

Model-averaging, but not flattened priors, benefitted to the model-informed precision dosing of oral kinase inhibitors in oncology

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Objective

- To report a comprehensive fit-for-purpose validation of the MIPD of **sunitinib** and **pazopanib** to predict $C_{min,ss}$ from any single concentration observed during an interdose interval.
- It includes the external validation of existing PK models and the possible advantage of **flattened priors** [1] or **model-averaging** [2]

Conclusion

- Model-averaging** should be preferred to the choice of a single model because of performance consistency across the evaluated scenarios.
- No benefit to flatten priors**
- The random **intra-individual variability** of PK **worsened** the quality of prediction at the **next cycle**.

Background

- Conventional therapeutic drug monitoring (TDM) of oral kinase inhibitors consists in comparing a concentration, measured exactly at the time of trough and steady-state, to a target value linked to efficacy and/or adverse events.
- With model-informed precision dosing (MIPD), a patient dose could be individualized with a TDM at any time, maximum a posteriori (MAP) Bayesian estimation of pharmacokinetics (PK) parameters, prediction of a trough concentration at steady-state ($C_{min,ss}$) and comparison to an efficacy target value. If predicted $C_{min,ss} > \text{target}$, the same dose is kept. If predicted $C_{min,ss} < \text{target}$, simulation *a posteriori* of a finite number of available dosing regimen and selection of a dose with a simulated $C_{min,ss} > \text{target}$.

Methods

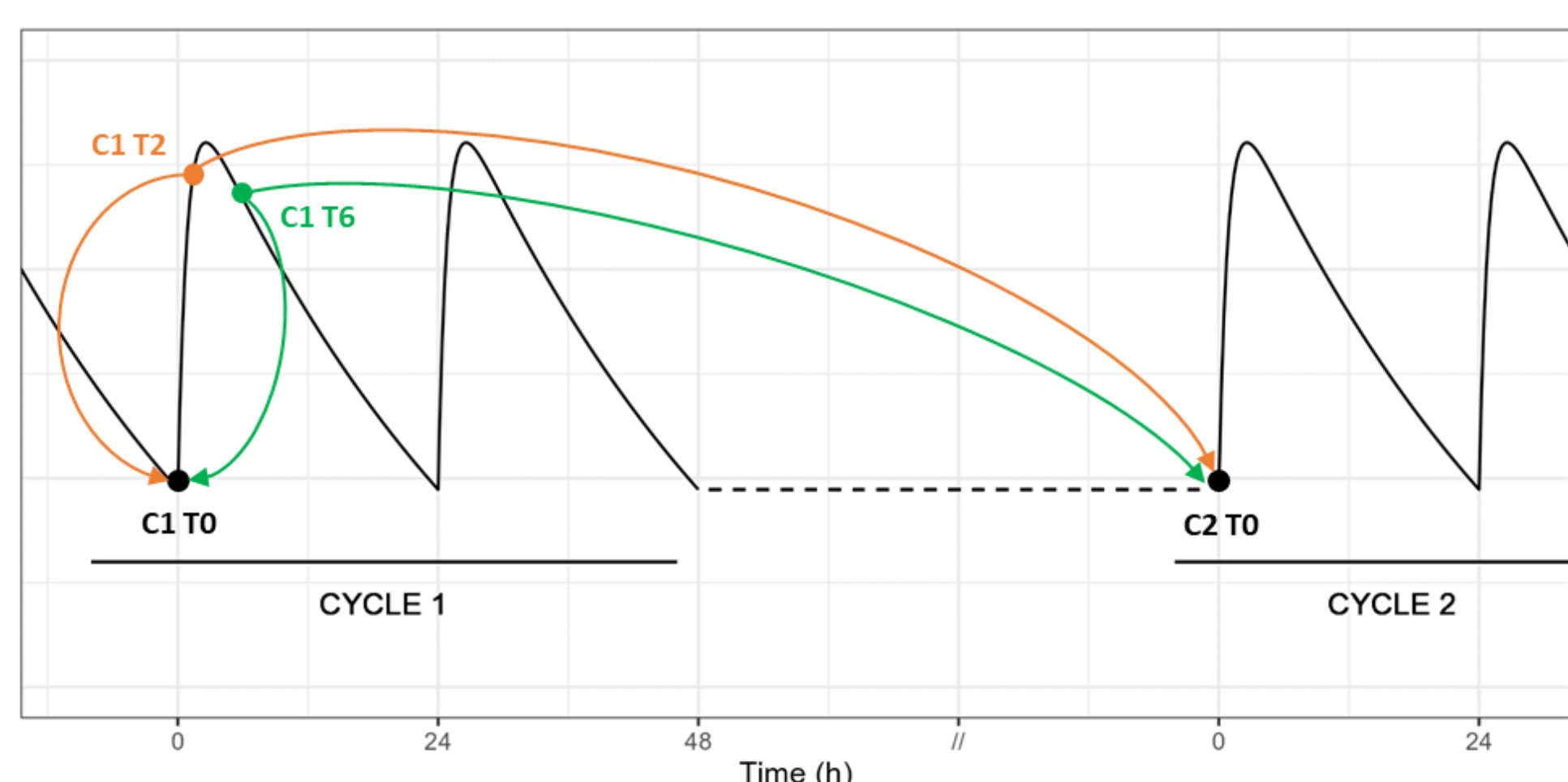


Figure 1. Methods: Prediction of $C_{min,ss}$ at the current (C1T0) and next cycle (C2T0).

- Single concentration data from 41 renal cancer patients treated with sunitinib or pazopanib, included in the SUP-R trial (NCT02555748), were analyzed.
- For each drug, four prediction scenarios were studied: concentrations measured 2 (C1T2) or 6 hours (C1T6) after an intake were analyzed in order to predict individual $C_{min,ss}$ either at the current cycle (C1T0) or at the next cycle (C2T0, 6 weeks later). The motivation was to evaluate the performance of predictions at the current cycle, and if this performance would still be valid at the next cycle with a possible dose modification informed by the estimated PK parameters (cf Figure 1).
- For each scenario, 5 or 6 models from the literature describing the PK of sunitinib (+ active metabolite ND-sunitinib) or pazopanib, respectively, were tested.
- In addition to single-model analyses, a model-averaging procedure was applied.
- Finally, each parameter estimation was conducted with four levels of flattened priors: 1 (original model), 0.3, 0.1, and 0.03.
- The quality of predictions was measured with bias (mean prediction error, MPE) and precision (root mean square error, RMSE).
- All the analyses were conducted using the R package mapbayr [3]

Results



Figure 2. RMSE and MPE (top and bottom panels, respectively) of the several scenarios for Sunitinib and Pazopanib (left and right panels, respectively).

- Sunitinib:**
 - Prediction of C1T0 from C1T2: RMSE ranging from 16.9% (Houk et al) to more than 70% (Khosravan et al).
 - Prediction of C1T0 from C1T6: RMSE ranging from 15.6% (Yu et al) to more than 70% (Khosravan et al).
 - Prediction of C2T0 was slightly worse than to predict C1T0 (~ +2% to +7% of RMSE, depending on the scenario).
 - Model averaging did not outperform any single model but had a consistent precision whatever the sampling time (C1T2 or C1T6) and the $C_{min,ss}$ to predict (C1T0 or C2T0), with RMSE between 20.0% and 23.5%.
 - Flattened priors did not markedly improve or worsen the predictions, except for models that initially performed very badly (e.g., RMSE decreased from >70% to 17.7% in a scenario with Khosravan et al [8]).
 - Bias varied between models and scenarios but was generally small, e.g. MPE between -3.1% to +4.9% with model-averaging depending on the scenario.
- Pazopanib:**
 - Performances similar or slightly worse than for sunitinib

Practical implementation

```
mod %>%
  adm_rows(amt = 100, ss = 1, ii = 24) %>%
  obs_rows(time = 17.5, DV = 3.4) %>%
  mapbayest(lambda = .1)

list(modA, modB, modC) %>%
  map(
    . %>%
      adm_rows(amt = 100, ss = 1, ii = 24) %>%
      obs_rows(time = 17.5, DV = 3.4) %>%
      mapbayest(lambda = .1)
  ) %>%
  model_averaging(estlist = .)

input$models %>%
  map(
    . %>%
      adm_rows(amt = input$dose, ss = 1, ii = input$ii) %>%
      obs_rows(time = input$stad, DV = input$obsconc) %>%
      mapbayest(lambda = input$prior)
  ) %>%
  model_averaging(estlist = .)
```

mrgsolve model

Data assembling on-the-fly

MAP-Bayes estimations

Iterate with several models

Average the predictions

Switch to Shiny environment

