

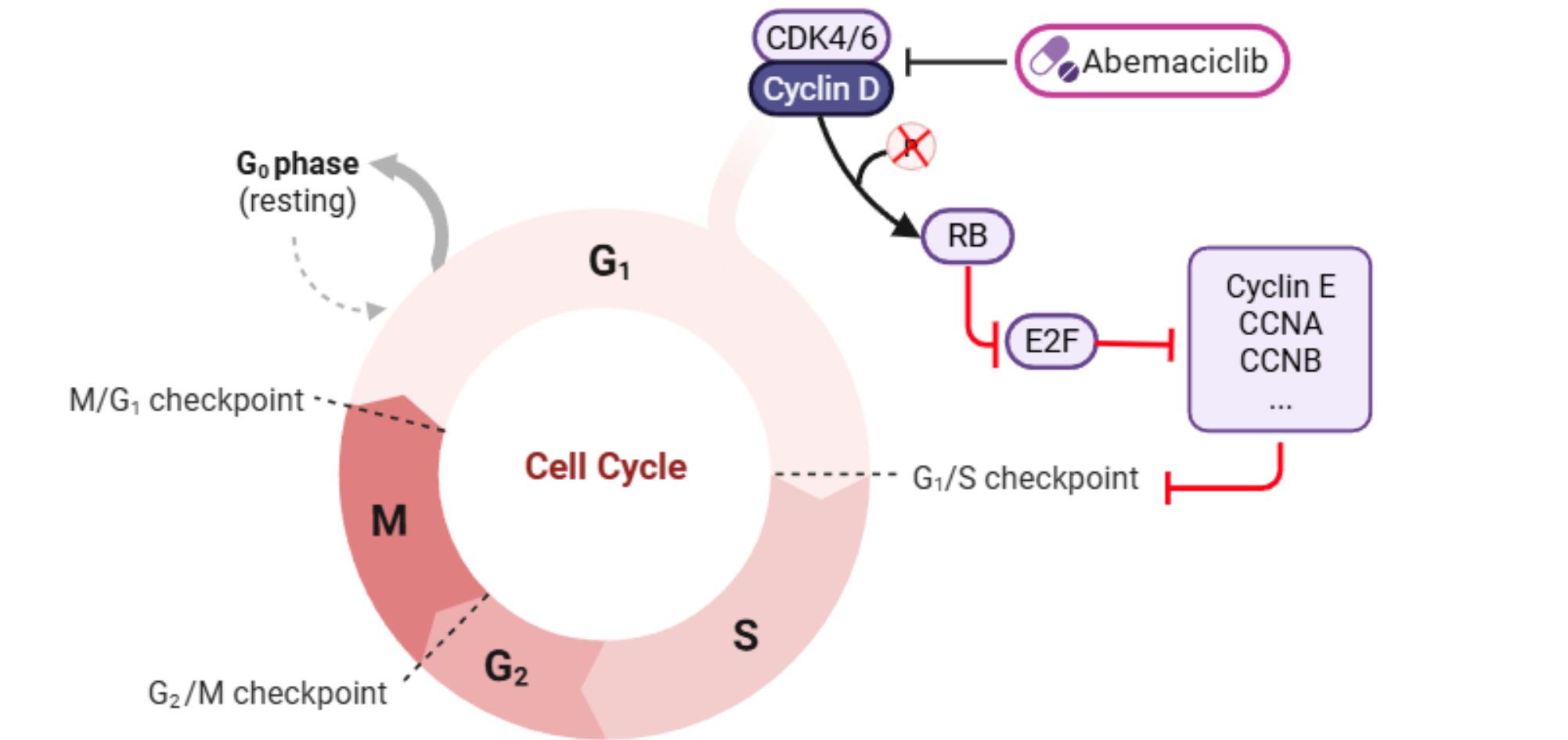
Linking Abemaciclib Exposure and Early Toxicity in HR+/HER2- Breast Cancer Patients: Insights from Real-World Data

Marylise STERLÉ^{1,2,3}, Bernard ROYER^{2,3,4}, Silvia ILIE⁵, Isabelle DESMOULINS⁵, Didier MAYEUR⁵, Manon REDA⁵, Audrey HENNEQUIN⁵, Jean-David FUMET^{2,5}, Leïla BENGRIE-LEFEVRE⁵, Courèche KADERBHAI⁵ and Antonin SCHMITT^{1,2,3}

¹Pharmacy Department, Centre Georges-François Leclerc, Dijon, France
²INSERM U1231, University Bourgogne Europe, Dijon, France
³Groupe de Pharmacologie Clinique Oncologique GPCO-Unicancer
⁴Pharmacology and Toxicology Laboratory, CHRU Besançon, Besançon, France
⁵Oncology Department, Centre Georges-François Leclerc, Dijon, France

INTRODUCTION

Abemaciclib is an oral cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, approved first for the treatment of HR+/HER2-advanced breast cancer. In April 2024, it became the only CDK4/6 inhibitor approved as adjuvant therapy for HR+/HER2- early breast cancer at high risk of recurrence.



Despite abemaciclib clinical benefits, its use is limited by adverse effects, especially hematologic disorders. The mechanisms underlying these toxicities remain poorly understood, and identifying contributing factors is key for optimizing treatment.

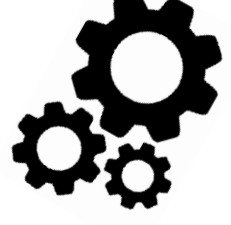
The aim of this study was to describe the pharmacokinetic/pharmacodynamic (PK/PD) relationships between abemaciclib plasma concentrations and the main adverse effects in a real-world population, to propose a target concentration for therapeutic drug monitoring (TDM).

PATIENTS & METHODS



A retrospective study
Between April 2021 and December 2023

All patient who began abemaciclib treatment in Dijon's clinical cancer center were included. As TDM of abemaciclib was routinely performed, assay results were available. The data required were collected from the patients' medical records.



Pharmacokinetic/Pharmacodynamic models development

Estimation of Model Parameters

Application of a non-linear mixed-effects regression approach. Using Monolix® Software¹: estimation of individual PK parameters by bayesian approach, using a previously published population PK model [1], and use as constants in the PK/PD models to estimate abemaciclib plasma concentrations.

¹ (Lixoft SAS, a Simulations Plus company)

Covariate

Covariate selection was carried out in several stages : graphically, using Pearson correlation tests and by a Forward/Backward approach.



Model evaluation

Based on the comparison between model objective function values, the ability of Monolix® to converge a parameter to a typical value of the population, the relative standard error (RSE) of parameter estimates and IIV and a graphical diagnostics.



Simulation

Based on the final PK/PD models to identify abemaciclib trough concentration (Cres) associated with neutropenia and thrombocytopenia ≥ grade 3.

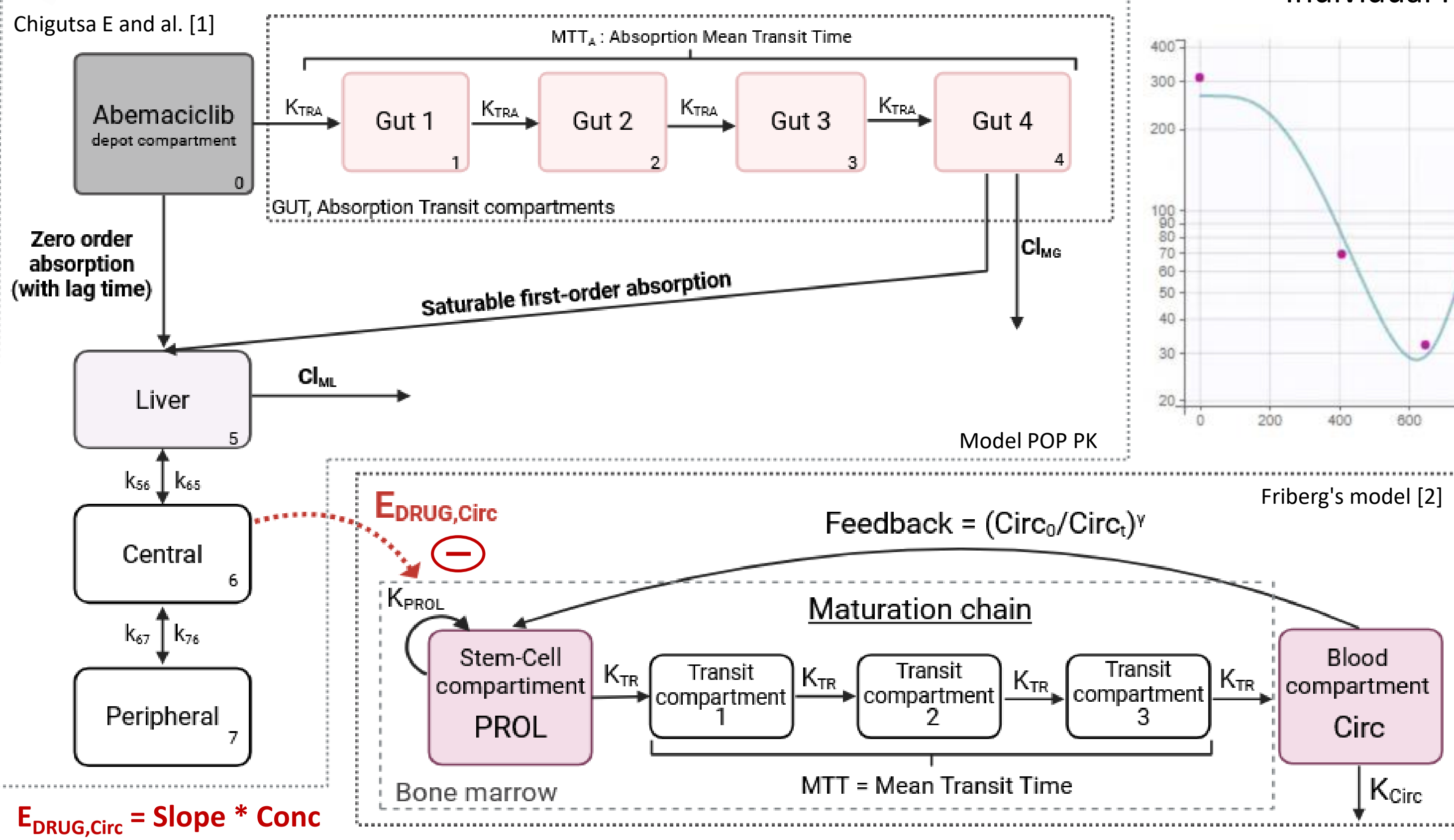
Using Simulx® Software¹ : 1,000 simulations of plasma neutrophil and platelet evolutions over 6 months for several Cres of abemaciclib were carried out. The proportions of patients with neutropenia and thrombocytopenia ≥ grade 3 were calculated for each Cres level.

A threshold of 20% of patients presenting the adverse effect was chosen.

RESULTS



Pharmacokinetic/Pharmacodynamic models development



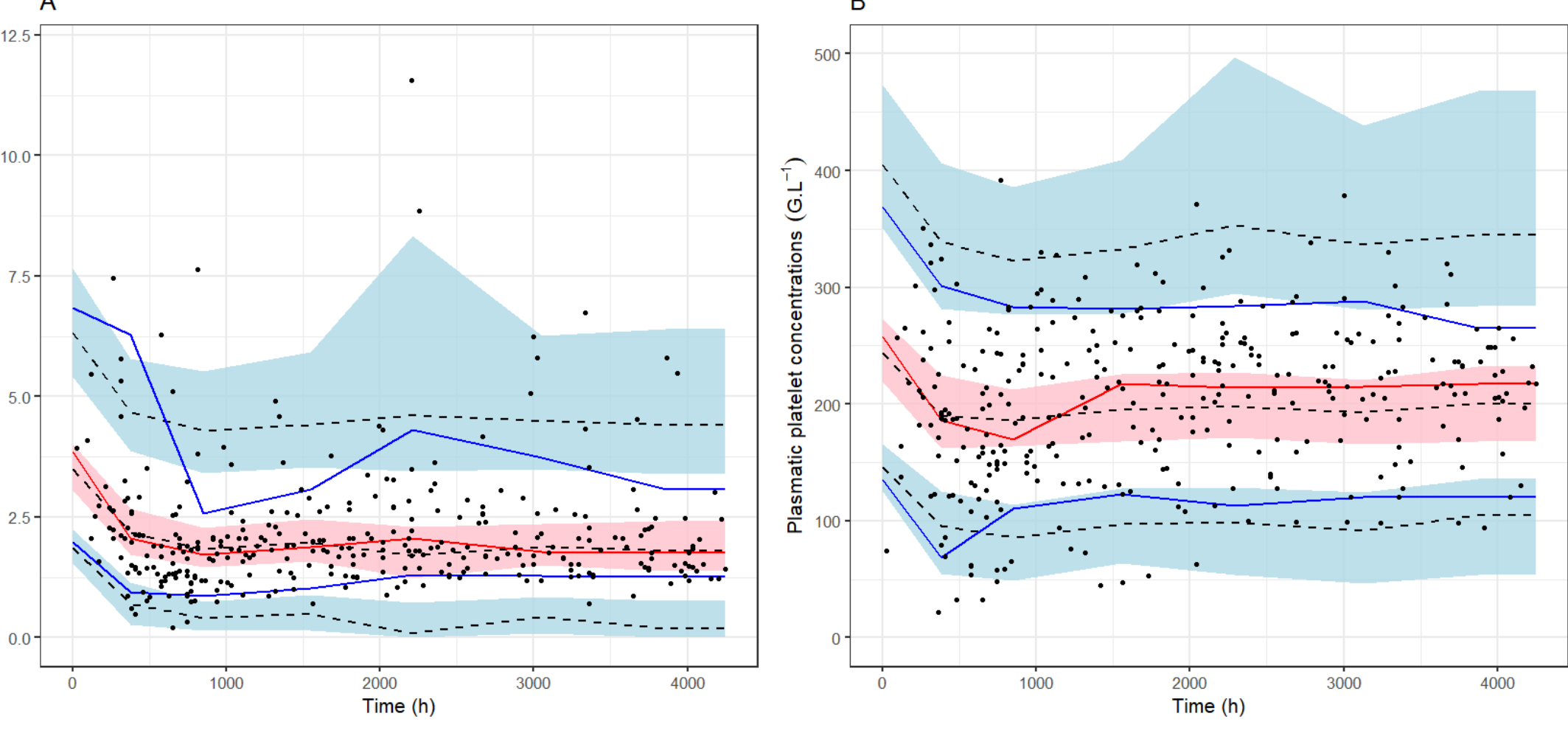
Pharmacokinetic/pharmacodynamic model describing abemaciclib effect on platelet and neutrophil plasma concentrations

Abemaciclib (compartment 0): depot compartment; Central (compartment 6): central compartment; Circ: compartment corresponding to circulating platelets/neutrophils; Circ₀: platelet/neutrophil level at time 0 in the Circ compartment; Circ_t: platelet/neutrophil level at time t in the Circ compartment; Cl_{MG}: gut clearance (metabolite formation in the gut); Cl_{ML}: hepatic clearance (metabolite formation in the liver); Conc: abemaciclib concentration; EDRUG: drug effect; γ (gamma): feedback mechanism; Gut 1, 2, 3, 4 (compartments 1, 2, 3, 4): absorption compartments; K_{Circ}: elimination rate of platelets/neutrophils from systemic circulation; K_{NY}: first-order rate constant from compartment N to compartment Y, K_{PROL}: stem cell proliferation rate, K_{TR}: maturation rate, K_{TRA}: absorption rate, Liver (compartment 5): liver compartment, MTT: maturation neutrophil/platelet mean transit time, MTT_A: absorption mean transit time; Peripheral (compartment 7): peripheral compartment, PROL: proliferation compartment, Slope: sensitivity to abemaciclib-induced neutropenia or thrombocytopenia

Individual Fit of Platelet Time Course

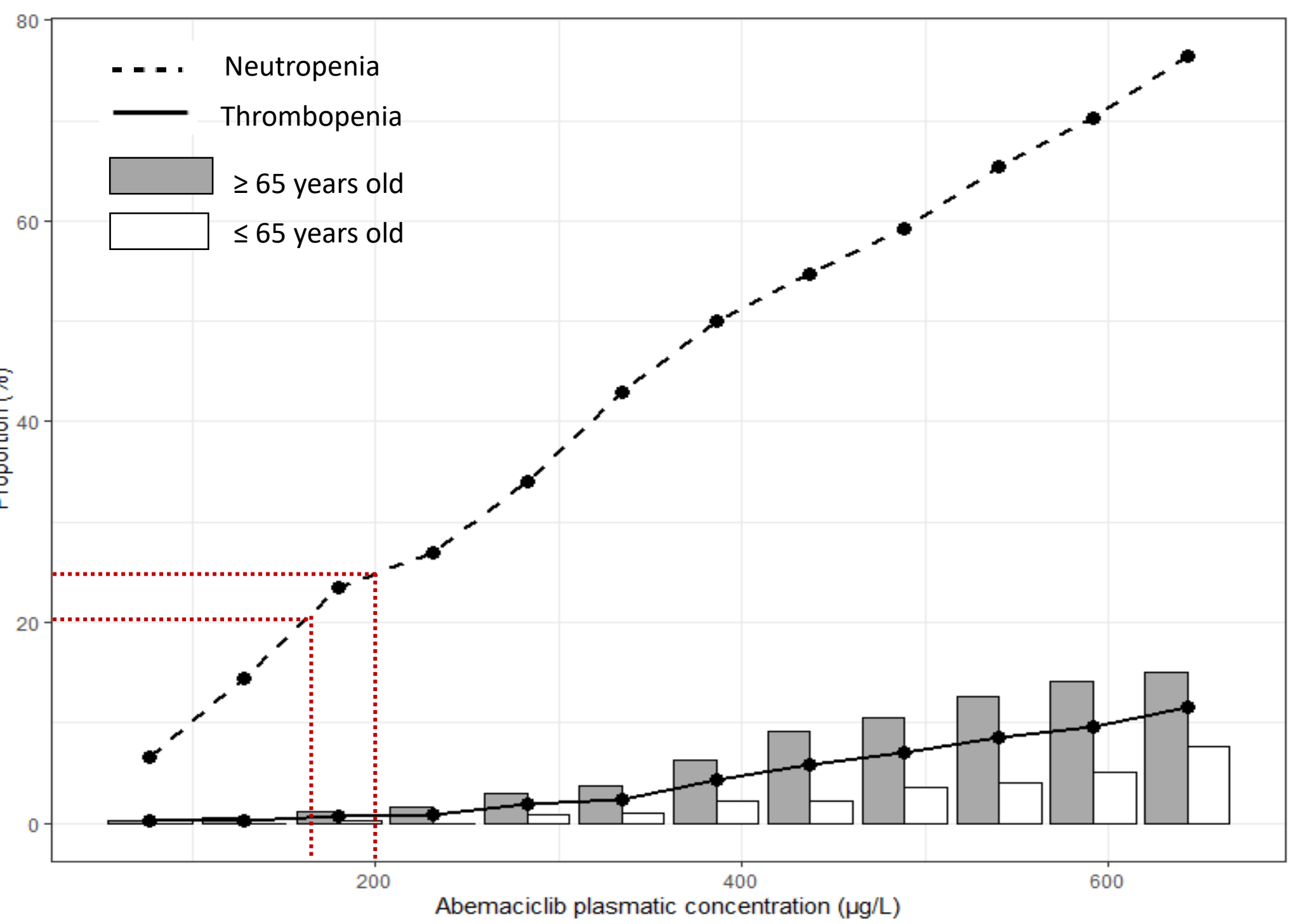
Individual Fit of Neutrophil Time Course

Model evaluation



Visual Predictive Check of Plasmatic Platelet Concentration (A) of Plasmatic Platelet Concentration (B) for final PK/PD model

Simulations



Risk of grade 3/4 neutropenia and thrombopenia depending on the abemaciclib residual concentration at steady-state

One thousand simulations of neutrophil and platelet kinetics were simulated at every Cres to 0 at 650 μg/L. The black dash line corresponds to the risk of grade 3 neutropenia. The black line corresponds to the risk of grade 3 thrombocytopenia and above in the general population, The grey bars represent the risk of grade 3 thrombocytopenia and above in patients over 65, and the white bars in patients under 65.

Models

Parameters	Neutrophils		Platelets	
	Final model	Final model	Final model	Final model
Circ _{0pop}	Estimate	RSE (%)	Estimate	RSE (%)
MTT _{pop}	3,56	6,16	247,13	5,07
v _{pop}	179,54	12,4	185,98	6,88
SLOPE _{Circpop}	0,26	15	0,39	6,98
β _{SLOPE_{AGE}}	0,22	13,8	0,091	19,9
IIV _{Circ₀}	/	/	2,12	35,8
IIV _{MTT}	43,64	11,4	37,84	10,1
IIV _v	41,01	20,66	40,76	13,6
IIV _{SLOPE_{Circ}}	54,46	16,1	34,64	17,9
Correlations	61,33	15,4	79,86	15,2
Residual error	Corr _{v/Circ₀}	/	-0,79	12,9
	b	0,24	/	0,16
				4,26

Population neutrophil/platelet PK/PD models parameter estimates

DISCUSSION

For the first time, we have described the evolution of neutrophils and platelets in patients treated with abemaciclib, using PK and PD models. By monitoring patients over 6 months, has enabled us to understand and describe the entire phenomena observed.

We identified a minimum target abemaciclib plasma concentration around 200 μg/L, above which more than 20% of patients would develop grade 3 and/or 4 neutropenia.

Regarding thrombocytopenia, the toxicity-related concentration is much higher than that observed for doses used in practice. However, we have shown that patients over 65 years of age are more likely to develop grade 3 thrombocytopenia and above.

Today, for abemaciclib, there is no real target range to predict efficacy and toxicity. Currently, it is the concentrations obtained in clinical trials which are used. Very few real-life studies have been carried out, which is why our study, and more specifically the determination of a minimum target concentration beyond which more than 20% of patients would present a grade ≥ 3 neutropenia, will enable us to refine the recommendations that will be made within the framework of TDM in routine clinical practice.

REFERENCES

[1] Chigutsa E and al., « Development and Application of a Mechanistic Population Modeling Approach to Describe Abemaciclib Pharmacokinetics. », *CPT Pharmacomet. Syst. Pharmacol.*, doi: 10.1002/psp4.12544.
[2] L. E. Friberg and al. « Model of Chemotherapy-Induced Myelosuppression with Parameter Consistency Across Drugs », *J. Clin. Oncol.*, sept. 2016, doi: 10.1200/JCO.2002.02.140.

CONCLUSION

Two PK/PD models describing the evolution of neutrophils and platelets as a function of time in patients treated with abemaciclib, based on real-life data, were developed. A target concentration linked to the onset of grade ≥3 neutropenia was identified, which could guide dosage adjustment during TDM

