Objective: Various pharmacokinetic/pharmacodynamic (PK/PD) models have been reported in the literature for describing the anti-tumor efficacy of antibody-drug conjugates (ADCs), with an assumption that ADCs act on the entire cell population (i.e., tumor volume). In the present work, a semi-mechanistic model was developed to incorporate the mechanism of action of a tubulysin payload that acts on dividing tumor cells in the mitotic phase. The new model was compared further with the widely used Simeoni and Jumbe models in terms of the model performance.

Methods: The serum ADC concentrations and tumor volumes from four patient-derived xenograft (PDX) mouse tumor models were fitted using the Simeoni, Jumbe and new models (Phoenix 6.4 NLME 1.3, Certara, St. Louis, Missouri, USA). The new model assumed that the local tumor ADC concentrations drove the efficacy and the ADC was distributed into the tumor by non-saturating pathways. In addition, the total tumor volume was divided into three cell populations: 1) resting, 2) mitotic, and 3) apoptotic tumor volumes, with only the mitotic tumor volume responsible for the tumor growth and inhibited by the ADC. To further account for the delay in the tumor growth inhibition, three transit compartments were added. The tumor static concentration (TSC) was estimated from all three models tested, and the model performance was compared using various diagnostic parameters.

Results: The new PK/PD model was able to successfully fit the tumor regression data and capture dose-dependent anti-tumor efficacy of the ADC in all four PDX models studied. In addition, the estimated TSC values from the Simeoni, Jumbe, and new models were found to be within 2-fold. When these three models were compared using Akaike information criterion, Bayesian information criterion, and visual predictive check, an improved model performance was observed with the new model.

Conclusions: A new semi-mechanistic model was developed by considering the ADC distribution into the tumor and the mechanism of action of the payload. This newly established model was shown to provide a better fit compared to the Simeoni and Jumbe models and may be suitable for modeling the anti-tumor efficacy of ADCs with anti-mitotic payloads.