Preclinical Tumor Dynamic Modeling of an Anti–Fucosyl-GM1 Antibody: Development of a Semimechanistic Model

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Objectives: Fucosyl-monosialoganglioside-1 (Fuc-GM1), a ganglioside expressed on the cell surface of small cell lung cancers (SCLCs), is a potential target for therapeutic approaches. A first-in-class, fully human IgG1 monoclonal antibody (mAb) targeting Fuc-GM1 is under investigation. The objective is to develop a semimechanistic preclinical tumor growth dynamic (TGD) model for this antibody, thus enabling Bayesian estimation of efficacious dose in patients with SCLC.

Methods: Experimental data from tumor growth in xenograft mice that received either placebo or 1 of 5 doses of anti–Fuc-GM1 mAb were analyzed. Commonly reported TGD models [1] were tested and compared using the population nonlinear mixed-effect modeling approach. The final model, derived from the Koch model [2], was selected based on considerations of the tumor-biology rationale such as the nonresponsive tumor fraction, mathematical justification such as Akaike information criterion and Bayesian information criterion, and the visual diagnostic plots. Phoenix 6.4.1 and its NLME 1.3 Quasi-Random Parametric Expectation Maximization (QRPEM) engine were used for data processing and modeling, respectively.

Results: Across the placebo and all 5 administered doses of anti–Fuc-GM1 mAb in xenograft mice, the mean (coefficient of variation, %) tumor exponential growth rate constant, tumor linear growth rate constant, nonresponse tumor volume, and drug potency effect were estimated as 0.114 (51%) 1/day, 122 (171.8%) mm$^3$/day, 117 (1.16%) mm$^3$, and 0.0642 (153%) kg/mg/day, respectively. The diagnostic plots suggested that the model adequately described the dose-dependent treatment effects of this antibody in the xenograft model (Figure 1). The output of this model is currently used as the prior probability for Bayesian model development.

Conclusion: An improved semimechanistic tumor dynamic growth model was developed to adequately describe the correlation between various doses of this antibody and preclinical efficacy in a xenograft model.

References: