Modeling of acquired resistance under TKI treatment

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1 – Objectives

Most patients under tyrosine kinase inhibitor (TKI) treatment will eventually develop resistance versus TKI drugs [1-3]. We developed a semi-mechanistic PK/PD model describing tumor growth inhibition and resistance under TKI treatment in xenograft mice. Based on model predictions, we aim at optimizing dosing and schedule of administration for patients acquiring resistance.

2a – Methods: *In vivo* experiments

Tumor growth inhibition (TGI) experiments were conducted in primary patient tumor (LXF A677) bearing mice receiving Erlotinib or Gefitinib treatment. Mice were randomized into treatment groups, control, 6.25mg/kg, 25mg/kg or 100mg/kg for each drug and treatment was daily orally administered for 14 days. Tumor volume was monitored over 30 days and sparse plasma PK data were collected (see Table I).

***In vivo* experiment**	
Tumor type	LXF A677
Duration	30 days
Dose groups (mg/kg/d)	Erlotinib: 0, 6.25, 25, 100 Gefitinib: 0, 6.25, 25, 100
Animals / Treatment group	8 animals
Days of dosing	Day 3 - 16
Plasma PK measurements	On day 10 & 16 At 0, 0.25, 0.5, 1, 2.5, 5, 10, 24 h
PK Sampling	1 sample/time point/dose group 1 sample/animal
Tumor volume measurement	Every 2-3 days

Table I: *Overview of the in vivo experiments conducted in LXF A677 tumor xenograft mice during 30 days.*

2b – Methods: Modeling approach

Two semi-mechanistic PK/PD models were developed with and without adaptive resistance and assuming a delay of drug response relative to drug exposure. The performance of the resistance model was compared to a classical TGI model [4]. The classical TGI model assumes a linear effect of plasma exposure on tumor cells, with a delay in disappearance of killed tumor cells as described elsewhere by Simeoni et al. [4]. In the acquired resistance model, we distinguish sensitive and acquired resistant cells in terms of sensitivity to treatment and growth rate. Parameter were estimated using Monolix v4.3.2 software [5]. Model discriminations was based on convergence (precision of the parameter estimates) and fitting criteria (residual error, Akaike information criterion and visual predictive checks).

2c – Methods: Simulation analyses

Simulation were performed in Berkeley Madonna v8.3.18 [6]. Developed model was used in a simulation mode to answer following questions from literature [3]:

- How does resistance affect tumor volume under and after treatment?
- What is the optimal dosing protocol to overcome resistance emergence?

3a – Results: Model structure & Parameter estimates

Model structure & evaluation

Classical TGI model Acquired resistance model

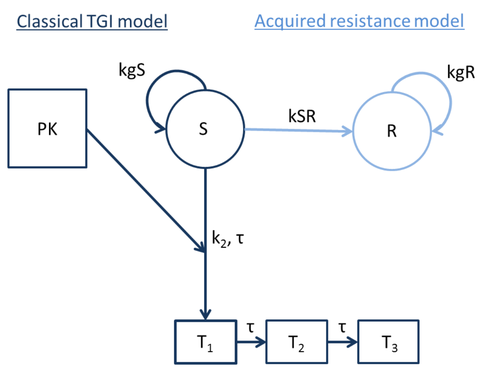

Figure I: *Classical TGI model (dark blue) and its resistance component (light blue). 'S' refers to sensitive cells and 'R' to resistant cells and 'T ' to transit compartments [4].*

Model evaluation	Classical TGI model	Acquired resistance model
# parameter	5	7
Residual error	0.162	0.136
AIC	7720	7560

Table II: *Comparing fitting criteria parameter for TGI model vs. TGI model + resistance*

Parameter estimation

TV: Tumor volume = $S + R + T_1 + T_2 + T_3$

kg: $\frac{2*\lambda_0*\lambda_1*TV}{2*\lambda_0*TV+\lambda_1}$

β : $\lambda_0 S*\beta = \lambda_0 R$ and $\lambda_1 S*\beta = \lambda_1 R$

Parameter	Fixed Effect (RSE %)		Random Effect (RSE %)	
$\lambda_0 S$ (1/d)	0.199 (10)		0.487 (18)	
$\lambda_1 S$ (mm³/d)	44.6 (10)		0.653 (11)	
k_2 (1/d)	Erlotinib: 1.85*10⁻⁴ (18)	Gefitinib: 6.07*10⁻⁴ (9)	Erlotinib: 0.655 (23)	Gefitinib: 0.2 (X)
τ (1/d)	1.52 (7)		0.1 (X)	
kSR (1/d)	4.23*10⁻⁴ (10)		0.2 (X)	
β	0.85 (18)		0.685 (18)	

Table III: *Parameter estimates. RSE is for Relative standard error. A non-linear growth model [7] was used to model the tumor growth.*

3b – Diagnostic tools

Observed vs. predicted

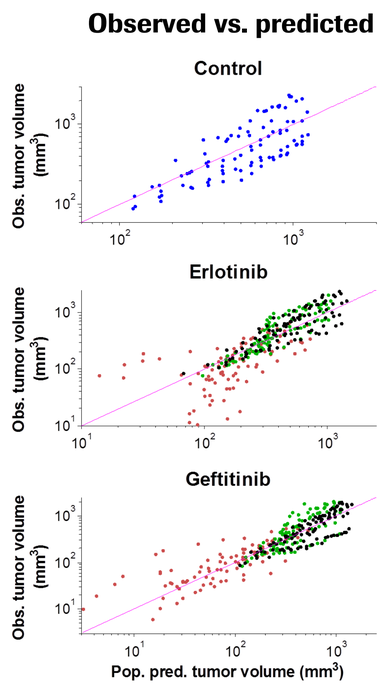

Figure II: *Observed vs. predicted tumor volume at 100mg/kg (red), 25mg/kg (green) and 6.25mg/kg (black).*

Prediction distribution

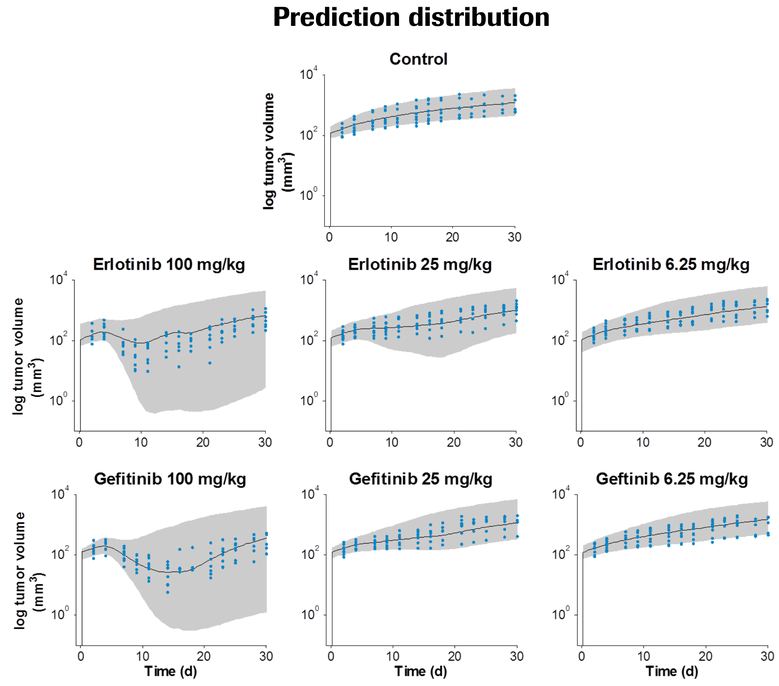

Figure III: *Prediction distribution plots. Blue dots are observed tumor volumes. The bold line is the median prediction and the grey area indicates the 95% confidence interval.*

3c – Results: Simulations

How does resistance affect tumor volume under and after treatment?

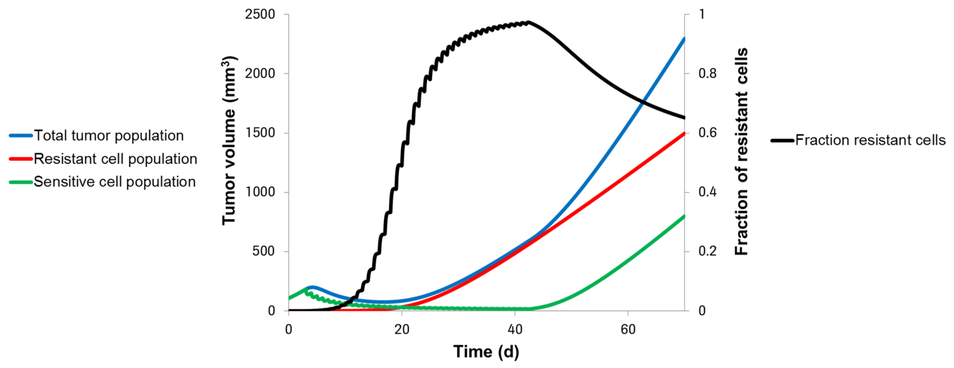

Figure IV: Simulated tumor volume after *daily dose from day 3 to day 43.*

- Resistant cells grow under treatment and total tumor volume increases
- Faster tumor growth is predicted after treatment due to the faster growing sensitive tumor cells.
- Fraction of resistant cell decreases when treatment stops

What is the optimal dosing protocol to overcome resistance emergence?

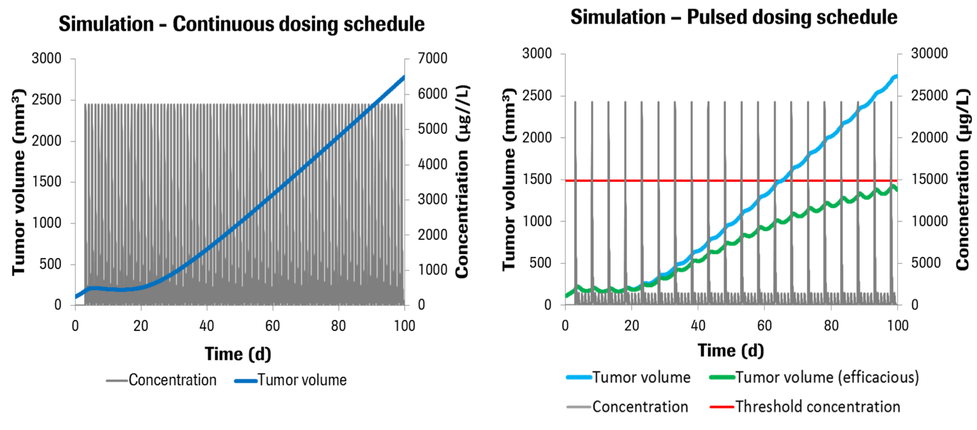

Figure V: Tumor volume changes *for three different scenarios:* ***a)*** *5x 1000ug per 5 days cycle continuous dosing,* ***b)*** *1x 4000ug + 4x 250ug per 5 days cycle pulsed dosing (blue) & pulsed dosing when resistant cells are affected by high plasma concentration (green).*

- Assuming the drug kills resistant cells with a lower potency as compared to sensitive cells, then pulse dosing is beneficial compared to continuous dosing if a threshold concentration is reached.

Conclusion

Tumor growth data in xenograft mice were better described with a model assuming adaptive resistance. The proposed resistance model can be used to explain tumor-regrowth during and after drug treatment and it allows to simulate impact of dosing regimen on tumor response [8,9].

The presented modeling results are consistent with findings from Chmielecki et al. [3]:

- Sensitive cells outgrow the resistant cells when treatment stops, leading to a decrease in the fraction of resistant cells. As a result, the tumor becomes again sensitive to TKIs treatment.
- Pulsed treatment can potentially be more beneficial than a continuous treatment, if the resistent cells are sensitives to high plasma drug concentrations. For the presented data set, it was not feasible to identify a killing parameter on the resistant cells. However in this Xenograft model, plasma concentration were still low compared to what is proposed in the pulsed dosing protocol of the ongoing clinical trial [10].

For a thorough evaluation, also safety aspects would need to be considered.

References

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