PK/PD Modeling of Soluble Ligand and Tumor Growth Inhibition for Anti-GITR Antibody mDTA-1 in Syngeneic Mouse Tumor Models

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Objectives: To characterize the PK/PD relationship of the soluble ligand, soluble glucocorticoid-induced TNFR-related protein (sGITR), and tumor growth inhibition for the anti-GITR antibody, murine DTA-1 (mDTA-1), in a Colon26 syngeneic mouse tumor model.

Methods: The relationship between serum mDTA-1 exposure and serum sGITR levels was evaluated in Colon26 syngeneic tumor mice following a single intravenous (i.v.) dose of 0.3, 1, 3, 10 or 15 mg/kg of mDTA-1. A one-compartment PK model with linear and non-linear (Michaelis-Menten) clearance was used to describe the PK of mDTA-1. The relationship between mDTA-1 exposure and sGITR was described using an Emax model. Tumor growth inhibition was described by an exponential model with first-order growth and second-order killing driven by mDTA-1 concentration, with first-order transit capturing delay of tumor cell death [1].

Results: The model-estimated maximal response (E_{\text{max}}) was 132 ng/mL sGITR. The mDTA-1 exposure to produce 50% of E_{\text{max}} (AUC_{50}) was 516 h·µg/mL, and the estimated baseline level of sGITR was 11.4 ng/mL. The linear clearance (CL), maximal elimination rate (V_{\text{max}}) and the Michaelis-Menten constant (K_m) of mDTA-1 were estimated to be 0.0082 mL/h, 0.38 µg/mL/h and 2.17 µg/mL, respectively. The estimated first-order growth rate (K_g), second-order tumor death rate (K_{\text{kill}}) and first-order rate constant of transit (k_1) were 0.0059 h^{-1}, 0.0078 (h·µg/mL)^{-1} and 0.012 h^{-1}, respectively. The tumor stasis concentration (TSC), derived from the model, was estimated to be 0.742 µg/mL.

Conclusions: The exposure-response relationship for sGITR and tumor growth inhibition following i.v. administration of mDTA-1 in tumor bearing mice were well described by Emax and tumor kinetic PK/PD models, respectively. The results were used in part to predict the minimal anticipated biological effect level (MABEL) and efficacious dose in patients.

Reference: