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 inside the cell, represents a novel and promising therapeutic approach in oncology
- An ADC was tested in a murine model, where mice were injected subcutaneously with PC3 human prostate tumor cells. After initial period of tumor growth ADC was administered, and tumors were measured over time
- The attempt to describe the tumor growth using previously published approach [1] was not successful in describing
  - Tumor growth pattern for individual animals
  - Delayed time for tumor regression
  - Quick tumor relapse following discontinuation of treatment
- A modified approach to address these complexities is presented

OBJECTIVES

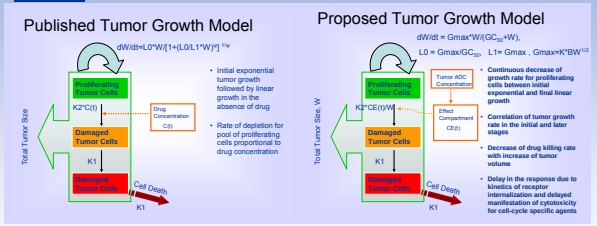
To develop a semi-mechanistic dynamic model of tumor growth and ADC effects in an in vivo murine xenograft model and to propose doses/regimens that optimize therapeutic efficacy

METHODS

STUDY DESIGN

- Mice injected subcutaneously with PC3 human prostate tumor cells
- When tumors reached 200-300 m3 (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)

MODELING



SIMULATIONS

To explore efficacy for different doses/regimens following simulations were performed:

- Doses
- 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

MODEL BUILDING

Model ID	Model Description: Tumor Growth Rate (mm3/day)	Model Description: ADT Tumor Killing Rate (mm3/day)	Minimization Status	Covariance Step Status	OFV	OFV Change	Post Hoc Diagnostics for Correlation between: Tumor Growth Rate and Baseline Tumor Weight	Post Hoc Diagnostics for Correlation between: Tumor Killing Rate and Dose level
201	Constant	K2*C(tumor)	S	N	6425	0	Yes	Yes
	Published model[1]	K2*C(tumor), K2*CE, etc.	N or S	N	-	>0	Yes	Yes
202	Constant	K2*CE	S	N	6402	-23	Yes	No
203	Constant	K2/W*CE	S	S	6316	-109	Yes	No
204	Constant*W	K2/W*CE	S	S	6379	-46	Yes	No
205	Constant*BW	K2/W*CE	S	S	6393	-32	-	No
206	Gmax*W/(GC$_{50}$+W)	K2/W*CE					Yes	No
207 (final Model)	Gmax*W/(GC$_{50}$+W), with Gmax=Constant*BW$^{1/2}$	K2/W*CE	S	S	6280	-145	No	No

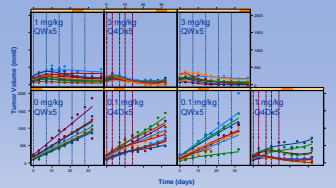
W: Tumor Weight; BW: Baseline tumor weight; S: Successful; N: not successful; -: Not applicable

Parameter Estimates for Final Model

Paramters: Label	Description	Unit	Estimate	Standard Error	Interindividual Variability: Estimate (CV%)	Standard Error (%)
BW	Mean Tumor Baseline Volume	mm3	136	4.9%	0.17 (41.2%)	19%
K	Maximum Growth Rate Gmax=K*BW$^{1/2}$	-	2.42	2.9%	0.0097 (9.87%)	61.30%
GC50	Tumor Volume corresponding to 1/2 Gmax	mm3	3.79	34.6%	-	-
K2	Tumor Killing Rate=K2/W*CE(t)	-	0.47	22.8%	0.404 (63.6%)	33%
KEO	Transition rate for Effect compartment	1/day	0.243	30.9%	-	-
K1	Tumor Death Rate	mm3/day	0.29	6.0%	-	-

METHOD=FOCE with INTERACTION

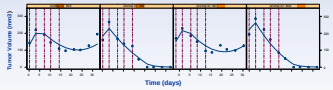
Predicted and Observed Tumor Growth Profiles



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

Representative Predicted and Observed Tumor Volumes

Dose: 3 mg/kg **Shedule: Q4Dx5**



The model described:

- Delay of tumor regression after initiation of drug treatment
- Quick onset of tumor relapse after discontinuation of treatment

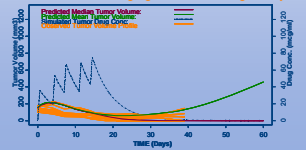
INTERNAL MODEL EVALUATION

- No deviation patterns in goodness-of-fit plots
  - PRED/IPRED/WRES/CWRES vs. DV/TIME
  - Predictive checks
- No dependence of parameters (ETAs) on
  - dose or dosing schedule
  - baseline tumor volume

EXTERNAL MODEL EVALUATION

Predicted and Observed Tumor Volume

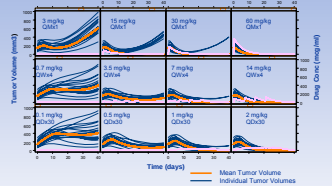
Validation Data: 6 mg/kg Q4Dx5, starting at day 17



The model can be extrapolated to predict the tumor respone from another experiment with

- Higher ADC dose level
- More aggressive tumors

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

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

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