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A pharmacometric framework for dose individualisation of sunitinib in GIST

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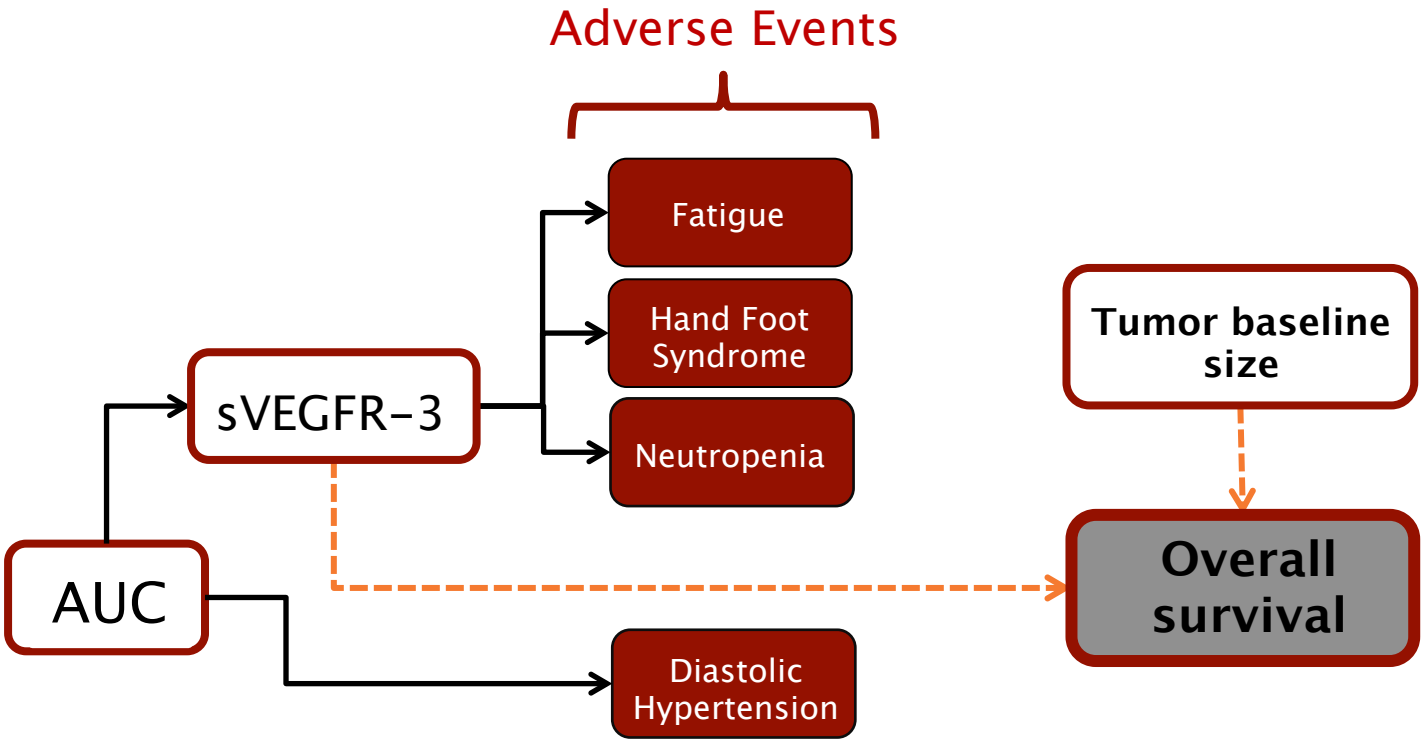
PAGE 2018 May 30

The pharmacometric framework
for sunitinib in GIST

Based on 303 patients



Hansson et al. PAGE 20 (2011) Abstr 2183.
Hansson et al. PAGE 21 (2012) Abstr 2364.
Hansson et al. 2013a. CPT Pharmacometrics Syst. Pharmacol.
Hansson et al. 2013b. CPT Pharmacometrics Syst. Pharmacol.

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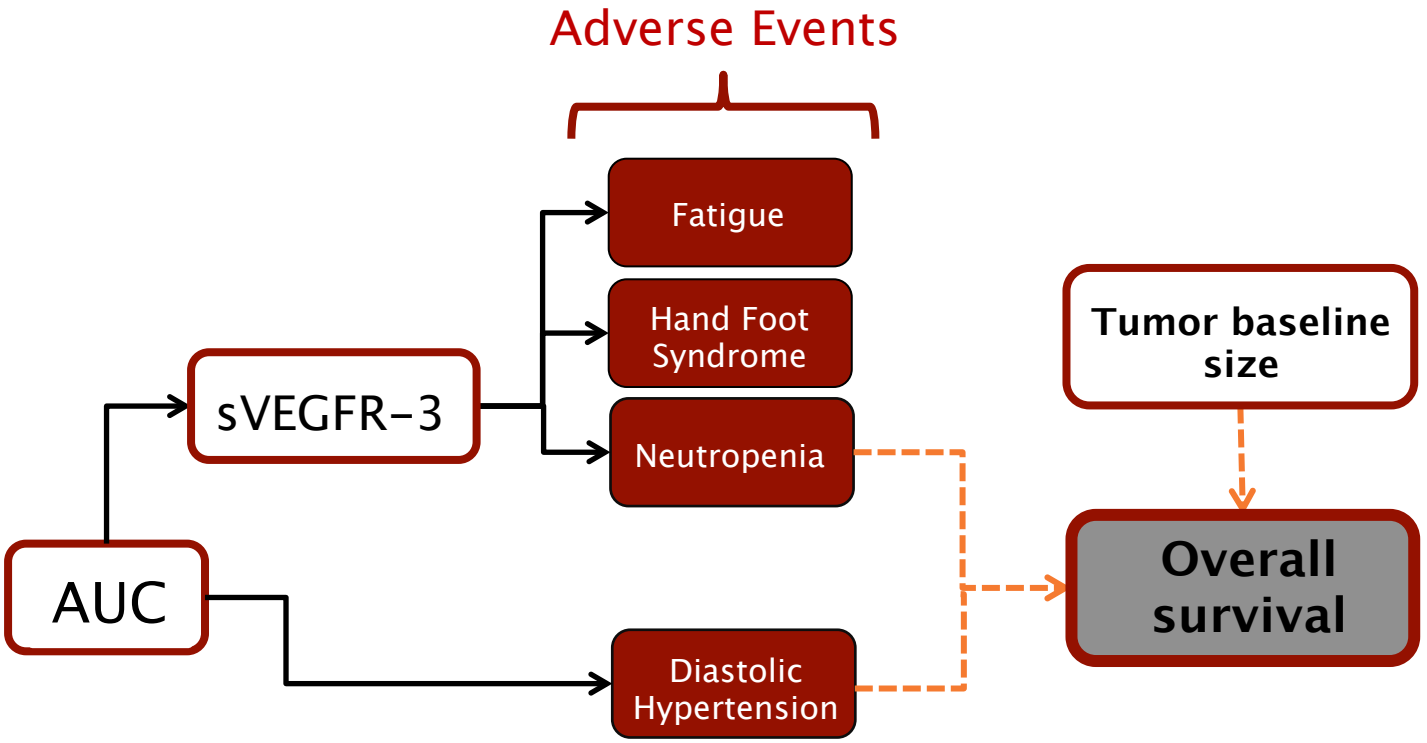

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Why use a pharmacometric framework?

Modeling

- Integrated understanding of the relationships between drug exposure, plasma biomarkers, adverse events, disease state, and long-term clinical outcome.

→ Valuable for identifying robust pharmacodynamic (PD) biomarkers and guide treatment decisions.

Simulations

- Allows for an interaction between treatment outcomes (e.g. toxicity-induced dose reductions may potentially impact efficacy).

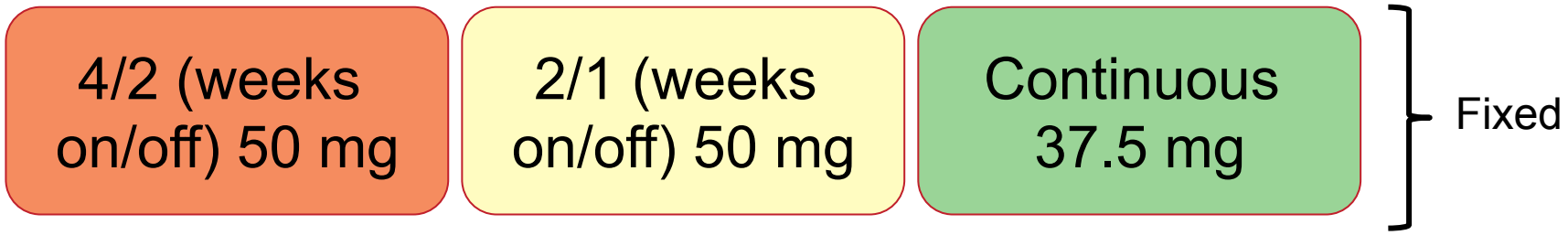
→ Realistic predictions of treatment outcomes under various dosing algorithms.

Hansson et al. 2013a. CPT Pharmacometrics Syst. Pharmacol.
Hansson et al. 2013b. CPT Pharmacometrics Syst. Pharmacol.
van Hasselt et al. 2015. CPT Pharmacometrics Syst. Pharmacol.
Schindler et al. 2017. CPT Pharmacometrics Syst. Pharmacol.

Sunitinib therapy in Gastro-Intestinal Stromal Tumors (GIST)

- **Sunitinib** is a Tyrosine-kinase inhibitor

- Various fixed dosing regimens are followed for GIST:



Demetri et al. 2006. Lancet.
George et al. 2009. Eur J Cancer.
Shen et al 2017. Oncol Ther.
FDA. SUNITINIB: FDA Prescribing Information.

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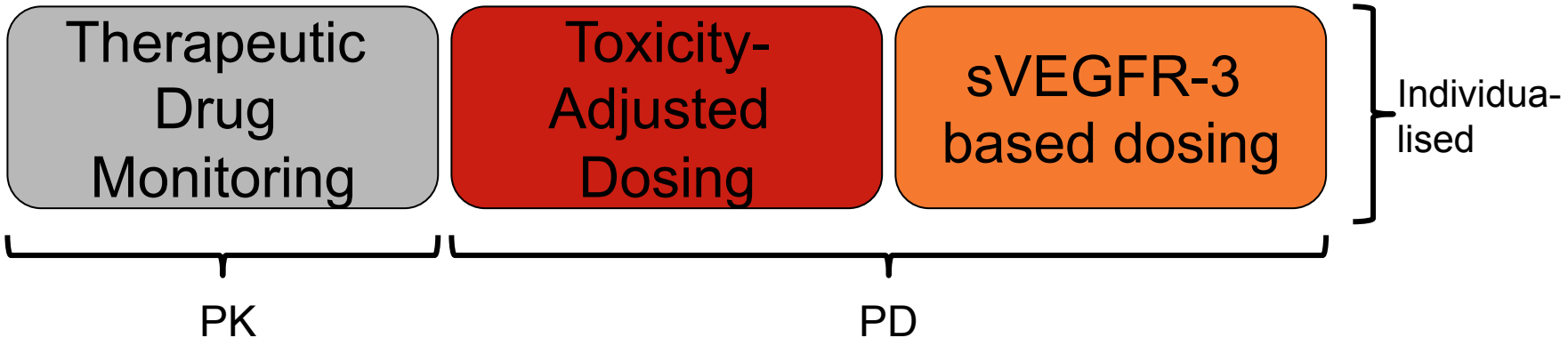
- **Various biomarkers have been suggested for dose-individualisation:**



- Css,min Sunitinib + SU12662
- Neutropenia
- Hypertension
- sVEGFR-3 changes

Hansson et al., 2013, *CPT: Pharmacometrics and Syst Pharmacology*
Lankheet et al., 2014, *Br J Cancer*
Sabanathan et al., 2017, *Cancer Chemother Pharmacol.*

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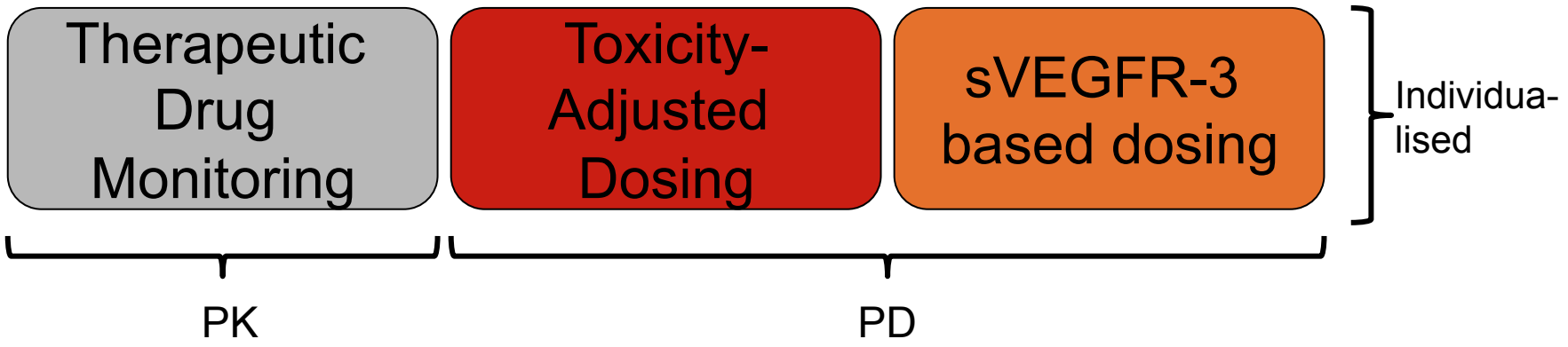
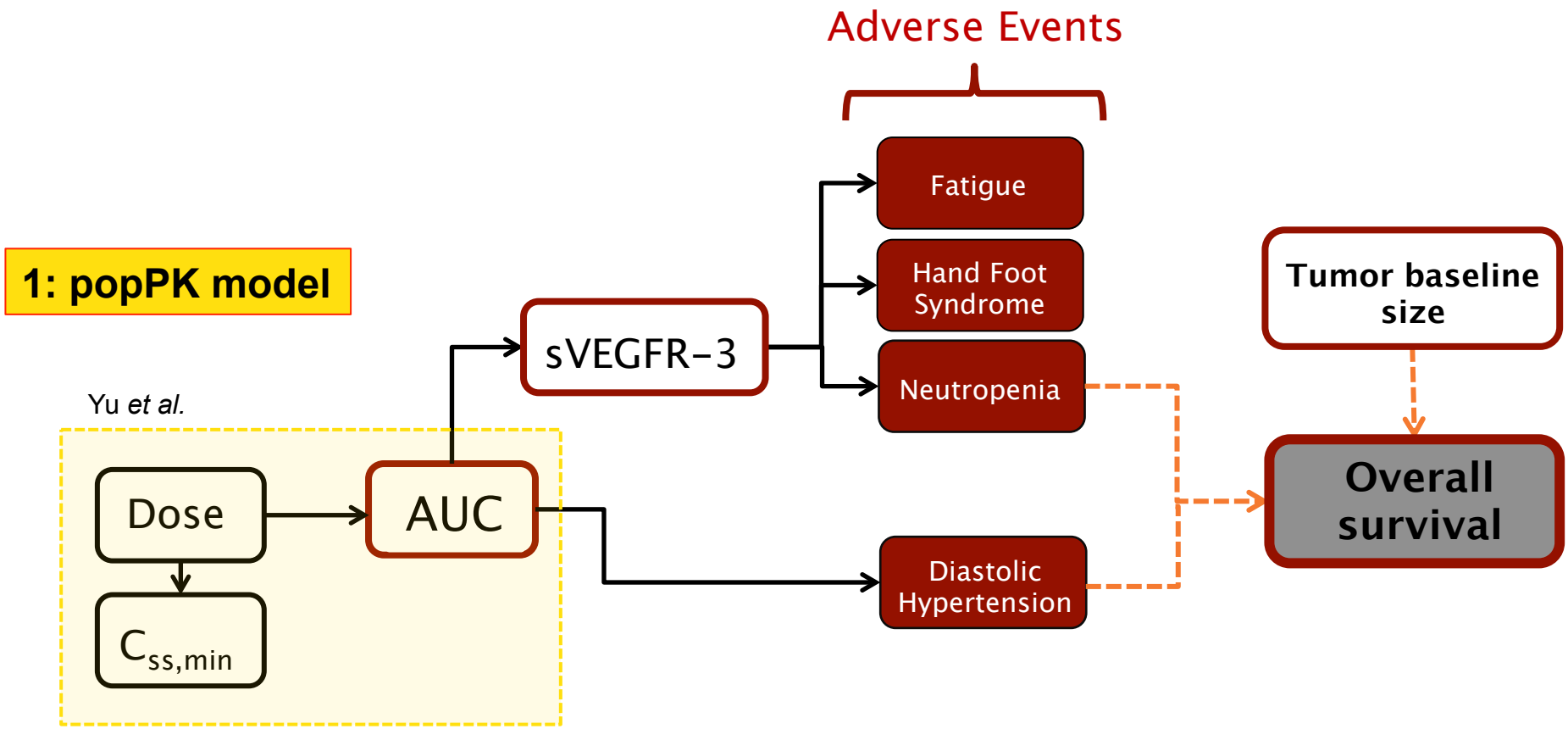
Objectives

Identify which biomarker could best be utilised for dose individualisation of sunitinib in GIST, to optimize the benefit/risk ratio.



Expansion of the framework



Hansson et al., 2013a, CPT: Pharmacometrics and Systems Pharmacology
Hansson et al., 2013b, CPT: Pharmacometrics and Systems Pharmacology
Yu et al, 2014, Br J Clin Pharmacol.

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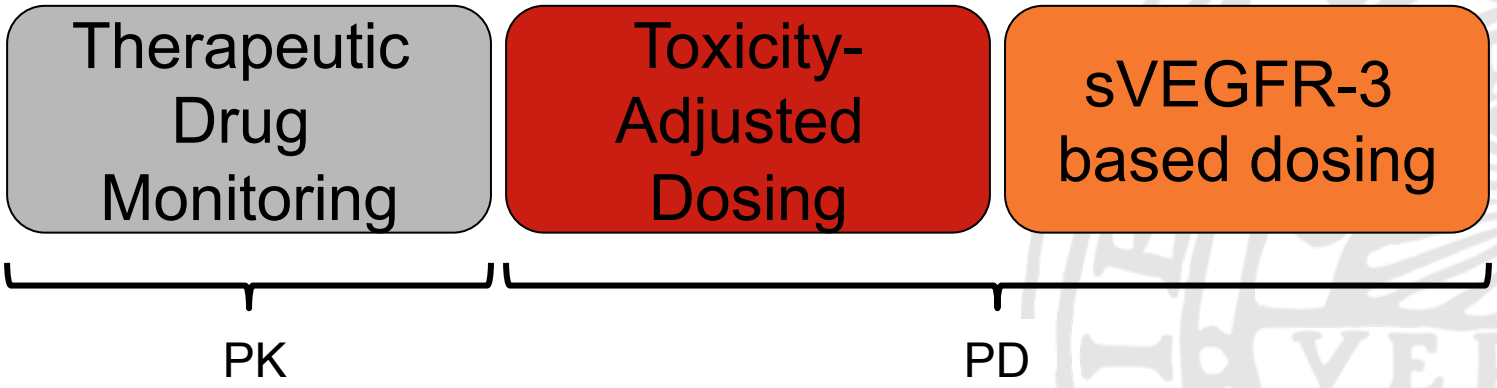
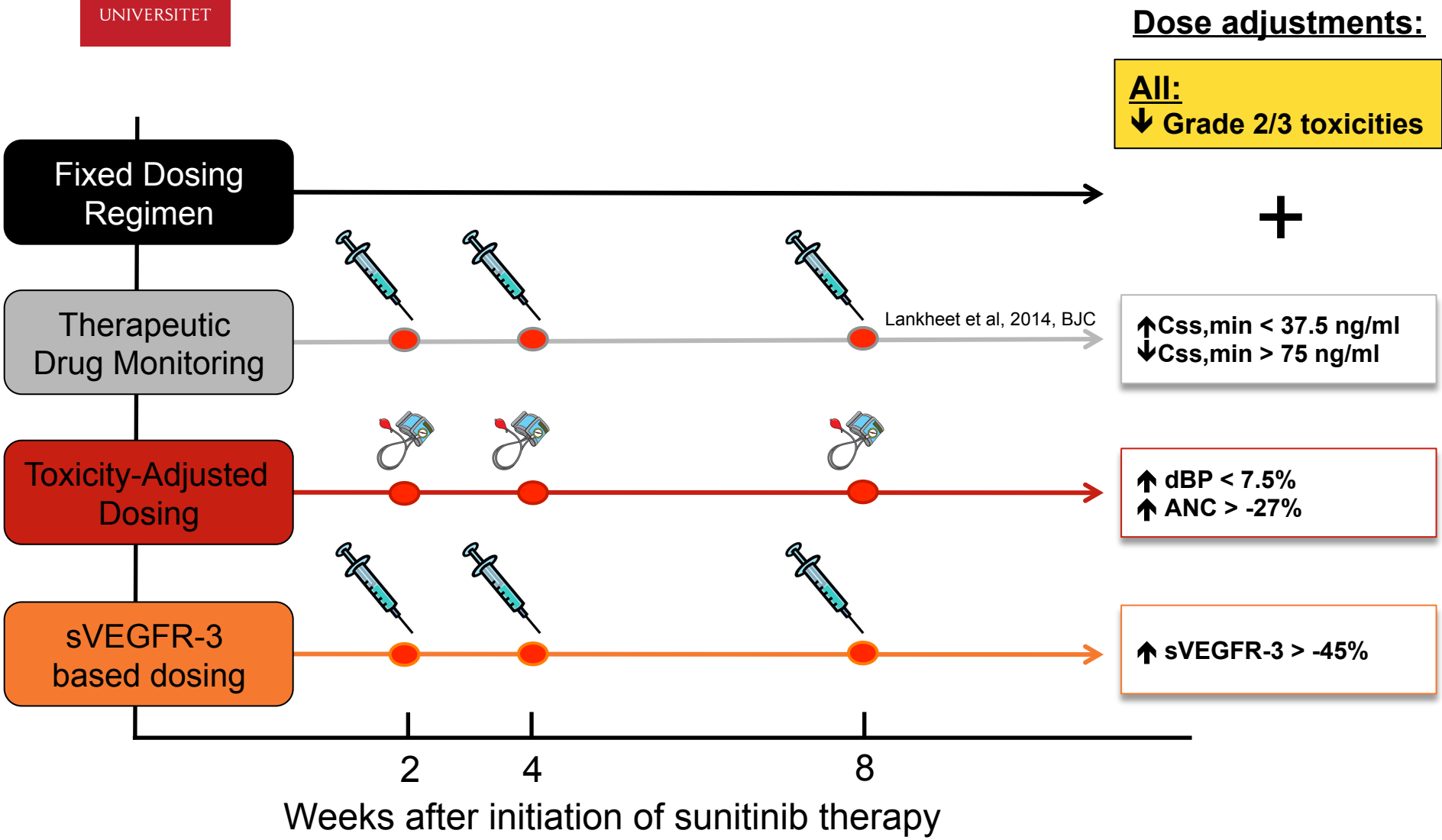
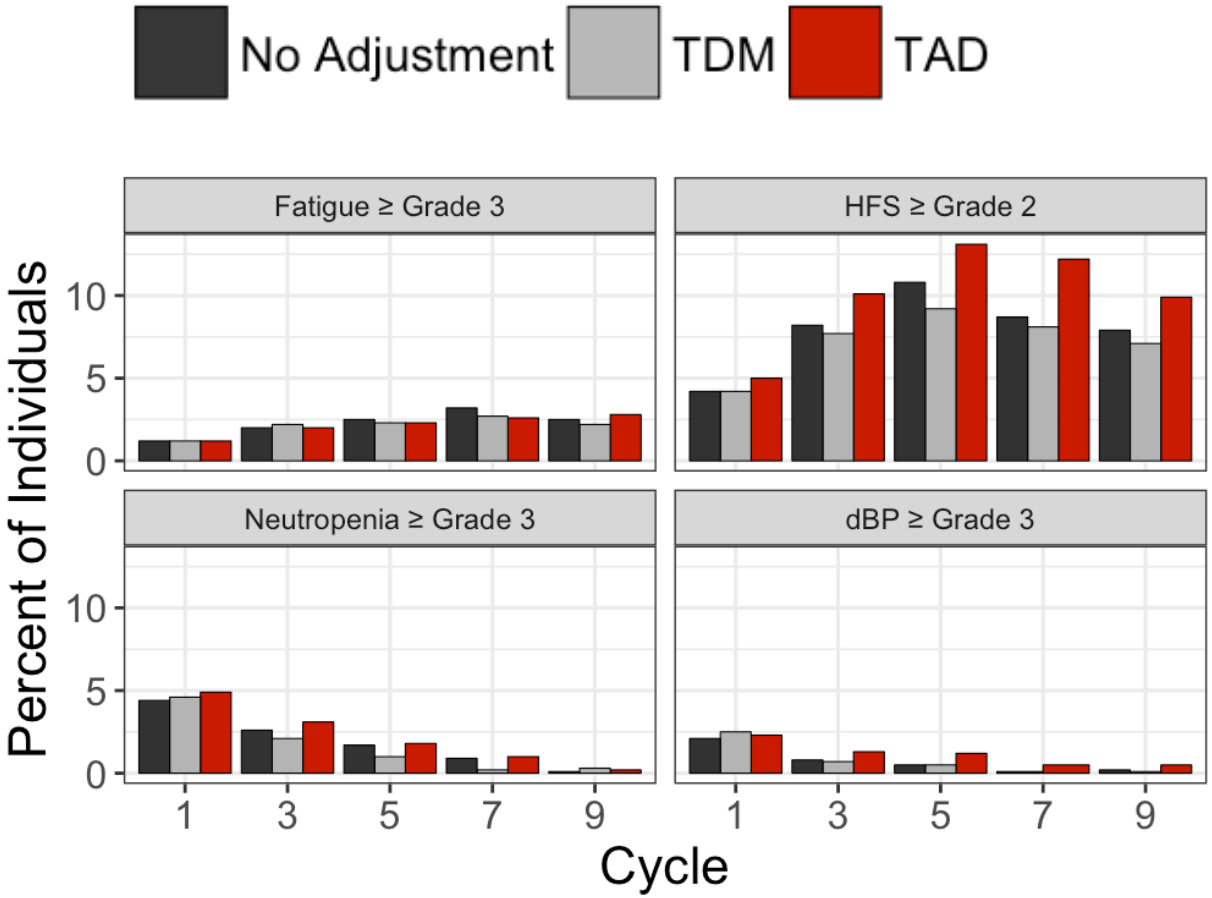
Biomarker-based dose adaptations



Schedule for dose individualisation



Comparison of biomarkers: adverse events



Daily observations of adverse events

Simulation with 1000 individuals

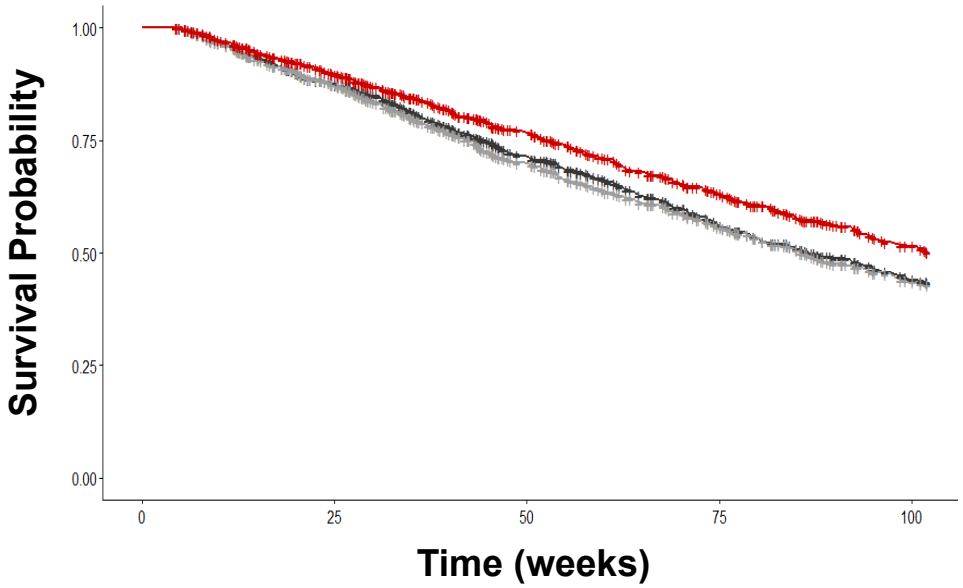
1 cycle = 6 weeks of sunitinib therapy

TDM= therapeutic drug monitoring, TAD = toxicity-adjusted dosing

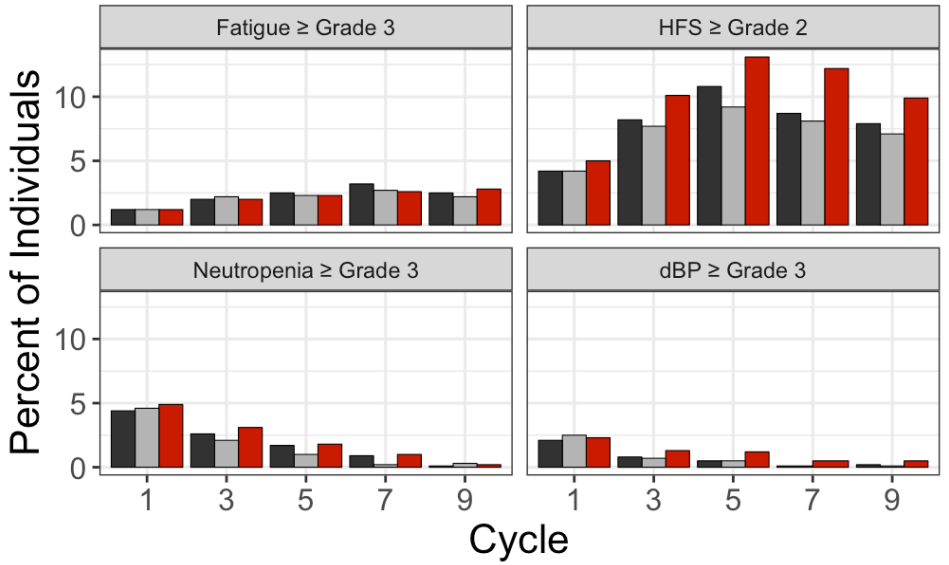
Comparison of biomarkers

No Adjustment TDM TAD

Overall Survival



Adverse Events

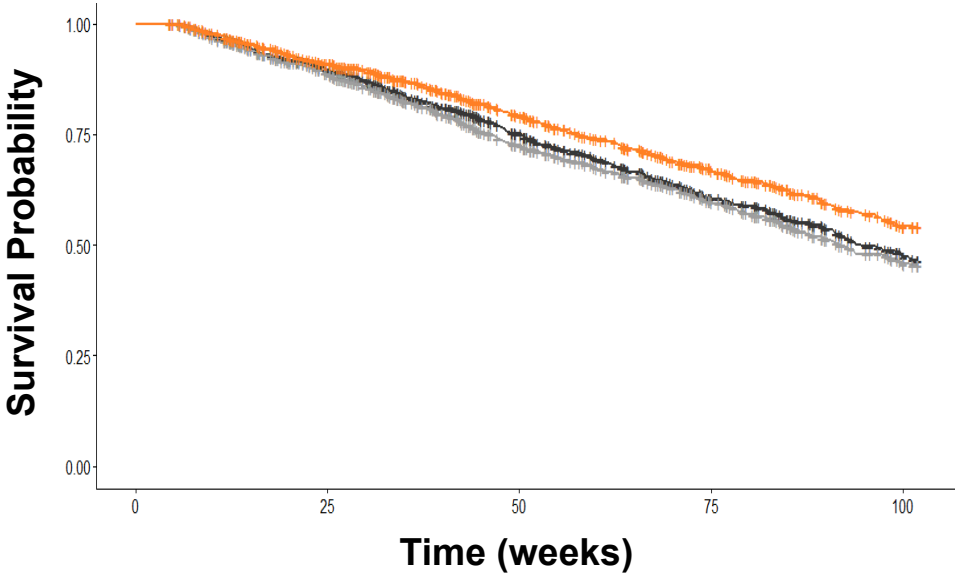


TDM= therapeutic drug monitoring, TAD = toxicity-adjusted dosing

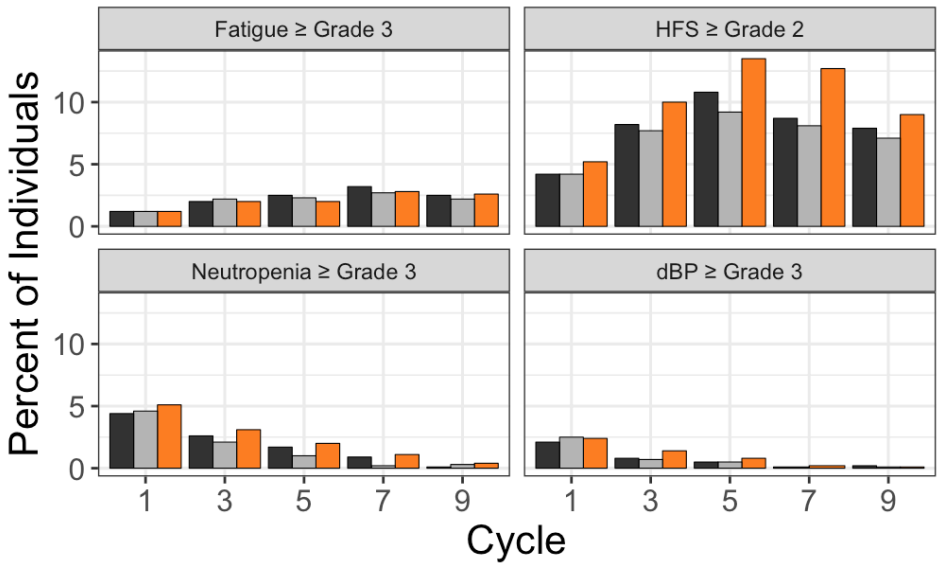
Comparison of biomarkers

No Adjustment TDM sVEGFR-3

Overall Survival



Adverse Events



TDM= therapeutic drug monitoring, sVEGFR-3 = sVEGFR-3 based dosing

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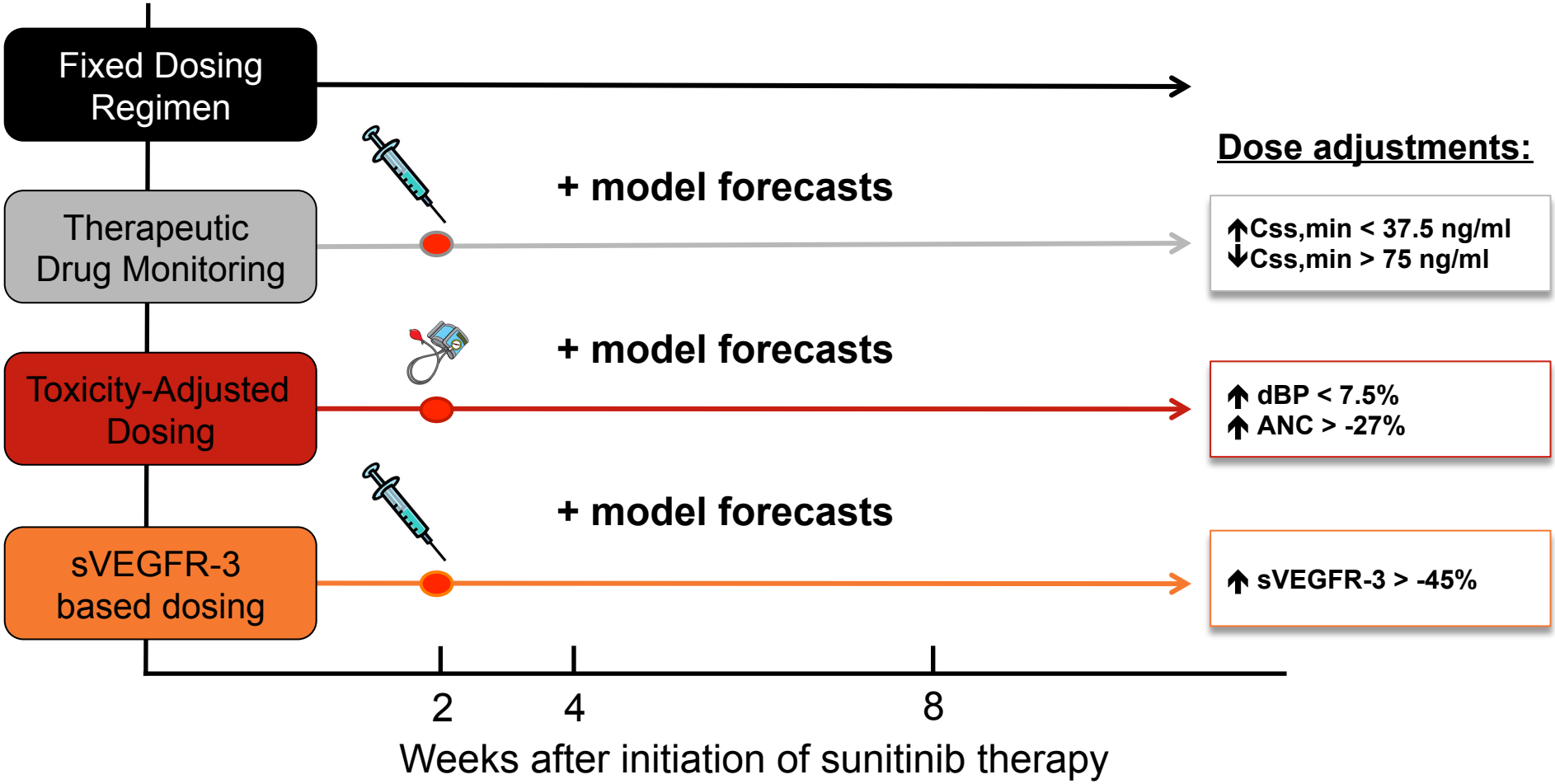
Model-based dose individualisation

Neutropenia

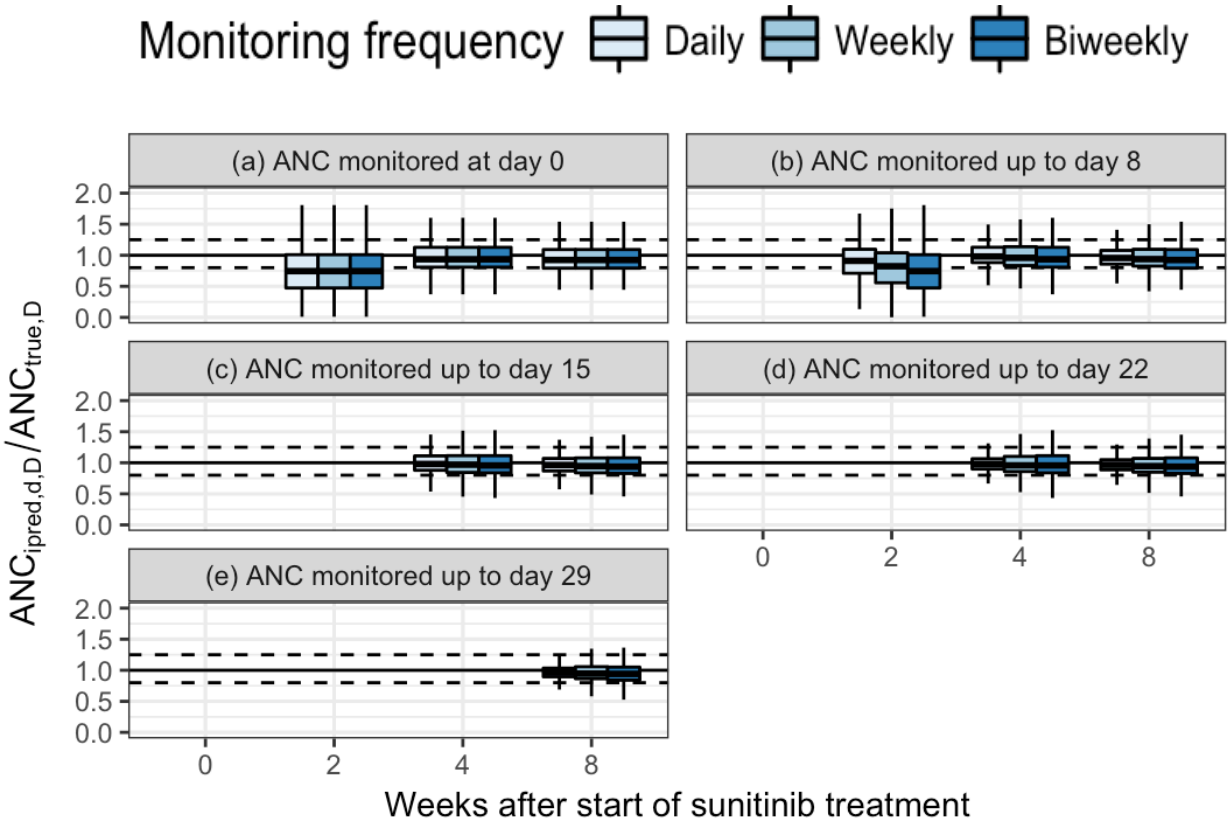
Diastolic Blood Pressure

sVEGFR-3

Schedule for dose individualisation



Accuracy of neutropenia forecasts



Accuracy at **Week 4**:

Daily:	**86%**
Weekly:	78%
Biweekly:	**74%**

$$ANC = \frac{ANC(t)\text{-}5}{5}$$

Results are based upon the CD schedule (37.5 mg)

Accuracy = 80-125% true value

* ANC = absolute neutrophil count

Netterberg et al., 2017, Cancer Chemother Pharmacol

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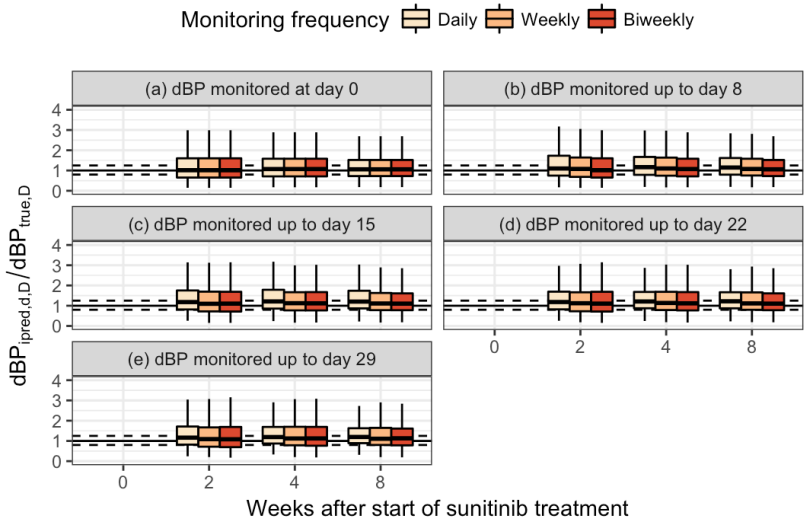
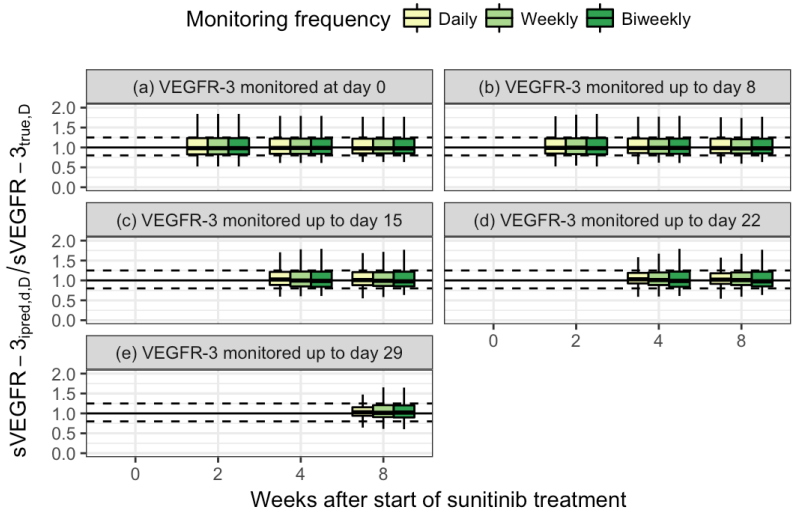
Accuracy of dBP and sVEGFR-3 forecasts





dBP = diastolic blood pressure

sVEGFR-3 = soluble VEGFR-3

Daily:	**35%**
Weekly:	28%
Biweekly:	**28%**

$$dBP = \frac{dBP(t)\text{-}BASE_{dBP}}{BASE_{dBP}}$$

Accuracy at **Week 4**:

Based on the CD schedule (37.5 mg)

Daily:	**75%**
Weekly:	67%
Biweekly:	**65%**

$$sVEGFR\text{-}3 = \frac{sVEGFR\text{-}3(t)\text{-}BASE_{sVEGFR\text{-}3}}{BASE_{sVEGFR\text{-}3}}$$

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Summary

1. A pharmacometric framework including both clinical outcomes and adverse effects provides an integrated approach to answer clinically relevant questions:
   - Provides an overview of the consequences of a dose change on multiple relevant outcomes
   - Enables consideration of interaction between variables

2. For sunitinib in GIST:
   - The suggested algorithm for TDM (concentration) was not predicted to improve OS
   - The suggested algorithm for Toxicity adjusted dosing (TAD) was predicted to improve OS
   - A sVEGFR-3 target was defined which resulted in similar OS and AEs as TAD
   - Next step: Optimize the biomarker cut-off points as well as the sampling schedules

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Summary

3. Neutrophil counts and sVEGFR-3 appear reliable for forecasting:
   - Early measurements shown to predict later measurements
   - Next step: The predictive performance of early measurements to predict individual hazard of death

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Acknowledgements

Radboud MC:
- Ingrid Desar
- Nielka van Erp

Metrum Research Group:
- Kyle T. Baron

Funding:
- Swedish Cancer Society
- European University Consortium for Pharmaceutical Sciences