# MODELING PHARMACOKINETICS AND BIOMARKER RESPONSE TO SUNITINIB AS POTENTIAL PREDICTORS OF EFFICACY IN PATENTS WITH METASTATIC COLORECTAL CANCER

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## Introduction and Objectives

Sunitinib is a multi-tyrosine kinase inhibitor currently tested in the treatment of metastatic colorectal cancer (mCRC) [1]. A thorough understanding of the dose-concentration-effect relationship is a prerequisite for the development of a PK/PD-guided treatment optimization strategy. Various studies reported a correlation between biomarker response (sVEGFR-2 and -3) and clinical outcome in cancer patients receiving sunitinib [2-5]. Another studies could identify the PK of sunitinib and SU12662 as predictor for the time-to-progression (TTP) and overall survival (OS) [6]. Our aim was to assess the relationship between PK of sunitinib, the biomarker response of sVEGFR-2 and -3, and TTP in mCRC patients.

## Patients and Methods

21 patients receiving a daily dose of 37.5 mg sunitinib on a 4-weeks on/2-weeks off treatment schedule in addition to FOLFIRI participated in this study (C-II-005). Blood samples were drawn at baseline and every two weeks for two therapy cycles. Sunitinib and the active metabolite SU12662 (the sum is referred to as 'active drug') concentrations were measured using LS-MS/MS. Both biomarkers, sVEGFR-2 and -3, were determined by validated ELISAs. Furthermore, TTP defined as day from first study medication to first assessment of progression was selected as clinical endpoint. If this information was not available data were censored to the last date the patient was confirmed to be progression-free [7]. A sequential PK/PD analysis was performed using NONMEM (version 7.1.2). Potential predictors for TTP were analyzed using Kaplan-Meier analysis, Cox regression and a model-based approach.

## PK/PD Results

**Pharmacokinetic model parameters**
Estimates, 90% bootstrap CI

| Parameter | Estimate (90% CI) | IIV (90% CI) |
|---|---|---|
| RPS | 1.91[a] | |
| MTT [h] | 1.48[a] | |
| N | 1.46[a] | 1.63 (0.91-2.39) |
| $k_a$ [$h^{-1}$] | 0.54[a] | |
| $CL/F_{Su}$ [L/h] | 38.1 (32.9-44.3) | 0.20 (0.14-0.25) |
| $V_1/F_{Su}$ [L] | 3090 (2708-3604) | |
| Q/F [L/h] | 0.47 (0.39-2.21) | |
| $V_2/F_{Su}$ [L] | 643[a] | |
| $CL/f_{aMet}$ [L/h] | 20.6 (17.5-24.8) | 0.15 (0.09-0.20) |
| $V_1/f_{aMet}$ [L] | 1680 (1221-2423) | |
| $Q/f_{aMet}$ [L/h] | 2.39 (1.35-3.89) | |
| $V_2/f_{aMet}$ [L] | 684 (653-905) | |
| Residual error model | | |
| $\sigma_{prop,Su}$ [%] | 25.9 (19.7-30.9) | |
| $\sigma_{prop,Met}$ [%] | 28.6 (24.1-31.7) | |

[a]fixed

| | |
|---|---|
| RPS | Ratio pre– to systemic metabolism |
| MTT | Mean transit time |
| N | Number of transit compartments |
| F | Bioavailability |
| $f_a$ | Fraction absorbed |
| $k_a$ | Absorption rate constant |
| CL | Clearance |
| V | Volume of distribution |
| Q | Intercompartmental clearance |

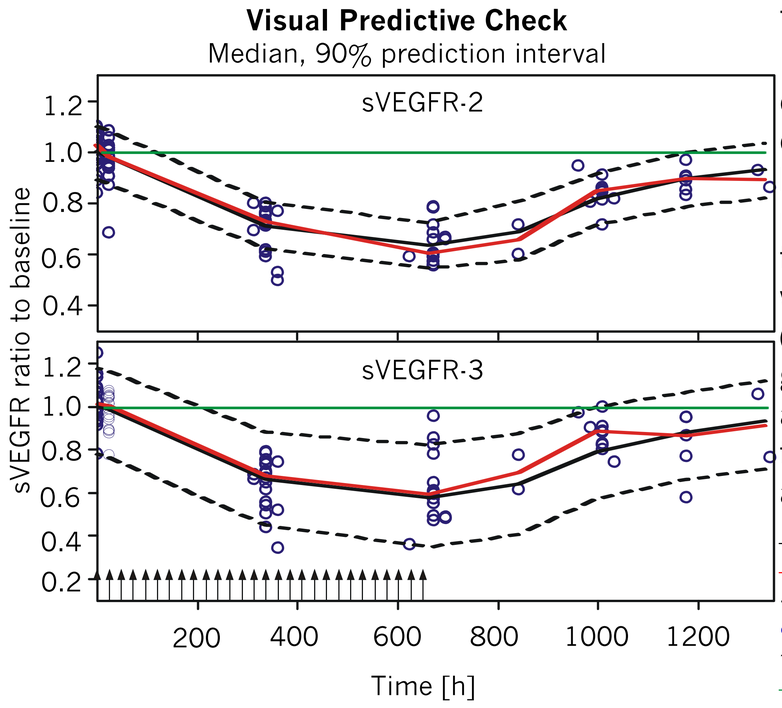
Based on a previous model developed for healthy volunteers [8] the PK model was adapted for mCRC patients. The concentration-time course of sunitinib and SU12662 could be sufficiently described by a two-compartment model for sunitinib and for SU12662 with transit compartments accounting for the delay in drug absorption.

**PK/PD model parameters**
Estimates, 90% bootstrap CI

| | sVEGFR-2 | | sVEGFR-3 | |
|---|---|---|---|---|
| Parameter | Estimate (90% CI) | IIV (90% CI) | Estimate (90% CI) | IIV (90% CI) |
| Baseline [ng/L] | 8951 (8330-9571) | 0.17 (0.10-0.21)<br>0.07 (0.05-0.09)[b] | 21,900 (17,922-27,029) | 0.51 (0.36-0.62) |
| α | 1.26 (1.02-1.51) | 0.45 (0.26-0.61) | 1.55 (1.12-2.12) | 0.55 (0.21-0.89) |
| $k_{out}$ [1/d] | 0.12 (0.10-0.13) | — | 0.12 (0.09-0.17) | — |
| $K_d$ [ng/L] | 4[a] | — | 4[a] | — |
| Residual error | | | | |
| $\sigma_{prop}$ [%] | 7.4 (5.8-9.1) | | 15.2 (11.9-17.7) | |

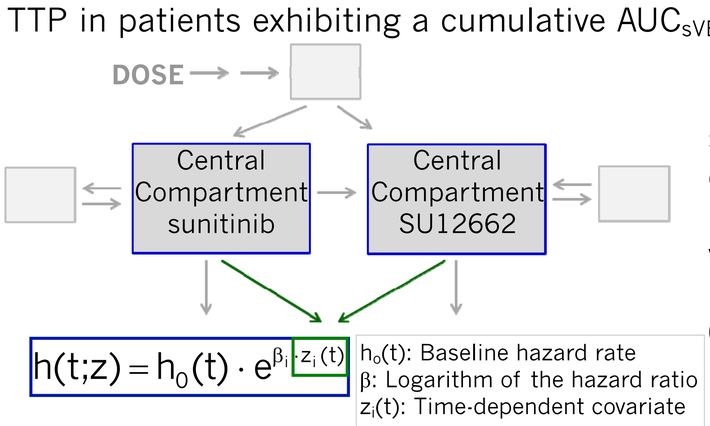
[a]fixed; [b]IOV on cycle; α: intrinstic activity; $k_{out}$: elimination rate constant; $K_d$: dissociation constant

Biomarker concentration-time courses could be well described by an indirect response model. Minimum concentration ratios relative to baseline (mean ± SD) were estimated as 0.64 ± 0.04 and 0.58 ± 0.11 for sVEGFR-2 and sVEGFR-3, respectively, which is comparable to the observed biomarker response (0.65 and 0.63, respectively).

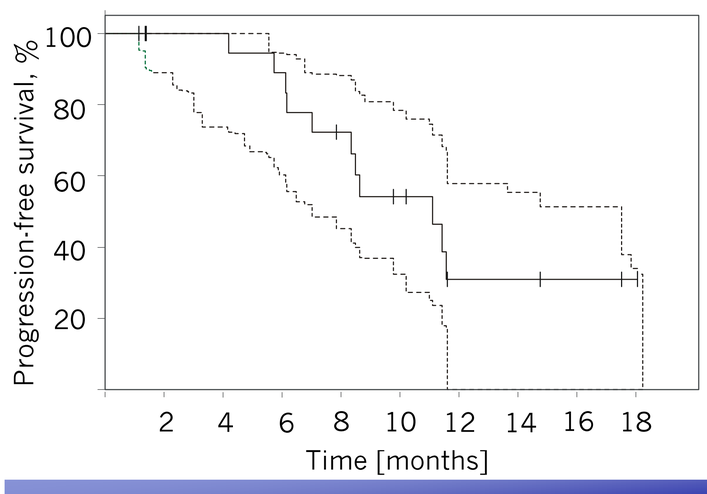



## Time-To-Event Analysis

Median TTP was 11.1 months for the mCRC patients receiving sunitinib in combination with FOLFIRI. Kaplan-Meier analysis revealed a trend of longer TTP in patients exhibiting a cumulative $AUC_{sVEGFR-2}$ after 4 weeks on treatment less than the median (8.5 vs. 11.5, p=0.1961). Age and the steady-state AUC of total active drug ($AUC_{ss}$) were identified as predictors for TTP using multivariate Cox regression with a Hazard ratio (HR) of 0.82 and 0.009 (p<0.001), respectively.




**Visual Predictive Check**
(median, 90% prediction interval)




**Time-To-Event model parameters**
Estimates, 90% bootstrap CI

| Parameter | Estimate (90% CI) |
|---|---|
| $h_0$ [$week^{-1}$] | 0.0234 (0.0121 to 0.0437) |
| β [ml/ng] | -0.722 (-1.644 to -0.336) |

TTP was best described using a parametric time-to-event model with an exponential distribution. The time-dependent concentration of unbound active drug was identified as best positive predictor for TTP (HR: 0.49 (95% CI: 0.27-0.88), p=0.013).

## Conclusions and Outlook

- The concentration-time profile of both active drug and biomarkers could be adequately described by the developed PK/PD models.
- Changes in plasma levels of both soluble receptors are highly correlated and the shapes of the concentration-time curves are comparable to observations in healthy volunteers [8].
- Active drug pharmacokinetics seemed to be more predictive for TTP in the investigated population than biomarker response.
- Further studies have to be performed to examine the predictive value of the biomarkers and pharmacokinetics in patients with other tumors exhibiting increased angiogenic activity.

## References

[1] Saltz et al. JCO 2007; 25:4793-9; [2] Burstein JCO 2008; 26:1810-6; [3] DePrimo et al. J Transl Med. 2007; 5:32; [4] Harmon et al. J Transl Med. 2011; 9:120; [5] Rini et al. JCO 2008; 26:3743-8; [6] Houk et al. Cancer Chemother Pharmacol 2010; 66:357-71; [7] Mross et al. Int J Clin Pharm Ther. 2011; [8] Lindauer et al. CPT 2010; 87:601-8

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