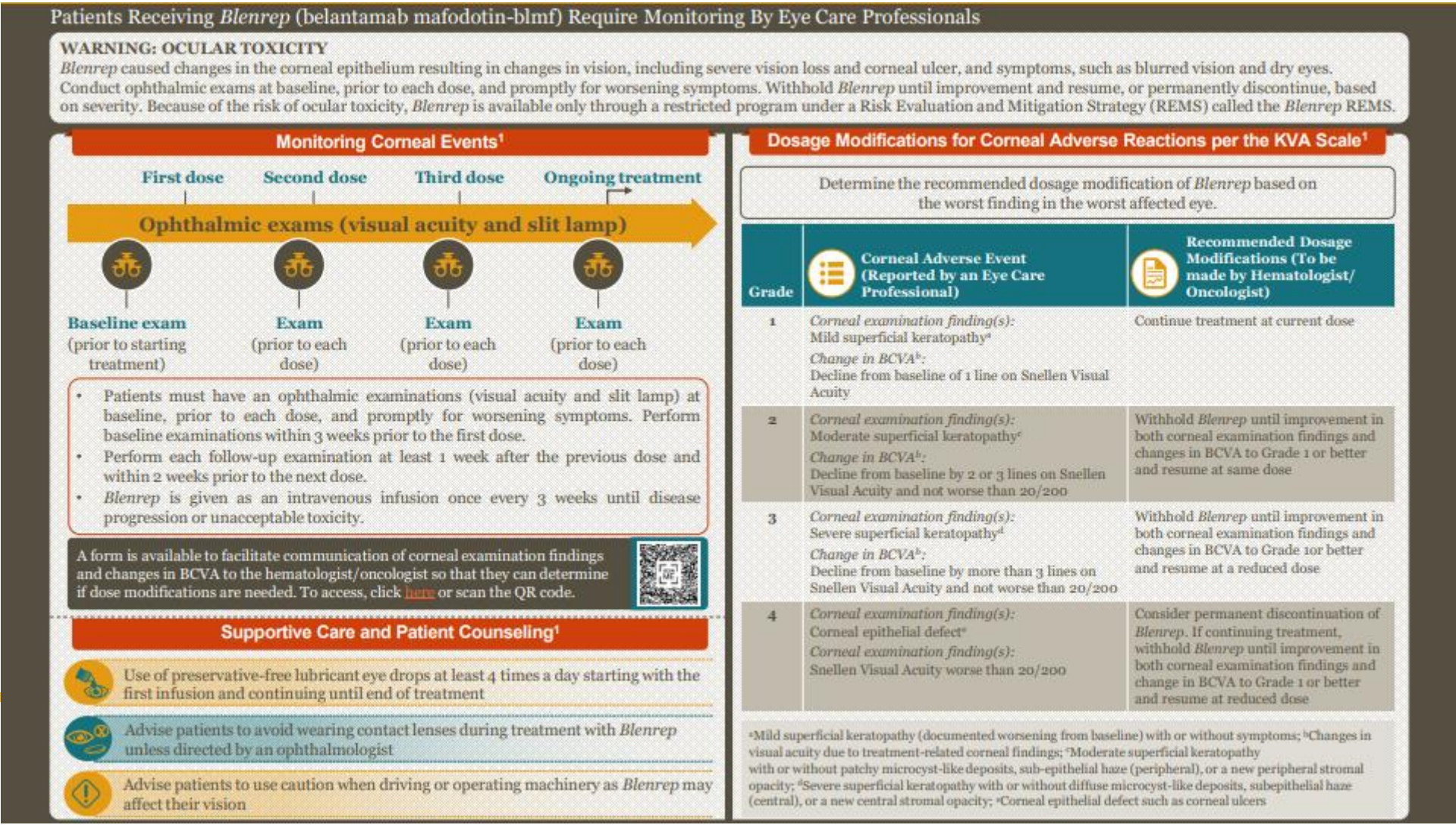
Risk Evaluation and Mitigation Strategy (REMS)



Patient Information

First Name:	Middle Initial:	Last Name:

Date of Birth (MM/DD/YYYY):	Phone:

Prescriber Information

First Name:	Last Name:

Phone:	Fax:	Email:

Eye Care Professional Information

First Name:	Last Name:	Credentials:

Phone:	Fax:	Email:

Information for Eye Care Professional

The prescriber will determine the recommended dosage modification of BLENREP based on the worst finding(s) in the worst affected eye.

During the ophthalmic exam, the eye care professional should:

- Assess the patient for corneal examination finding(s) and decline of best corrected visual acuity (BCVA).
- Determine the most severely affected eye as both eyes may not be affected to the same degree.
- Report the grade for the worst eye for examination finding(s) and BCVA to the treating physician by using Table 1 Corneal Adverse Reactions for KVA Scale, which was used in the clinical trial.

Corneal Examination Findings and Best Corrected Visual Acuity

Please refer to Table 1 for information on relevant examination findings for BLENREP.

Date of Assessment: _____

Section 1: For Baseline Examination Only

- What are the current best corrected Snellen visual acuity results?

  OD ___/___ OS ___/___

Eye Care Professional Consult Request Form

First Name:	Middle Initial:	Last Name:	Date of Birth (MM/DD/YYYY):

Section 2: For Follow-Up Examinations

- What are the current best corrected Snellen visual acuity results?

  OD ___/___ OS ___/___

- Were there findings upon corneal examination and/or visual acuity assessment? ☐ Yes ☐ No

  If **Y**, please check affected eyes:

  ☐ **OD**
  ☐ **OS**
  ☐ **OU**

Corneal Examination Findings and Change in BCVA from Baseline for Right Eye

	Corneal Examination Findings *Check One*	**Changes in BCVA from Baseline (per Snellen Visual Acuity)** *Check One*
Right eye (OD)	☐ No change from baseline ☐ Mild superficial keratopathy ☐ Moderate superficial keratopathy ☐ Severe superficial keratopathy ☐ Corneal epithelial defect	☐ No change from baseline ☐ Decline from baseline of 1 line on Snellen Visual Acuity ☐ Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200 ☐ Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200 ☐ Snellen Visual Acuity worse than 20/200
	Additional Corneal Examination Findings:	

Corneal Examination Findings and BCVA Changes from Baseline for Left Eye

	Corneal Examination Findings *Check One*	**Changes in BCVA from Baseline (per Snellen Visual Acuity)** *Check One*
Left eye (OS)	☐ No change from baseline ☐ Mild superficial keratopathy ☐ Moderate superficial keratopathy ☐ Severe superficial keratopathy ☐ Corneal epithelial defect	☐ No change from baseline ☐ Decline from baseline of 1 line on Snellen Visual Acuity ☐ Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200 ☐ Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200 ☐ Snellen Visual Acuity worse than 20/200
	Additional Corneal Examination Findings:	

Section 3: What is the current grading from the examination finding(s) and BCVA? *(Report the grade for the worst eye by checking the box.)*

Table 1. Corneal Adverse Reactions for KVA Scale.[a]

Report the grade for the worst eye by checking the box	Grade	Corneal Adverse Reaction
☐	**Normal**	*Corneal examination finding(s)* Cornea clear / No change from baseline *Change in BCVA[b]:* No decline from baseline of 1 line on Snellen Visual Acuity
☐	**Grade 1**	*Corneal examination finding(s)* Mild superficial keratopathy[c] *Change in BCVA[b]:* Decline from baseline of 1 line on Snellen Visual Acuity
☐	**Grade 2**	*Corneal examination finding(s):* Moderate superficial keratopathy[d] *Change in BCVA[b]:* Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200
☐	**Grade 3**	*Corneal examination finding(s):* Severe superficial keratopathy[e] *Change in BCVA[b]:* Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200
☐	**Grade 4**	*Corneal examination finding(s):* Corneal epithelial defect[f] *Change in BCVA[b]:* Snellen Visual Acuity worse than 20/200

[a] Adapted and modified from the Prescribing Information.
[b] Changes in visual acuity due to treatment-related corneal findings.
[c] Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.
[d] Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
[e] Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.
[f] Corneal epithelial defect such as corneal ulcers.

ELAHERE™
mirvetuximab soravtansine-gynx
injection 100 mg

Today's date: __/__/____

Ocular Assessment Form

This is an optional tool to help support eye care for patients prescribed ELAHERE

TO BE COMPLETED BY THE PRESCRIBING ONCOLOGIST OR PATIENT

ONCOLOGIST		PATIENT	
Name		Name	
Facility		Date of birth	
Phone		Patient ID	
Fax/email			

TO BE COMPLETED—AND SUBMITTED TO THE PRESCRIBING ONCOLOGIST—BY THE EYE CARE PROVIDER

Please select the appropriate option:

☉ Baseline exam ☉ Scheduled follow-up exam ☉ Follow-up due to patient-reported symptoms

Note: As part of their treatment with ELAHERE, your patient is being prescribed ophthalmic topical steroids that may elevate intraocular pressure.[1-4]

Symptom Assessment

☉ Patient reports the following new or ongoing ocular symptom(s): ☉ No symptoms reported

Visual Acuity[1]

	Baseline exam		Current exam	
	Right eye	Left eye	Right eye	Left eye
Best corrected distance visual acuity	20/	20/	20/	20/
Entering distance visual acuity Were corrective lenses worn during the assessment? ☉ Yes ☉ No	20/	20/	20/	20/

Ophthalmic Exam[1]

☉ No abnormal findings

Finding	Severity of finding	Right eye	Left eye	Action
Keratitis/ keratopathy	Nonconfluent superficial keratitis	☉ Yes	☉ Yes	Monitor
	Confluent superficial keratitis	☉ Yes	☉ Yes	If yes for either eye, notify prescribing oncologist[a]
	Cornea epithelial defect	☉ Yes	☉ Yes	
	3-line or more loss in best corrected visual acuity	☉ Yes	☉ Yes	
	Corneal ulcer	☉ Yes	☉ Yes	
	Stromal opacity	☉ Yes	☉ Yes	
	Best corrected distance visual acuity of 20/200 or worse	☉ Yes	☉ Yes	
	Corneal perforation	☉ Yes	☉ Yes	
Uveitis	Grade 1/rare cell in anterior chamber	☉ Yes	☉ Yes	Monitor
	Grade 2/1-2+ cell or flare in anterior chamber	☉ Yes	☉ Yes	If yes for either eye, notify prescribing oncologist[a]
	Grade 3/3+ cell or flare in anterior chamber	☉ Yes	☉ Yes	
	Grade 4/hypopyon	☉ Yes	☉ Yes	

[a]Reporting exam findings to the treating oncologist can guide the need for dose modification of ELAHERE due to ocular adverse events.[1]

Additional Information	Eye Care Provider: *(Name and Contact Information)*

UCLA Stei

Ocular substudy of DREAMM-2

- 30 patients
- Monocular prophylactic corticosteroid eye drops
- Preservative-free artificial tears 4-8x/day OU
  - Treated eye: grade 3 - 29% @2.5.4mg/kg, 42% @3.4mg/kg
  - Untreated eye: grade 3 – 18% @2.5mg/kg, 50% @3.4mg/kg
  - Median time to keratopathy onset similar
- Conclusion: steroids are ineffective

Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, Abdallah AO, Callander N, Lendvai N, Sborov D, Suvannasankha A, Weisel K, Karlin L, Libby E, Arnulf B, Facon T, Hulin C, Kortüm KM, Rodríguez-Otero P, Usmani SZ, Hari P, Baz R, Quach H, Moreau P, Voorhees PM, Gupta I, Hoos A, Zhi E, Baron J, Piontek T, Lewis E, Jewell RC, Dettman EJ, Popat R, Esposti SD, Opalinska J, Richardson P, Cohen AD. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020 Feb;21(2):207-221. doi: 10.1016/S1470-2045(19)30788-0. Epub 2019 Dec 16. PMID: 31859245.

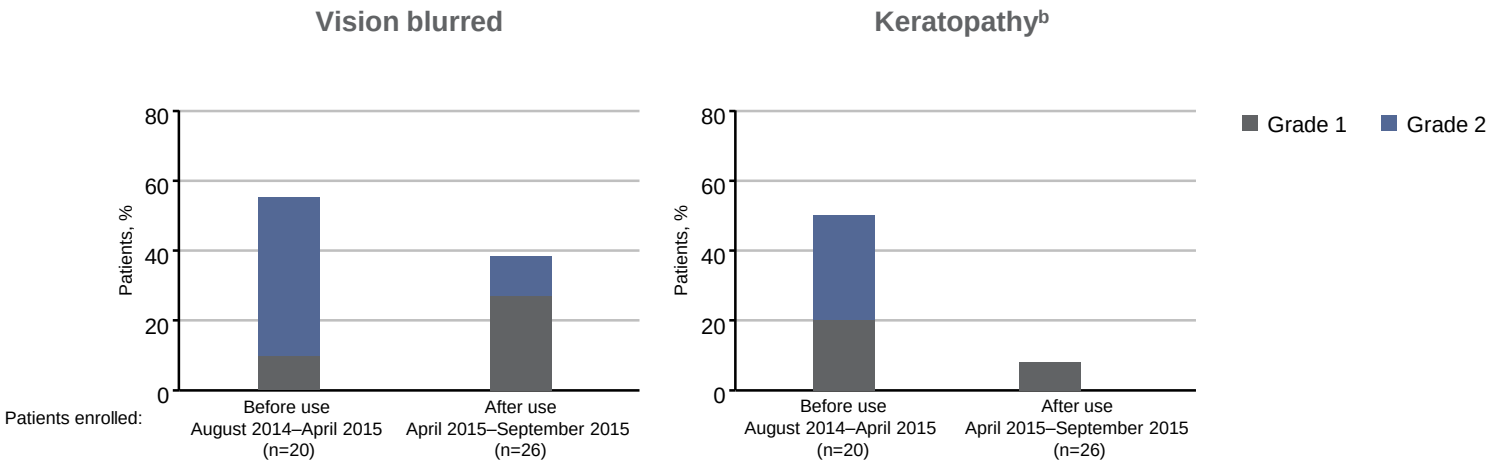
Other ADC studies suggest topical steroids may be of some benefit

- 3 out of 22 references reported some benefit in patients with corneal AEs
  - One was associated with reduced incidence
  - Poorly studied – does not seem promising

Adherence to Preventative Measures Decreased the Incidence and Grade of Visual Disturbances With MIRV[1]

Prophylactic use of preservative-free lubricating eye drops and other preventive measures—including avoiding the use of contact lenses, cleaning the exterior eye area, using warm compresses, and wearing sunglasses in daylight—were implemented in the phase 1 first-in-human study[1,2,a]

Comparison of Ocular AEs Before and After Use of Preservative-Free Lubricating Eye Drops[2]



Mandating the use of daily lubricating eye drops and additional ocular management procedures subsequently decreased both the incidence and grade of ocular AEs with MIRV[1]

AE, adverse event; MIRV, mirvetuximab soravtansine.

[a]ClinicalTrials.gov identifier: NCT01609556.[3] [b]Keratopathy included corneal cyst, corneal disorder, corneal deposits, corneal epithelial microcysts, keratitis, keratopathy, limbal stem cell deficiency, and punctate keratitis.[2]

1. Moore KN, et al. *J Clin Oncol*. 2017;35(10):1112-1118. **2.** Moore KN, et al. Presented at: 2016 American Society of Clinical Oncology Annual Meeting; June 3–7, 2016; Chicago, Illinois. Abstract 5567. **3.** ClinicalTrials.gov identifier: NCT01609556. Updated February 17, 2021. Accessed September 2, 2022. https://clinicaltrials.gov/ct2/show/NCT01609556.

So what else can be done?

- I don't really know!
  - Until the mechanism is better understood we don't have a good strategy
- I have tried amniotic membrane placement without success (n = 1)
- Bandage contact lenses have not been reported to be of any benefit
- Cooling masks and vasoconstrictors during the infusion don't really seem to make a big impact
- Active studies looking at autologous serum tears with some anecdotal reports of success (seems promising)

CJO JCO

Original Article

Reversible HER2 antibody-drug conjugate-induced ocular toxicity

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Objective: To report 3 cases of reversible epitheliopathy induced by A166—a human epidermal growth factor receptor (HER2)-targeted antibody-drug conjugate (ADC) therapy for resistant HER2 tumours.

Methods: Advanced HER2 tumour patients were enrolled in A166 phase I/II clinical trial using Bayesian logistic regression model dose escalation. Key exclusion criteria were ≥grade 2 (G2) corneal pathology, severe organ disease, and other cancer therapy within 4 weeks. Eye exams were performed at baseline, regularly scheduled intervals, and additionally upon A166-induced ocular symptoms. Topical therapy with autologous serum tears (ASTs) was implemented based on visual acuity, symptoms, and slit lamp exam. A166 was withheld if ≥G2 ocular toxicity developed; if status improved to ≤G1, A166 therapy was resumed. Visual acuity, corneal exam, and subjective comfort were recorded.

Results: After ≥2 cycles of A166, 6 eyes of 3/23 enrolled patients developed whorl pattern epitheliopathy suggestive of limbal stem cell (LSC) dysfunction requiring cessation of A166 despite positive tumour response. Patients 1 and 3 received 3.6 mg/kg A166 dose, and patient 2 received 3.0 mg/kg. Topical steroids (2/4 eyes) failed to improve epitheliopathy. Adding ASTs improved vision, ocular comfort, and whorl pattern epitheliopathy in 6/6 eyes within 3 weeks. Patient 1 continues to improve on ASTs; patient 2 withdrew from the study; and patient 3 resumed A166 therapy.

Conclusion: A166 precipitates LSC *dysfunction*-like epitheliopathy. Combination therapy including aggressive lubrication, withholding drug, and ASTs help reverse toxicity. Recognizing that ADC-induced epitheliopathy can respond to ocular management may enable cancer patients to continue lifesaving therapy.

Antibody-Drug Conjugates (ADCs)

- What are ADCs?
- Ocular adverse events with ADCs
- Management of ocular adverse events
- Discussion

OCULAR AEs ASSOCIATED WITH ADCs

What c e events

s?

- There are

TABLE 3. SUMMARY OF THE INCIDENCE OF OCULAR AEs ACROSS ALL REFERENCES

Adverse event	*Number of references (of 22) citing AE*
Blurred vision	10
Keratitis (including punctate)	8
Dry eye	7
Corneal microcysts/microcystic epithelial changes	5
Corneal deposits/inclusions	4
Conjunctivitis/keratoconjunctivitis	3
Decreased visual acuity	2
Unspecified keratopathy	2
Optic neuropathy	2
Eye irritation	2
Diplopia	2
Corneal epithelial defect/damage	1
Unspecified ocular toxicity	1
Ocular surface disease	1
Swollen tear duct	1
Increased lacrimation	1
Conjunctival hemorrhage	1
Eye redness	1
Ocular bleeding (location unspecified)	1
Uveitis (bilateral)	1
Iridocyclitis	1
Photophobia	1
Cataract	1
Cortical blindness	1
Scotoma	1
Nonspecific retinopathy	1
Eye pain	1
Floaters	1
Retinal vein occlusion	1

Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular Adverse Events Associated with Antibody-Drug Conjugates in Human Clinical Trials. J Ocul Pharmacol Ther. 2015 Dec;31(10):589-604. doi: 10.1089/jop.2015.0064. Epub 2015 Nov 5. PMID: 26539624; PMCID: PMC4677113.

Why does this happen?

- We still don't know!
  - Direct vs. indirect delivery of payload to epithelial cells causing necrosis
    - On target (antibody-mediated delivery)
    - Off target (delivery of an unconjugated cytotoxin)
  - Until we know the exact mechanism it will be challenging to develop a mitigation strategy

What will patient's complain of?

Dry eye

Blurred vision

What are things ECPs should look for and ask during an exam?

- OBJECTIVE CHANGE IN VISION
- WORSENING DRY EYE OR KERATOPATHY
- MEC'S: Microcyst-like epithelial changes

What diagnostic tests should be done?

- BCVA – perform refraction
  - Refraction will commonly fluctuate but as long as BCVA is similar to baseline treatment can continue

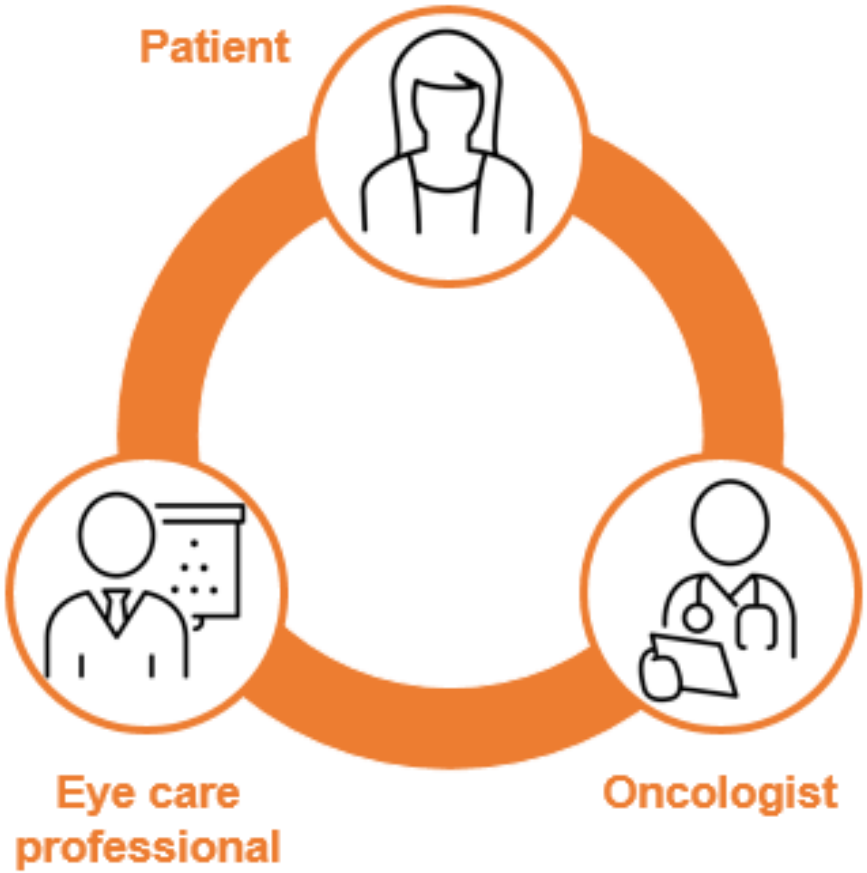
- Slit lamp exam
  - Once epithelial cysts have involved mid-periphery or center treatment must be held until improvement

    (Belantamab guidelines) – other future guidelines may differ

How should you manage these patients?

- Evolving treatment algorithms
  - In general infusions are given every 3 weeks
  - Eye exam performed < 3 weeks prior to first infusion
  - Follow-up exam at least 1 week after previous dose and within 2 weeks prior to next dose
- PFATs 4-8x/day is the best we have for now
- Studies with ASTs are ongoing and seem promising

Communication with Heme/Onc is critical



Questions?

Thank You!

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