Exposure-Safety Markov Modeling of Ocular Adverse Events in Patient Populations Treated With Tisotumab Vedotin

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Objectives

- To describe the time course of grade ≥2 ocular AEs using Markov modeling in patients with solid tumors who were treated with TV mono or in combination with other treatments
- To evaluate the effect of TV exposure on grade ≥2 risk of ocular AEs as well as covariate effects on risk of grade ≥2 ocular AEs
- To evaluate the effect of alternate dosing regimens of TV on the risk of ocular AEs

Conclusions

The discrete time Markov model reasonably described the observed time course of ocular AEs, as well as transition probabilities, following treatment with TV mono or combination therapy

Of the multiple covariates modeled, results indicated that implementation of the Eye Care Plan significantly reduced the risk of grade ≥2 ocular AEs, whereas other multipliers did not lead to a statistically significant reduction of risk

The model predicted a higher probability of grade ≥2 ocular AEs with increased dose intensity at a Q2W dosing schedule compared with Q3W[4]

Background

- TV is a TF-directed ADC composed of 1) a fully human monoclonal antibody specific for TF, 2) the microtubule-disrupting agent MMAE, and 3) a protease-cleavable linker that covalently links MMAE to the antibody
  - In tumor cells, TF has been shown to promote tumor growth, angiogenesis, and metastasis[1,2]
- TV has an established dosing regimen of 2.0 mg/kg Q3W in cervical cancer[3]
  - Continued efforts are being made to further optimize the dose intensity of TV driven by the hypothesis that increased dose intensity may lead to increased efficacy[4]
  - Previous modeling work suggests that the more frequent 1.7 mg/kg Q2W dosing regimen can achieve a higher dose intensity and may enhance clinical activity in noncervical cancers[4]
  - The 1.7 mg/kg Q2W dose is being evaluated clinically in the ongoing innovaTV 207 trial[5]
- With increased dose intensity, the risk of safety signals also increases. Here, we present how increased dose intensity of TV impacts one the key AEs of special interest

Methods

- Data from 7 studies of TV in patients with advanced solid tumors were used for modeling[5-18]
- The final popPK model is shown in **Figure 1**
  - Model-based simulations assessed the safety profile of TV at alternative dosing regimens in 757 patients
  - The exposure-ocular model was a discrete time Markov model (2-state) with a first-order Markov element and interindividual variability on baseline probabilities

Ocular AE Dataset

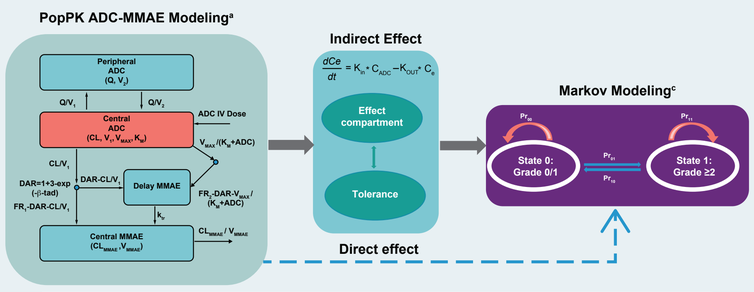
- Ocular AE data used to generate the Markov model are inclusive of both TV mono and in combination with other treatments across all tumor types
- **Table 1** shows the number of patients at various dose levels and schedules who experienced at least one grade ≥2 ocular AE
  - Patients treated with TV in combination with pembro and carbo reported similar grade ≥2 ocular AEs relative to TV mono

Table 1. Dosing Regimen and Sample Size of Patient Datasets

TV regimen	Grade ≥2 OAE, n (%)	Total patients, N
innovaTV 207[5-7]		
0.9 mg/kg 3Q4W mono	7 (15)	46
1.7 mg/kg Q2W mono	1 (17)	6
2.0 mg/kg Q3W mono	22 (26)	86
innovaTV 208[8]		
0.9 mg/kg 3Q4W mono	20 (23)	86
1.2 mg/kg 3Q4W mono	1 (13)	8
innovaTV 204[a,9,10]		
2.0 mg/kg Q3W mono	27 (27)	101
innovaTV 205[11,12]		
0.9 mg/kg 3Q4W mono	9 (27)	33
1.3 mg/kg Q3W + bev	3 (50)	6
1.3 mg/kg Q3W + carbo	0	6
1.3 mg/kg Q3W + pembro	2 (33)	6
2.0 mg/kg Q3W + bev	8 (89)	9
2.0 mg/kg Q3W + carbo	13 (33)	40
2.0 mg/kg Q3W + pembro	24 (32)	74
innovaTV 206[13,14]		
1.5 mg/kg Q3W mono	0	3
2.0 mg/kg Q3W mono	3 (15)	20
innovaTV 201[15-17]		
0.3 mg/kg Q3W mono	0	3
0.6 mg/kg Q3W mono	0	3
0.9 mg/kg Q3W mono	0	3
1.2 mg/kg Q3W mono	0	3
1.5 mg/kg Q3W mono	0	3
1.8 mg/kg Q3W mono	1 (33)	3
2.0 mg/kg Q3W mono	53 (31)	170
2.2 mg/kg Q3W mono	1 (14)	7
innovaTV 202[18]		
0.9 mg/kg Q3W mono	2 (67)	3
1.2 mg/kg Q3W mono	1 (17)	6
1.2 mg/kg 3Q4W mono	8 (62)	13
1.2 mg/kg Q3W mono	3 (5)	6
2.0 mg/kg Q3W mono	1 (25)	4

[a]Details of the ocular Eye Care Plan can be found in the published protocol of the innovaTV 204 study on Clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT03438396. The prophylactic Eye Care Plan was introduced during the conduct of the study leading to results reflective of a mixture of ocular AE rates prior to and post-Eye Care Plan implementation.

Figure 1. Final PopPK and Transition Model



Exposure model[b]	Transform[b]
Direct effect	linear, E_{max}, power
Effect compartment	linear, E_{max}, power
Tolerance model (modulating cmt)	linear, power
Indirect response (stimulate K_{OUT})	linear, E_{max}

[a]Two-compartment ADC model with parallel linear and Michaelis–Menten elimination, a delay compartment, and a one-compartment MMAE model.[19] [b]Varying combinations of the exposure models and transformations applied to both ADC and MMAE. Logit(F_{i1}) = β_{i1} + f(exposure of ADC) + f(exposure of MMAE), where exposure = actual daily-C_{max} and daily-C_{avg} and concentration in effective compartment. [c]The transition probability from state i to j (Pr_{ij}) for j=0 or 1: Pr_{i0} = 1 – F_{i1} and Pr_{i1} = F_{i1}, where the F_{ij} are cumulative probability density functions.

Results

Best-fitting Model

- The Base model (Model 1) described ADC using a hyperbolic function of C_e
- When estimating the effect of MMAE and ADC simultaneously on the risk of grade ≥2 ocular AEs (Model 2), the opposing directionality of the exposure-response effects indicated the 2 were not separately identifiable
  - Parameter estimates suggested that ADC was associated with significant elevation of risk, while MMAE was associated with significant lowering of risk
- Given the potential parameter identifiable issues in Model 2 as well as the lack of a clear scientific rationale for counterintuitive effect of MMAE on risk of AE, ADC alone was chosen as the exposure metric in the base model (Model 1)
- The Final model (Model 3) was developed by adding covariates to Model 1 as proportional factors on the effect of C_e (**Table 2**)

Table 2. AIC and Objective Model Function

Model	Description	Objective function	AIC
1	**Base model (Model 1):** 2 state; effect compartment, E_{max} ADC only; IIV on baseline	5638.663	5650.663
2	**Model 2**: 2 state; effect compartment, E_{max} ADC only, linear function for MMAE; IIV on baseline	5594.443	5608.443
3	**Final model (Model 3):** E_{max}; effect compartment of ADC, differing conditional effect across states; IIV on baseline; covariate model	5499.285	5525.285

Covariate Effect and Effect of Exposure on Ocular AE Risk

- Incidence of ocular AEs with TV combination regimens were consistent with rates seen with TV mono (**Figure 2**)
  - Relative to TV mono, there was a directional increase in the risk of ocular AEs with TV in combination with bev, however, this increase was not significant
- Use of prophylactic treatment and the introduction of the Eye Care Plan were associated with a reduced risk of ocular AEs
  - Baseline prophylactic eye care was the only factor impacting risk

Model Application: Grade ≥2 Ocular AEs in Alternative Dosing Regimens

- Higher dose intensities appeared to be associated with a higher risk of grade ≥2 ocular AEs[4] (**Figure 3**)
  - A Markov modeling approach has the potiental to predict the toxicity of alternative treatment regimens

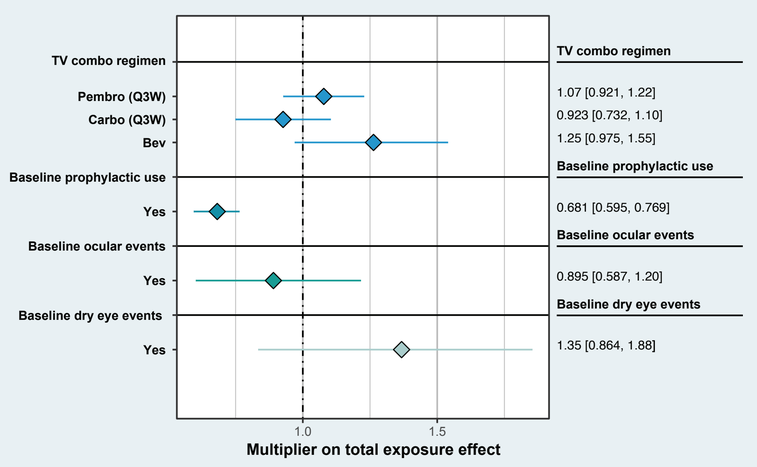
Model Evaluation: Visual Predictive Check and Evaluation of Transition Probability

- The final Markov model provided a reasonable description of observed grade ≥2 ocular AE data (**Figure 4**)

Model Evaluation: Time-to-Event of First Grade ≥2 Ocular AE

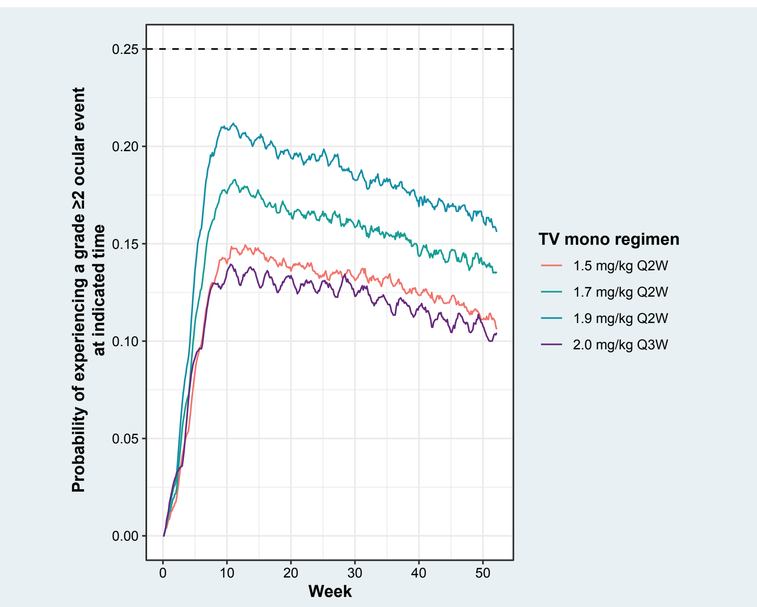
- The final model reasonably characterized the timing of ocular AEs (**Figure 5**)
  - Most first grade ≥2 ocular AEs happened approximately 14–21 weeks after therapy initiation
  - The AE profile was similar between mono and combination therapies

Figure 2. Ocular AE Final Model[a] (N=757)



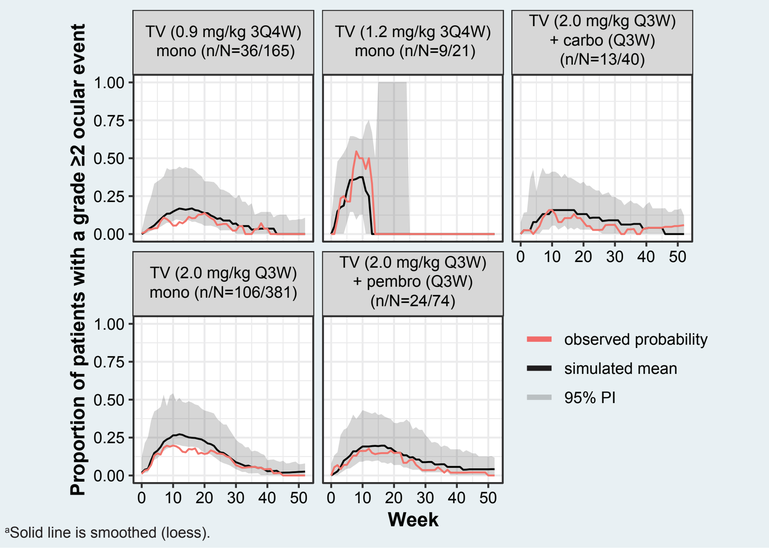
[a]Mean and 90% CI of indicated effect as a proportional effect (relative to the reference patient) on the total exposure effect on the log-odds of transition. The reference patient, who was treated with TV mono, was studied prior to the Eye Care Plan and had no baseline ocular events or baseline dry eye events.

Figure 3. Combined Simulations: Predicted Ocular AEs in Noncervical Cancers[a]



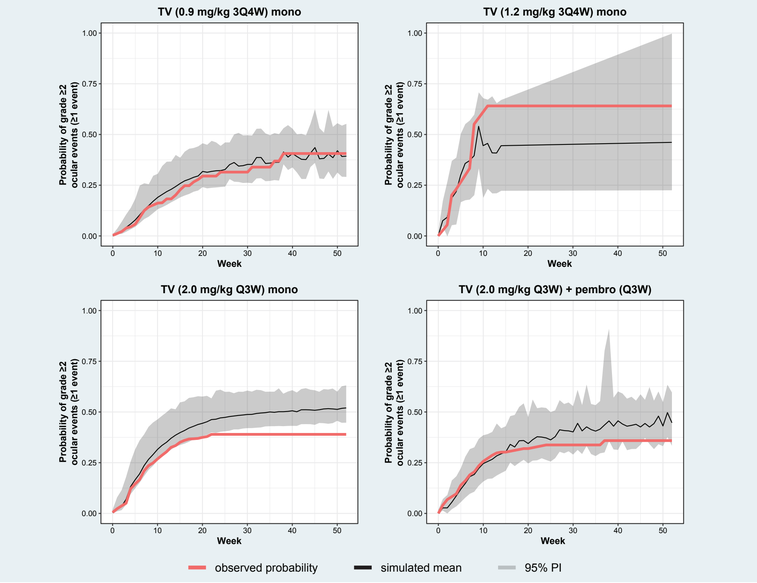
[a]Lines indicate the mean probability for those remaining in the simulated trial at the indicated week.

Figure 4. Visual Predictive Check[a]



[a]Solid line is smoothed (loess).

Figure 5. Time-to-Event of First Grade ≥2 Ocular AE



Abbreviations

3Q4W, days 1, 8, and 15 of a 28-day cycle; ADC, antibody-drug conjugate; AE, adverse event; AIC, Akaike information criterion; AUC, area under the time-concentration curve; bev, bevacizumab; C_{avg}, average concentration; carbo, carboplatin; C_e, effect compartment; CI, confidence interval; CL, clearance; C_{max}, maximum concentration; cmt, compartment; C_{trough}, trough concentration; DAR, drug-antibody ratio; E_{max}, maximal effect; FR_1, fraction of ADC non-specific elimination to the central compartment; FR_2, fraction of ADC target-mediated elimination to the delay compartment; IIV, inter-individual variability; IV, intravenous; K_M, Michaelis–Menten constant; K_{OUT}, first order degradation rate of response; MMAE, monomethyl auristatin E; mono, monotherapy; OAE, ocular adverse event; pembro, pembrolizumab; PI, prediction interval; popPK, population pharmacokinetics; Pr, transition probability; Q, inter-compartmental clearance; Q2W, days 1 and 15 of a 28-day cycle; Q3W, day 1 of a 21-day cycle; TF, tissue factor; TRAE, treatment-related AEs; TV, tisotumab vedotin; V, volume; V_{max}, maximum volume.

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Disclosures

YSF, CP, AG, IS, and MG are employees of and have equity in Genmab. RG, JV, CO, LN, and WDH are employees of and have equity in Seagen Inc. DP is an employee of Metrum Research Group, which is a paid consultant for Seagen and Genmab.

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