Integrating distribution to tumor tissue into a dynamic PK/PD model to evaluate the anti-cancer effect of erlotinib in patient-derived LXFA 677 tumor xenograft mice

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1 – Objective

Development of a dynamic PK/PD model to describe the anticancer effect of erlotinib in patient-derived LXFA 677 tumor xenograft mice as a function of drug concentration in tumor tissue

2 – Methods

Two independent experiments were conducted in female NMRI nu/nu mice implanted with human LXFA677 primary patient tumors. For assessing tumor growth inhibition, a repeated oral dose study with 100, 25, 6.25 mg/kg/d of erlotinib was conducted. Tumor volume was monitored twice weekly during and after drug treatment and a sparse plasma PK sampling scheme (2 observations per mouse) was implemented (experiment I). In a second study aiming to assess the drug distribution to the tumor tissue, a staggered sampling approach was applied. For each mouse, a single sampling time point for drug concentration in plasma and tumor was obtained after oral administration of 100 mg/kg/d for single and repeated dose (experiment II). A dynamic PK/PD model was developed relating the time course of the tumor volume to the exposure in the tumor. Concentration in the tumor was directly linked to the effect. Population analyses were performed using MONOLIX v3.2 [1].

	Experiment I	Experiment II
Dose groups (mg/kg)	6.25/25/100	100
Rhythm of administration	Repeated dose (28 days)	Unique and repeated dose (5 days)
PK samples	2 PK samples per mouse (plasma concentration only)	1 PK sample per mouse (plasma and tumor concentration)
Tumor size evaluation	~Every 3 days	Day one or four (depending on the rythm)

Table I: Experiment overview

	Experiment I	Experiment II
Number of mice	56	96
# PK samples in plasma	87	64
# PK samples in tumor	0	64
Tumor size evaluation	746	288

Table II: Dataset

3 – Results: PK modeling Experiment II

First step: Estimate PK parameters in Experiment II where observations are available in plasma and tumor compartment
Second step (PKPD modeling): In Experiment I, parameter related to the PK in the tumor compartment are fixed

Observed PK samples:
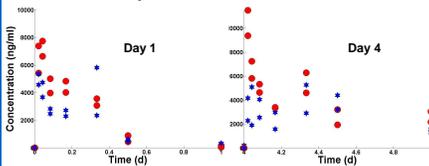
Figure I: Observed plasma PK samples (red points) and tumor PK samples (blue star) for unique (left) and repeated (right) administration in Experiment II

Modeling results:
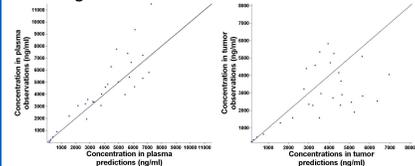
Figure II: Observed vs. Predicted individual concentration in plasma (left) and tumor (right) in Experiment II

2 – Methods: Flow chart for PD model selection final model
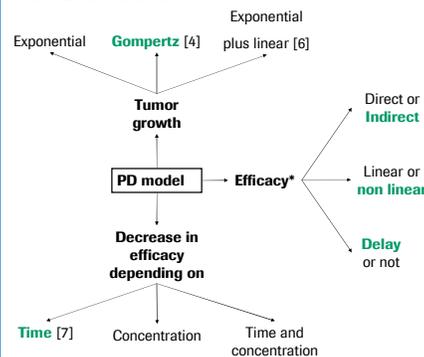
*Interface [3] can be related to indirect and non linear effect

References:
[1] Kuhn E, Lavielle M. "Maximum likelihood estimation in nonlinear mixed effects models" Computational Statistics and Data Analysis, vol. 49, No. 4, pp 1020–1038, 2005
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[3] Meille C, Iliadis A, Barbolosi D, Frances N, Freyer G. An interface model for dosage adjustment connects hematotoxicity to pharmacokinetics. Journal of Pharmacokinetics and Pharmacodynamics (2008) 35 (6):619-633
[4] Norton L, Simon R, Brereton HD, Bogden AE. Predicting the course of Gompertzian growth. Nature. 1976 Dec 9;264(5586):542-5.
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[6] Koch G, Walz A, Lahu G, Schropp J. Modeling of tumor growth and anticancer effects of combination therapy. J Pharmacokinet Pharmacodyn. (2009) 36(2):179-97
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PK diagram (center):

PK

- KL: tumor growth rate
- V0: initial tumor size
- Theta: maximum tumor size
- Alpha, Beta: interface model parameters
- R: decrease in efficacy
- Tau: mean transit time

- KA: absorption constant rate
- CL: clearance from the central compartment
- Vc: volume of distribution in the central compartment (plasma)
- Vt: volume of distribution in the tumor compartment
- Q: intercompartmental clearance

PD

Interface [3] (Alpha, Beta)

Tumor Growth — Gompertz [4]

KL, Theta

3 – Results: PKPD modeling Experiment I

	Fixed effect	r.s.e (%)	Random effect	r.s.e (%)
KA (d^{-1})	52	x	x	x
CL (L.d^{-1})	0.968	16	0.3	x
Vc (L)	0.0848	25	0.6	x
Vt (L)	0.0558	x	0.4	x
Q (L.d^{-1})	3.48	x	x	x
a1 (ng.ml^{-1})	100	x	x	x
b1	0.46	3	x	x
KL (d^{-1})	0.0494	9	0.337	15
V0 (mm^3)	114	8	0.409	13
Theta (mm^3)	3510	13	0.25	x
Alpha (mL.ng^{-1}.d^{-1})	2.77	18	0.2	x
Beta (d^{-1})	0.00035	x	0.2	x
R (d^{-1})	0.0386	19	x	x
Tau (d^{-1})	8.9	19	0.1	x
b2	0.166	4	x	x

Table III: Parameter estimate for the PKPD modeling in Experiment I

Figure III: Observed vs. predicted individual tumor size for PK (up) and PD (down) in Experiment I

Figure IV: VPC [5] of the tumor size depending on the dose group (control, 100mg/kg, 25mg/kg and 6.25mg/kg from left to right and up to down) in Experiment I. Blue points are observed values, blue line is median prediction and pink areas are 50% and 95% confidence interval of the prediction.

4 – Discussion

PK model
- The PK model fitted the data well in both experiments. The PK parameter estimates were similar, but volume of distribution in the tumor (Vt) was highly correlated to the observed tumor size in the PK experiment (data not shown). Further improvement is expected when using the observed tumor volume as a covariate on the Vt.
- The plasma/tumor PK model was built with data from only one dose (Experiment II). The same kinetics were assumed at different dose levels and the tumor related PK parameters were fixed in Experiment I.

PD model
- For unperturbed tumor growth, various tumor growth models were tested. The best model fit was obtained with a Gompertz model [4], despite the plateau phase was not observed.
- The design of the experiment (tumor observation before treatment start) allowed to separate parameters related to unperturbed tumor growth to parameter related to efficacy.
- The drug effect was well described by using the interface model [3] associated with signal transduction cascade [2]. A good precision in efficacy-related parameter estimates was achieved.

Conclusion:
Linking efficacy to the exposure at the tumor compartment improved the PKPD modeling by accounting separately for the delay due to distribution to the biophase and the delay triggered by biological cascade. This approach is useful for profiling and discriminating compounds in early development.