UPPSALA
UNIVERSITET

PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3 and sKIT as Biomarkers of Tumor Response and Overall Survival Following Sunitinib Treatment in GIST

Emma K. Hansson[1], Paul Westwood[1], Michael Amantea[2], Jonathan French[2], Brett Houk[2], Peter A. Milligan[2], Mats O. Karlsson[1], Lena E. Friberg[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Sweden
[2]Pfizer Global R&D

PAGE 2011 June 9

UPPSALA UNIVERSITET

Exposure - biomarker - response

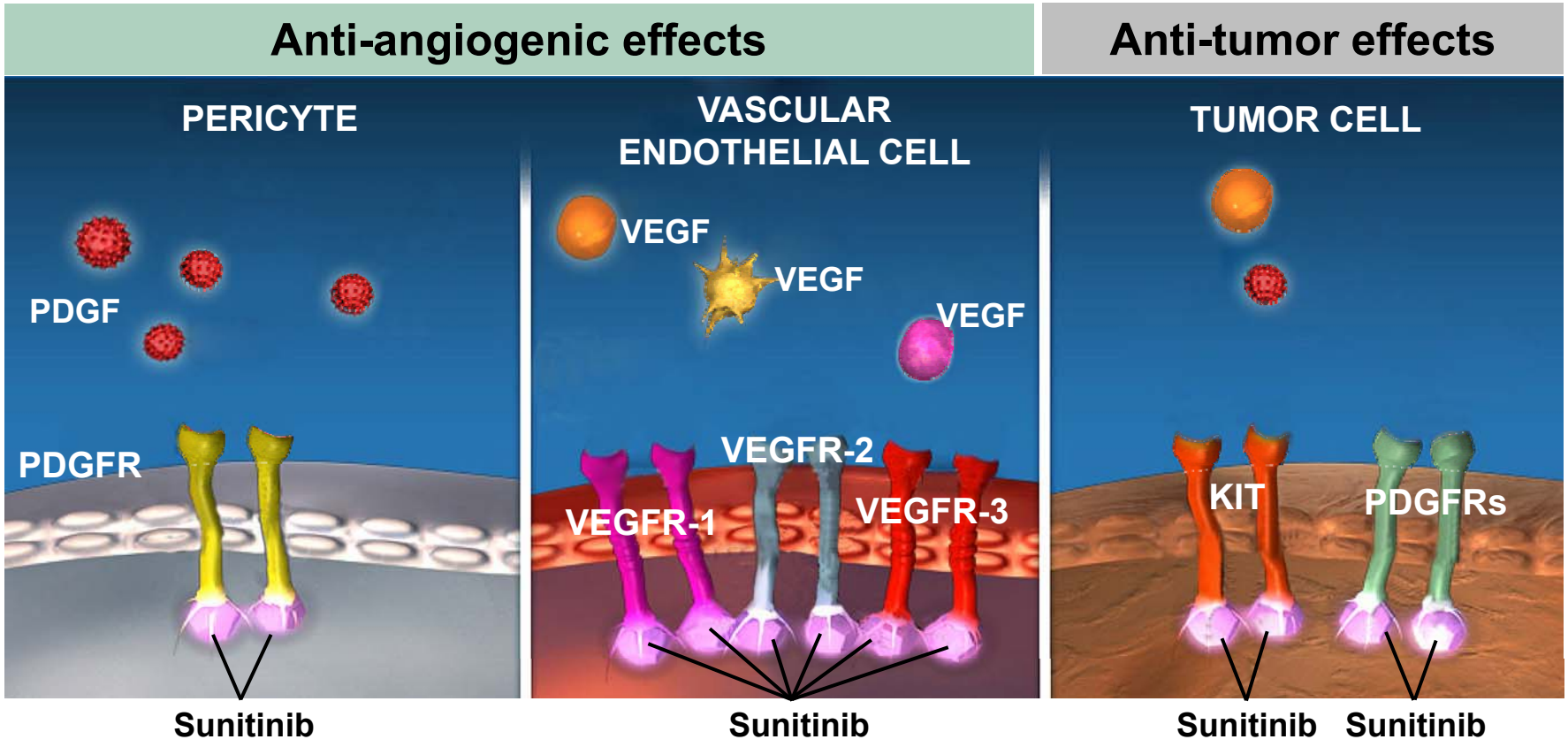
Selection of an optimal dose in the area of targeted drugs in oncology is a challenge.

A characterized **Exposure - biomarker - response** relationship may:

- Enable dose optimization
- Facilitate prediction and monitoring of clinical response
- Provide an understanding of the mechanism of action
- Act as an early indicator of safety issues
- Improve efficiency of clinical trials (surrogate endpoint)

UPPSALA UNIVERSITET

Sutent® - sunitinib malate



Multi targeted inhibition of receptor tyrosine kinases on tumor cells, pericytes and endothelial cells results in anti-angiogenesis and reversal of tumor growth

UPPSALA UNIVERSITET

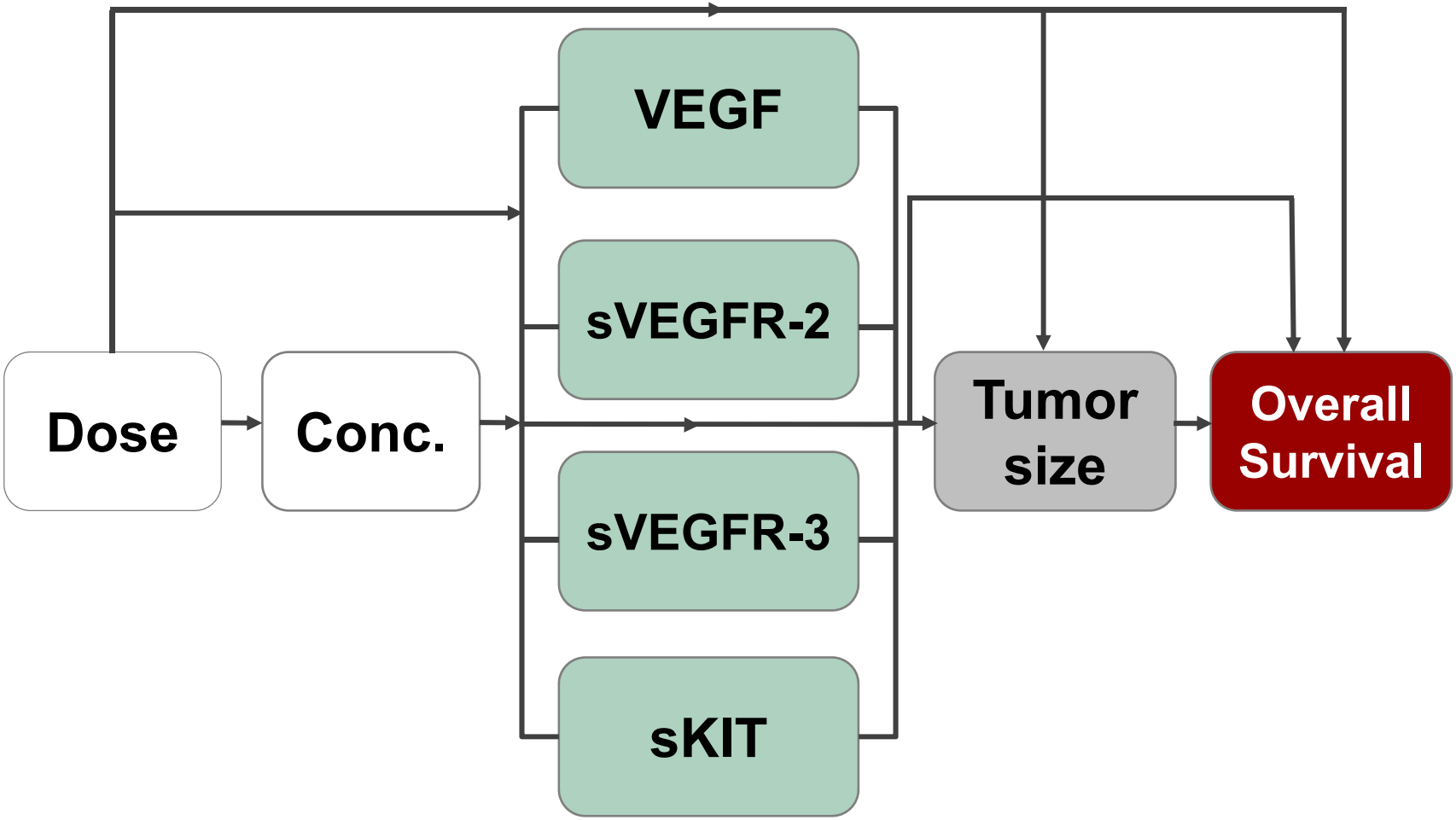
Objectives

To investigate **Exposure-Response Relationships** following sunitinib (Sutent®) treatment in imatinib-resistant GIST (gastro intestinal stromal tumors) with focus on the potential biomarkers **VEGF, sVEGFR-2, sVEGFR-3 and sKIT**

- Are the factors predictive of tumor size dynamics?
- Are the factors predictive of overall survival?

UPPSALA UNIVERSITET

Objectives

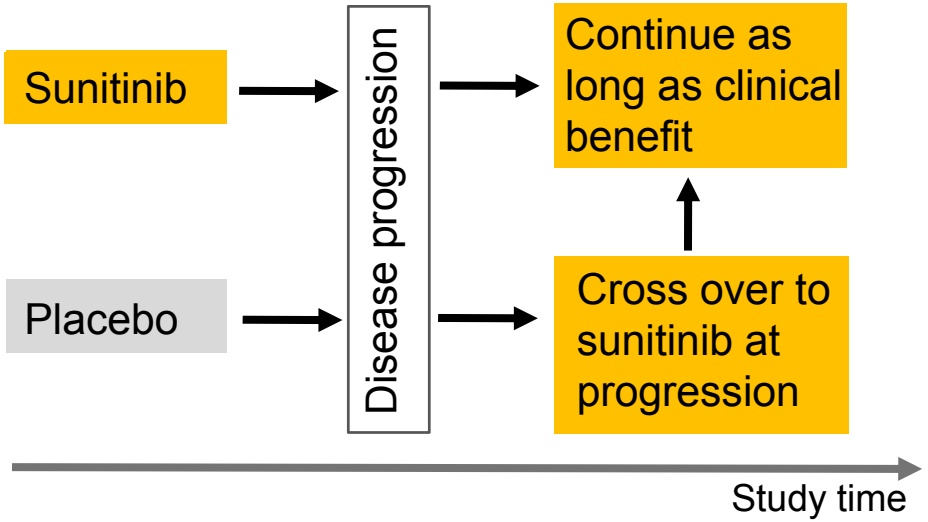


UPPSALA UNIVERSITET

Sunitinib data

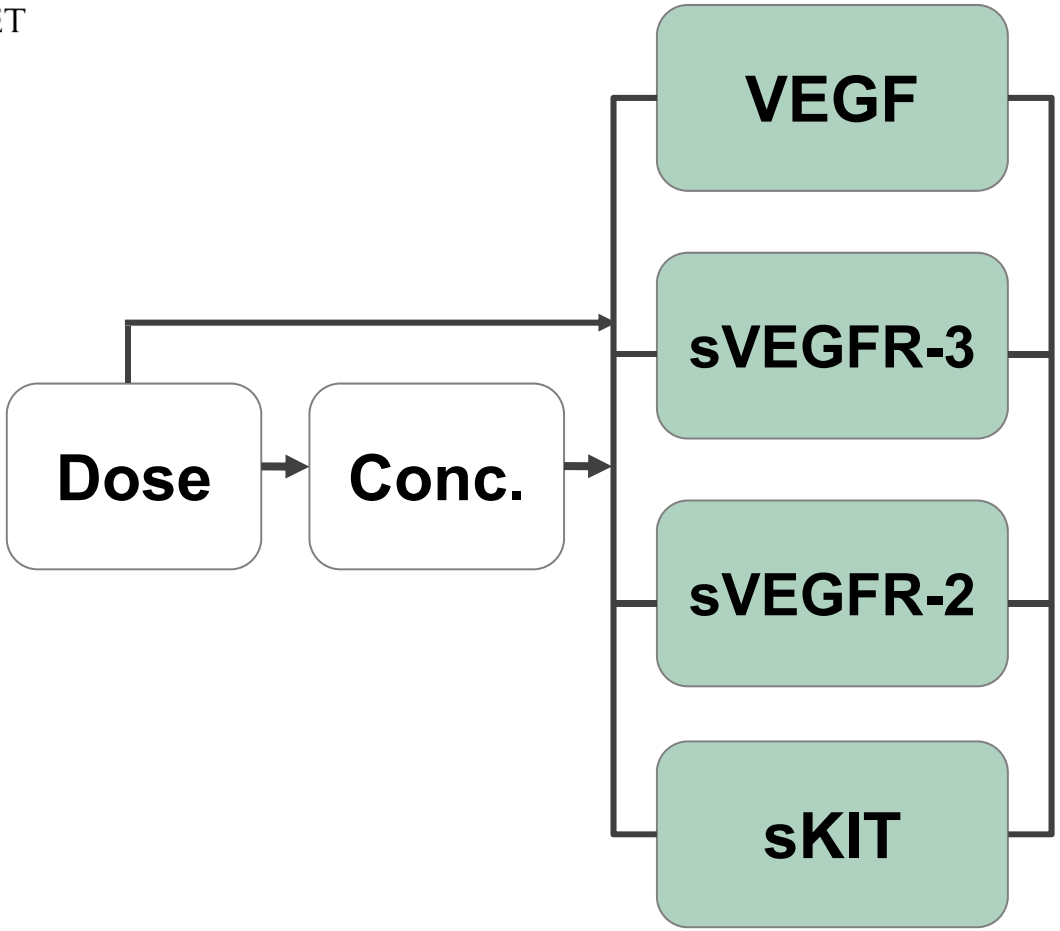
Indication	Imatinib-resistant or intolerant GIST
n	300
Studies	4 phase I to phase III studies[1-4]
Dose (mg)	0, 25, 37.5, 50, 75 qd
Schedule (weeks on/off treatment)	4/2, 2/1, 2/2 and continuous treatment
PK	Individual PK parameters[5]
Biomarker sampling (cycle:day)	1:0, 1:14, 1:28; 2:1, 2:28; 3:1, 3:28 etc
Tumor assessment (cycle:day)	1:0, 1:28; 2:28; 3:28 etc

Study design for placebo controlled study



[1] George S. et al., Europ J of Cancer. 2009
[2] Shirao K. Et al., Invest New Drugs. 2010
[3] Demetri G.D. et al., Lancet. 2006
[4] Maki R.G. et al., ASCO. 2005
[5] Houk B. et al., Clin Cancer Res. 2009

UPPSALA
UNIVERSITET



UPPSALA UNIVERSITET

Results
Biomarker models

Inhibition K_{out} $\frac{dBM}{dt} = K_{in} - K_{out}\left(1 - \frac{I_{max} \cdot C}{IC_{50} + C}\right) \cdot BM$

Inhibition K_{in} $\frac{dBM}{dt} = K_{in}\left(1 - \frac{I_{max} \cdot C}{IC_{50} + C}\right) - K_{out} \cdot BM$

Linear DP

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

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

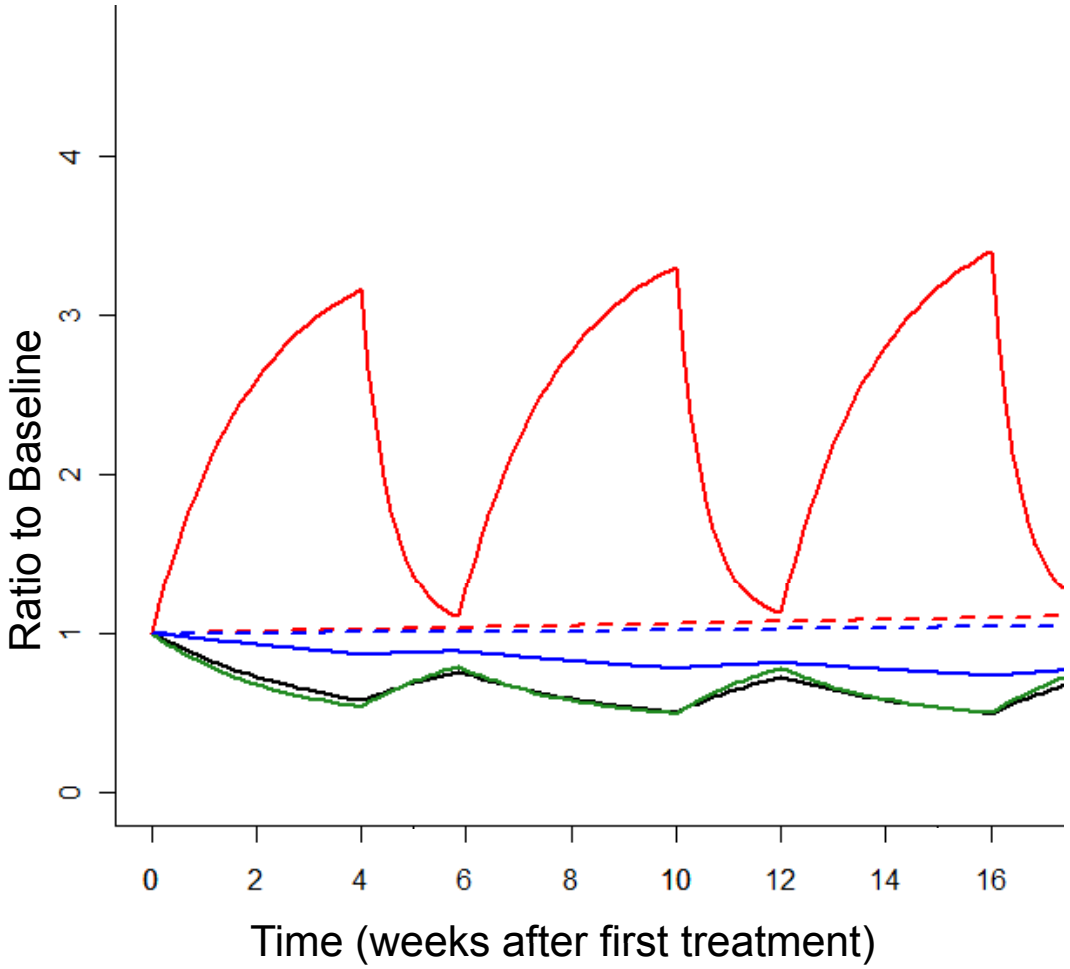
	VEGF		sVEGFR-2		sVEGFR-3		sKIT	
Parameter	**Estimate**	**% IIV**	**Estimate**	**% IIV**	**Estimate**	**% IIV**	**Estimate**	**% IIV**
Base (pg/mL)	59.8	50	8660	19	63900	43	39200	50
MRT (days)	3.75	**24**	23.1	**24**	16.7	**24**	101	27
I_{max}	1 FIX	-	1 FIX	-	1 FIX	-	1 FIX	-
IC_{50} (mg/L)	**0.042**	50	**0.042**	43	**0.042**	63	**0.042**	240
γ	3.31	-	1.54	-	-	-	-	-
DP_{slope} ($month^{-1}$)	**0.026**	171	-	-	-	-	**0.026**	172
Res Error (%)	45	-	12	-	22	-	23	-
Res Error (pg/mL)	-	-	583	-	-	-	-	-

IC_{50} correlations: VEGF, sVEGFR-2, sVEGFR-3 75-90 %

DP = Disease progression, MRT = Mean Residence Time = $1/K_{out}$

UPPSALA UNIVERSITET

Biomarker Model Predictions



Biomarker	Model
VEGF	- K_{out}
sVEGFR-2	- K_{in}
sVEGFR-3	- K_{in}
sKIT	- K_{in}
sKIT DP	Linear
VEGF DP	Linear

DP = Disease progression

UPPSALA UNIVERSITET

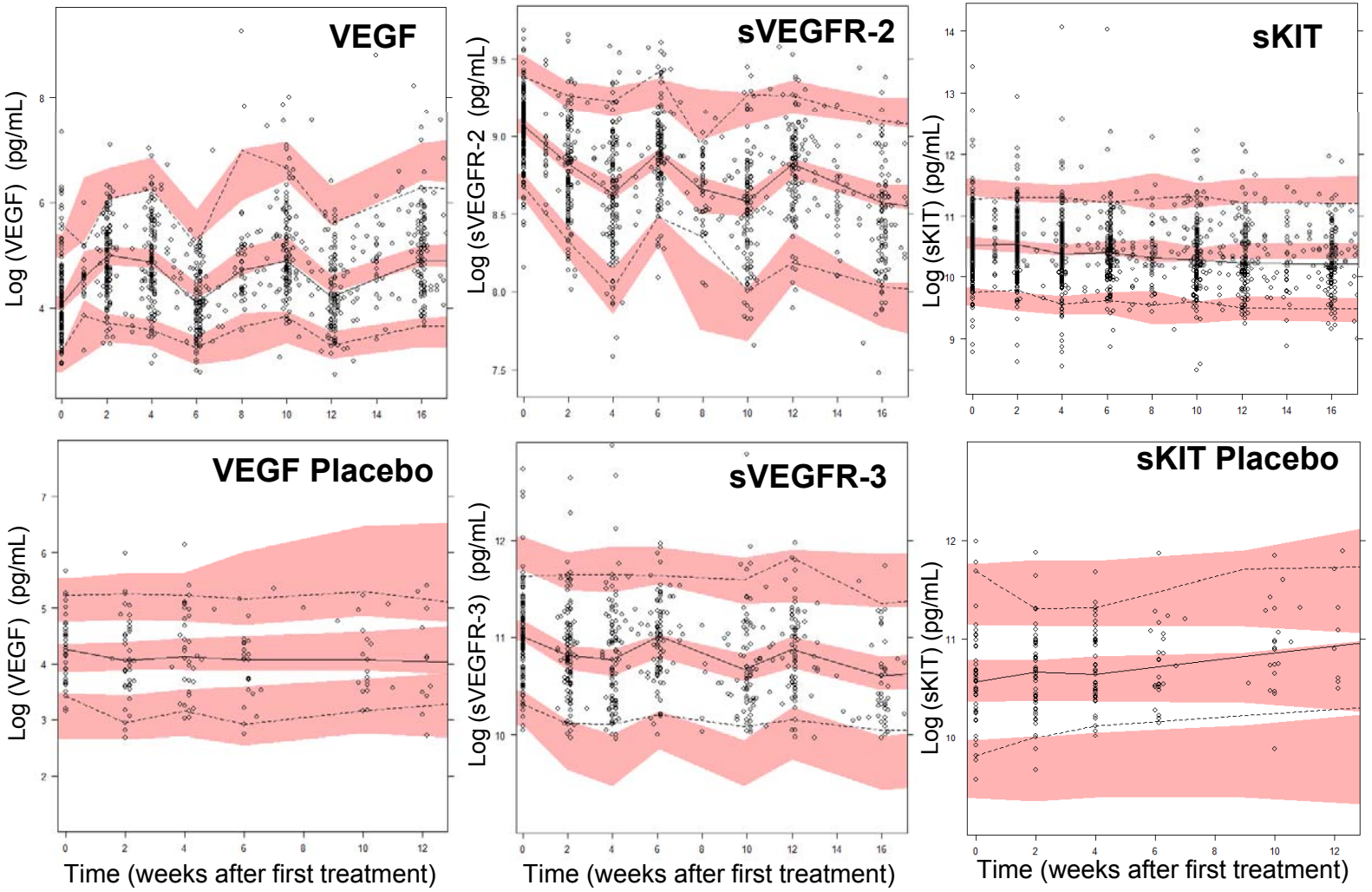
VPC Biomarker Model

n simulations = 500

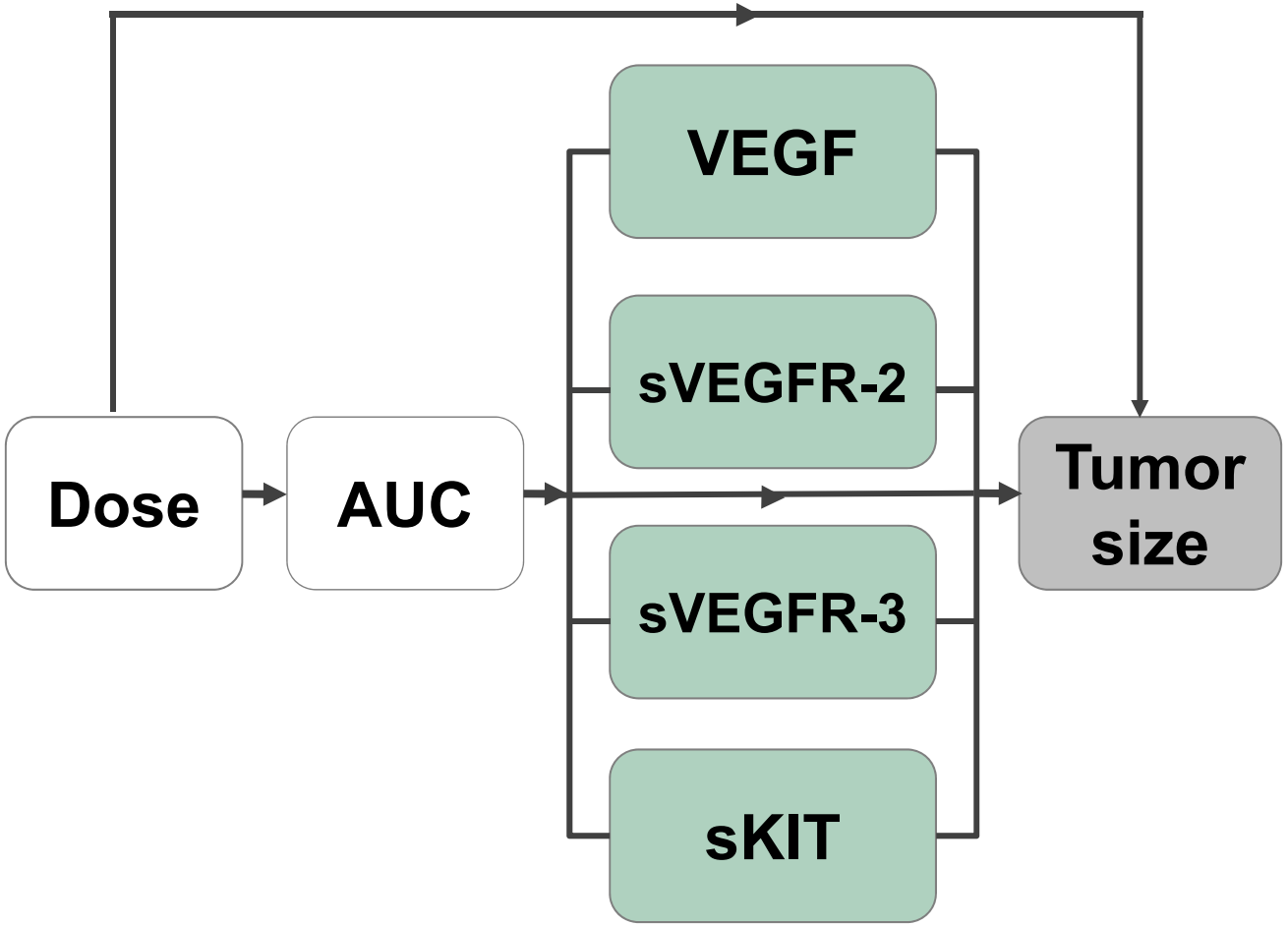
Confidence intervals for the simulated data's 5th,50th and 95th percentiles

50th percentile of the observed data

5th and 95th percentiles of the observed data



UPPSALA
UNIVERSITET



UPPSALA UNIVERSITET

Tumor growth inhibition model[6]

Tumor growth rate | Cell kill rate

$$\frac{dy(t)}{dt} = K_G \cdot y(t) - (K_{Drug} \cdot AUCss_{0\text{-}24} + \mathbf{K_{BM} \cdot BM_{REL}}) \cdot R(t) \cdot y(t)$$

$$R(t) = e^{-\lambda t}$$

$$y(0) = y_0 + \varepsilon^{7}$$

$$BM_{REL} = \frac{BM(t) - Base}{Base}$$

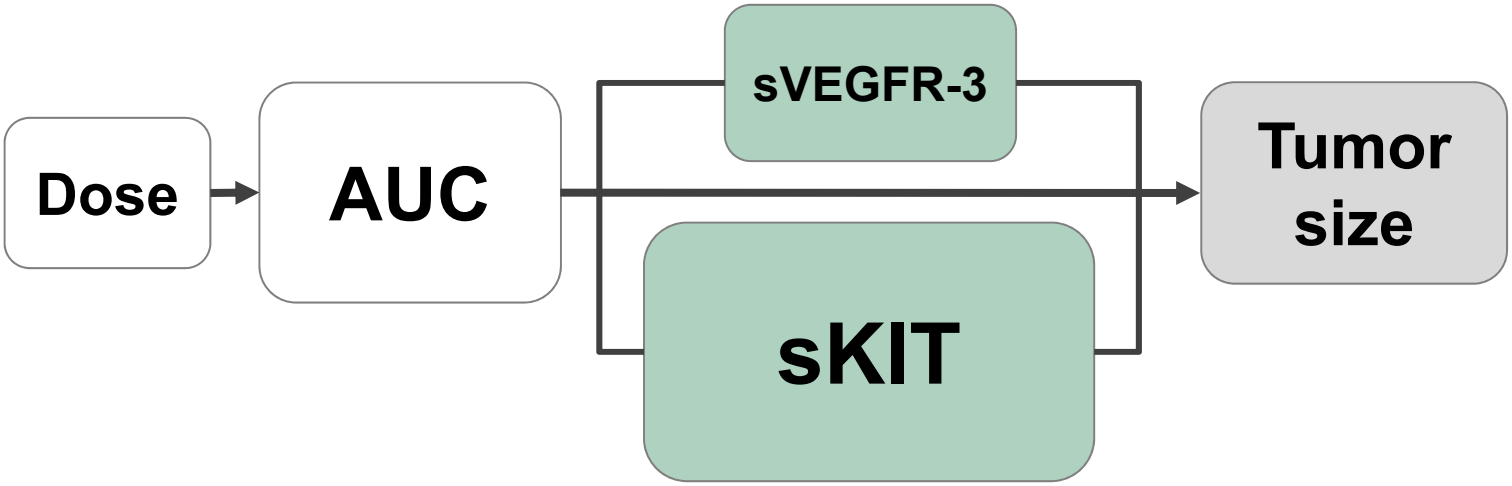
K_G = tumor growth rate (week^{-1})
K_{Drug} = tumor size reduction rate (AUC^{-1} week^{-1})
K_{BM} = tumor size reduction rate (week^{-1})
λ = rate constant of resistance appearance (week^{-1})

[6] Claret L. et al. JCO. 2009:27, 4103-4108
[7] Dansirikul et al J Pharmacokinet Pharmacodyn 2008

UPPSALA UNIVERSITET

Results
Tumor model

Parameter	Estimate	RSE (%)	IIV (CV %)	RSE (%)
K_G (week^{-1})	0.012	10	54	19
K_{Drug} (week^{-1} x AUC^{-1})	0.0050	40	119	12
K_{sKIT} (week^{-1})	-0.0028	14	243	16
K_{sVEGR3} (week^{-1})	-0.037	21	-	-
λ (week^{-1})	0.022	27	-	-
Res error (%)	13	9.7	-	-



UPPSALA UNIVERSITET

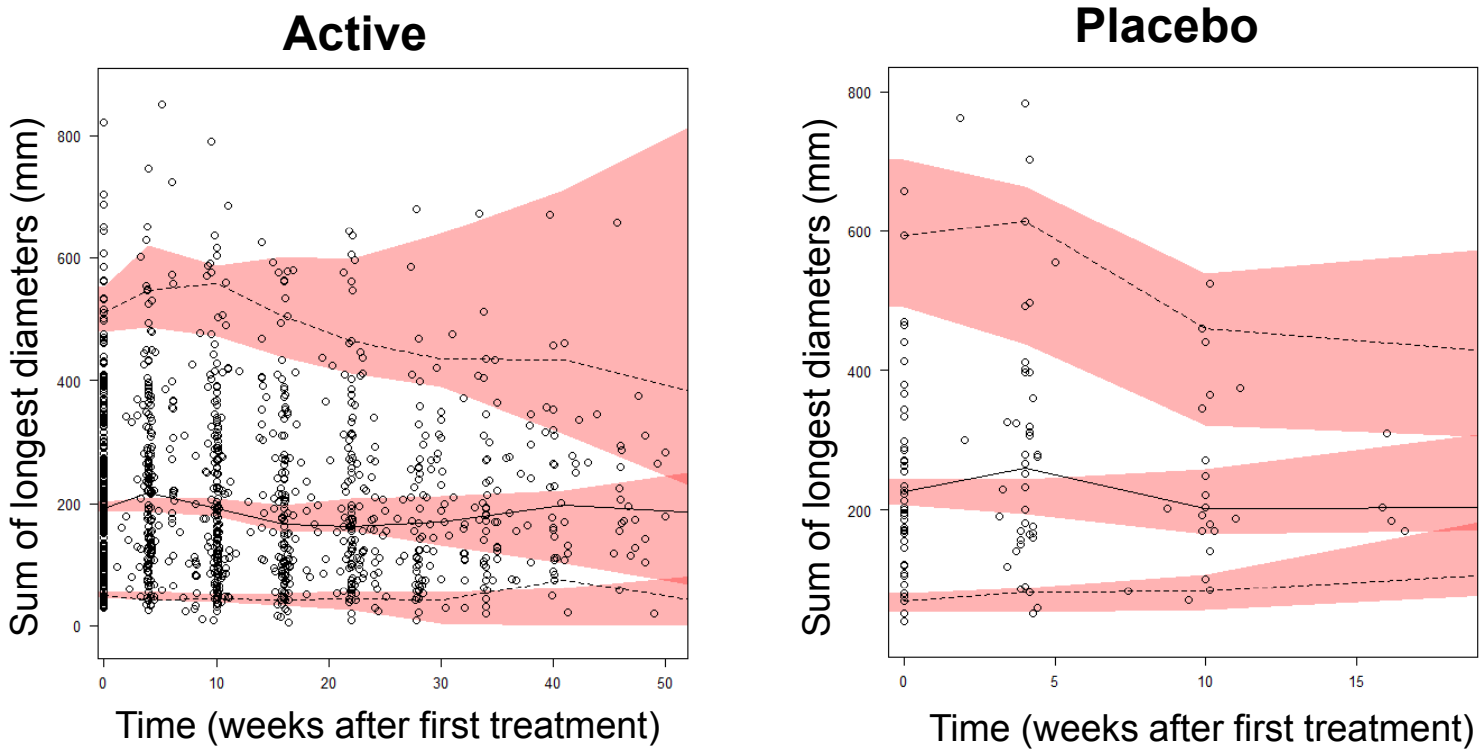
VPC Tumor model

n simulations = 500

Confidence intervals for the simulated data's 5th,50th and 95th percentiles

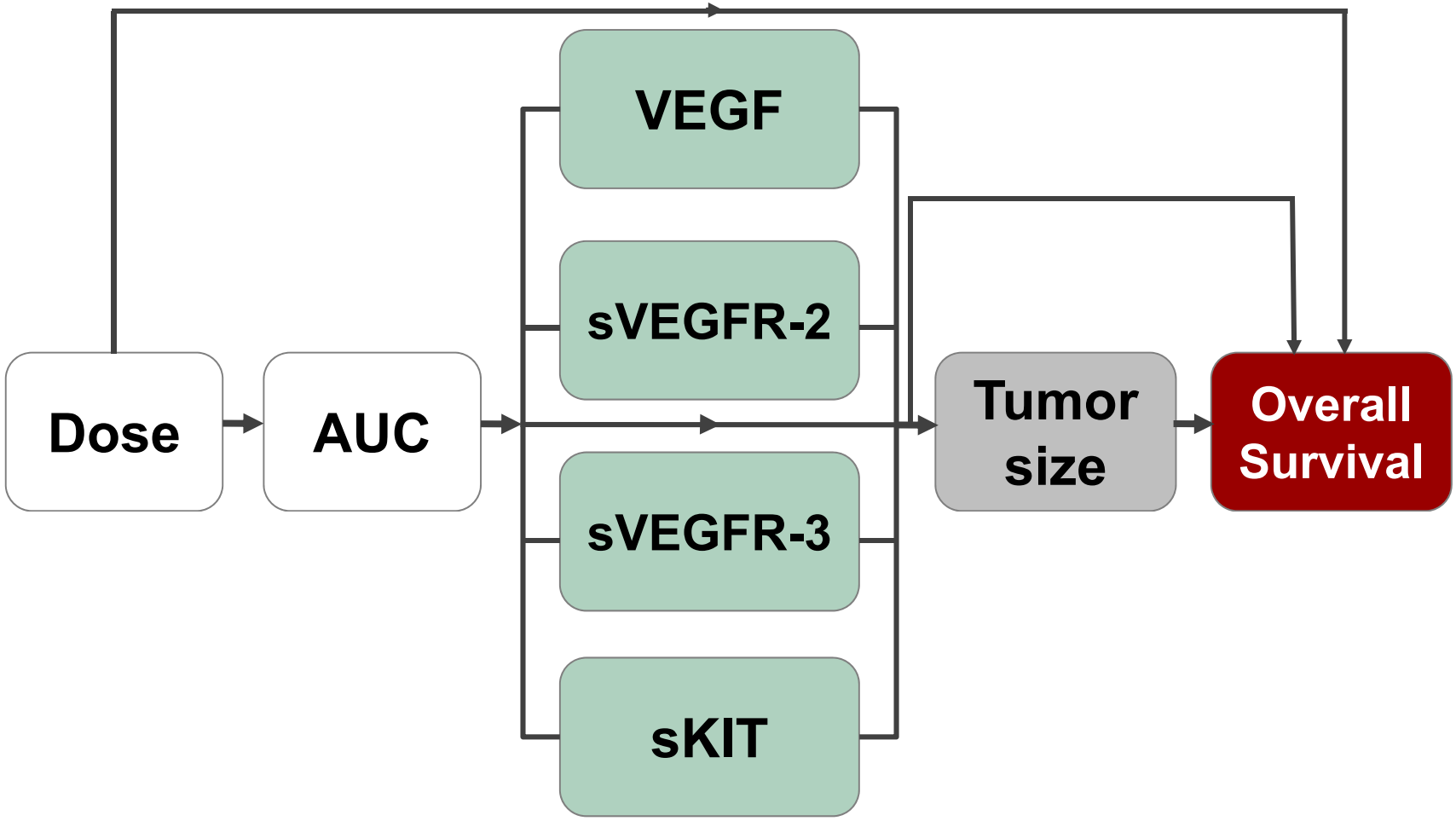
50th percentile of the observed data

5th and 95th percentiles of the observed data



Drop out, dependent on progressive disease, tumor size and time, was taken into account in the simulations

UPPSALA UNIVERSITET



UPPSALA UNIVERSITET

Survival model

Data: n = 300 163 events (54 %)

Parametric survival model (exponential, weibull, gompertz, log-logistic)

Time varying predictors

- Dose
- AUC
- $BM_{REL} = \frac{BM(t) - Base}{Base}$
- $Tumor_{REL} = \frac{y(t) - Base}{Base}$

Constant predictors

- BM = Base
- Tumor = Base
- $Tumor_{REL_6} = \frac{y(6) - Base}{Base}$ $Tumor_{REL_{12}} = \frac{y(12) - Base}{Base}$

Biomarker time courses and tumor size were extrapolated until time of death /censoring

UPPSALA UNIVERSITET

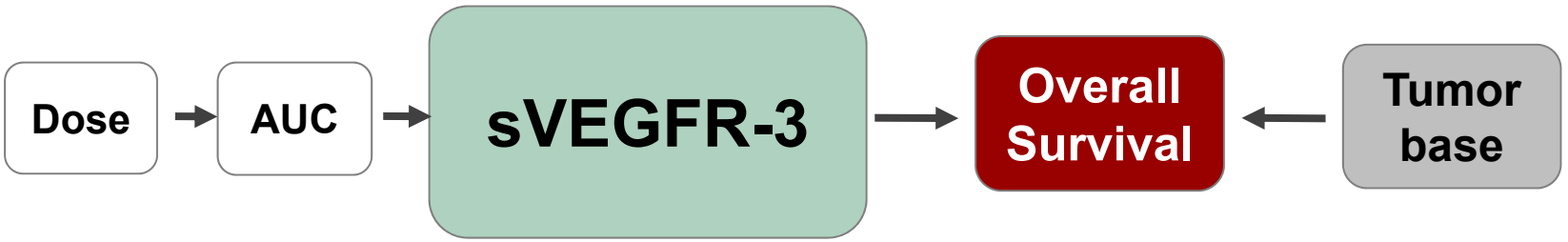
Results
Survival model

Final survial model:

- Weibull distribution
- BM_{REL} ↑ sVEGFR-3 response ↓ h(t)
- Baseline tumor size ↑ baseline ↑ h(t)

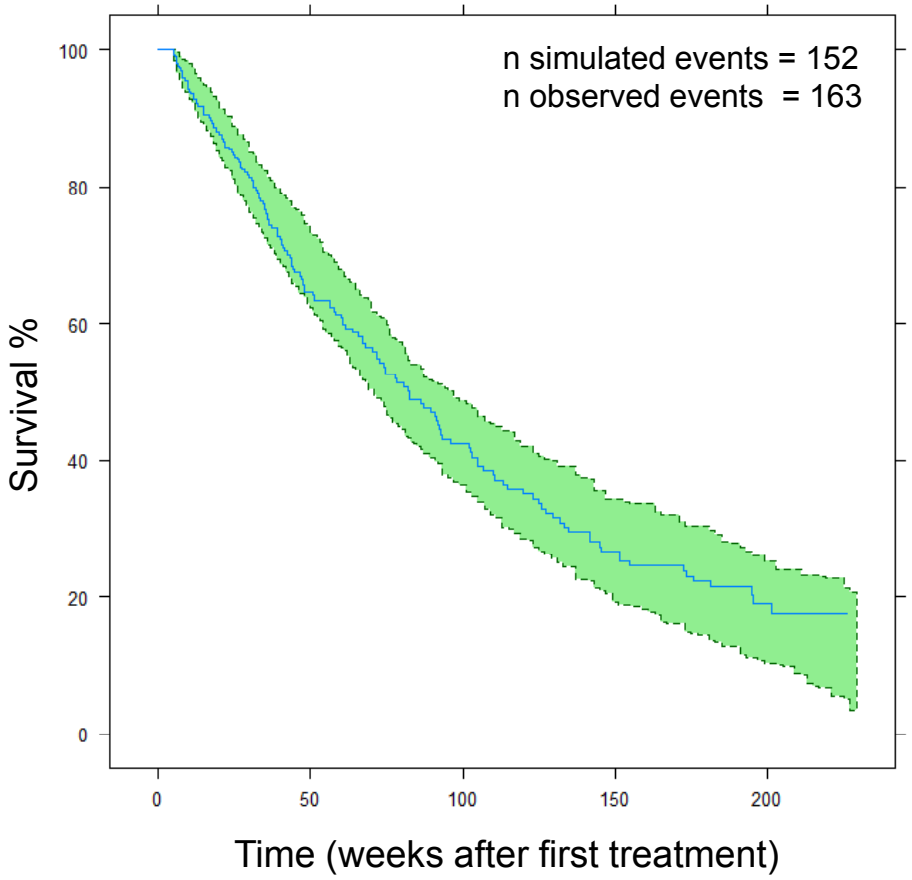
Parameter	Estimate	RSE (%)
λ(week^{-1})	0.0059	47
α	1.2	7
θ_1 sVEGFR-3	-3.8	16
θ_2 Tumor baseline (mm)	-0.0024	28

$$h(t) = \lambda\alpha t^{(\alpha-1)} \cdot e^{(-\theta_1 \cdot \text{sVEGFR-3} + -\theta_2 \cdot \text{Tumor base})}$$



UPPSALA UNIVERSITET

Simulations Survival model



n simulations = 200
Kaplan-Meier plot of observed data
95 % prediction intervals of the Kaplan-Meier plot

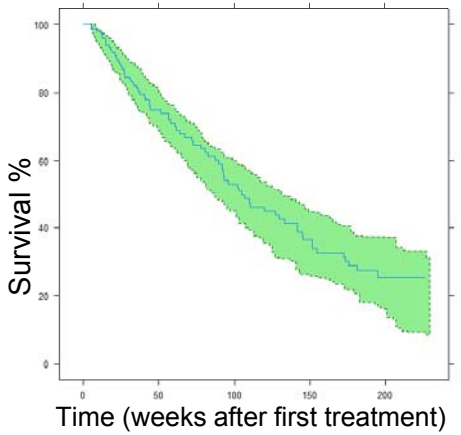
Random censoring was assumed

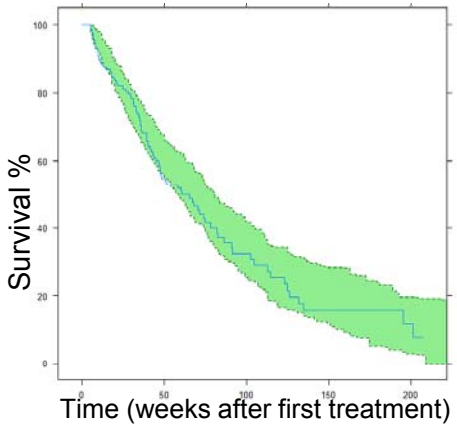
UPPSALA UNIVERSITET

Simulations Survival model

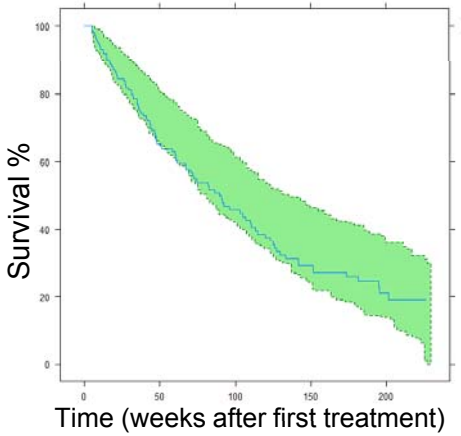
Below median | **Above median**

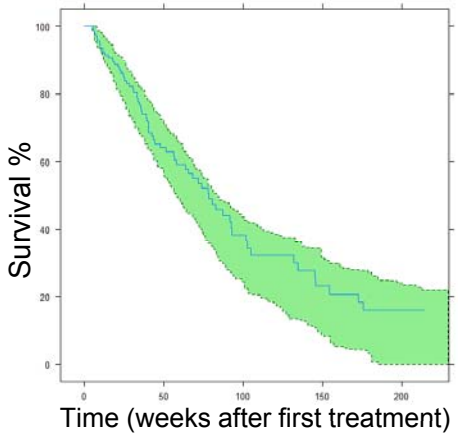
Baseline tumor size





VEGFR-3

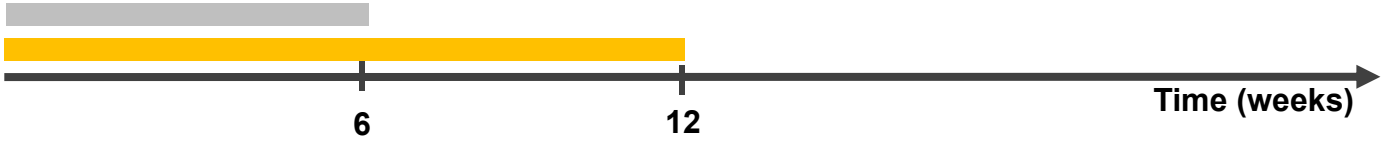




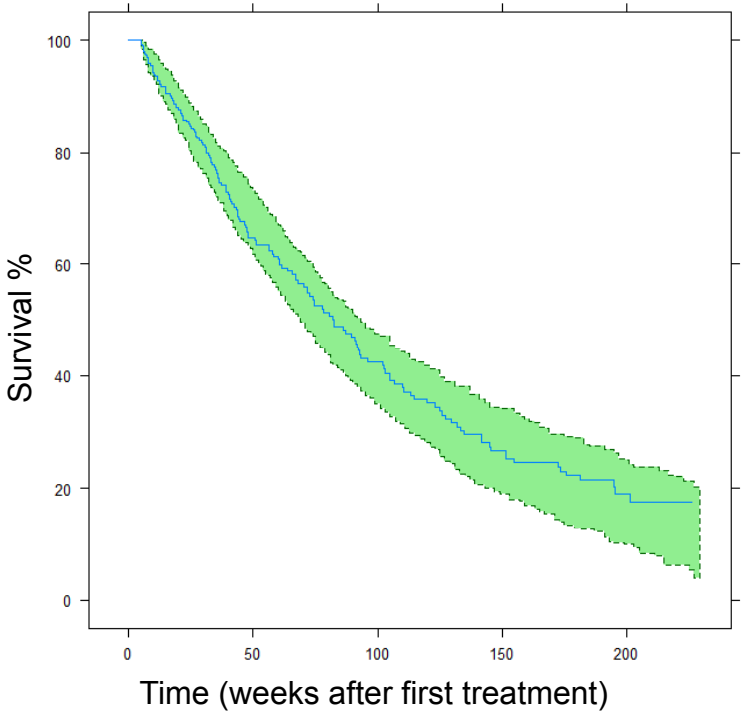
n simulations = 200
Kaplan-Meier plot of observed data
95 % prediction intervals of the Kaplan-Meier plot

UPPSALA UNIVERSITET

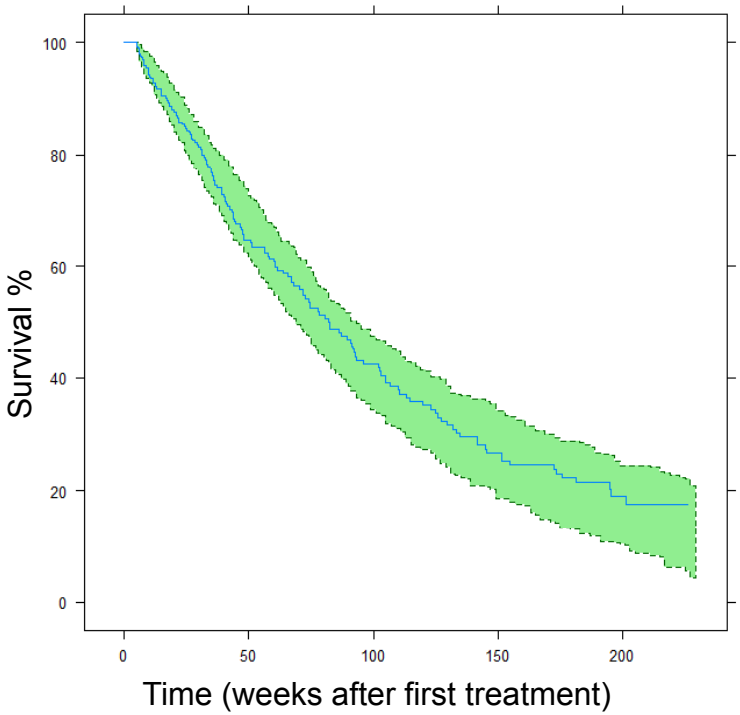
Prediction from first treatment cycles



sVEGFR-3
1:st & 2:nd treatment cycle



sVEGFR-3
1:st treatment cycle



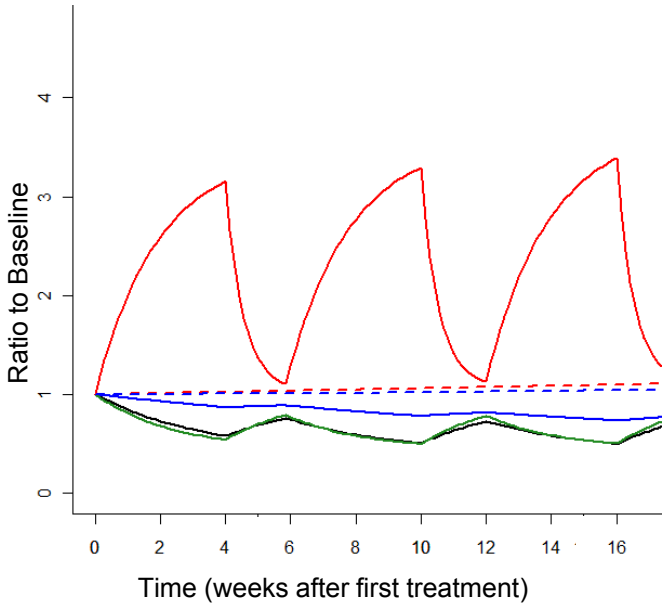
n simulations = 200
Kaplan-Meier plot of observed data
95 % prediction intervals of the Kaplan-Meier plot

UPPSALA UNIVERSITET

Discussion

sKIT has previously been reported as a biomarker of time to progression and overall survival based on results from a traditional statistical analysis[9].

The developed modeling framework allowed integration of the whole biomarker time course and the response, thereby enabling identification of other biomarker relationships.



[9] De Primo. et al., CCR. 2009

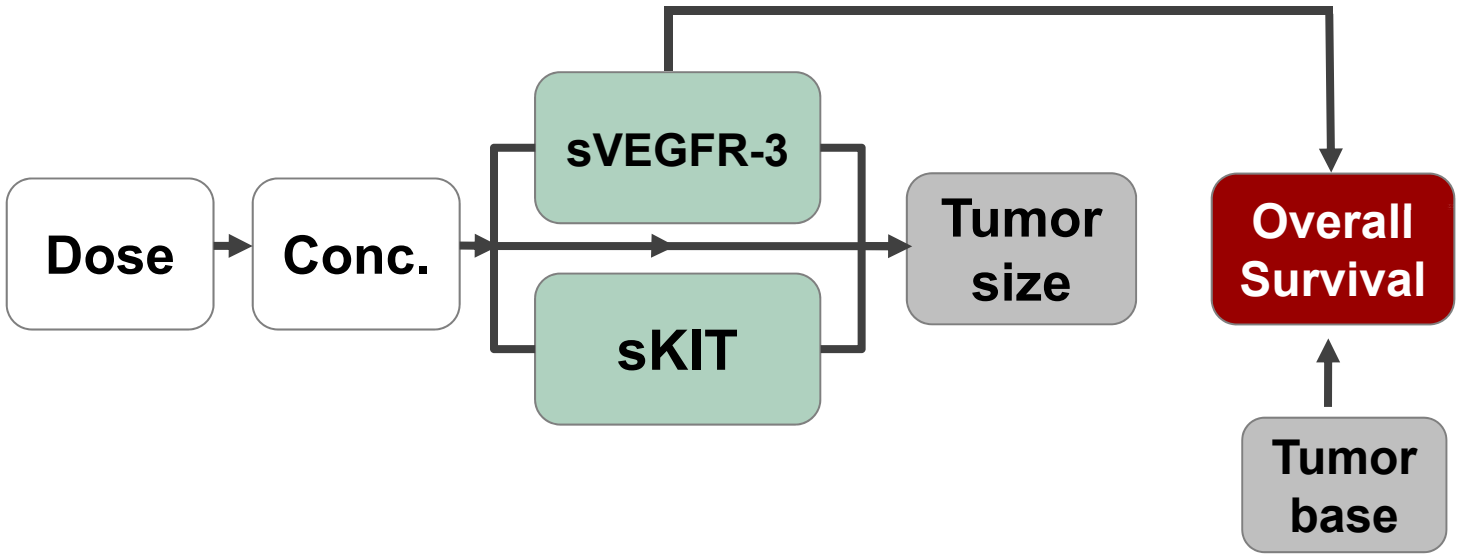
UPPSALA UNIVERSITET

Conclusion

The developed modeling framework allowed integration of the whole biomarker time course and the response.

The identified relationships indicate a potential use of **sKIT, sVEGFR-3** and **tumor baseline** as biomarkers of treatment response.

sKIT could be hypothesized to be a marker for the inhibitory effect of sunitinib on KIT and sVEGFR-3 for the anti-angiogenic activity.



UPPSALA UNIVERSITET

Acknowledgements

- Pfizer ltd
- Swedish Cancer Society