PKPD-Modeling of VEGF, sVEGFR-1, sVEGFR-2, sVEGFR-3, sKIT and tumor size following axitinib treatment in metastatic renal cell carcinoma (mRCC) patients

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Background and Objectives

- Axitinib (Inlyta®) is a multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties, approved for the treatment of metastatic renal cell carcinoma (mRCC). Axitinib inhibits vascular endothelial growth factor (VEGF) receptors 1, 2 and 3.
- A modeling framework characterizing the relationships between dose, exposure, biomarkers (VEGF, sVEGFR-2,3 and sKIT) has been developed for patients with gastro-intestinal stromal tumor (GIST) treated with sunitinib, another tyrosine-kinase inhibitor [1].
- The aims of the present study are:
  - ✓ To characterize the time-course of five biomarkers (VEGF and its soluble receptors sVEGFR-1,2,3, as well as sKIT) in mRCC patients treated with oral axitinib.
  - ✓ To investigate potential longitudinal relationships between sunitinib dose, AUC, biomarkers and tumor size, as determined by the sum of longest diameters (SLD)
  - ✓ To compare these relationships to sunitinib in GIST patients [1].

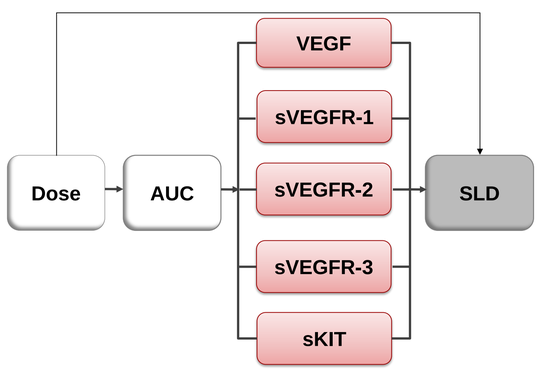

Fig.1: Investigated relationships

Methods

Patients and Data (Table 1)

Patients	Cytokine-refractory Japanese patients with mRCC (n=64)
Dose	Starting dose: 5 mg BID (range: 1.6-16.4 mg/day)
Schedule	Continuous in 4-week cycles
PK	Individual PK parameters
Biomarker sampling	Pre-dosing, day 1 of cycles 2-7 and end of treatment (n = 436 for each biomarker, longest sampling duration: 89 weeks)
SLD assessment	Baseline and every 8 weeks (n = 476, longest sampling duration: 104 weeks)

Biomarker Models

- Indirect response models (IDR) were fitted to log-transformed biomarker data. Models for each biomarker were developed separately and finally combined into a joint model to explore correlations.

Inhibition k_{out} (VEGF):

$$\frac{dBM}{dt} = K_{in} - k_{out}\left(1 - \frac{I_{max} \cdot AUC^{\gamma}}{AUC_{50}^{\gamma} + AUC^{\gamma}}\right) \cdot BM(t)$$

Inhibition K_{in}(sVEGFR-1,2,3, sKIT):

$$\frac{dBM}{dt} = K_{in}\left(1 - \frac{I_{max} \cdot AUC^{\gamma}}{AUC_{50}^{\gamma} + AUC^{\gamma}}\right) - k_{out} \cdot BM(t)$$

Linear disease progression

$$DP(t) = Base \cdot \left(1 + DP_{slope} \cdot t\right)$$

$$K_{in} = DP(t) \cdot k_{out}$$

Tumor Model

- Dose, daily AUC and model-predicted relative change from baseline in the biomarkers (VEGF, sVEGFR-1,2,3) were evaluated as drivers for the change in SLD using a longitudinal tumor growth inhibition (TGI) model [2].
- The probability of dropout was taken into account during simulations and described by a logistic regression model including the predictors daily AUC, observed SLD at dropout, time since start of the study and a 20% increase in SLD since nadir.

Estimation and simulations were performed using NONMEM 7.2.

Results

Biomarker Models

- VEGF and sVEGFR-1,2,3 data were adequately described by IDR models.
- A common AUC_{50} was estimated for sVEGFR-2 and sVEGFR-3. The individual AUC_{50} parameter for VEGFR-1,2 and 3 were highly correlated (80-99%).
- No drug effect was identified to influence sKIT concentrations.

Table 2: Final parameter estimates (IIV, %CV) for axitinib biomarker models in mRCC patients as compared to sunitinib in GIST patients [1]

	VEGF		sVEGFR-2		sVEGFR-3		sVEGFR-1	
	Axitinib	Sunitinib	Axitinib	Sunitinib	Axitinib	Sunitinib	Axitinib	Sunitinib
Base (pg/mL)	64.7 (44)	59.8 (50)	8910 (15)	8660(19)	19700 (47)	63900 (43)	83.4 (18)	Data not available
MRT (=1/k_{out}, days)	0.549 (-)	3.75 (24)	18.9 (72)	23.1 (24)	6.08 (-)	16.7 (24)	0.673 (-)	
AUC_{50} (µg·h/L)	348 (40)	1000 (50)	722[a] (45[b])	1000 (43)	722[a] (45[b])	1000 (63)	1400 (45[b])	
Hill	1 FIX	3.31 (-)	0.704 (-)	1.54 (-)	1 FIX	1 FIX	1 FIX	
DP_{slope} ($month^{-1}$)	0.0456 (92)	0.0261 (171)	-	-	-	-	-	
Res Error (%)	36.9 (-)	44.6	17.3 (-)	12.0	23.7 (-)	21.9	20.2 (-)	
Res Error (pg/mL)	-	-	-	-	1430 (-)	-	-	

IIV = Inter-individual variability; DP = Disease Progression, MRT = Mean Residence Time = 1/k_{out}. Relative standard errors of parameter estimates for axitinib were less than 35% for fixed and random effects, except for $MRT_{sVEGFR-1}$ (51%). [a] Common drug effect parameter for sVEGFR-2 and 3; [b] The IIV in AUC_{50} for VEGFR-1, 2 and 3 was quantified using a common variability term.

Tumor Model

- SLD time-course was well-characterized by a TGI model. Using the model-predicted relative change in sVEGFR-3 from baseline ($sVEGFR\_3_{REL}$) as driver of the change in tumor size best described the data.

$$\frac{dSLD}{dt} = K_G \cdot SLD(t) - K_{sVEGFR\_3} \cdot sVEGFR\_3_{REL} \cdot e^{-\lambda \cdot t} \cdot SLD(t)$$

- Using daily AUC and sVEGFR-3 as predictors did not significantly improve the fit compared to sVEGFR-3 alone.

Results (cont'd)

Table 3: Final parameter estimates for the tumor model

Parameter	Estimate	RSE (%)	IIV (CV %)	RSE (%)
K_G (wk^{-1})	0.00101	14	175	12
K_{sVEGFR_3} ($wk^{-1} \cdot AUC^{-1}$)	179 (1)	13	14.9	45
λ (wk^{-1})	0.124	14	73.3	15
Residual error (%)	10.8	8.6	36.2	24

K_G : SLD increase rate constant; $K_{sVEGFR-3}$: SLD reduction rate constant induced by the drug ; λ : resistance appearance rate constant

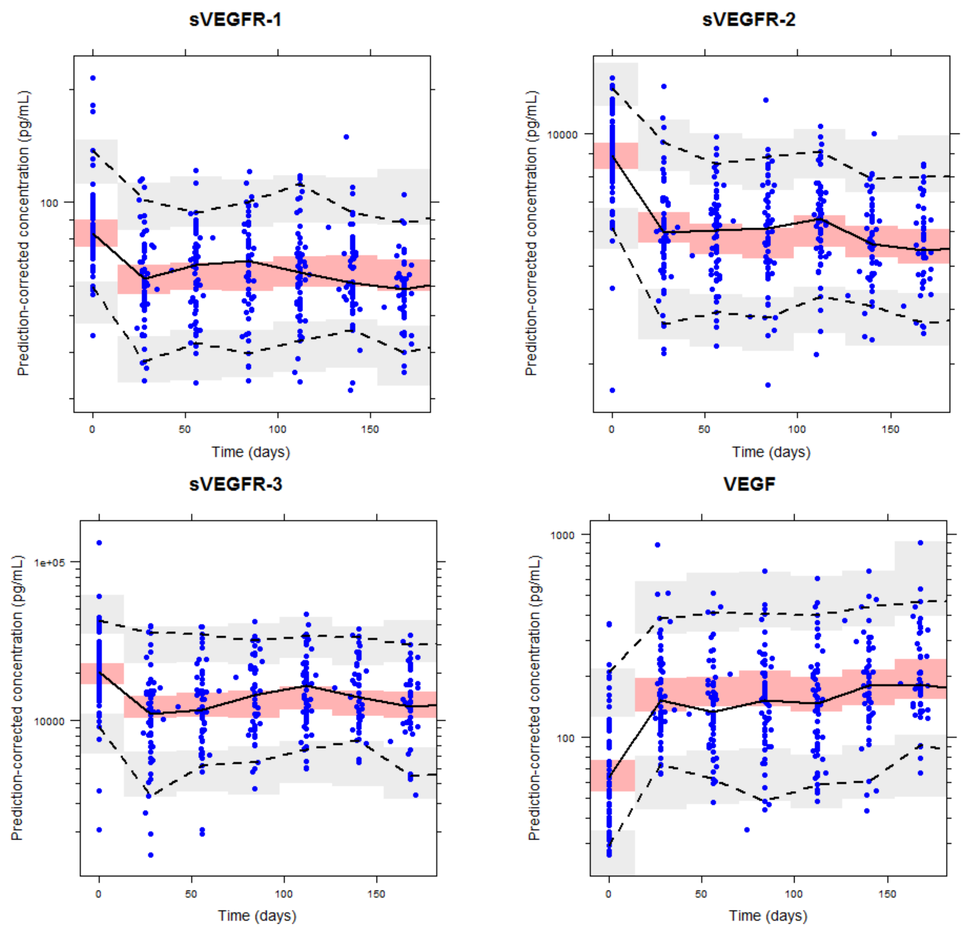

Fig.2: Prediction-corrected visual predictive checks of the final biomarker models based on 500 simulations. *Median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median, 5th and 95th percentiles of the simulated data.*

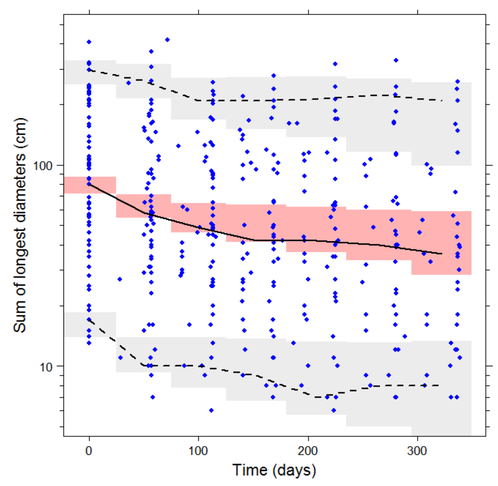

Fig.3: Visual predictive checks of the final tumor model based on 500 simulations. *Median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median, 5th and 95th percentiles of the simulated data. Dropout was taken into account in the simulations.*

Discussion and Conclusions

- The modeling framework proposed by Hansson et al. for GIST patients treated with sunitinib successfully described the relationships between exposure, biomarkers and tumor size in mRCC patients treated with axitinib. sVEGFR-1 was added to the framework.
- Axitinib did not have a significant effect on sKIT, unlike sunitinib in GIST patients.
- sVEGFR-3 baseline values in mRCC was typically lower than in GIST but similar to those observed in metastatic colorectal cancer [3]. MRT of VEGF, sVEGFR-2 and 3 were shorter in mRCC than in GIST.
- sVEGFR-3 was the best predictor of change in tumor size for axitinib in mRCC and has also been identified as a significant predictor for sunitinib in GIST patients.

References

[1] Hansson et al. PAGE 20 (2011) Abstr 2183 [www.page-meeting.org/?abstract=2183

[2] Claret et al. J Clin Oncol (2009) 27 : 4103-4108

[3] Kanefendt et al. PAGE 21 (2012) Abstr 2354 [www.page-meeting.org/?abstract=2354]

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