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

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BACKGROUND

- Antibody-drug conjugate (ADC), where an antibody binds specifically to a receptor overexpressed on tumor cells, and by internalization delivers a small molecule toxin to the cell.

- An ADC was tested in a murine model, where mice were injected subcutaneously with PC3 human prostate tumor cells. After an initial period of tumor growth, the ADC was administered, and tumors were measured over time.

STUDY DESIGN

- Mice injected subcutaneously with PC3 human prostate tumor cells
- When tumors reached 200-300 mm³ (Day 21), 7 groups of mice (10/group) were administered ADC:
  - Dose levels: 0.1, 1, 3 mg/kg
  - Dosing frequencies: QWx5, Q4Dx5 for each dose level
- Control group dosed with drug–free vehicle by QWx5
- Tumor volume monitored up to at least one week after discontinuation of treatment (Day 32-40)

OBJECTIVES

To develop a semi-mechanistic dynamic model of tumor growth and ADC effects in an in vivo murine xenograft model and to propose doses/regimens that optimize therapeutic efficacy.

METHODS

MODEL BUILDING

Published Tumor Growth Model

Proposed Tumor Growth Model

SIMULATIONS

To explore efficacy for different doses/regimens following simulations were performed:
- Dose: 0.1, 0.5, 1, and 2 mg/kg/day
- Frequency of dosing: QD, QW, and QM
- 20 individuals simulated for each regimen (Dose*Frequency) (12 regimens)

RESULTS

Parameter Estimates for Final Model

Predicted and Observed Tumor Growth Profiles

The model adequately described both tumor progression and regression patterns with and without treatment.

SIMULATIONS

Target tumor drug concentration for tumor eradication: ~20 mcg/mL
- Tumor re-growth starts at tumor drug concentration: ~5-10 mcg/mL
- 12 mg/kg Q2W would eradicate tumors in all animals
- Higher drug doses greatly reduce variability of tumor response to treatment

SUMMARY OF MODEL FEATURES

- Semi-mechanistic tumor growth model
- Continuous decrease of growth rate for proliferating cancer cells
- Initial stage: exponential growth
- Late stage: linear growth
- Delay in tumor regression upon drug treatment modeled by an effect compartment
- Effect compartment may represent the internalization process and the delayed cytotoxicity with cell-cycle specific agents
- The rate of conversion of proliferating tumor cells to damaged tumor cells
- Proportional to tumor effect-compartment concentration
- Inversely proportional to tumor weight

CONCLUSIONS

- The enhanced semi-mechanistic tumor growth model was proposed with modifications based on biological understanding of tumor dynamics
- The population PK/PD model described the dynamics of tumor growth in placebo and ADC-treated animals, during treatment and after its discontinuation
- Simulations based on the model allowed to define target tumor ADC concentrations and to optimize dose regimens for further development

REFERENCES