POTENTIAL MECHANISM FOR OCULAR ADVERSE EVENTS OBSERVED WITH TISOTUMAB VEDOTIN

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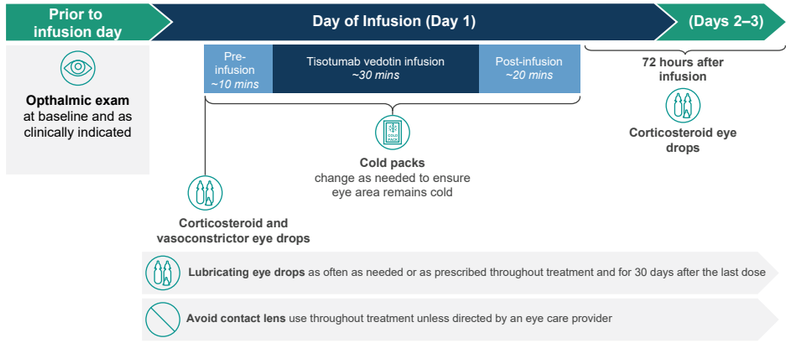
BACKGROUND

- Tisotumab vedotin (TV) is a TF-directed ADC composed of the mAb, tisotumab, conjugated to the cytotoxic payload, MMAE
- TF levels are elevated in solid tumors[1] and TF is expressed in the ocular epithelium[2,3]; therefore, ocular AEs can occur in patients treated with TV
- TV monotherapy was granted accelerated approval by the US FDA for adult patients with r/mCC with disease progression on or after chemotherapy[4]
  - Approval was based on results for tumor response rate and durability of response in the pivotal, multicenter, open label, international study innovaTV 204
  - TV has a boxed warning for ocular toxicity as part of the USPI[4]
- 54% patients in the innovaTV 204/GOG-3023/ENGOT-cx6 (innovaTV 204) study experienced at least 1 ocular AE
  - Most common ocular AEs observed were conjunctivitis, dry eye, and keratitis; majority were Grade 1 or 2 events[5]
  - All patients were required to follow a mandatory eye care plan to mitigate risk of and manage potential ocular AEs[5,6]

innovaTV 204 REQUIRED EYE CARE PLAN[5]



Adapted from Kim SK, Ursell P, Coleman RL, Monk BJ, Vergote I. Mitigation and management strategies for ocular events associated with tisotumab vedotin. Gynecol Oncol. 2022;165(2):385-92, with permission from Elsevier.

- Patients instructed to contact care team if ocular symptoms occurred during treatment
- Prompt referral to opthalmologist for new or worsening ocular symptoms
- Adherence to the Required Eye Care Plan along with collaboration with ophthalmologists and dose modifications based on pre-specified guidelines were employed to reduce risk of ocular AEs
- Clinicians should refer to the USPI for most up-to-date safety information including the Required Eye Care

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Abstract #192; International Gynecologic Cancer Society (IGCS); September 29-October 1, 2022

NONCLINICAL EVALUATION OF OCULAR AEs OBSERVED WITH TV

IN VITRO TISSUE CROSS-REACTIVITY (TCR) STUDY

Species	Epithelial cell type stained	Location of observed membrane staining	Staining intensity and frequency
Human	Eye (cornea, conjunctiva, lens)	Cornea/conjunctiva: membrane staining observed on entire circumference of stained cells with corneal staining on superficial layers, conjunctival staining in all layers. Lens: membrane staining on basal and apical surface of cells.	Weak to strong (1+ to 3+) Frequent (>75–100% of cells)
Cynomolgus monkey	Eye (conjunctiva, lens)	Conjunctiva: membrane staining observed on entire circumference of stained cells. Lens: membrane staining on apical surface of cells.	Weak to strong (1+ to 3+) Frequent (>75–100% of cells)

Note: Frozen normal human and cynomolgus monkey tissues (n=3 donors per species) were stained with TV or tisotumab antibody at 0.5 or 2 ug/mL. Staining location, intensity, and frequency were evaluated.

4-point scale used to assess staining intensity (1+ = weak, 2+ = moderate, 3+ = strong, 4+ = intense)

- TV and tisotumab antibody bind to cryosections of human and cynomolgus monkey ocular tissues, including conjunctival and corneal epithelium

REPEAT-DOSE 13-WEEK CYNOMOLGUS MONKEY TOXICITY STUDY

Test item	Dose level (mg/kg)	Number of animals with ocular symptoms	
		Males	Females
Vehicle Control	0	0	0
TV	1	0/5	0/5
	3	1/5	0/5
	5	4/4*	3/5
Tisotumab	25	0/5	0/5

Note: Animals dosed once every three weeks for 5 doses

* 1 animal euthanized early due to adverse skin lesions, not included in ocular symptom evaluation

- Ocular findings in cynomolgus monkeys observed with TV, but not with tisotumab antibody
  - At 3 and 5 mg/kg of TV, reddened or partially closed eyes and reddened conjunctiva were observed
  - Binding/inhibiting TF at 5-fold higher doses with the tisotumab antibody alone did not lead to ocular symptoms

Disclosures

Thank you to our patients and their families for their participation in the innovaTV 204 study, and to all research personnel for their support of this important trial. Medical writing support was provided by Sarah Canestaro, MS (contract medical writer) Seagen Inc.

The innovaTV 204 study was funded by Genmab A/S and Seagen Inc. and sponsored by Genmab, Gynecologic Oncololgy Group (GOG), and European Network for Gynaecological OncologicalTrials group (ENGOT). IV reports consulting fees from Agenus, Akesobio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, Jazzpharma, Karyopharm, Mersana, MSD, Novocure, Novartis, Oncoinvent, OncXerna, Sanofi, Seagen, Sotio, Verastem Oncology, Zentalis; research support from Oncoinvent, Amgen, Roche; travel expenses from Karyopharm. SK reports consultancy from Bayer, Eli Lilly, Seagen Inc. and research funding from Seagen Inc.

OCULAR AEs OBSERVED IN innovaTV 204[5]

Occurrence of ocular AEs in innovaTV 204 regardless of causality	Patients (N=101) n (%)	
	Any Grade	Grade ≥3
Pts with ≥1 ocular AE	55 (54)	3 (3)
Ocular AE in ≥3 patients		
Conjunctivitis	31 (31)	0
Dry eye	25 (25)	0
Keratitis	11 (11)	0
Blepharitis	7 (7)	0
Punctate keratitis	6 (6)	0
Increased lacrimation	4 (4)	0
Ocular hyperemia	4 (4)	0
Blurred vision	3 (3)	0
Entropion	3 (3)	0
Meibomitis	3 (3)	0
Ulcerative keratitis	3 (3)	3 (3)

- Inflammatory, symptomatic, with most confined to the ocular surface
- 4 patients experienced changes in visual acuity of which 75% resolved at last follow up
- Median time to onset of first ocular AE was 1.4 months (IQR 0.7–2.0) and median time to resolution was 0.7 months (0.3–1.6)
- Majority (86%) of the observed 138 ocular AEs related to TV resolved within 30 days after last TV dose
- 5% patients discontinued treatment due to ocular AEs

CONCLUSIONS

- Ocular AEs observed with TV in the pivotal innovaTV 204 study were primarily mild to moderate, confined to the ocular surface, and symptomatic
- Impact to visual acuity was low, and majority (86%) of ocular AEs were reversible
- Nonclinical study data show that while both tisotumab antibody and TV bind to ocular tissues (in vitro TCR Study), only dosing with TV resulted in ocular AEs (Cynomolgus Monkey Toxicity study)
  - Ocular AEs observed with TV are potentially driven by directed delivery of MMAE to TF-expressing cells in the ocular epithelium
  - This mechanism is potentially distinct from keratopathies with other ADCs which were due to non-antigen mediated uptake by corneal epithelial cells[5]
- Careful monitoring/reporting of ocular symptoms, adherence to the Eye Care Plan, and dose modifications can mitigate risk of ocular AEs observed with TV

Abbreviations

ADC: antibody-drug conjugate, AEs: adverse events; FDA: Food and Drug Administration, IQR: interquartile range, mAb: monoclonal antibody; MMAE: monomethyl auristatin E, r/mCC: recurrent or metastatic cervical cancer, TCR: tissue cross-reactivity study, TF: tissue factor, TV: tisotumab vedotin, US: United States, USPI: United States prescribing information

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