

Covariate Analysis of Metabolizing Enzymes and Efflux Transporters and Model based Therapeutic Drug Monitoring in Females Receiving Olaparib

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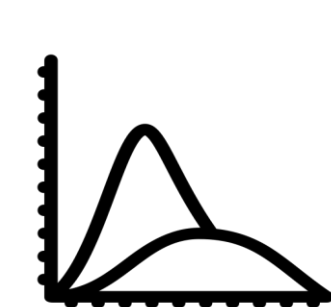
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Background

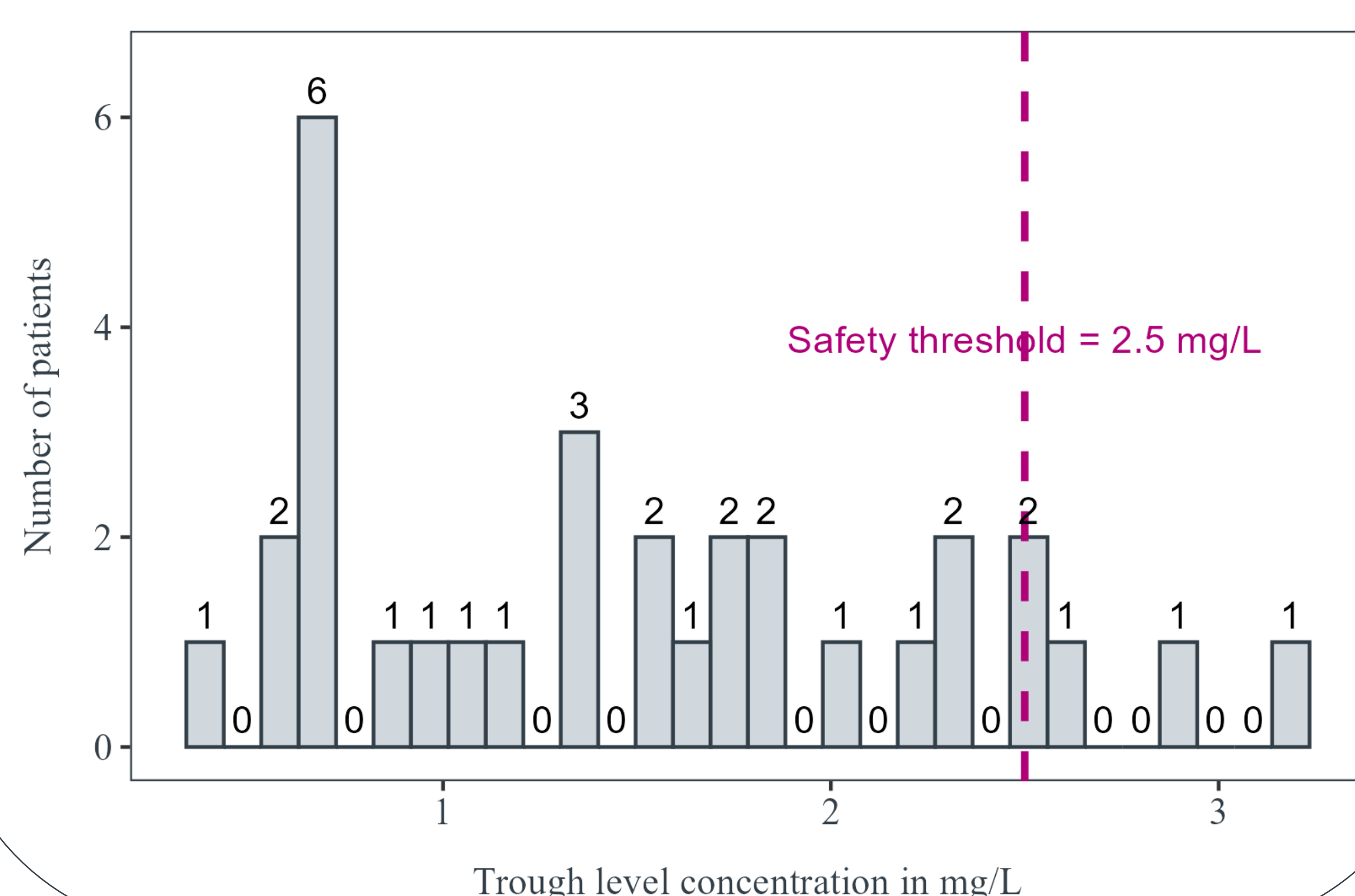
Olaparib is an inhibitor of Poly-ADP-Ribose-Polymerase (PARPi) approved for the treatment of ovarian cancer with BRCA1/2 mutation, HER2-negative breast cancer, pancreatic cancer, and metastatic prostate cancer. The standard dose is 300 mg twice daily which is reduced for patients with moderate renal impairment [1] or after the occurrence of a severe adverse drug reaction (ADR). Usually, other individual factors are not considered potentially resulting in inappropriate dosing bearing the risk of ineffective treatment on one hand or exceeding toxic levels accompanied by ADRs on the other hand. Focusing on toxic levels and the occurrence of ADRs, the question arises whether the need for a dose reduction can be anticipated based on routine measurements in the form of therapeutic drug monitoring (TDM).

Predictions for TDM

Mean predicted PK parameters for patients being treated with the standard dose

	c_{max} [mg/L]	11.2 (1.82)
	t_{max} [h]	1.49 (0.20)
	AUC_{0-12h} [mg*h/L]	58.6 (16.5)
	c_{min} [mg/L]	1.52 (0.76)

In the literature, a minimum concentration of 2.5 mg/L at 12 hours post-dose is considered a safety threshold in olaparib treatment [3]. Exceeding this level has been associated with an increased risk of adverse drug reactions, most commonly anemia [4]. The correlation between progression-free survival and exposure or maximum concentration remains inconclusive, as existing studies show conflicting results.



Study overview

Enrolled Patients

N = 32
♀ = 100%
Age [years]: 59 [42 – 73]
Weight [kg]: 62 [48 – 102]

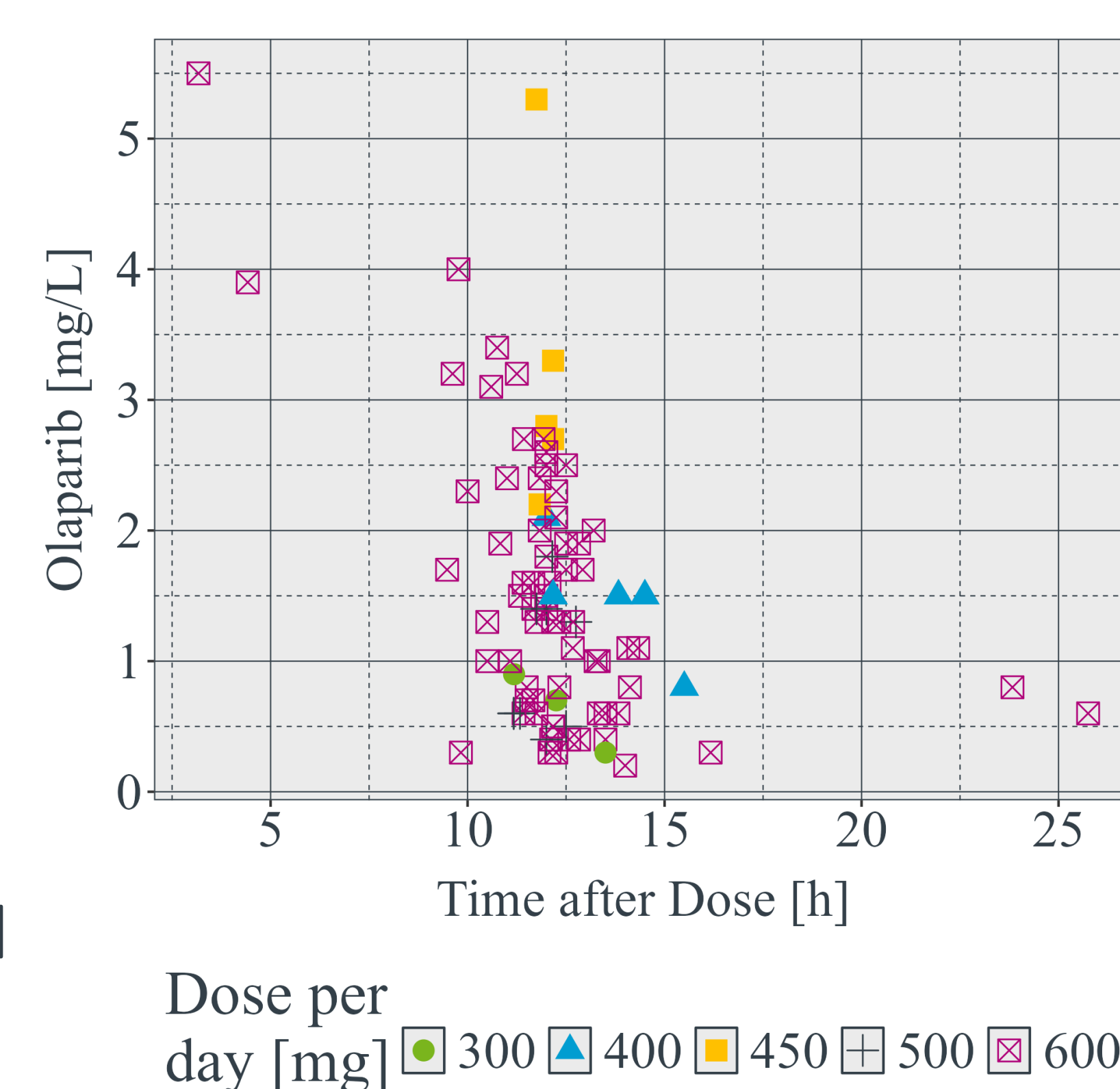
Standard dose

N = 25 / 32
300 mg
1 – 0 – 1

Samples

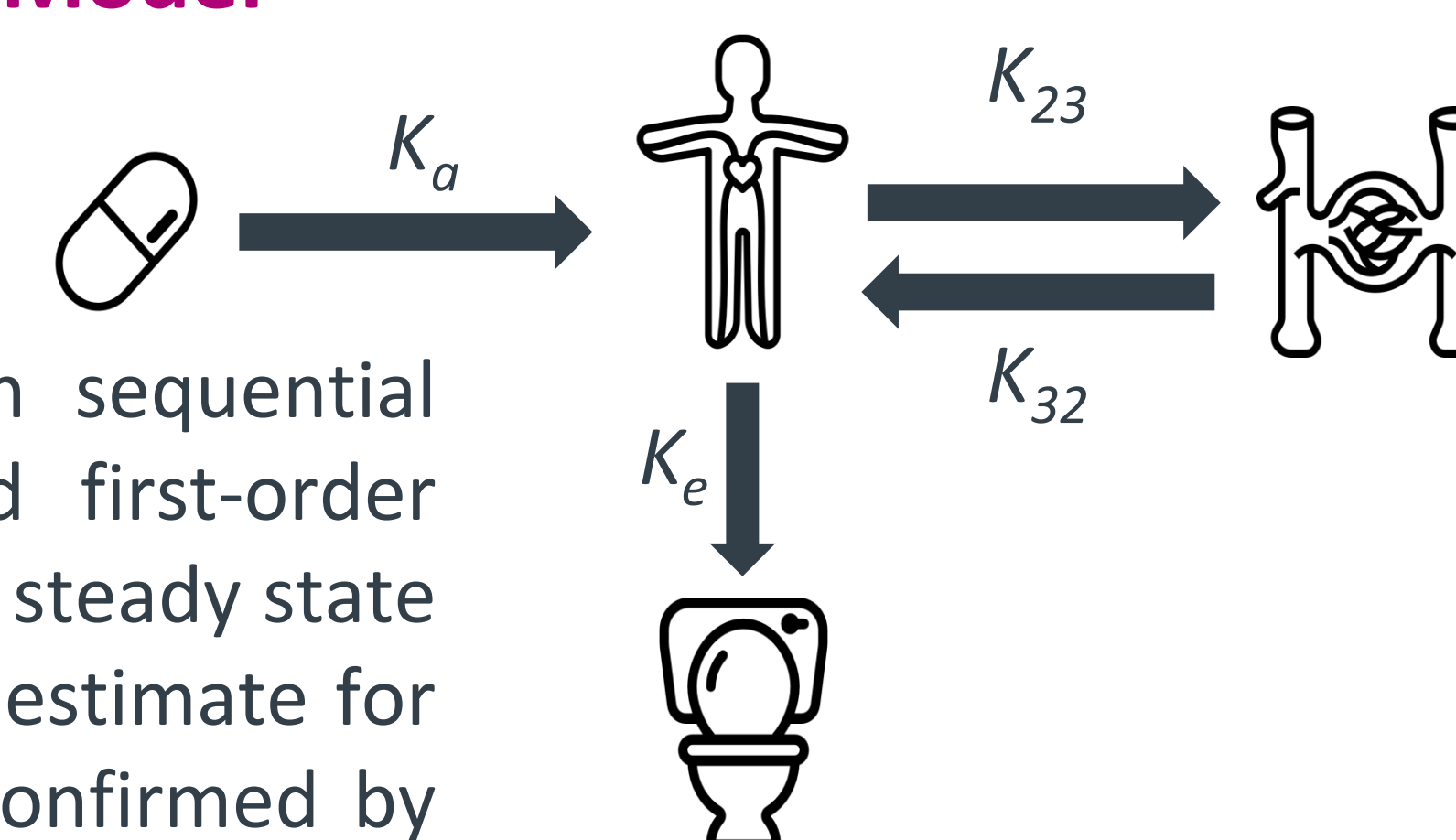
Total N = 90
Per patient 4.5 [1 – 9]
Standard dose N = 68
Time period ~ 1 year

Measurements by LC-MS/MS [2]



POP PK Model

The population pharmacokinetic model was based on a published validated model by Zhou et. al. [5]. The model consisted of two compartments with sequential zero- and first-order absorption and first-order elimination which is reduced by 15% in steady state due to auto-inhibition. The parameter estimate for the clearance was re-estimated and confirmed by bootstrap analysis (N=1000).



Covariate analysis

Olaparib is mainly metabolized by CYP3A4/5 and an inhibition or induction of these enzymes lead to significant changes in AUC and c_{max} [3]. Also the efflux transporters ABCB1 [6] and ABCG2 are responsible for olaparib-resistance in cancer cells. Up to three single nucleotide polymorphisms (SNPs) can occur in ABCB1, with increasing SNP count associated with decreased transporter activity. The number of SNPs was evaluated as both a continuous and a categorical covariate. Due to the limited sample size, covariate analysis did not reveal significant effects.



CYP-Metabolism
CYP3A4*22
TC (4) vs. CC (28)

CYP3A5
IM (2) vs. PM (30)



ABC-Transporter
ABCB1*(1236C>T | 3435C>T | 2677G>T/A)
Number of SNP from 0 to 3 (19|3|4|6)

ABCG2*421C>A
CC (22) vs. AC/CA (10)

Conclusion and perspective



The population pharmacokinetic (popPK) model was successfully reconstructed and adapted to predict AUC_{0-12h} , t_{max} , c_{min} , and c_{max} based on measured trough concentrations. The predicted values align well with pharmacokinetic parameters reported in the literature [3], supporting the model's suitability for further model based therapeutic drug monitoring (TDM).



Ongoing patient recruitment aims to achieve a more balanced covariate distribution and, through increased sampling per patient, allowing an estimation of inter-occasion variability (IOV) observed in clinical practice.

References

- [1] Rolfo C, et.al.: Clin Pharmacokinet 58:1165–74 (2019)
- [2] Canil G, et al.: Pharmaceutics 15(5): 1524 (2023)
- [3] Dirix L, et al.: Clin Ther 38(10): 2286–99 (2016)
- [4] van der Kleij MBA, et.al.: Clin Pharmacokinet 62:1333–64 (2023)
- [5] Zhou D, et al.: Clin Pharmacokinet 58(5): 615–25 (2019)
- [6] Vaidyanathan A, et al.: Br J Cancer 115(4): 431–441 (2016)

Abbreviations

ADR	Adverse Drug Reaction
PARPi	Inhibitor of Poly-ADP-Ribose-Polymerase
popPK	Population Pharmacokinetic
SNP	Single Nucleotide Polymorphism
TDM	Therapeutic Drug Monitoring

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