Population Modeling of Tumor Growth in a Murine Xenograft Model Following Administration of Biologic Drug Candidate

L. Zhao*, G. Robbie, D. Jackson, J. Gooya, M. Camara, E. Gibiansky

MedImmune, Gaithersburg, MD, U.S.A.

Objectives: To propose a semi-mechanistic dynamic model of tumor growth and antibody-drug conjugate (ADC) effects in a murine xenograft model and to propose doses/regimens that optimize therapeutic efficacy based on the model.

Methods: Mice were injected subcutaneously with PC3 human prostate tumors. When tumors reached 200-300 m^3, 7 groups of mice (10/group) were administered the ADC (3 dose levels x 2 dose frequencies, plus 1 control group) and tumor volumes were measured over time. Tumor ADC concentrations from a separate experiment were used for population exposure-response modeling. The model of tumor growth and drug effects suggested previously [1] could not adequately describe the response in individual animals across the doses. The model was modified to account for i) the continuous decrease of growth rate for proliferating cells between the initial exponential and final linear growth, ii) correlation of tumor growth rate in the initial and later stages; iii) the decrease of drug killing rate with increase of tumor volume, and iv) delay in the response due to kinetics of receptor internalization and delayed manifestation of cytotoxicity for cell-cycle specific agents. The proposed model was both internally and externally validated with additional experimental data. Simulations of different dosing regimens were performed and new experiments with optimized efficacy proposed.

Results: The model for tumor volume consists of proliferating tumor cells and a number of transit compartments that represent compromised (non-proliferating) cells and delayed cell death. The rate of growth of proliferating cells is described by a sigmoidal (Emax) function of volume of proliferating cells. The converting rate of proliferating cells to compromised tumor cells is proportionally related to the ADC concentration in the effect-compartment and reciprocally related to tumor volume. The model described both tumor progression and regression patterns with and without treatment. The model was able to predict the response of the experiment with more aggressive tumors and higher doses than used for model building. Simulations established trough ADC tumor levels necessary for tumor stasis and eradication. They also suggested that less frequent treatment with higher dosing amount will improve the therapeutic response. The optimal dosing regimens suggested by the model were used in the further studies.

Conclusions: The population PK/PD model described the dynamics of tumor growth with and without ADC treatment. New features improved the model, and predicted the response patterns of individual animals. The developed model predicted the external data, and simulations based on the model allowed to define target tumor ADC concentrations and to optimize dose regimens for further development. Thus, the proposed model is a useful tool for projecting tumor response to treatment to facilitate drug development process.

References:

[1] Simeoni, M et al. Clinical Cancer Research 2004; 64, 1094-1101.