A Model-based Framework to Address Dose Modifications: Accounting for Dose Modifications in Exposure-Response Analyses in Oncology for Brigimadlin Development

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Objectives

Model-based exposure-response (ER) analyses are a cornerstone of dose optimization in the Project Optimus era in oncology drug development, yet often do not directly address the causal questions of clinical interest. Dose modifications due to safety and tolerability lead to feedback in the dose-exposure-safety relationship, where safety outcomes and doses have time-varying confounding. Failure to account for this feedback in standard model-based ER analyses may lead to unrealistic simulations (i.e., too high of exposure and safety risks), reducing the credibility of model-based inferences. Semi-mechanistic pharmacometric models are an important tool for model informed drug development and Project Optimus, in particular, to help extrapolate to new dosing regimens or populations. Based on the case example of safety-based dose modifications of brigimadlin, a potent, oral murine double minute 2 homolog-tumor protein 53 antagonist, we aimed to:

- Characterize the relationship between safety endpoints and dose modifications
- Perform dynamic simulations of exposure and safety that account for dose modifications
- Support causal inferences for hypothetical dosing regimens, specifically, the risk-benefit tradeoff of a high initial dose with likely subsequent dose reductions.

Methods

The analysis included the data of brigimadlin administered once every three weeks (Q3W) from Study 1403-0001 (datacut Nov 2021, NCT03449381), a phase Ia/Ib, open label, multicenter, dose-escalation study in patients with advanced or metastatic solid tumors.

Statistical Models

A Bayesian model of the probability of dose modification as a function of platelet and neutrophil counts (side effects of this class of drugs) was developed to characterize the dynamic and probabilistic nature of dose decisions. The dose modification model was a composite of one categorical model for the dose decision and one time-to-event (TTE) model for the length of the dose delay.

Dose decision model

The dose decision had four categories:

1. *No change*: no dose change and no delay.
2. *Dose reduction*: a dose reduction without delay.
3. *Dose delay*: a delay with no dose change.
4. *Dose delay and reduction*: a dose reduction with delay.

A categorical regression was used to model the 'dose decision' outcome, which assumed the probability of dose decision for the next dose was mediated through the platelet and neutrophil counts 21 days after the current dose and that the previous drug dose had no direct causal effect.

Dose delay model

According to the study protocol, any dose administered more than 3 days after the scheduled time (21 days after last dose) was considered as a delay. A TTE model was developed for the length of the dose delay using a Weibull distribution with platelet and neutrophil counts 21 days after dose as predictors.

Semi-Mechanistic Models

Previously developed population pharmacokinetic-pharmacodynamic (PKPD) platelet and neutrophil models were used.

Figure 1: Schematic of the two-compartment pharmacokinetic model for brigimadlin concentration.

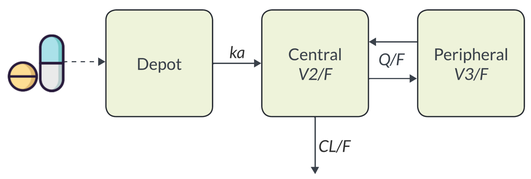


Figure 2: Schematic of the pharmacodynamic (platelet and neutrophil counts) models [1].

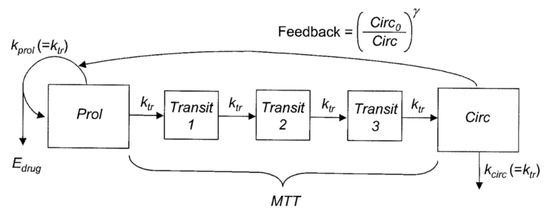
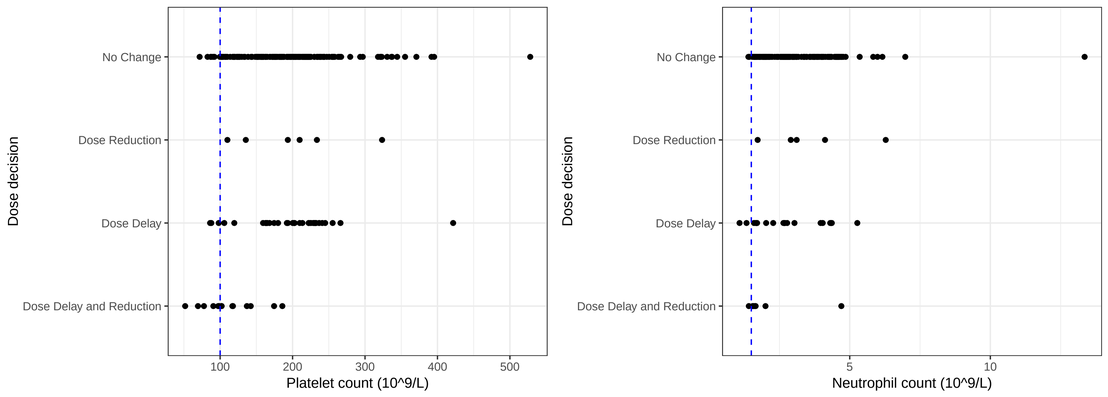


Figure 3: Observed dose decision versus platelets and neutrophils, showing physician discretion in dose modifications.

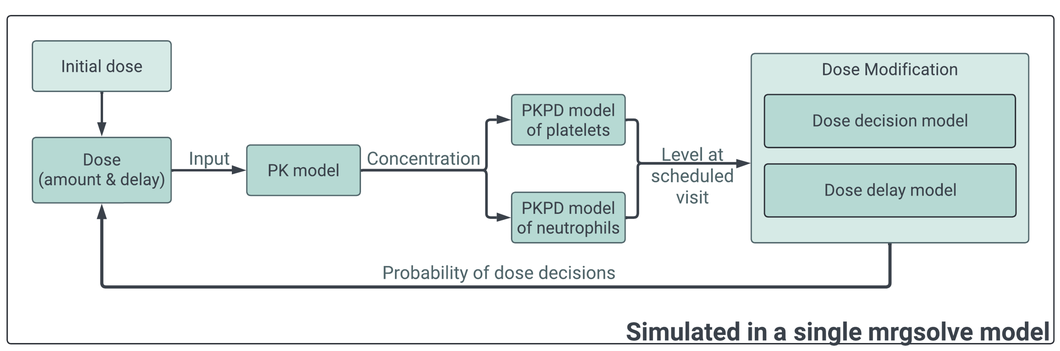


The blue dashed lines are thresholds specified in the study protocol which triggered dose modifications.

Simulations

- Semi-mechanistic ordinary differential equation (ODE) models
  - PK: two-compartment with first-order absorption and linear elimination
  - Platelets and Neutrophils: myelosuppression models with a proliferating, three transit, and circulating compartments [1]
- Simulation workflow
  - mrgsolve package in R [2]
  - Dose to exposure: population PK model
  - Drug exposure to platelets and neutrophils: PKPD models
  - Dose decision and dose delay: dose modification models
- Simulation design
  - Resample covariate and random effect values from the trial population
  - 45 mg Q3W initial dose
  - Simulated platelet and neutrophil counts 21 days after each dose were monitored and used for decision making for the next dose
  - 30 mg and 20 mg dose reduction levels
  - After two reductions, discontinue simulation for participant

Figure 4: Schematic representation of dynamic simulation and implied causal model.



Results

Dose delays and reductions were estimated to occur more frequently with lower platelet and neutrophil counts (**Figure 5** for platelets, neutrophils not included here); additionally, the delays were longer with lower counts (**Figure 6** for platelets, neutrophils not included here). Simulated patient profiles with dynamic dosing regimens adequately captured the qualitative trajectories of dose decisions, exposure, platelet, and neutrophil counts (**Figure 7**). The simulations including dose modifications were able to predict rates of thrombocytopenia and neutropenia that more closely matched the rates observed in patients than simulations without dose modifications (**Figure 8**). Under the observed initial dose with consideration of dose modifications, the predicted rate of thrombocytopenia ≥ Grade 3 was 21.6%, compared to the observed rate of 24.6%, while for neutropenia ≥ Grade 3 the predicted rate was 13.8% compared to the observed rate of 17.5%. When not accounting for the dose modifications, the risk of thrombocytopenia ≥ Grade 3 was vastly overpredicted (**Figure 8**).

Figure 5: Model predicted probabilities of dose decision versus platelets.

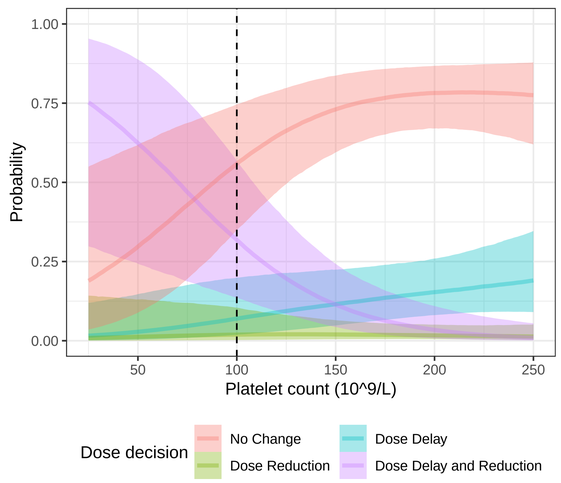
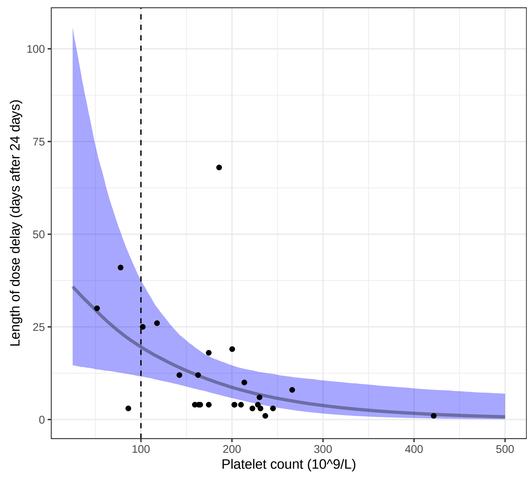
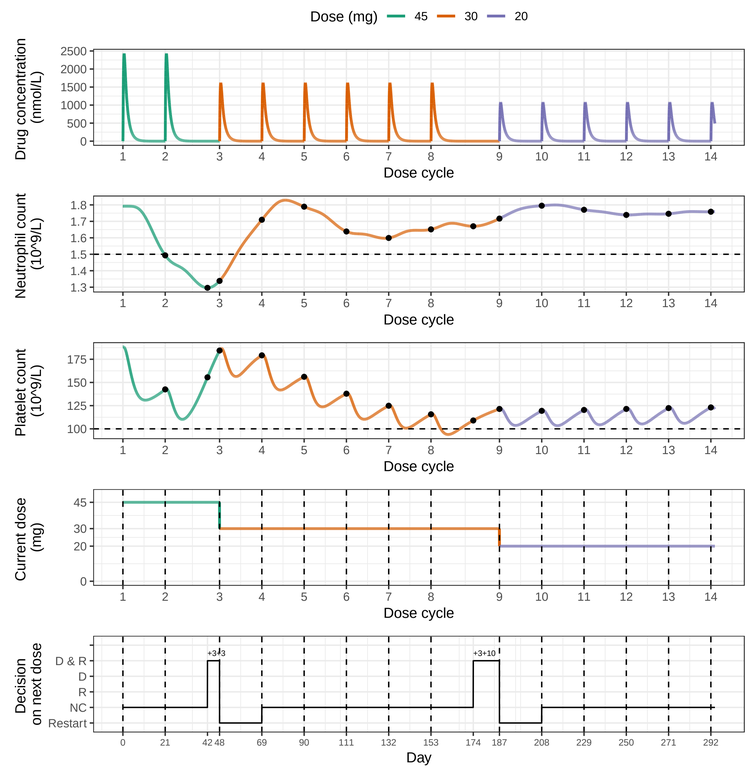


Figure 6: Model predicted length of dose delay versus platelets.



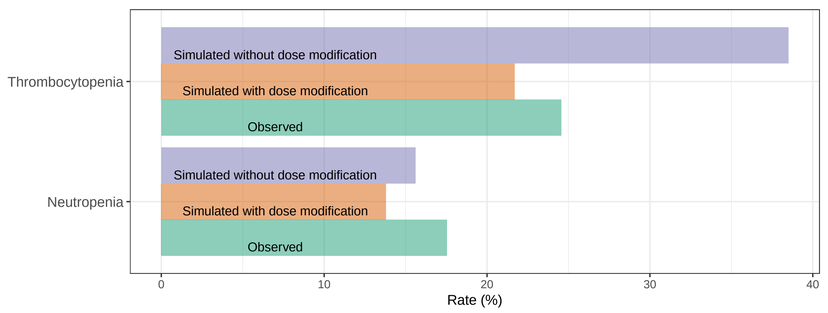
The ribbons represent 90% CIs. The dashed lines are thresholds specified in the study protocol which triggered dose modifications. The black points represent the observed data.

Figure 7: A representative profile of the simulated brigimadlin concentration, neutrophils, platelets, current dose, and dose decision.



The vertical dashed lines represent dose events. The horizontal dash lines are thresholds specified in the study protocol which triggered dose modifications. The black points indicate the simulated neutrophils and platelets that were monitored and used for decision making on the next dose. D = dose delay, R = dose reduction, D & R = dose delay and reduction, NC = no change.

Figure 8: Comparison of the simulated and observed rates of thrombocytopenia ≥ Grade 3 and neutropenia ≥ Grade 3 given initial dose of 45 mg.



Conclusion

- The integration of the statistical dose modification model and semi-mechanistic models improved the concordance between model predictions and observed data compared to the semi-mechanistic models alone.
- A simulation framework was developed that supports simulation of dosing histories and evaluation of novel dosing regimens, including the effects of a higher initial dose.
- Similar modeling and simulations strategies can be used in the future to support a variety of drug development questions in oncology indications with greater clinical relevance than semi-mechanistic or statistical modeling alone.

References

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[2] Baron, K.T., Gillespie, B., Margossian, C., Pastoor, D., Denney, B., Singh, D., Le Louedec, F. and Waterhouse, T. *mrgsolve: Simulate from ODE-Based Models*. Metrum Research Group (2021).

Acknowledgements

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