

Revealing the complexity of monoclonal antibodies exposure-response relationship in metastatic colorectal cancer patients while mitigating confounding factors

S. Lobet¹, G. Paintaud^{2,3}, T. Lecomte^{1,4}, D. Ternant^{2,3}

¹Inserm UMR 1069, N2COx, Tours University, France; ²Pilot Centre for Therapeutic Antibodies Monitoring (PiTAM), CHRU Tours, France; ³Inserm U1327, ISCHEMIA, Tours University, France; ⁴Gastroenterology and Digestive oncology Department, CHRU Tours, France

INTRODUCTION

Monoclonal antibodies (mAbs) like **cetuximab (CTX)** and **bevacizumab (BV)** are key treatments for metastatic colorectal cancer (mCRC) [1]

Understanding the exposure-response (ER) relationship of these mAbs, and of oncology in general, remains complex and controversial:

- Conventionally: $\nearrow$ [mAbs] associated with better clinical response ("exposure-driven" relationship) $\rightarrow$ $\nearrow$ Survival (PFS) (as shown in several studies of CTX [2-4] and BV [5-7])
 - However: some authors has suggested the absence of an ER relationship for CTX [8-9] and BV [10-11]
- $\rightarrow$ these discrepancies may be explained by cofounding factors [12-13], such as :
- baseline disease status ("prognostic-driven" relationship)
 - dynamic phenomena like target engagement and disease improvement over time ("response-driven" relationship)

Objectives : Challenge conventional approaches to describing and interpreting ER analysis

MATERIALS & METHODS

Data from phase II multicenter studies in patients with mCRC

 102 patients

 400mg/m² loading dose
250 mg/m² weekly (QW)

 CTX serum conc. (N=91;n=1296)
ELISA; LLOQ = 0,75 mg/L
PFS (N=91)

 137 patients

 First line treatment
5mg/kg every 2 weeks (Q2W)

 BV serum conc. (N=130;n=486)
ELISA; LLOQ = 0,61 mg/L
PFS (N=130)

Model development using Monolix Suite 2021 R1 [14]

1) Pharmacokinetic model development

- to describe joint kinetics of these mAbs and their targets
- Several TMDD model approximations (MM, QSS, IB) tested
- compared to previous published models

2) Time-to-progression (TTP) model development

- to describe the risk of progression
- TTP data modeled using parametric approach for baseline hazard (h_0)
 $\rightarrow$ Exponential, Weibull, log-logistic, and Gompertz distribution compared

3) Joint PK-TTP model development:

- to describe the relationship between PK and PFS : $h(t) = h_0(t) \times LINK$
- three possible links between mAb conc., target level and $h(t)$ tested
 - (i) no link : $LINK = 1$ (No link model)
 - (ii) mAb conc. as an inhibitor on h_0 : $LINK = 1 - \frac{C_1}{C_{50} + C_1}$ (C link model)
 - (iii) target levels as an inhibitor on h_0 : $LINK = \frac{R}{R_{50} + R}$ (R link model)
- C_{50} and R_{50} are unbound mAb conc. and target levels leading to a 50% $\searrow$ or $\nearrow$ respectively, on h_0
- parameters estimated using a sequential approach

4) Mitigation strategies applied to exposure response analysis

- to account baseline prognostic-driven and response-driven factors on the ER
 - time-varying CL component added to first-order CL term on the base model
 - association of TTE with PK parameters tested, using TTP as covariates
 - association of CL with TTP tested, using CL as a covariate of $h(t)$

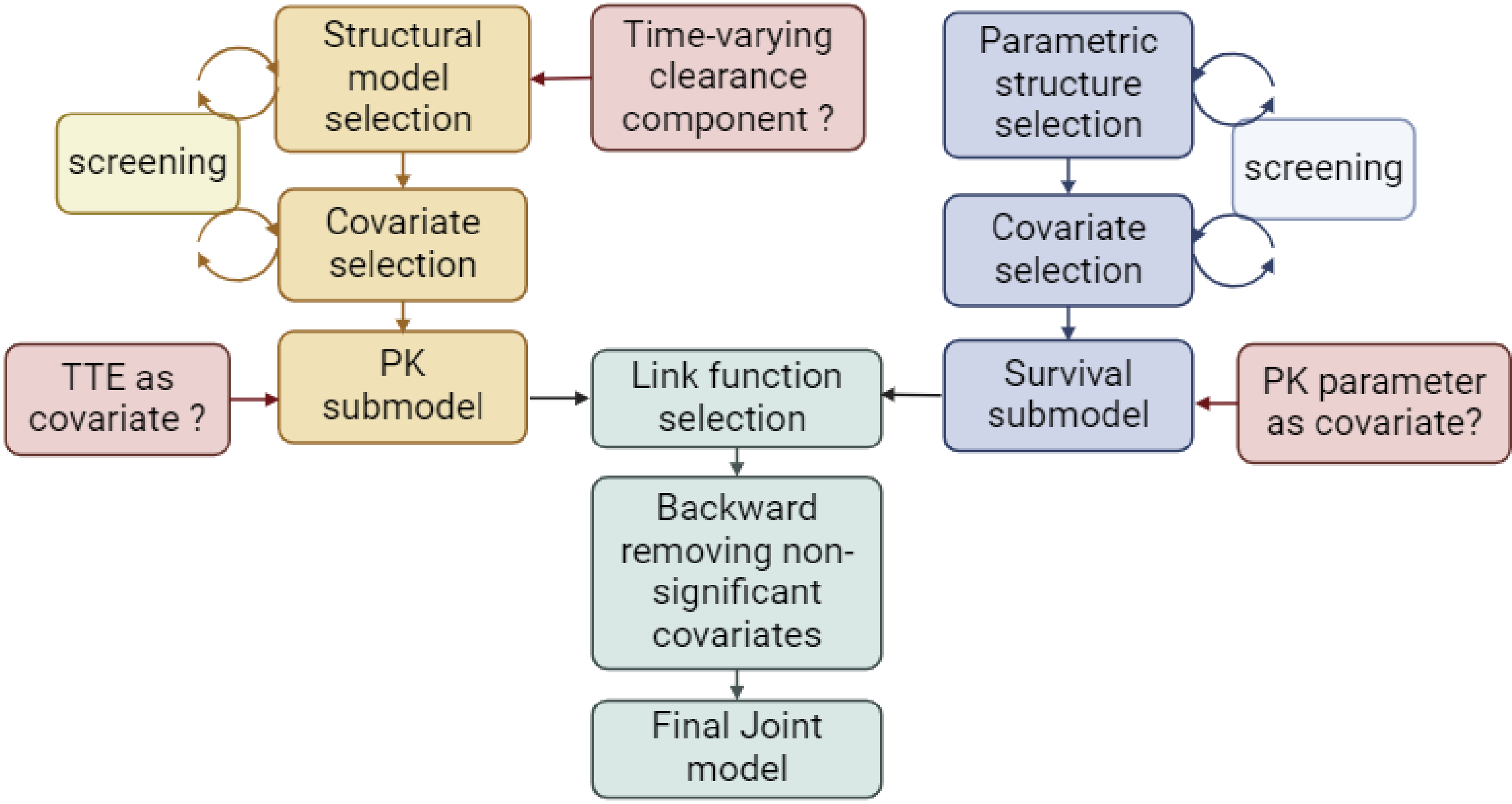


Figure 1 : Strategy Development for Modeling the Exposure-Response Relationship

RESULTS

Table 1 : Population parameters of TMDD and joint PK-TTP models for CTX and BV in mCRC patients

	CETUXIMAB [15]	BEVACIZUMB [16]
Target-mediated Pharmacokinetics		
TMDD model	QSS approximation	QSS approximation
R_0 (nM)	106 ($> cEGFR \approx 0.45$ nM [8],[17])	7.7 ($> cVEGF \approx 0.005$ nM [5],[7],[18])
k_{int} (day ⁻¹)	0.83 ($> \times 4$ $k_e = 0.17$)	0.48 ($> \times 10$ $k_e = 0.04$)
K_{ss} (nM)	1.5	10
k_{deg} (day ⁻¹)	0.81	0.93
Antigen burden on R_0	No covariate (CEA, P=0.73)	$R_{0,TV} = R_{0,pop} \cdot \left(\frac{CEA}{65}\right)^{0.061} \cdot e^{0.32 \cdot cVEGF} \cdot e^{0.22 \cdot EHM}$
Clinical status on CL	$CL = 0.43 + 0.059 \cdot e^{-0.048 \cdot t}$ $\searrow$ AIC ($\Delta AIC = -18.26$) $\searrow$ R_0 (38 nM)	$CL = CL_0 = 6.6$
Clinical status on V_1	$CL_{0,TV} = CL_{0,pop} \cdot \left(\frac{ALB}{38}\right)^{-0.85} \cdot \left(\frac{TTP}{181}\right)^{-0.12} \cdot e^{0.2 \cdot SEX(H)}$	$CL_{TV} = CL_{pop} \cdot \left(\frac{HT}{169}\right)^{4.0} \cdot \left(\frac{ALB}{37}\right)^{-0.78}$
	$V_{1,TV} = V_{1,pop} \cdot \left(\frac{BSA}{1.81}\right)^{1.1}$	$V_{1,TV} = V_{1,pop} \cdot \left(\frac{HT}{169}\right)^{3.6}$
Joint PK-TTP model		
$h_0(t)$	$\frac{1.5}{543} \cdot \left(\frac{t}{543}\right)^{0.5}$ (Weibull model)	$\frac{2.4}{334} \cdot \left(\frac{t}{334}\right)^{1.4}$ (Log-logistic model)
Link	$\frac{R}{0.13 + R}$	$\frac{R}{0.14 + R}$
Antigen burden on h_0	No covariate	$e^{0.81 \cdot cVEGF}$
Clinical status on h_0	$e^{3.9 \cdot CL}$	$e^{2.0 \cdot CL}$
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Figure 2: Simulation of the influence of R_0 on mAb concentrations, targets and PFS

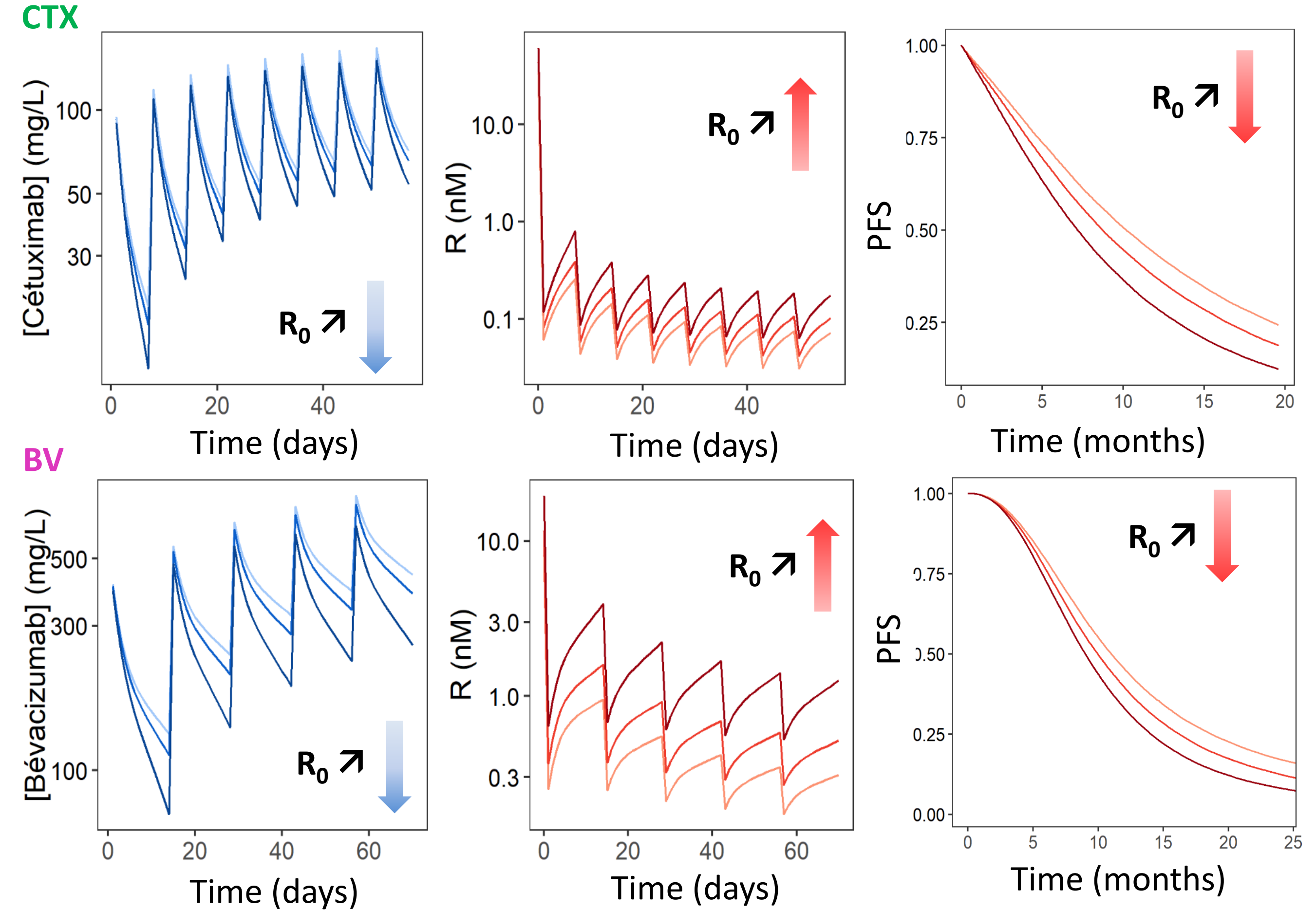
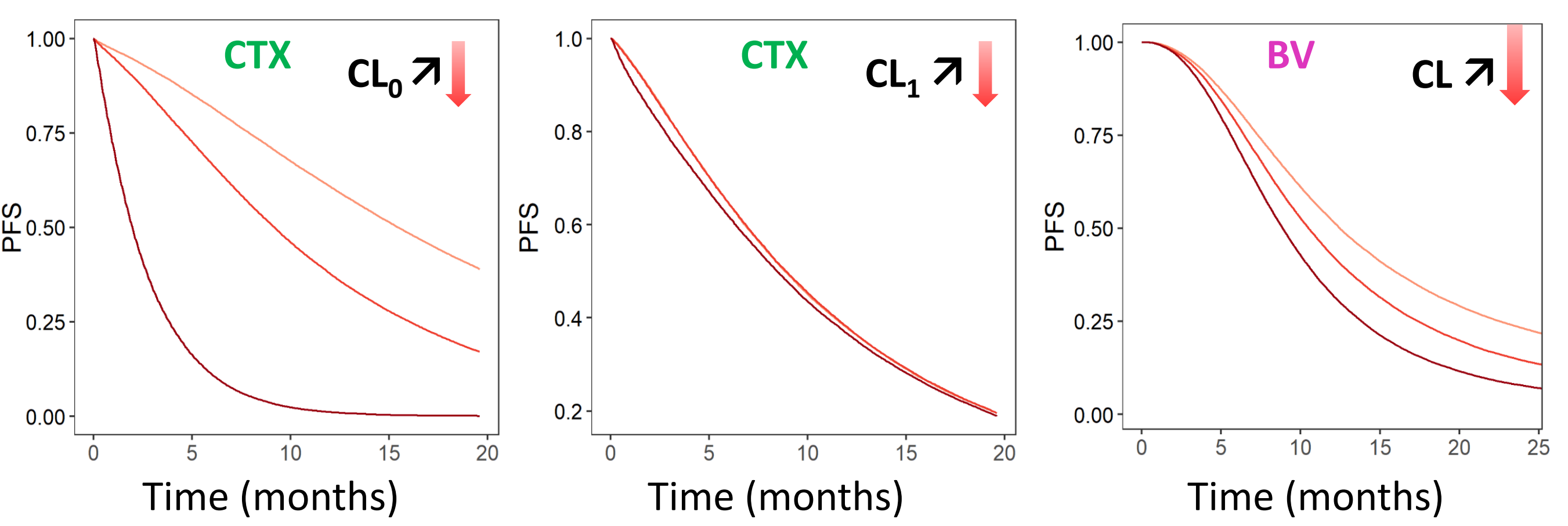


Figure 3: Simulation of the influence of CL on PFS



CONCLUSIONS

- First studies to show the relationship between mAb concentrations, target engagement and clinical efficacy by mitigating potential sources of bias.
- Highlights the complexity of the ER relationship of BV and CTX, and for anticancer mAbs in general.
- Description of both target kinetics and a patient's pathophysiology might therefore be the cornerstone for a better understanding of this relationship.

CONTACT : sarah.lobet@etu.univ-tours.fr

REFERENCES

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