

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

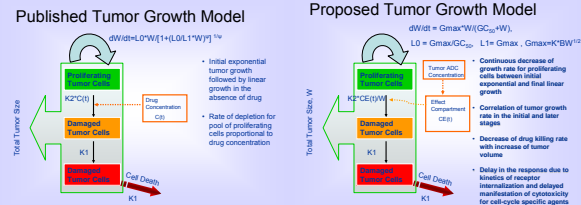
To develop a semi-mechanistic dynamic model of tumor growth and ADC effects in an vivo murine xenograft model and to propose doses/regimens that optimize therapeutic efficacy

METHODS

STUDY DESIGN

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

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	Tumor Growth Rate (mm ³ /day)	ADT Tumor Killing Rate (1/day)	Internalization Constant (1/day)	Conversion (1/day)	Drug Status	OVF	DFV	Post Hoc Diagnostics for Correlation between Tumor Growth Rate and Baseline Tumor Weight	Tumor Killing Rate per Dose Level
201	Constant	K2*W	S	N	N	6428	5	Yes	Yes
202	Published model	K2*W	S	N or S	N	6462	-13	Yes	Yes
203	Constant	K2*W	S	S	S	6319	-105	Yes	No
204	Constant	K2*W	S	S	S	6279	-48	Yes	No
205	Constant	K2*W	S	S	S	6363	-32	Yes	No
206	Constant	K2*W	S	S	S	6363	-32	Yes	No
207 (Final)	Constant	K2*W	S	S	S	6286	-145	No	No

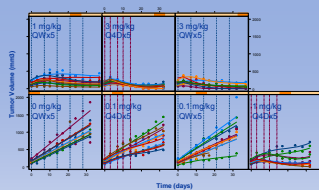
W: Tumor Weight; BW: Baseline tumor weight; S: Successful; N: Not successful; - : Not applicable

Parameter Estimates for Final Model

Label	Description	Parameters			Interindividual Variability	
		Unit	Estimate	Standard Error	Estimate (CV%)	Standard Error (%)
BW	Mean Tumor Baseline Volume	mm ³	136	4.9%	-	-
K	Maximum Growth Rate Gmax*K ² BW ^{1.2}	-	242	2.9%	0.0087 (9.87%)	61.30%
GC50	Tumor Volume corresponding to 1/2 Gmax	mm ³	3.79	34.6%	-	-
K2	Tumor Killing Rate K2*W ²	-	0.47	22.8%	0.404 (83.6%)	33%
KED	Transition rate for Effect compartment	1/day	0.243	-	-	-
K1	Tumor Death Rate	mm ³ /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



The model described:

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

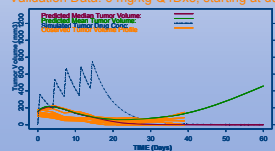
INTERNAL MODEL EVALUATION

- No deviation patterns in goodness-of-fit plots
 - PRED/IPRED/WRES/CVRES 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

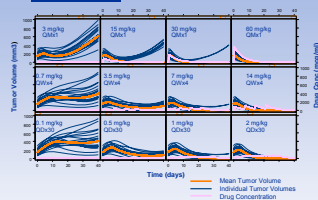
Validation Data: 6 mg/kg Q4Dx5, starting at day 17



The model can be extrapolated to predict the tumor response 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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