

Application of a population pharmacokinetic model of olaparib in patients with recurrent glioblastoma and non-small cell lung cancer

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BACKGROUND

Clinical studies combining molecularly-targeted drugs with radiotherapy (RT) have largely failed to improve patient outcomes in cancer. A potential reason is the insufficient consideration given to treatment scheduling. Often, schedules are selected based on previous monotherapy or combination regimens with chemotherapy. Mathematical modelling is a viable approach to explore alternative schedules to enhance synergy between therapies and investigate associated toxicities.

OBJECTIVES

1. Evaluate the ability of a published olaparib PopPK model¹ to accurately predict olaparib concentrations in patient populations not used in the model development.
2. Apply this model to investigate the effects of different dosing schedules in patients treated with concurrent olaparib and radiotherapy.

METHODS

OPARATIC trial simulations

- Plasma measurements of olaparib 75 hours after administration in 45 patients with recurrent glioblastoma from 3 dose cohorts (100 mg OD, 150mg OD, 200mg BID) were obtained².
- Each dose cohort was simulated using the olaparib PopPK model¹ (adapted to have a single absorption rate).
- Plasma and peripheral concentrations were compared with observed concentrations.

CONCORDE-A trial simulations

- Drug and radiotherapy administration timings obtained from 13 patients with non-small cell lung cancer (NSCLC) in 3 dose cohorts (100 mg 3 times a week, OD, BID)³.
- Patient schedules were simulated using the olaparib PopPK model¹.
- Alternative dosing regimens were simulated to align radiotherapy with the peak peripheral concentration of olaparib, to be interpreted as a surrogate for peak tumour concentration.
- Concentrations were compared between equivalent regimens.

RESULTS

OPARATIC trial

- Observed plasma concentrations across all three cohorts fall within the 95% CI of predicted plasma concentrations.

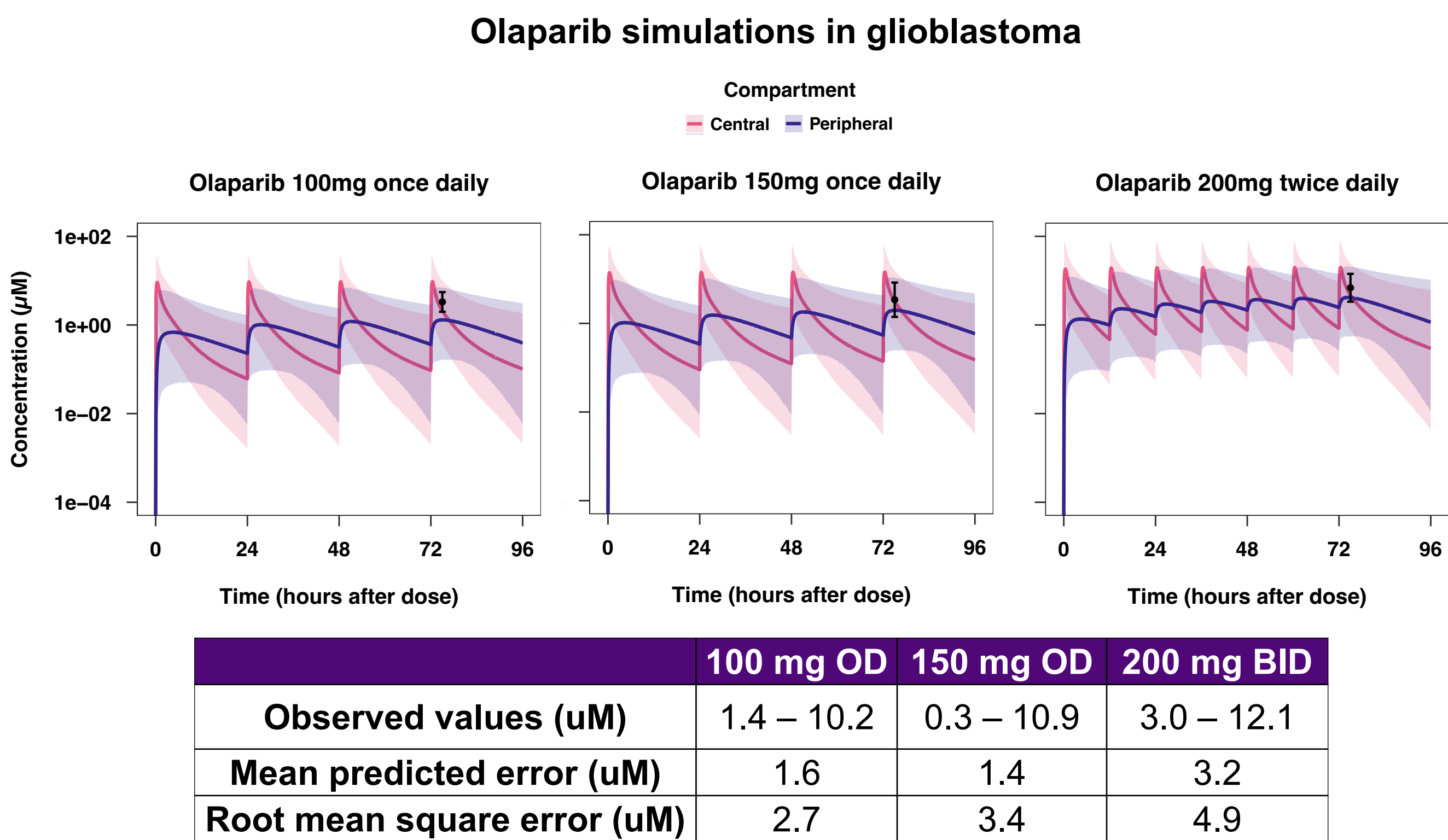


Figure 1. Simulated plasma and peripheral concentration–time curves of olaparib from the OPARATIC trial. Dosing schedules shown over four days, overlaid with observed mean plasma concentrations in glioblastoma patients at 100mg OD (left), 150mg OD (middle), 200mg BID (right). Solid lines and shaded areas represent predicted mean concentrations and their associated variability (95% CI), respectively.

RESULTS

CONCORDE-A trial patients

- Predicted olaparib plasma concentrations at radiotherapy administration times remained similar across dose levels.
- Predicted olaparib peripheral concentrations at radiotherapy administration times increased with more frequent dosing.

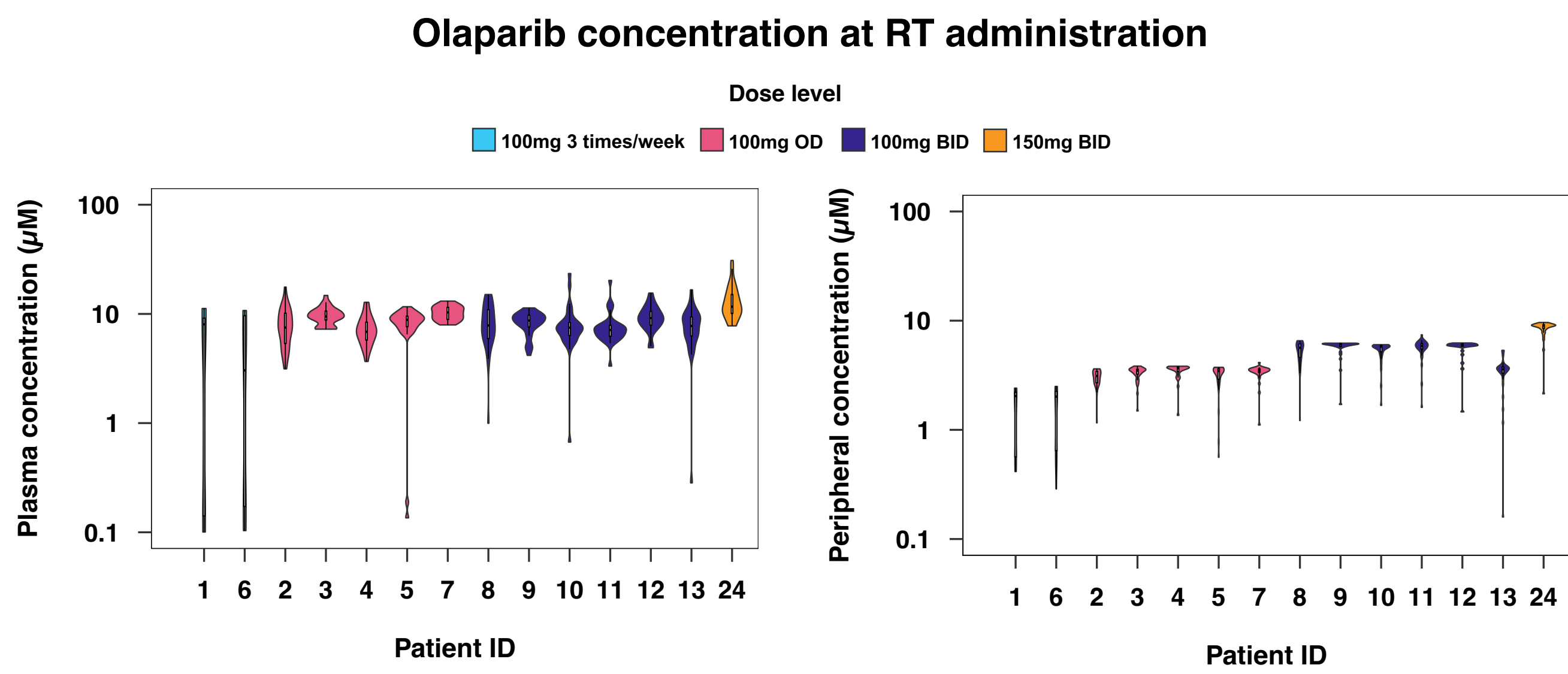


Figure 2. Simulated concentrations of olaparib at radiotherapy administration times. Plasma concentrations (left) and peripheral concentrations (right) are simulated separately for each patient in the CONCORDE-A trial.

Investigating alternative schedules

- OD olaparib dosing 5 hours before radiotherapy could achieve higher peripheral drug concentrations at the time of radiotherapy administration than the equivalent dose in a BID schedule.

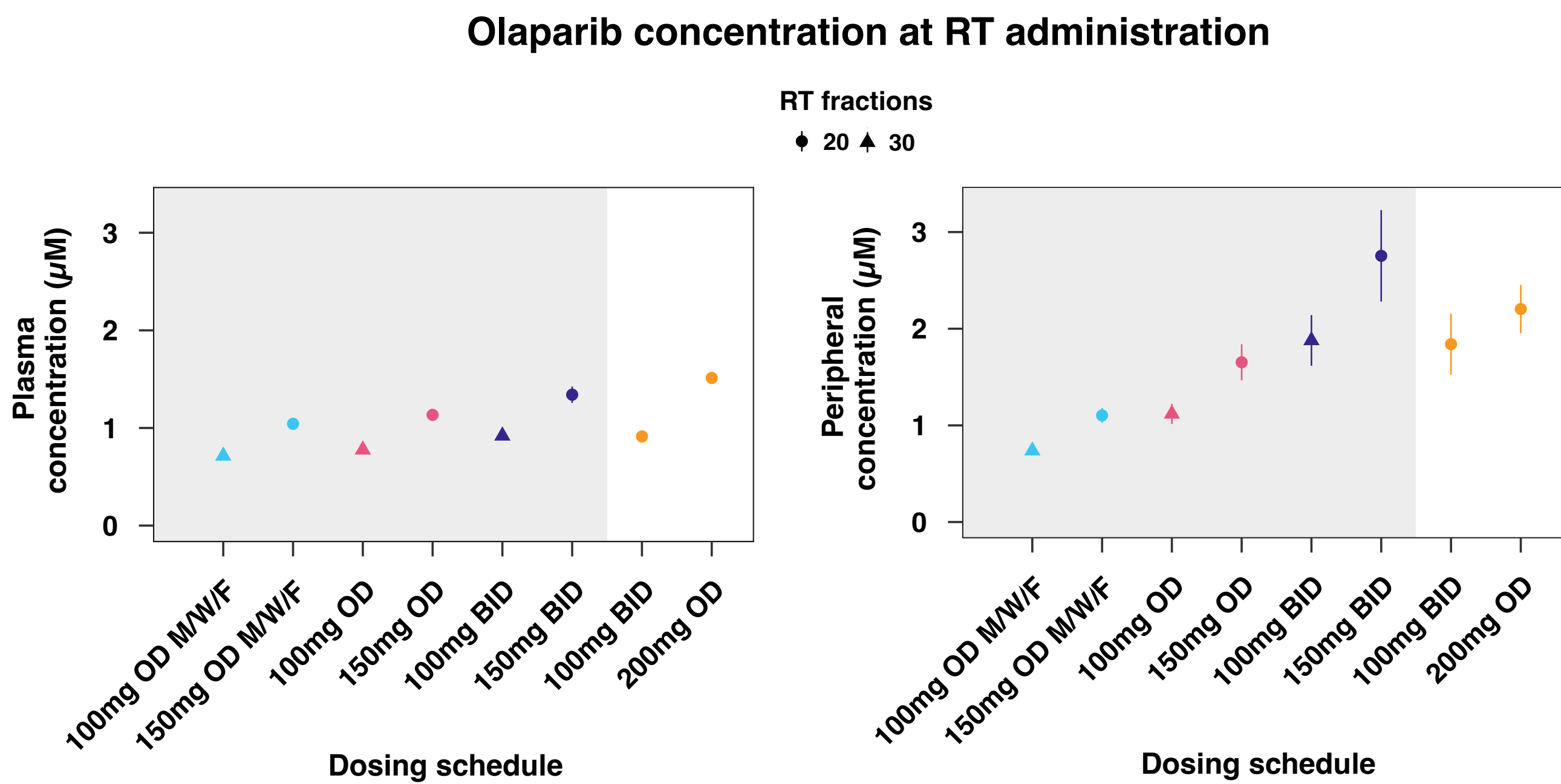


Figure 3. Simulated concentrations of olaparib at radiotherapy administration times under hypothetical schedules. Simulated plasma (left) and peripheral (right) concentrations (uM) at radiotherapy administration from equivalent olaparib dosing regimens, specified by the same colours, under a 4-week schedule (20 RT fractions) or 6-week schedule (30 RT fractions).

CONCLUSIONS

- The olaparib PopPK model was able to predict plasma concentrations in recurrent glioblastoma patients.
- In NSCLC patients, alternative schedules to those administered in the CONCORDE-A trial show that higher olaparib concentrations at radiotherapy administration could be achieved.

FUTURE DIRECTIONS

- Model the relationship between olaparib plasma and tumour PK.
- Understand the relationship between olaparib concentrations and adverse effects in NSCLC using toxicity data from CONCORDE-A trial.
- With a finalised PKPD model, conduct preclinical investigation of effects of different olaparib and RT schedules.

REFERENCES

1. Zhou D, et al. Bridging Olaparib Capsule and Tablet Formulations Using Population Pharmacokinetic Meta-analysis in Oncology Patients. *Clin Pharmacokinet.* 2019 May;58(5):615-625.
2. Hanna C, et al. Pharmacokinetics, safety, and tolerability of olaparib and temozolomide for recurrent glioblastoma: results of the phase I OPARATIC trial. *Neuro Oncol.* 2020 Dec 18;22(12):1840-1850.
3. Walls GM, et al. CONCORDE: A phase I platform study of novel agents in combination with conventional radiotherapy in non-small-cell lung cancer. *Clin Transl Radiat Oncol.* 2020 Sep 22;25:61-66.