

External evaluation of a PK/PD model describing the time course of paclitaxel and neutropenia in patients with advanced non-small cell lung cancer

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Background and Objectives

Paclitaxel (PTX) exhibits complex pharmacokinetics (PK) with high interindividual variability as well as severe toxicity, namely neutropenia, which makes PTX an appealing drug for dose individualisation. In [1], the concentration-time course of PTX and the resulting neutropenia were previously described by a PK/pharmacodynamic (PD) model. Based on this model, a dose individualisation algorithm was developed. Subsequently, a

clinical trial (CEPAC-TDM, EUDRACT: 2010-023688-16) was performed to evaluate whether the proposed dosing algorithm was able to reduce grade 4 neutropenia without reducing treatment efficacy. The aim of the work here presented is to externally validate the previously described PK/PD model using the data collected from the CEPAC-TDM study.

Methods

Patients in the CEPAC-TDM study received PTX once every 3 weeks for up to 6 cycles in a 3 h infusion in a dose of either:

➤ **Arm A:** 200 mg/m² (n = 183) or

➤ **Arm B:** according to the published algorithm [1] (n = 183). The first dose was individualised based on sex and age. Subsequent doses were adapted based on the grade of neutropenia and on the time above the threshold plasma concentration of 0.05 µmol/L ($T_{C>0.05}$). $T_{C>0.05}$ was estimated using the developed PK/PD model (Fig 1).

In both arms patients received cisplatin or carboplatin in addition and doses of both drugs were reduced in case of severe toxicity.

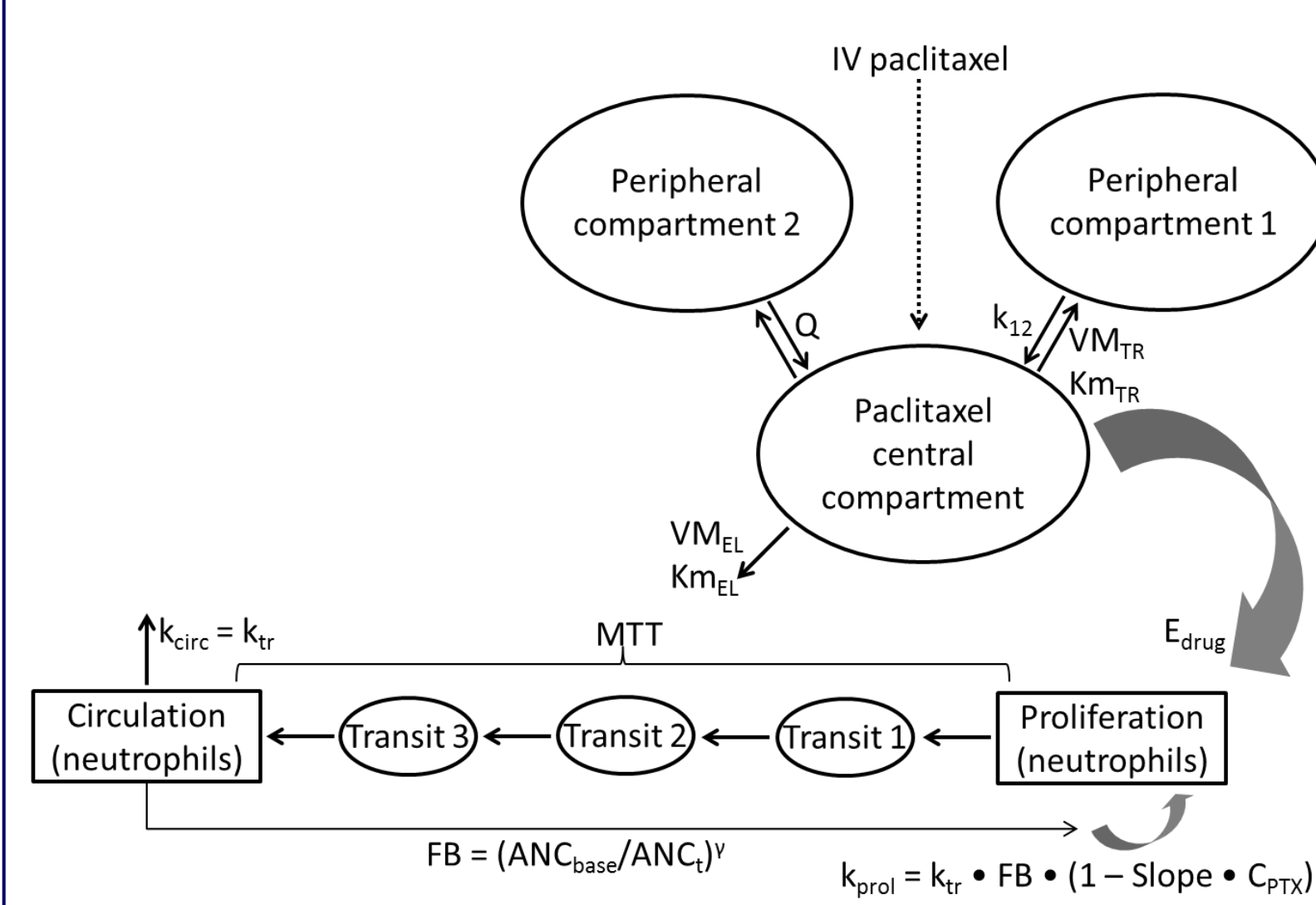


Figure 1: PK/PD model published by Joerger et al [1] describing the PTX plasma concentration and neutrophil-time profiles. **ANC**=absolute neutrophil count; **ANC_{base}**=baseline ANC; **ANC_t**=ANC at time t; **C_{PTX}**=PTX plasma concentration; **E_{drug}**=drug effect; **FB**=feedback; **k_{circ}**=degradation rate constant; **Km_{EL}**=C_{PTX} at half VM_{EL}; **Km_{TR}**=C_{PTX} at half VM_{TR}; **k_{prol}**=proliferation rate constant; **k_{tr}**=transition rate constant; **MTT**=mean transition time; **Q**=intercompartmental clearance; **Slope**=sensitivity to PTX; **VM_{EL}**=max. elimination capacity; **VM_{TR}**=max. transport capacity; **γ**=feedback constant.

PTX concentration (PK) was measured 24 h after drug administration only in Arm B, while neutrophil counts (PD) were obtained in both arms shortly before and 15 ± 2 days after drug administration.

PTX and neutrophil concentrations were visually explored and the proposed PK/PD model was evaluated with respect to the data from the CEPAC-TDM study using basic goodness of fit plots and prediction-corrected visual predictive checks (pcVPC) (NONMEM 7.3, PsN 4.2 and Xpose4 4.5.3). The MAXEVAL=0 function was used to allow for Bayesian estimation of individual parameters.

Results

- Overall, higher doses of PTX were administered in both sexes in the conventional Arm A (median dose Arm A: 368 mg; Arm B: 285 mg).
- Comparable exposure and neutrophil-time course were observed between sex in Arm B. However, a more profound reduction of neutropenia was achieved in Arm B compared to Arm A for females than for males (Fig 2).

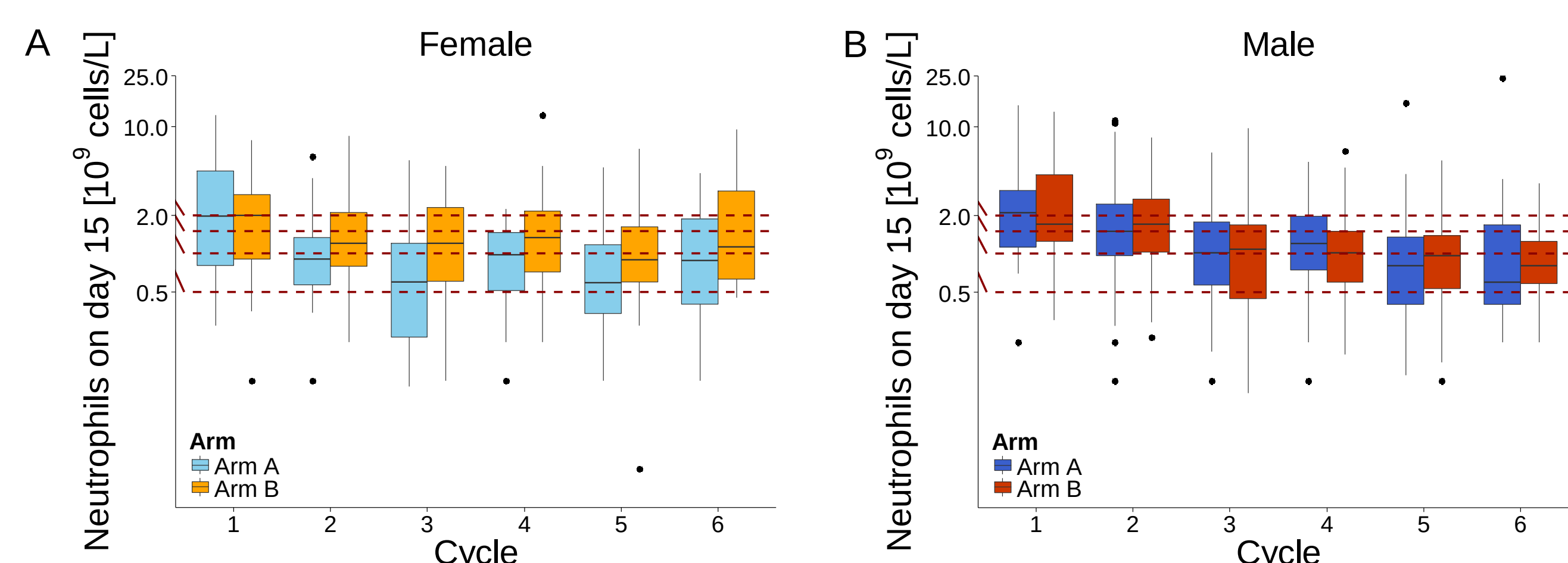


Figure 2: Boxplots of neutrophil count on day 15 ± 2 vs. cycles for A) females and B) males, each stratified by arm; boxes: inter-quartile range (IQR), including median; whiskers: range from the hinge to the highest value within 1.5 • IQR; points: data beyond the whiskers; red lines: neutropenia grade 1-4

- The PK model showed a good fit to the observed data on the individual level (Fig 3A). The observation vs population prediction plot show reduced correlation (Fig 3B), which can be explained by the sampling strategy (only 24 h after drug administration).

Results (cont.)

- An underprediction (negative bias) of the PK model is seen (Fig 5A), which is less profound in females (Fig 3B). The superior fit for females was expected since females preponderated in model development [1].

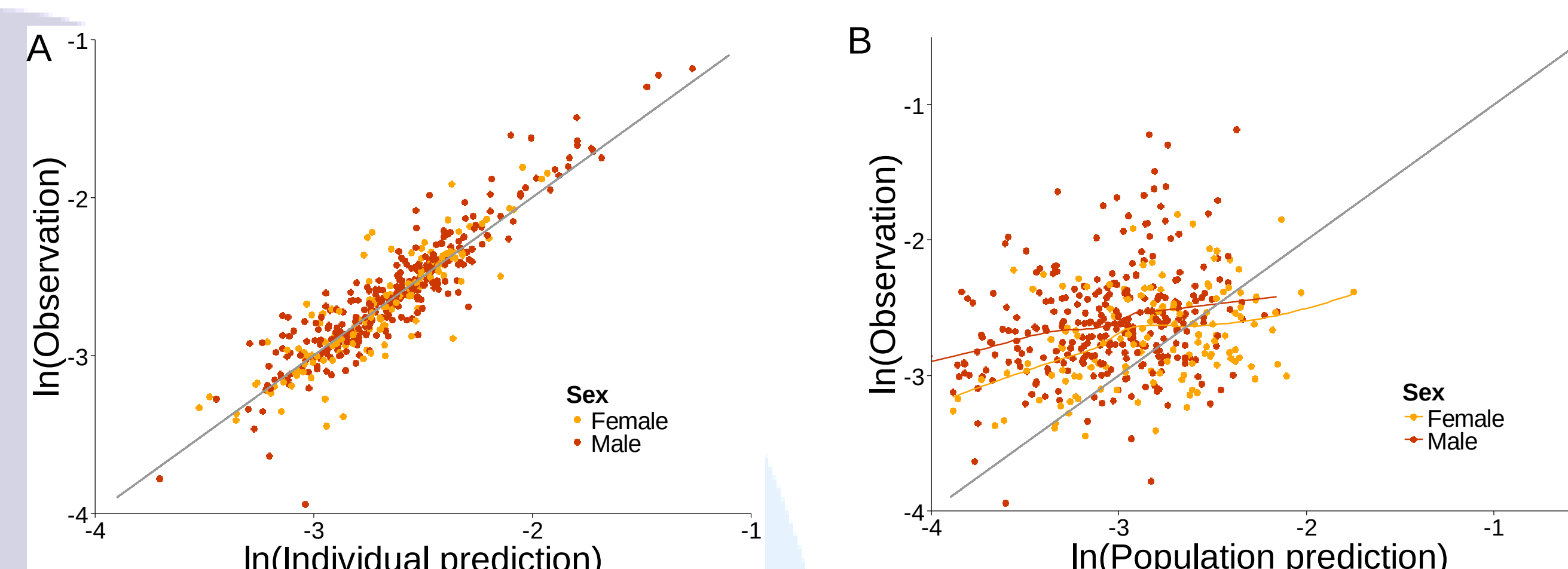


Figure 3: Basic goodness of fit plots for PK of PTX in Arm B (observation) vs model prediction. A) population prediction and B) individual prediction, respectively; grey line: line of identity

- Individual prediction was overall able to successfully describe the neutrophil data (Fig 4A). However, when comparing over cycles underprediction in the first and overpredicted in the later cycles was observed.
- Examining weighted residuals over time (Fig 4B) and the pcVPC (Fig 5B) an overprediction was found especially for later treatment cycles. This increasing misspecification is compatible with bone marrow exhaustion.
- In addition it can be seen that the observations on day 15 are more affected by the overprediction than the neutrophil data after 21 days.

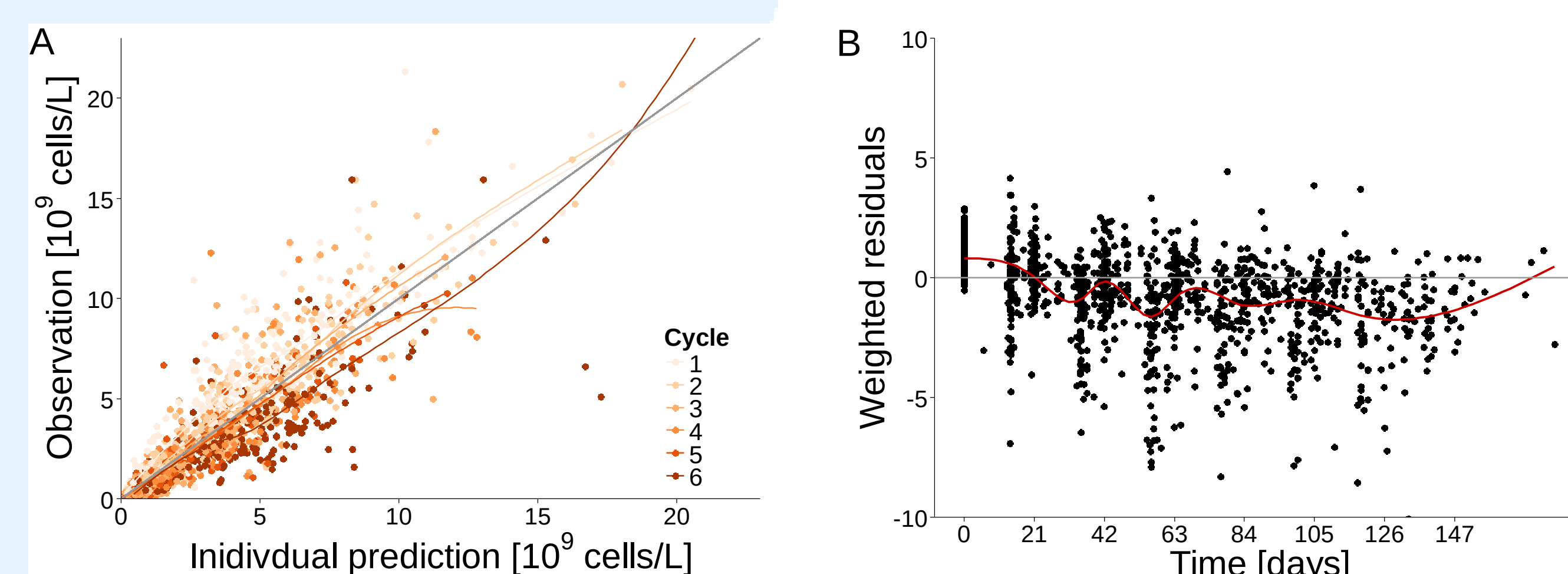


Figure 4: Basic goodness of fit plots for neutrophil count in Arm B. A) Observation vs individual model prediction, stratified by cycle; B) weighted residuals vs time (red line: smooth function); grey line: line of identity

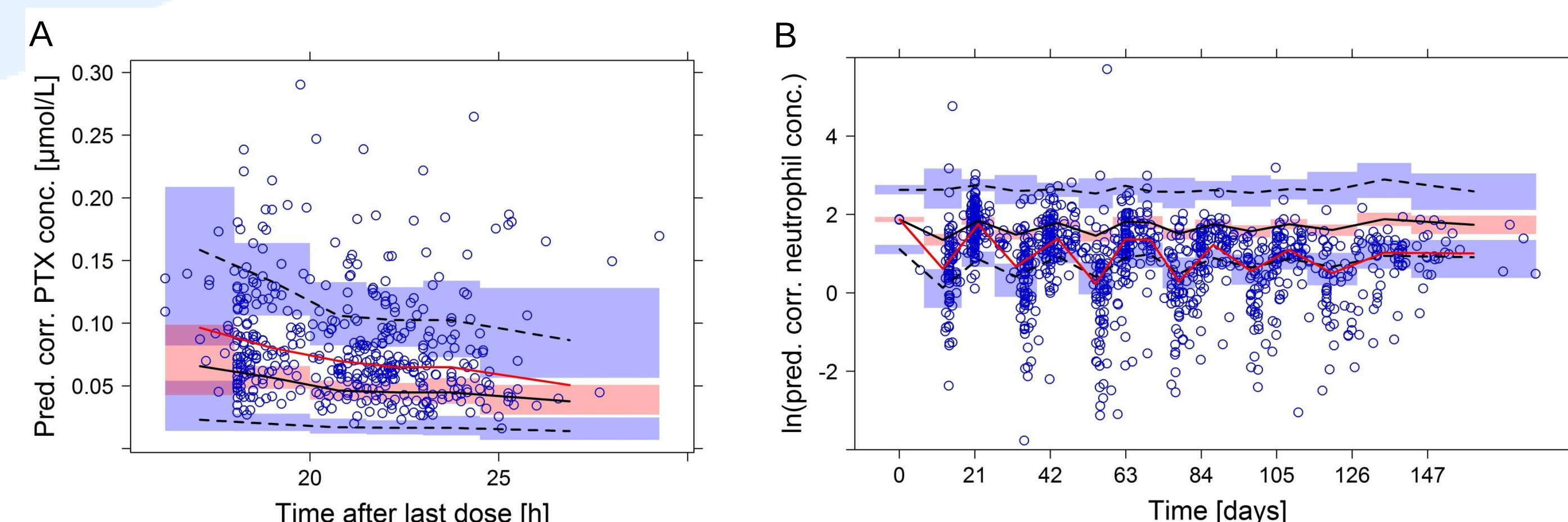


Figure 5: Prediction-corrected visual predictive check (pcVPC) of A) PK and B) PD model for Arm B; blue circles: observed neutrophil concentrations; red line: median of observations; black lines: median (solid), 5th, 95th percentiles (dashed) of the simulations; shaded areas: 90% confidence intervals for the prediction lines

Discussion and Conclusions

- Population prediction of the PTX plasma concentration are slightly underpredicted which might partly cause the overprediction of the PD model.
- The PK/PD model will be refined to take into account bone marrow exhaustion.
- The refined PK/PD model will be used to fine-tune the proposed 3-weekly dosing algorithm.

References:

[1] M. Joerger, S. Kraff, A.D.R. Huitema, et al. Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: a pharmacokinetic-pharmacodynamic simulation study. *Clin. Pharmacokinet.* 51: 607–17 (2012).



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