



Objectives

To investigate the predictive ability of drug exposure, circulating biomarkers and tumor size on overall survival (OS) in axitinib-treated metastatic renal cell carcinoma (mRCC) patients.

Background

- Axitinib (Inlyta®) is an anti-angiogenic tyrosine kinase inhibitor with activity towards the vascular endothelial growth factor (VEGF) receptors VEGFR-1, 2, 3. It is approved in the treatment of mRCC.
- Pharmacometric models describing the relationships between axitinib exposure, circulating biomarkers (VEGF, sVEGFR-1,2,3 and sKIT) and tumor sum of longest diameters (SLD) have been developed previously in axitinib-treated mRCC [1].

Methods

Patients and Data

- Data were available from a phase II study [3] including 64 Japanese patients with cytokine-refractory mRCC treated with axitinib at a starting dose of 5 mg b.i.d. Dose increase or reduction was based on individual safety and tolerability.
- Patients were followed-up for OS for a median duration of 65 weeks.

Previously developed models for biomarkers and SLD [1]

- Biomarkers:
 - Indirect response models with inhibition of the loss (VEGF) or the production (sVEGFR-1,2,3) of response driven by axitinib daily AUC.
 - No significant effect of axitinib on sKIT.
- SLD: tumor growth inhibition model, where the response is driven by the model-predicted relative change in sVEGFR-3 from baseline.

Overall survival model

- Parametric time-to-event models were fitted to the OS and censoring data.
- Baseline hazard distributions were investigated as constant, Weibull, Gompertz, log-normal and log-logistic.
- Predictors of OS were tested alone and in combination (Table 1).

Table 1: Investigated predictors on overall survival

Patient characteristics	Baseline Eastern Cooperative Oncology Group (ECOG) status
Exposure-related	Daily AUC
Biomarker-related	$BM(t)$ $\Delta BM(t) = BM(t) - BM_0$ $BM_{rel}(t) = \frac{BM(t) - BM_0}{BM_0}$ $BM_{rel,week\ 4} = \frac{BM_{week\ 4} - BM_0}{BM_0}$
SLD-related	SLD_0 $SLD(t)$ $\Delta SLD(t) = SLD(t) - SLD_0$ $SLD_{rel}(t) = \frac{SLD(t) - SLD_0}{SLD_0}$ $SLD_{rel,week\ 6} = \frac{SLD_{week\ 6} - SLD_0}{SLD_0}$

BM: biomarkers, i.e. VEGF, sVEGFR-1, 2 and 3

- Patients were assumed to stay on treatment until time of death or censoring.

Conclusions

- The SLD time-course best predicted OS in axitinib-treated mRCC patients. These results differ from those in sunitinib-treated GIST patients, where sVEGFR-3 relative change from baseline was a better predictor of OS than SLD [2].
- In the next step, the developed modeling framework (Fig.1) will be extended to include safety biomarkers (e.g. diastolic blood pressure). Such framework can potentially be used for monitoring drug response and guiding dose individualization.

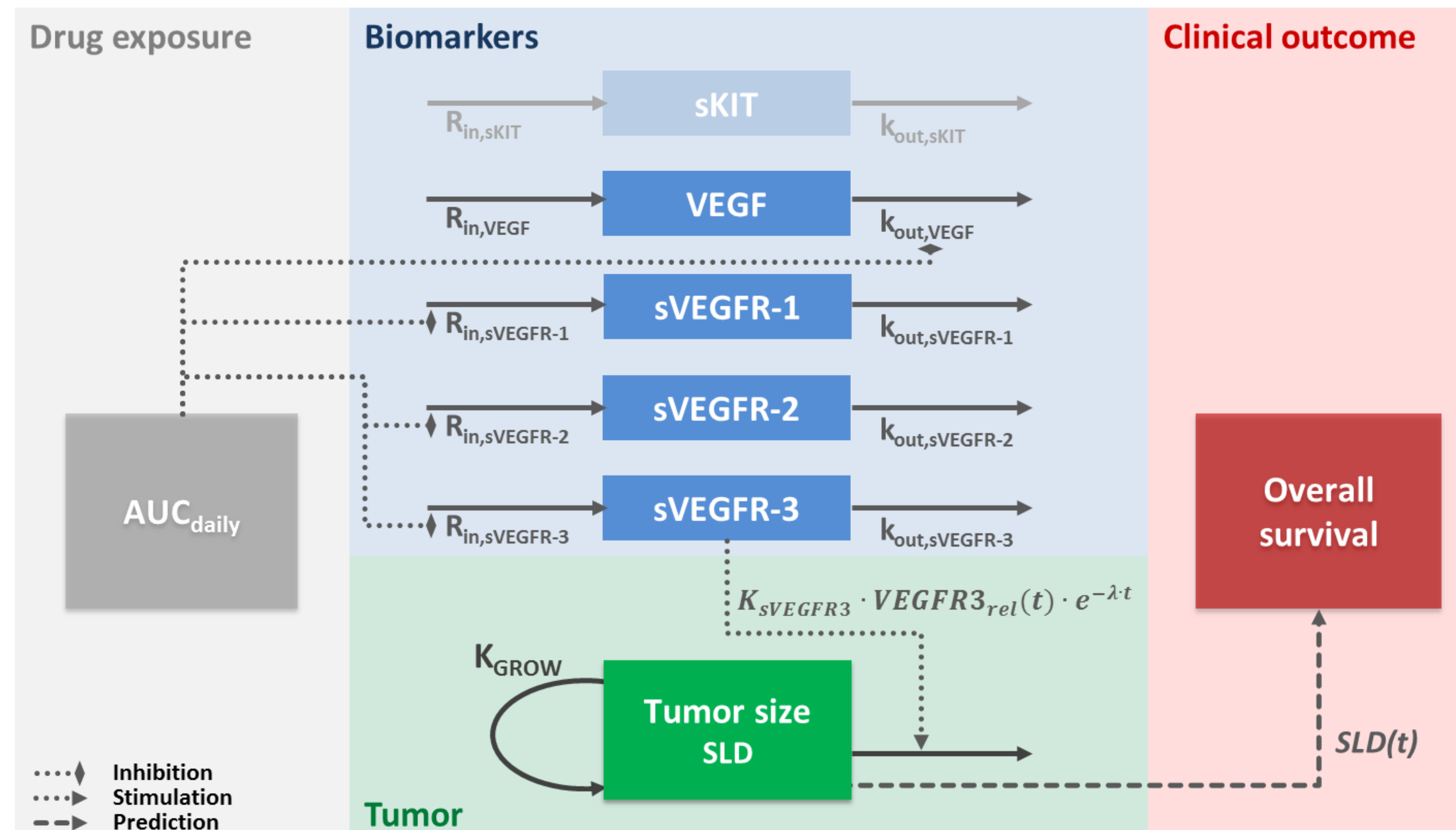


Fig. 1: Schematic representation of the modeling framework for axitinib in mRCC

Results

- The baseline hazard for OS was best described by a log-logistic distribution. A competing log-logistic function described the hazard of being censored.
- The SLD time course (SLD(t)) was the most significant predictor for OS (dOFV = -21.7) and was included in the final OS model (Eq.1, 2, Table 2, Fig.2). Larger SLDs were associated with a lower survival probability.

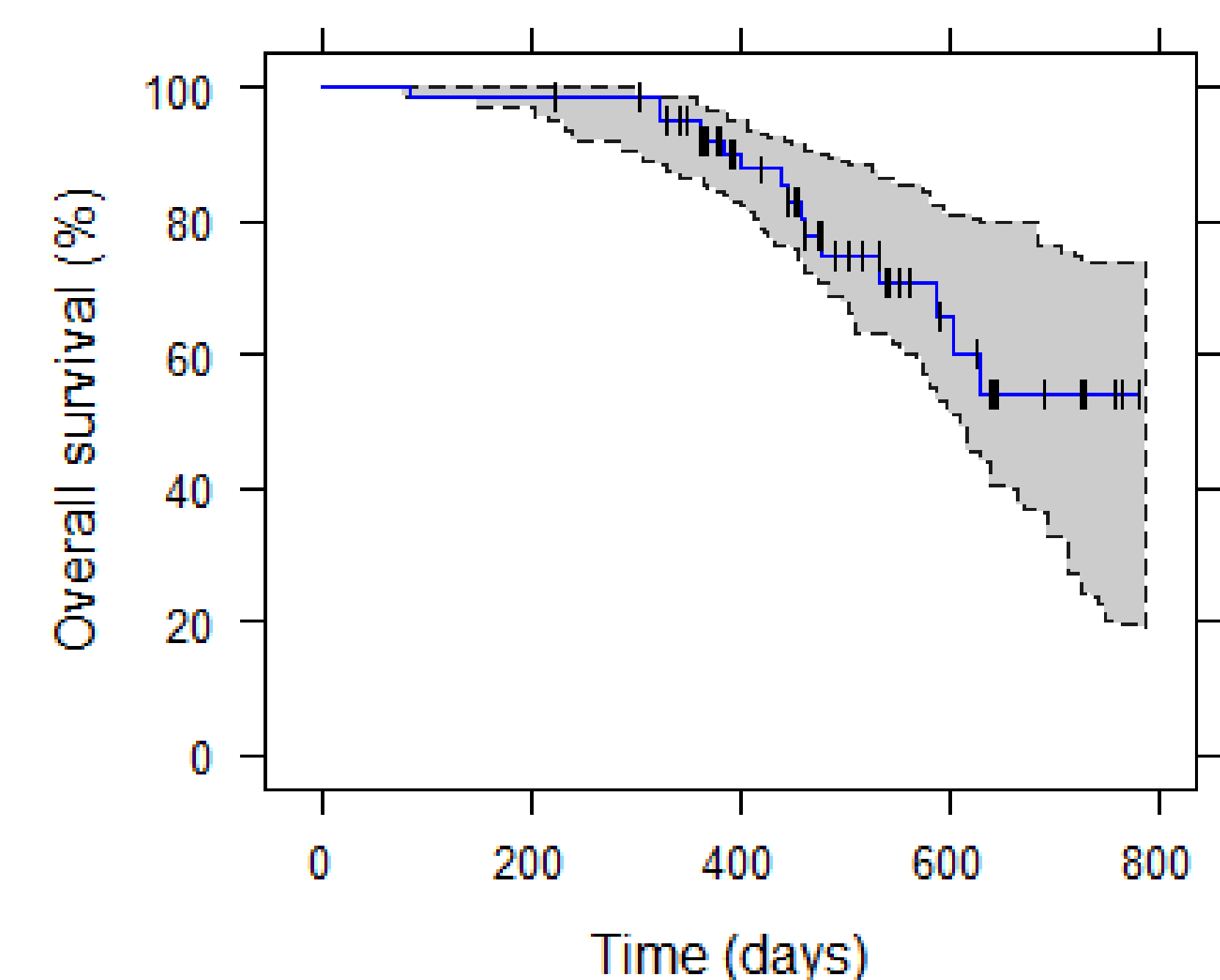
$$h(t) = \frac{\psi^{\frac{1}{\gamma}} \cdot t^{\frac{1}{\gamma}-1}}{\gamma \cdot (1 + (\psi \cdot t)^{\frac{1}{\gamma}})} \cdot e^{\beta_{SLD} \cdot SLD(t)} \quad (Eq.1)$$

$$\psi = e^{-\beta_0} \quad (Eq.2)$$

Table 2: Final OS model parameter estimates

Parameter	Estimate (RSE%)
β_0	7.05 (3.0)
γ	0.297 (21)
$\beta_{SLD} \text{ (mm}^{-1}\text{)}$	0.0123 (20)

Fig.2: Visual predictive check for the Kaplan-Meier survival curve. The observed Kaplan-Meier curve (blue line) is compared to the 90% confidence interval (shaded area) derived from model simulations (200 samples) of the survival model including the SLD time-course as predictor. Vertical black lines represent censored observations



- In the univariate analysis, statistically significant predictors of OS also included baseline SLD (dOFV=-12.8). However, when SLD(t) was included in the model none of the other predictors further improved the fit.

References

- [1] Schindler et al. PAGE (2013) ; Abstr 2859
[2] Hansson et al. CPT :PSP (2013). 2 ; e84
[3] Tomita et al. Eur J Cancer (2011); 47: 2592-2602

Acknowledgement: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.

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