

Quantifying the exposure-toxicity relationship of [¹⁷⁷Lu]Lu-PSMA-I&T using a population PK-PD model

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Introduction

- [¹⁷⁷Lu]Lu-PSMA-I&T is a proven effective radioligand therapy that prolongs survival in patients with metastatic castration resistant prostate cancer (mCRPC).
- It targets the prostate-specific membrane antigen (PSMA) highly expressed on mCRPC cells.
- While [¹⁷⁷Lu]Lu-PSMA has a favorable overall toxicity profile, dose-limiting hematological toxicities do occur in a subset of patients.
- Considerable variability is present in pharmacokinetics (PK), particularly in tumor and bone exposure.

Aim

To quantify the relationship between [¹⁷⁷Lu]Lu-PSMA-I&T exposure in bone and bone metastases, and its impact on neutrophil counts using a semi-physiological population pharmacokinetic-pharmacodynamic (PK-PD) model

Conclusion

- The population PK-PD model quantified the [¹⁷⁷Lu]Lu-PSMA-I&T exposure-neutrophil relationship of treated mCRPC patients, highlighting substantial variability in bone exposure and feasibility of predicting individual neutrophil counts.
- Further optimization could help predict individual neutropenia from first-cycle data and establish toxicity thresholds to guide personalized treatment.

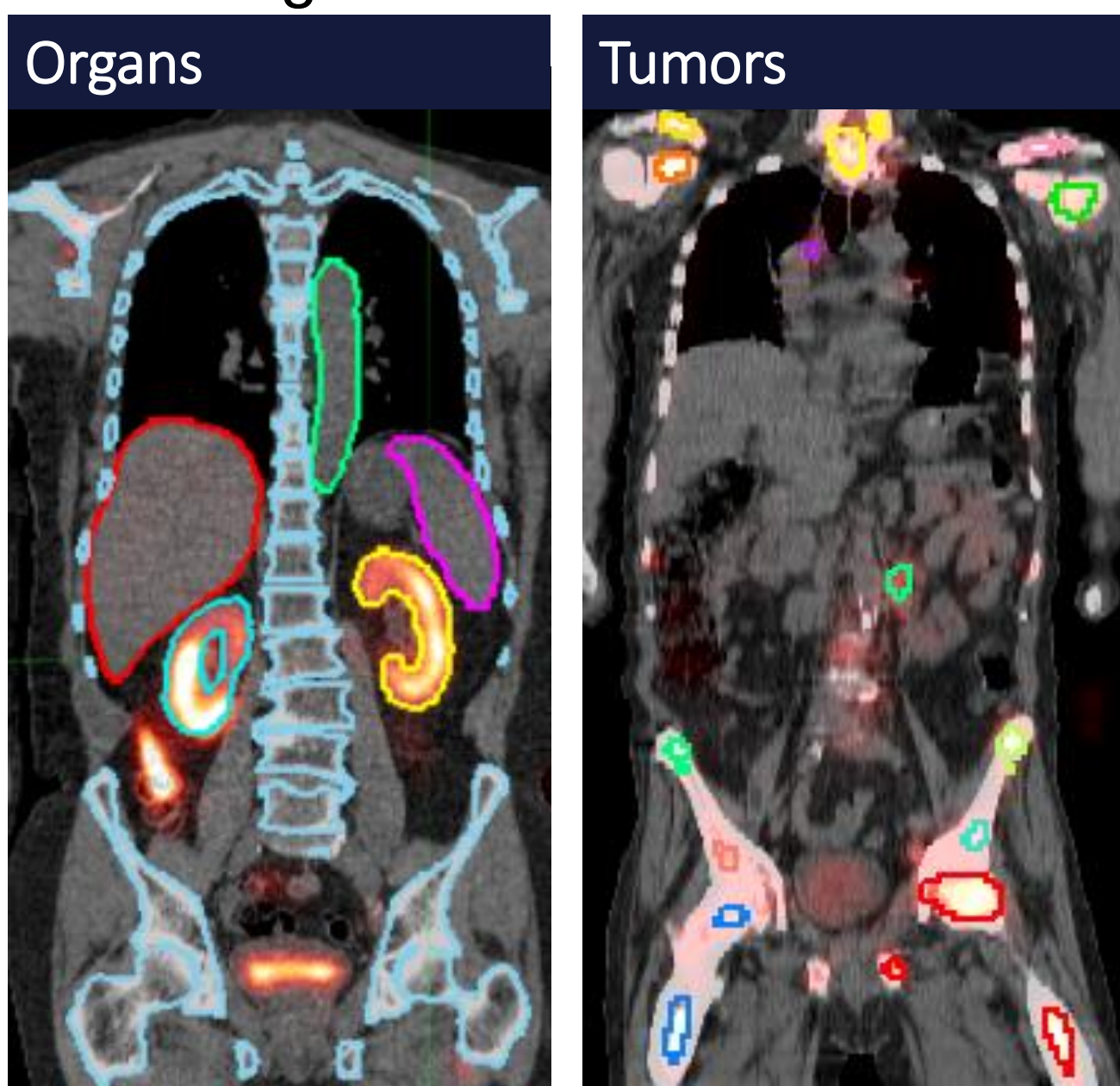
Methods & Clinical Data

Table 1. Patient characteristics and study information

Characteristic	Median [range]
Patients (n)	139
Treatment schedule (n)	4x6 (~10 patients) and 2x2 (12 weeks interval) weeks
Injected radioactivity (MBq)	7385 [3693, 7763]
SPECT-CT scan times (h)	4, 24, 144
Weight (kg)	81.3 [57.0, 120.0]
Age (years)	74 [50, 91]
Neutrophils at baseline (10 ⁹ /L)	4.1 [1.3, 12.6]
Patients neutrophils (10 ⁹ /L) < 1.5 (%)	7.2%
Cycles per patient (n)	3.2 [1-8]
Volume of segmented tumors (mL)	243.7 [3.5, 2764.1]
Distinct tumor type per patient (n)	
• Bone metastasis	134
• Liver metastasis	26
• Primary tumor and nodal metastasis	88

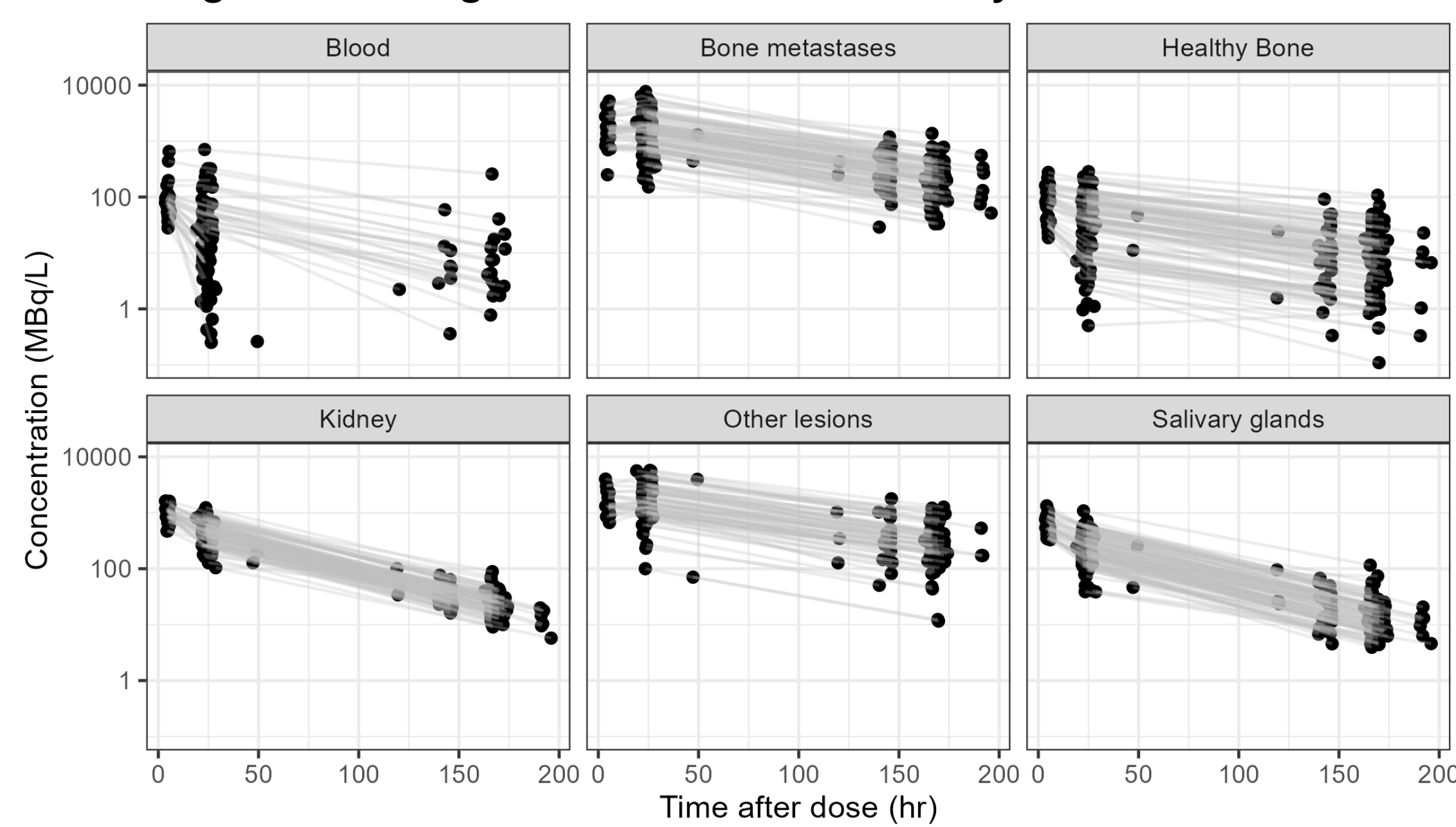
Data from patients receiving [¹⁷⁷Lu]Lu-PSMA-I&T (September 2019-March 2024). Baseline values measured at study inclusion, unless stratified per cycle. Neutrophil levels were included up to 3 months post-treatment.

Figure 1. Semi-automatic organ and tumor segmentation on SPECT/CT



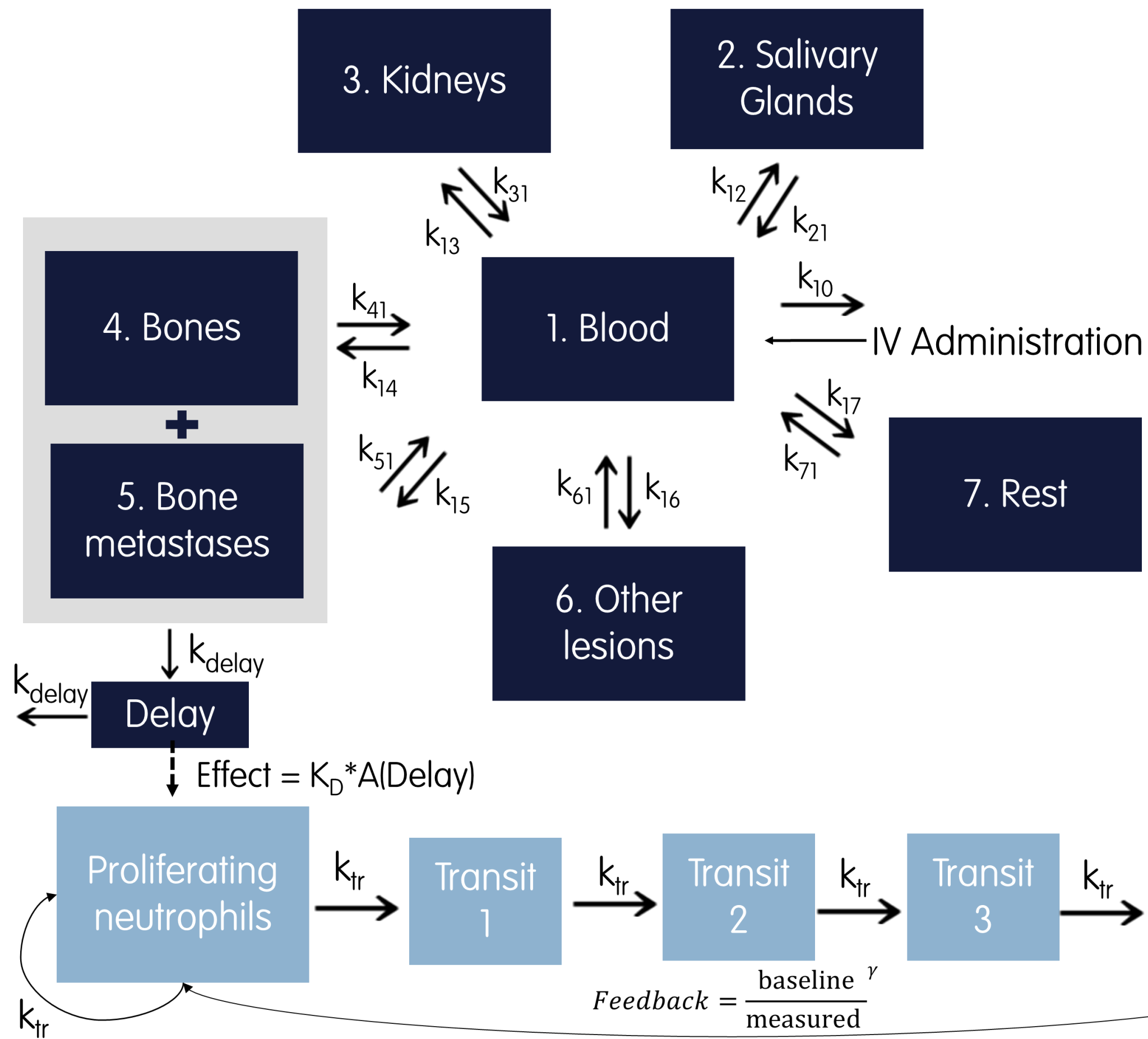
MIM (version 7.3.6) was used to acquire volumes (L) and mean uptake (MBq/L) in organs and tumors (≥2.5mL).

Figure 2. Concentration (MBq/L) time curves of segmented organs and tumors after cycle 1



Model Structure & Parameters

Figure 3. Schematic overview of the final model structure



A previously developed PK-model was optimized and expanded [1]. A previously developed PD-model was used to sequentially link the activity in bones (healthy bone and bone metastases compartment) to patient neutrophil data (using NONMEM 7.5) [2]. The total activity in bones was corrected for decay.

Table 2. Final estimates of important PK-PD parameters

Parameter (PK)*	Estimate (RSE%)	Estimate (RSE%)
	Population parameters(θ)	Inter-individual variability (CV(%))
k ₁₄ (h ⁻¹)	0.0170 (16.2)	151 (19.4)
k ₄₁ (h ⁻¹)	0.0218 (4.41)	
k ₁₅ (h ⁻¹)	0.0299 (12)	67.1 (17.6)
k ₅₁ (h ⁻¹)	0.0214 (2.19)	
Decrease tumor uptake cycle 2, 3 and 4-8 (%)	75.2 (7.9), 59.1 (8.03), 58.7 (9.38)	
Tumor volume effect bone metastases and other lesions**	0.963 (1.34), 1.06 (2.93)	
IOV on tumor uptake	-	30.3 (15.8)
Parameter (PD)		
Baseline neutrophils (10 ⁹ /L)	4.21 (3.77)	40.0 (12.5)
Mean transit time (MTT) (h)	179 (12.7)	
Slope effect (K _D) (MBq ⁻¹)	0.000627 (21.5)	
Gamma	0.113 (21.4)	
k _{delay} (h ⁻¹)	0.000448 (20.8)	151 (39.1)
Residual unexplained variability		
Proportional error neutrophils		25.8 (4.4)

PK-PD model was developed sequentially (PK-parameters were fixed when estimating PD-parameters).
*Not all parameters are shown. **Covariate was included as power function $P_{cov} = P_{pop} * \frac{COV_{\theta_{cov}}}{COV_{median}}$

Model Evaluation & Simulations

Figure 4. Example of individual GOF-plots

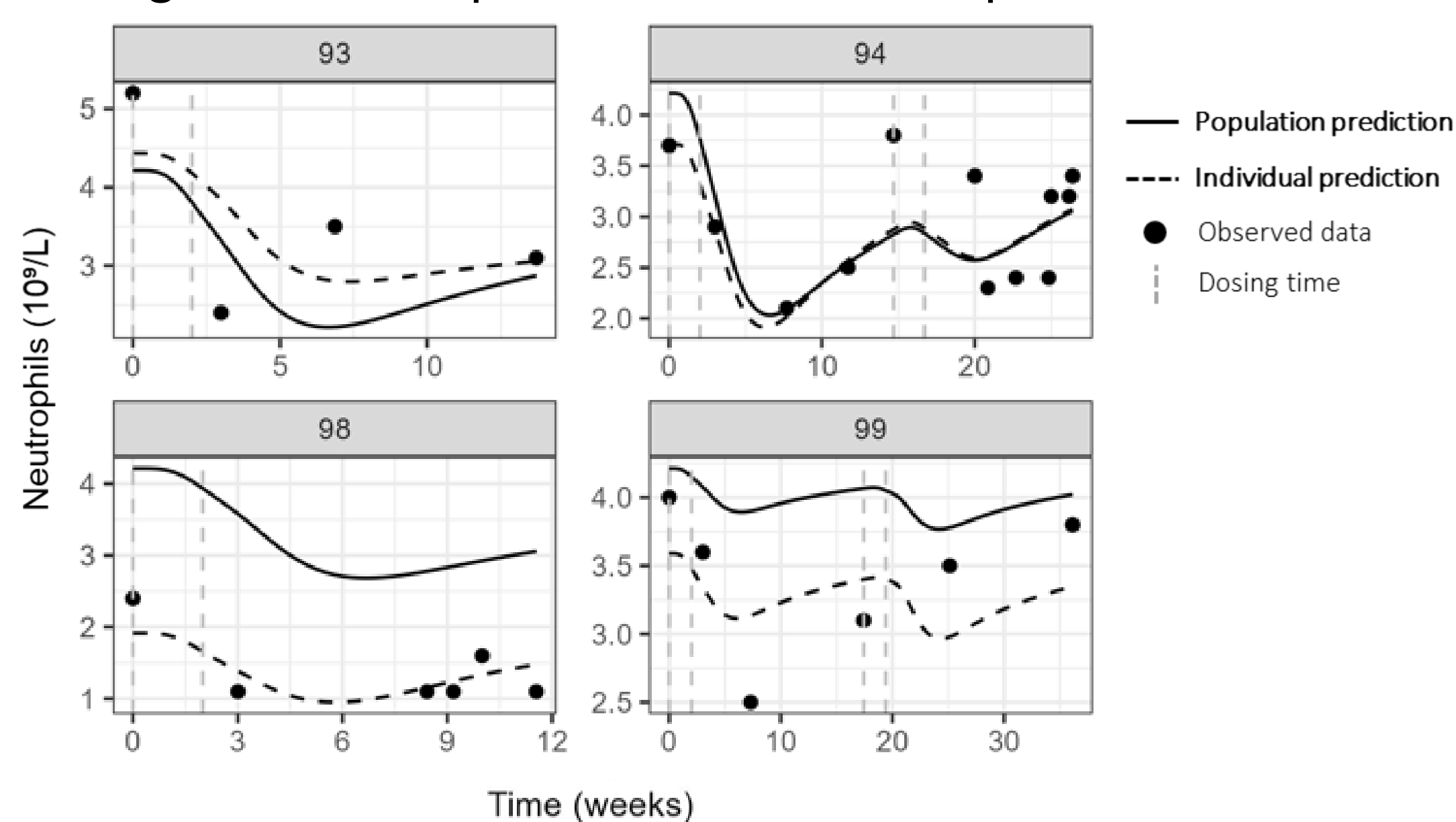


Figure 5. GOF-plots of neutrophil counts

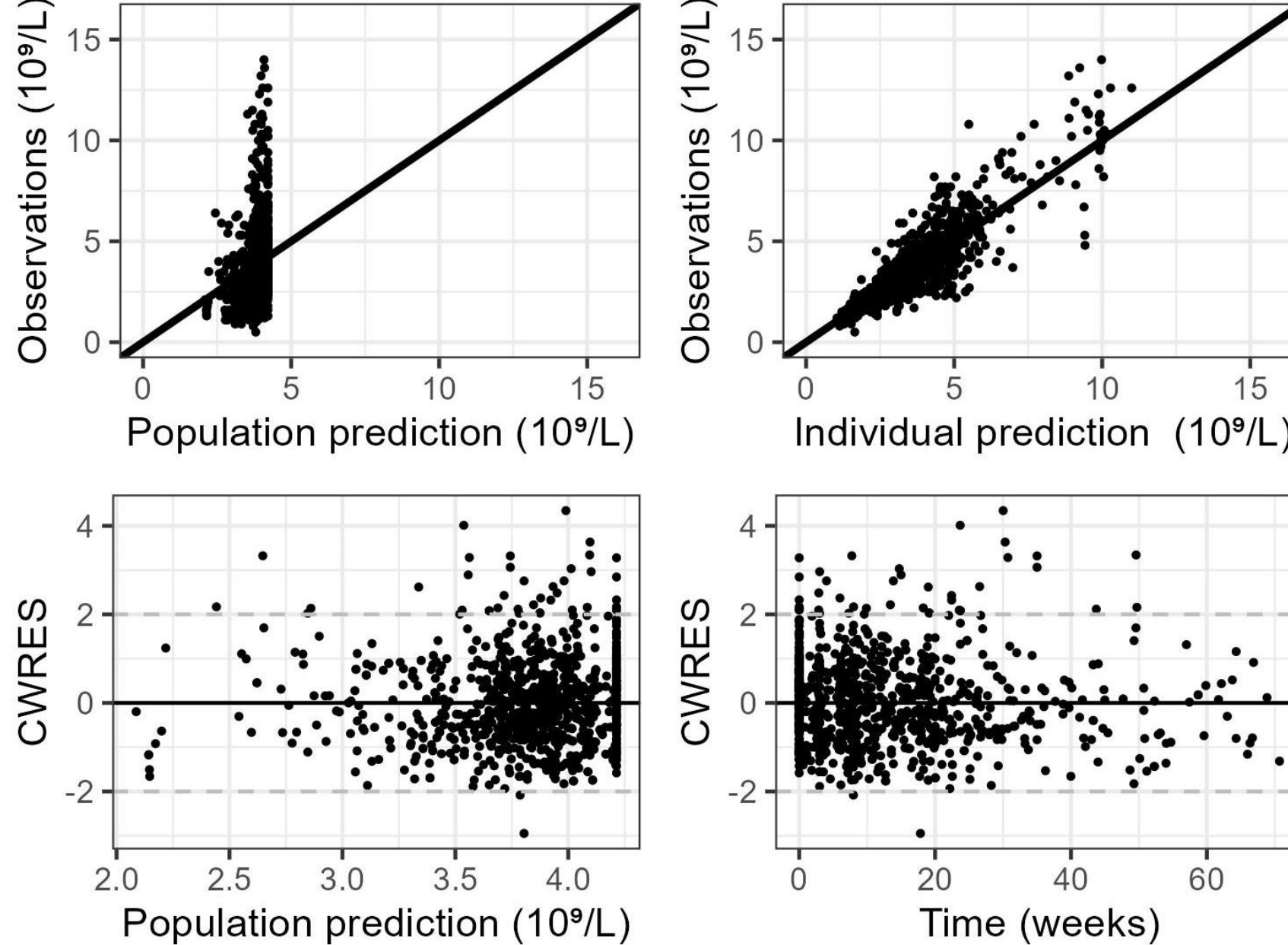


Table 3. Percentage of patients with clinically relevant neutrophil counts ≤1.5 (10⁹/L) observed and predicted by model simulations (n=1000)

Observed	Median simulated	Lower PI (10%)	Upper PI (90%)
7.2%	8.0%	5.1%	10.9%