

Population Pharmacokinetics of rituximab in elderly patients with Chronic Lymphocytic Leukemia

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INTRODUCTION

Rituximab is a monoclonal antibody that binds specifically to the **CD20 present in the surface of normal and neoplastic B lymphocytes**.

Rituximab PK is characterized by a saturable target-mediated elimination.

Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is considered as the standard front-line treatment for patients with chronic lymphocytic leukaemia (CLL).

OBJECTIVES

To develop a population pharmacokinetic (PopPK) model for rituximab administered in elderly patients with CLL.

To assess relationships between Pop PK parameters and potential individual factors of variability.

METHODS

- In elderly Chronic Lymphocytic Leukaemia therapy (CLL, CLL 2007 SA; registered at www.clinicaltrials.gov as NCT00645606)¹, four monthly courses of full FCR with two additional rituximab doses on day 14 of cycles 1 and 2 administrations in induction phase were followed by either rituximab maintenance treatment consisting in intravenous rituximab (500 mg/m²) every 8 weeks for up to 2 years or observation.
- Rituximab concentrations in serum samples were measured using validated enzyme-linked immunosorbent assay (LLOQ=0.20 mg/L, ULOQ = 9.0 mg/L).
- Population pharmacokinetic (PopPK) model was performed with Monolix software version 2018R2 (Lixoft®, Antony, France).
- PK model was a 2 compartment structural model with irreversible binding of rituximab to latent target².

RESULTS

dataset

958 rituximab concentrations were collected from 69 patients.

Tab. 1. Patients' characteristics

Baseline characteristics		n	Median	Range
Age	[years]	-	71	64-86
Sex (F/M)		25/44	-	-
Body Weight	[kg]	-	72	39-121
Body surface area	[m ²]	-	1.83	1.29-2.42
Binet stage B/C*3		46/23	-	-

*Binet stage B and C: active chronic lymphocytic leukemia requiring treatment; B, 3 or more areas of lymph-node involvement without anemia or thrombocytopenia; C, Presence of anemia and/or thrombocytopenia

- The two-compartment structural model with linear and non-linear target-mediated elimination link to CD20 target-antigen maturation, satisfactorily described the data (Fig. 2.).

- Age, body weight, body surface area, corporal mass index, total lymphocyte counts have no influence on rituximab pharmacokinetics.
- A higher k_{in} value was observed in Binet stage C compared with Binet stage B (0.193 vs 0.126, $p=4.67 \times 10^{-5}$) (Tab.2).

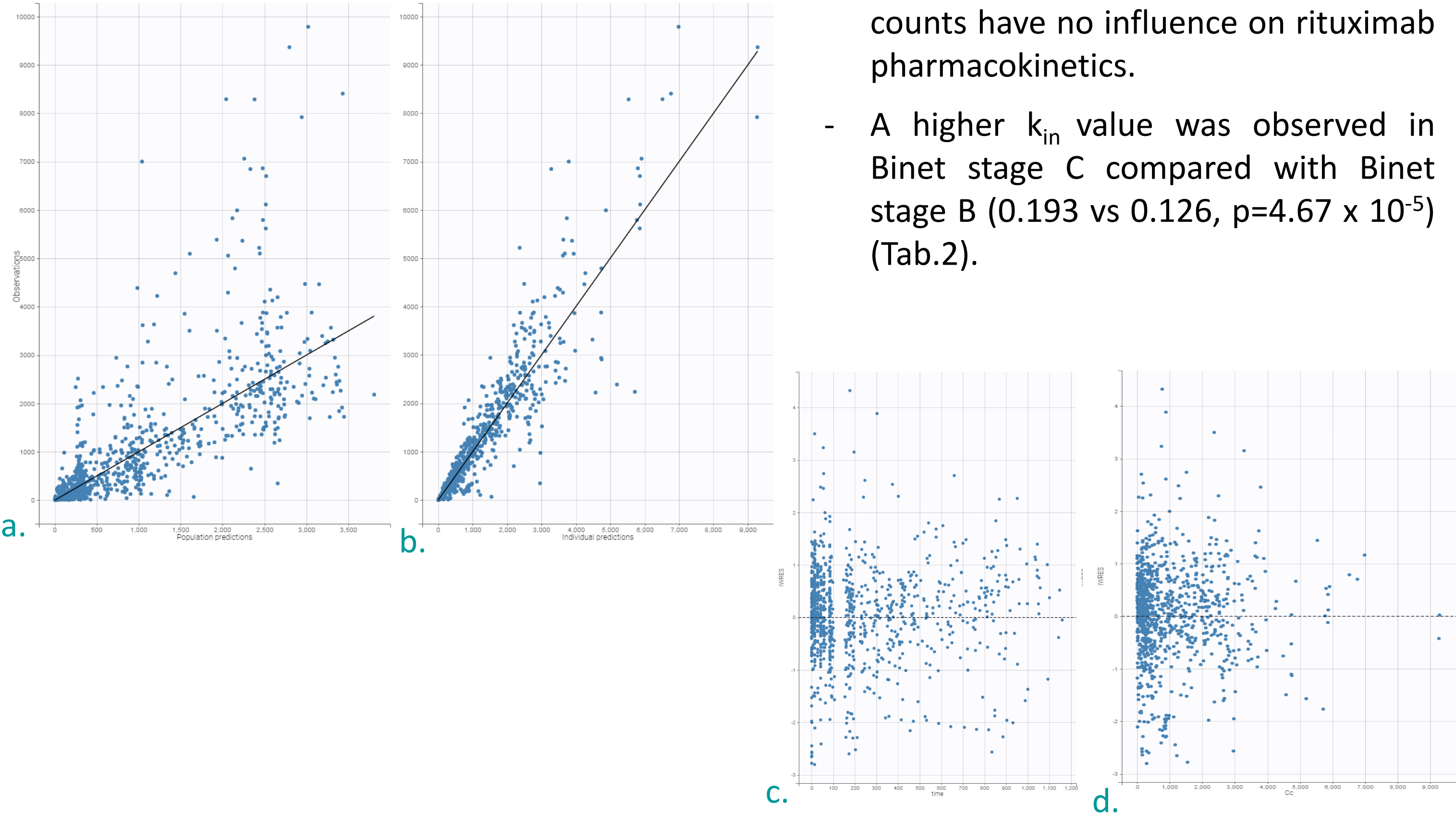


Fig. 1. Goodness of fit plots. Graphs of the observed concentrations versus population predicted concentrations (a) and versus individual predicted concentrations (b), individual weighted residuals versus time (c) and versus individual predicted concentrations (d).

PK model

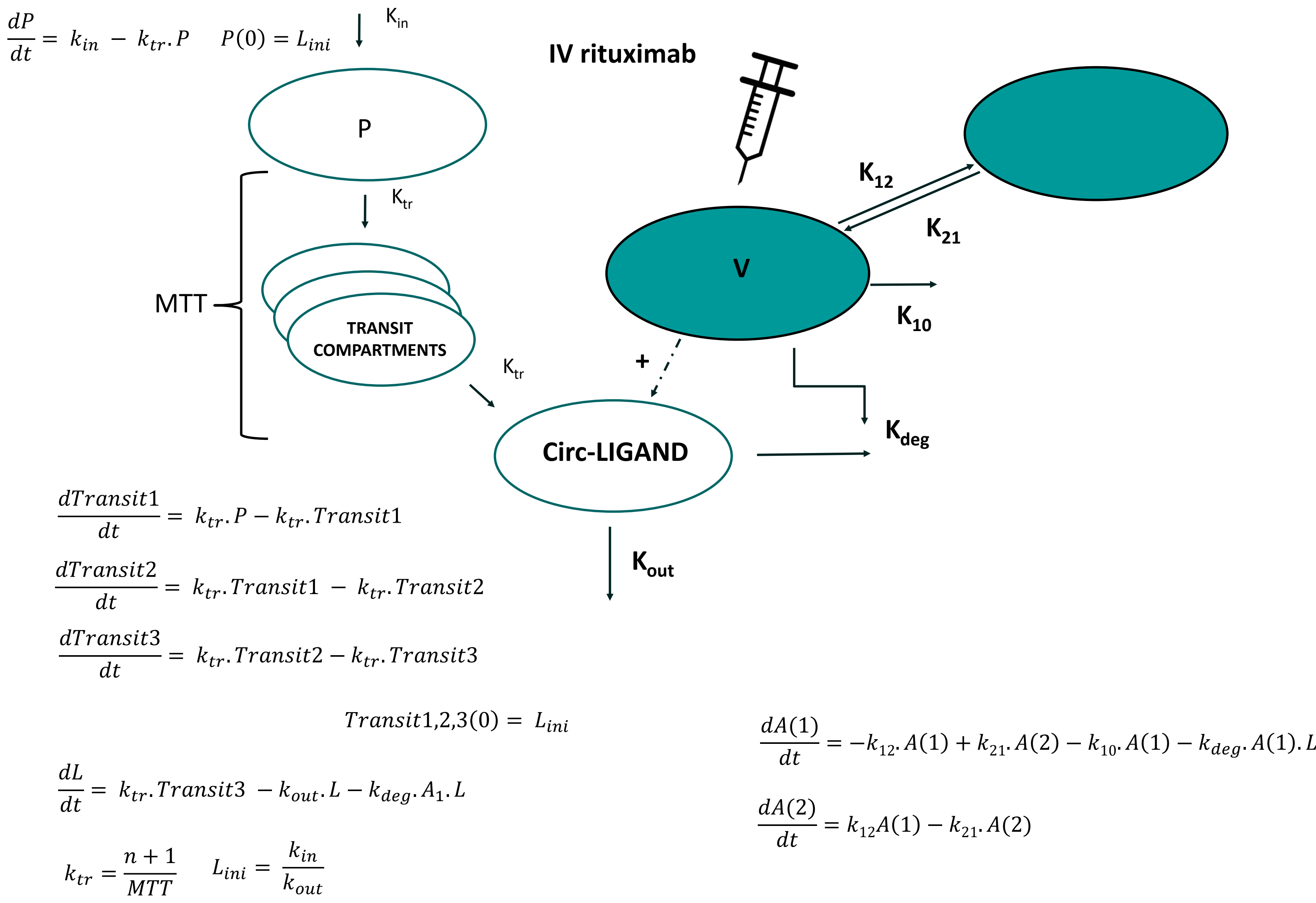


Fig. 2. Schematic of the pharmacostatistical model linking a two-compartment pharmacokinetic model to CD20 target-antigen maturation. The CD-20 target-antigen turnover consists of one compartment that represented proliferative cells (P), three transit compartments with maturing cells (Transit compartments) and a compartment of circulation observed blood cells (Circ-ligand) available for rituximab binding. V, distribution volume, K_{10} , elimination rate constant, k_{12} and k_{21} intercompartmental constants, zero-order production rate constant of target antigen k_{in} , first-order rate constant of rituximab-independent death of latent target antigen k_{out} , mean maturation time MMT and rituximab target-mediated elimination rate constant k_{deg} .

Tab. 2. Final PK model parameter estimates

Parameter		Estimate (%RSE)	p
Fixed effects			
V	[L]	2.846	5
k_{10}	[d ⁻¹]	0.057	6
k_{12}	[d ⁻¹]	0.113	4
k_{21}	[d ⁻¹]	0.078	7
MTT	[d]	7.828	5
k_{in}	[nmol.d ⁻¹]	0.126	12
Binet stage C on k_{in}		0.673	25
k_{out}	[d ⁻¹]	1.877E-04	7
k_{deg}	[nmol ⁻¹ .d ⁻¹]	1.561E-04	13
Interindividual and residual variability			
ω_v (%)		0.39	10
ω_{k10} (%)		0.43	11
ω_{k12} (%)		0.35	16
ω_{kin} (%)		0.58	12
ω_{kdeg} (%)		0.53	18
σ_{prop} (%)		0.34	3

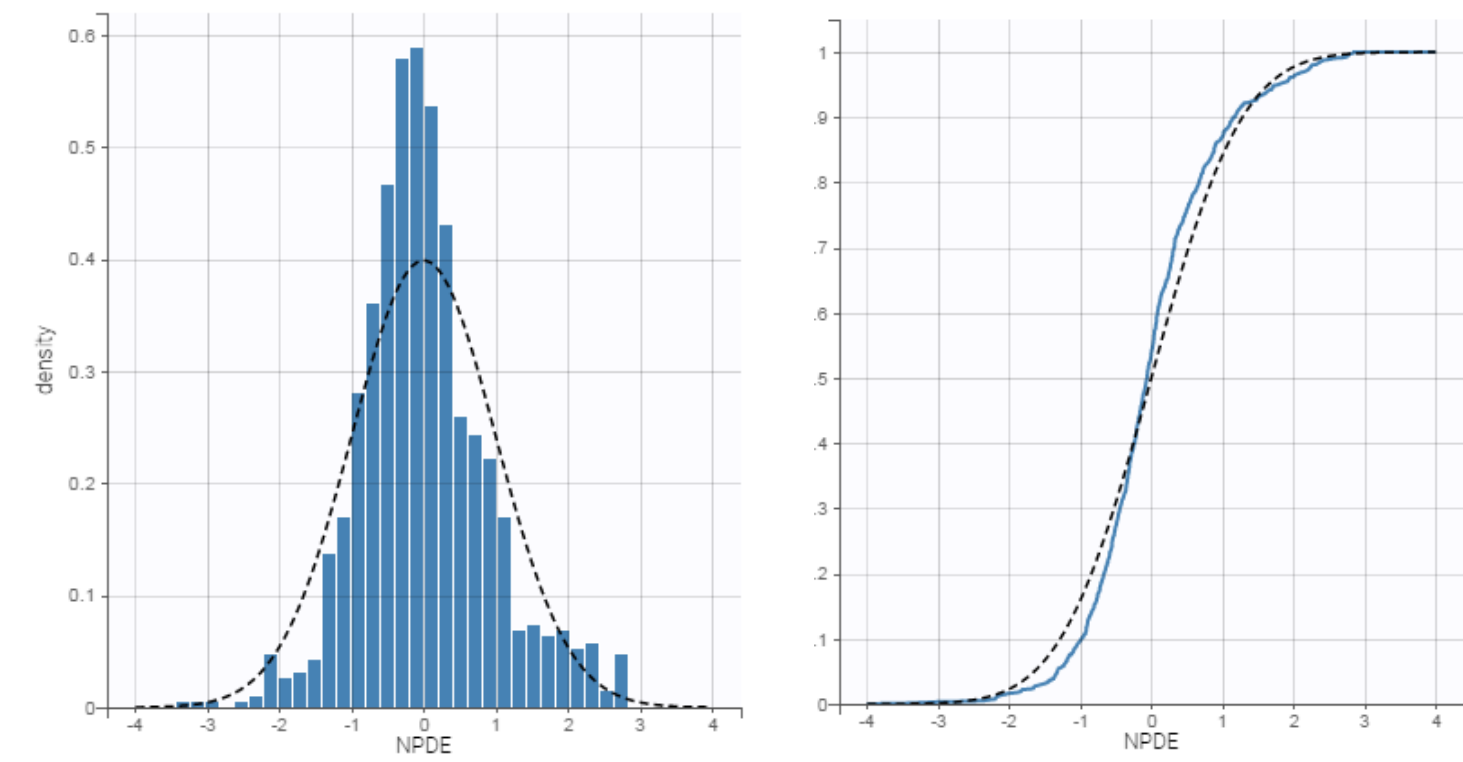


Fig. 3. NPDE distribution

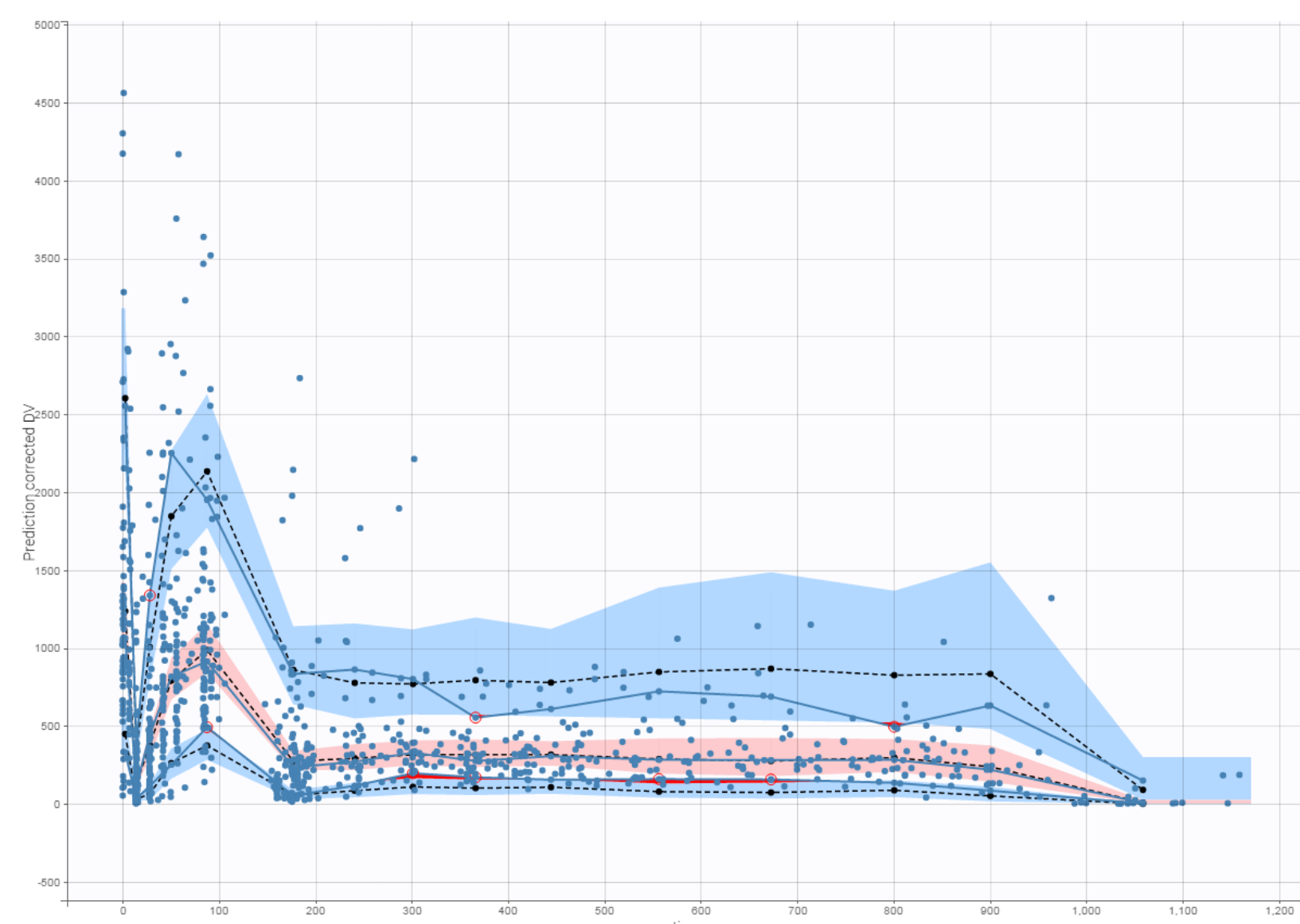


Fig. 4. Corrected Visual Predictive Check

CONCLUSION

In this study, we confirmed that the rituximab PK in elderly patients with CLL is satisfactorily described using a semi-mechanistic model including the maturation process of B-cells available for rituximab binding. B cells were considered as latent because CD-20 counts (target antigen) were not available over the time course of this study. In this population the gravity score influenced the PK of rituximab, in the manner that the most serious patients have the lower rituximab concentrations.

PERSPECTIVES

The next step of this study will be to assess the influence of the exposure to rituximab on the progression-free survival and to propose an optimize regimen for rituximab maintenance therapy in this population based on the model developed.

REFERENCES

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³Binet JL et al, A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981 Jul 1;48(1):198-206.