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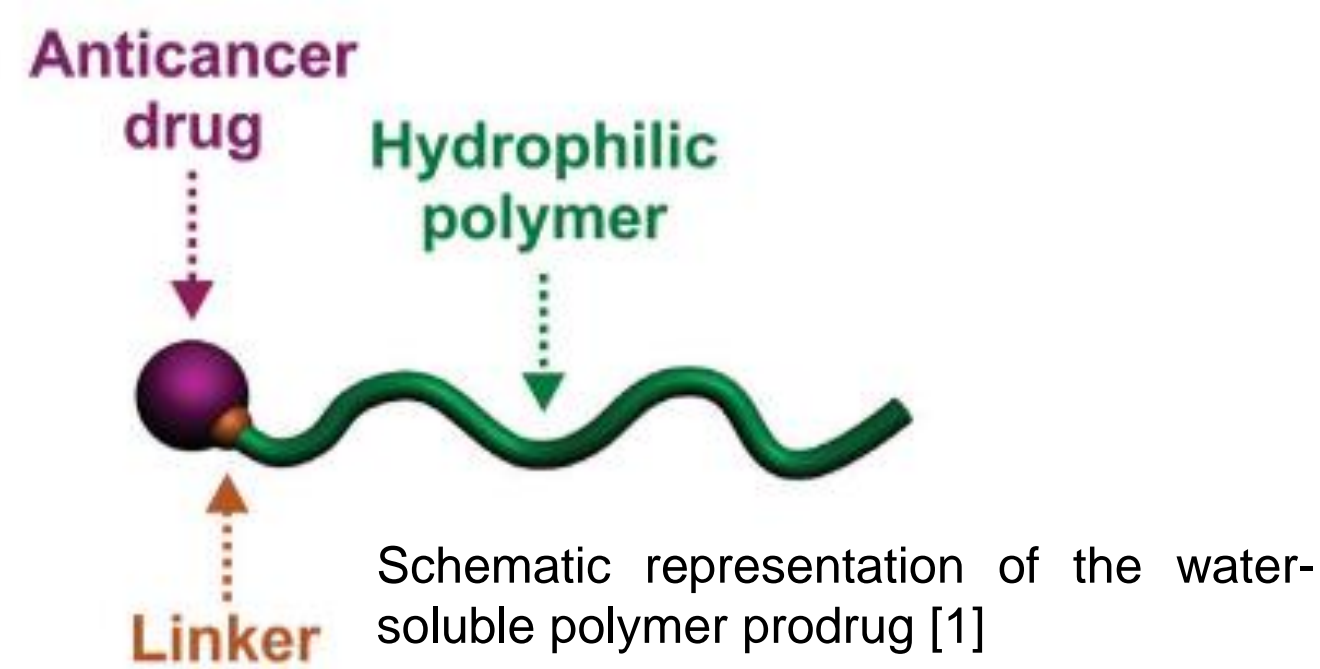
PK/PD MODELLING TO ADVANCE THE PRECLINICAL DEVELOPMENT OF A NOVEL POLYMER PRODRUG IN ONCOLOGY

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MOTIVATIONS & OBJECTIVES

- Taxanes such as **Paclitaxel** (PTX) are considered essential chemotherapeutics for the treatment of solid tumors. PTX formulations have been explored to **increase efficacy**, to **reduce toxicities** and have **improved pharmacokinetics** (PK).
- PTX linked to polyacrylamide (PTX-PAAm) is a new polymer prodrug which could result in an **effective** and **tolerable** anticancer treatment allowing for **subcutaneous** (SC) administration.



OUTLINE

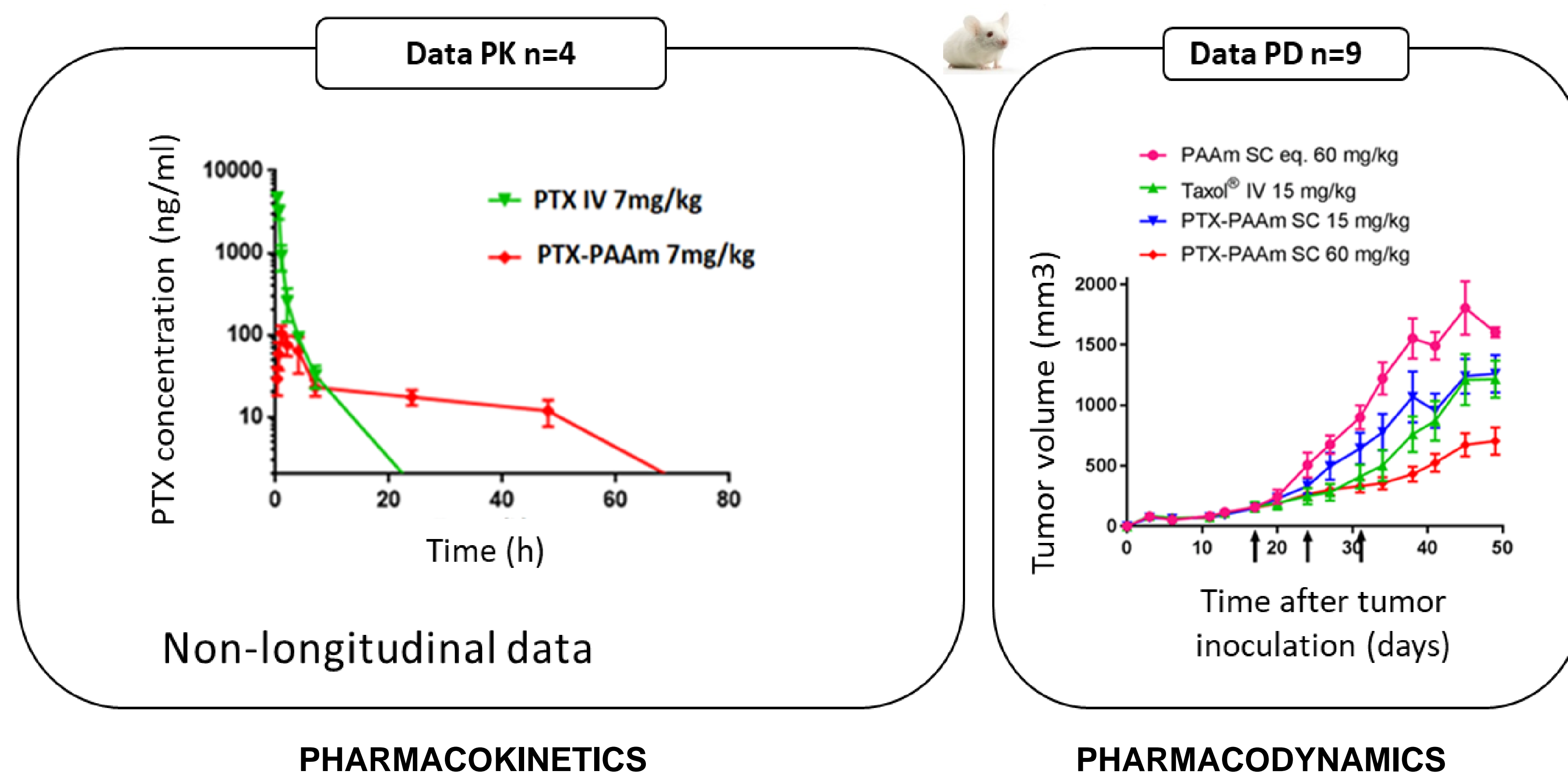
PK/PD modeling: **dose regimen optimization**

METHODS

SOFTWARES (version 2023R1)



EXPERIMENTAL BACKGROUND



PK/PD MODEL WAS BUILT GRADUALLY

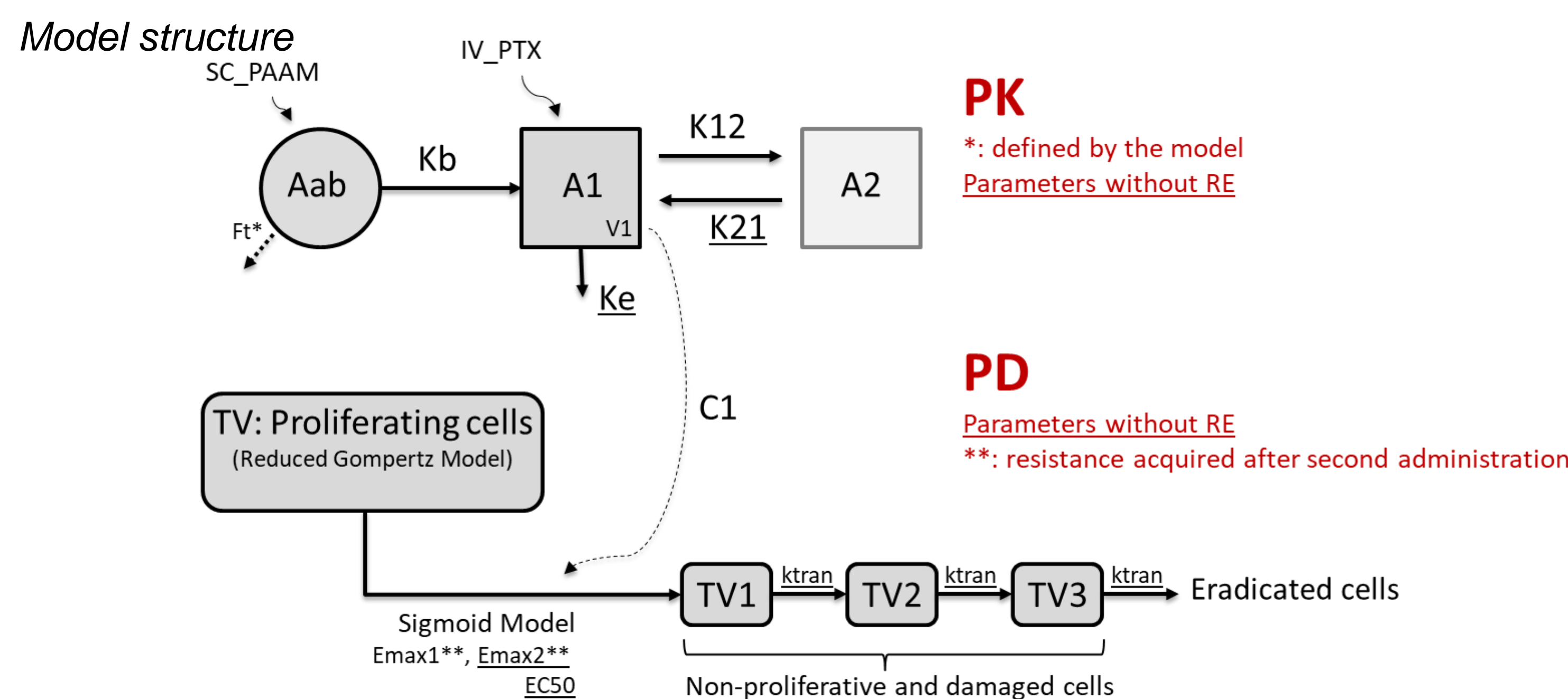
- (1) Pop-PK Model
- (2) Natural Tumor growth Model
Exponential, Power Law, Logistic & Gompertz's Models
- (3) PTX efficacy on cancer cells
Simeoni, Log Kill, Norton Simon & Treshold killing Models
- (4) Resistance model investigation

PK/PD MODEL WAS SELECTED ON

Numerical criteria
Objective function value (OFV) - Relative Standard Errors (RSE)
Graphical criteria
Visual Predictive Check (VPC) - Individual fits – Obs. vs Pred.

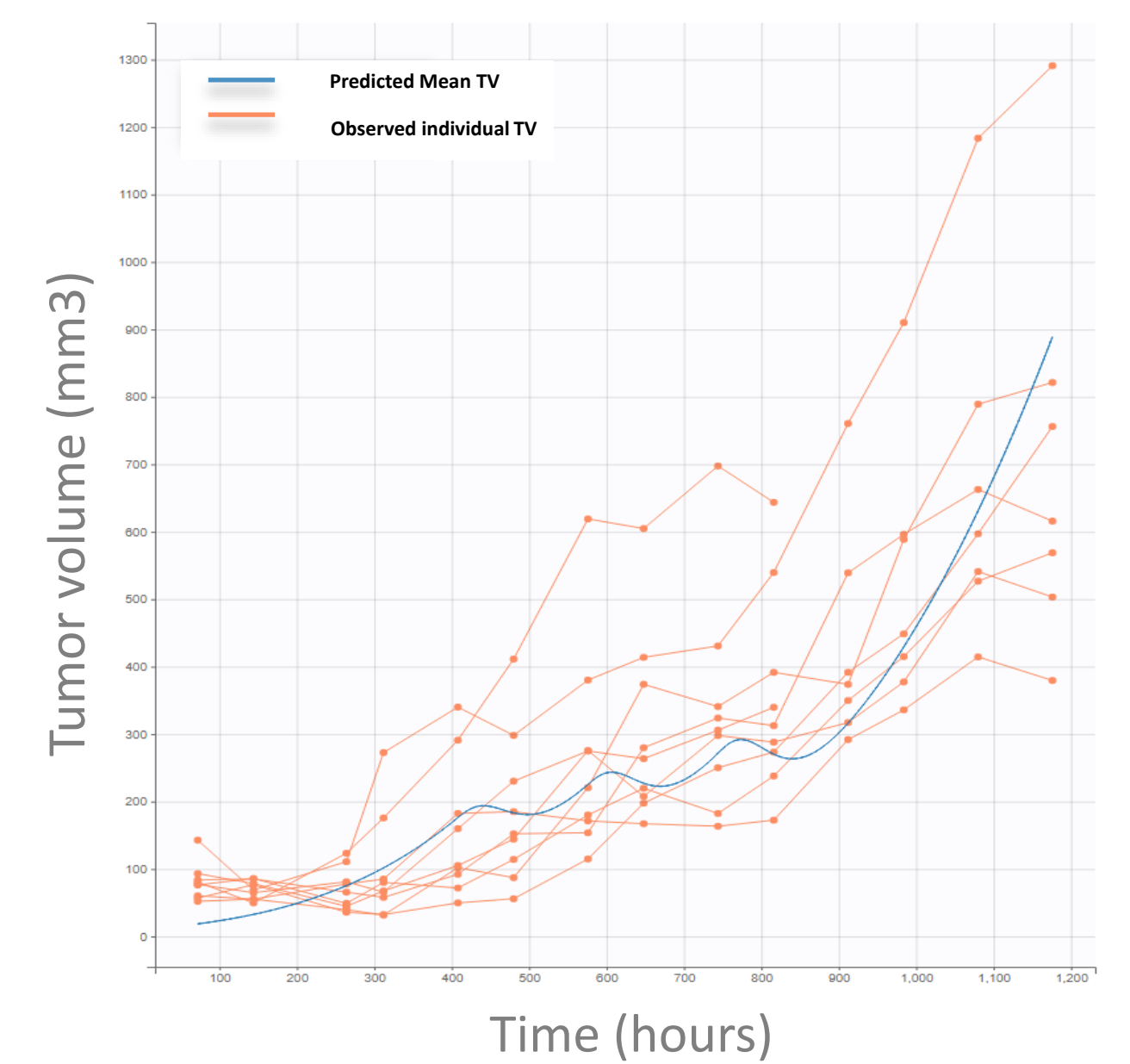
RESULTS

Final PK/PD MODEL

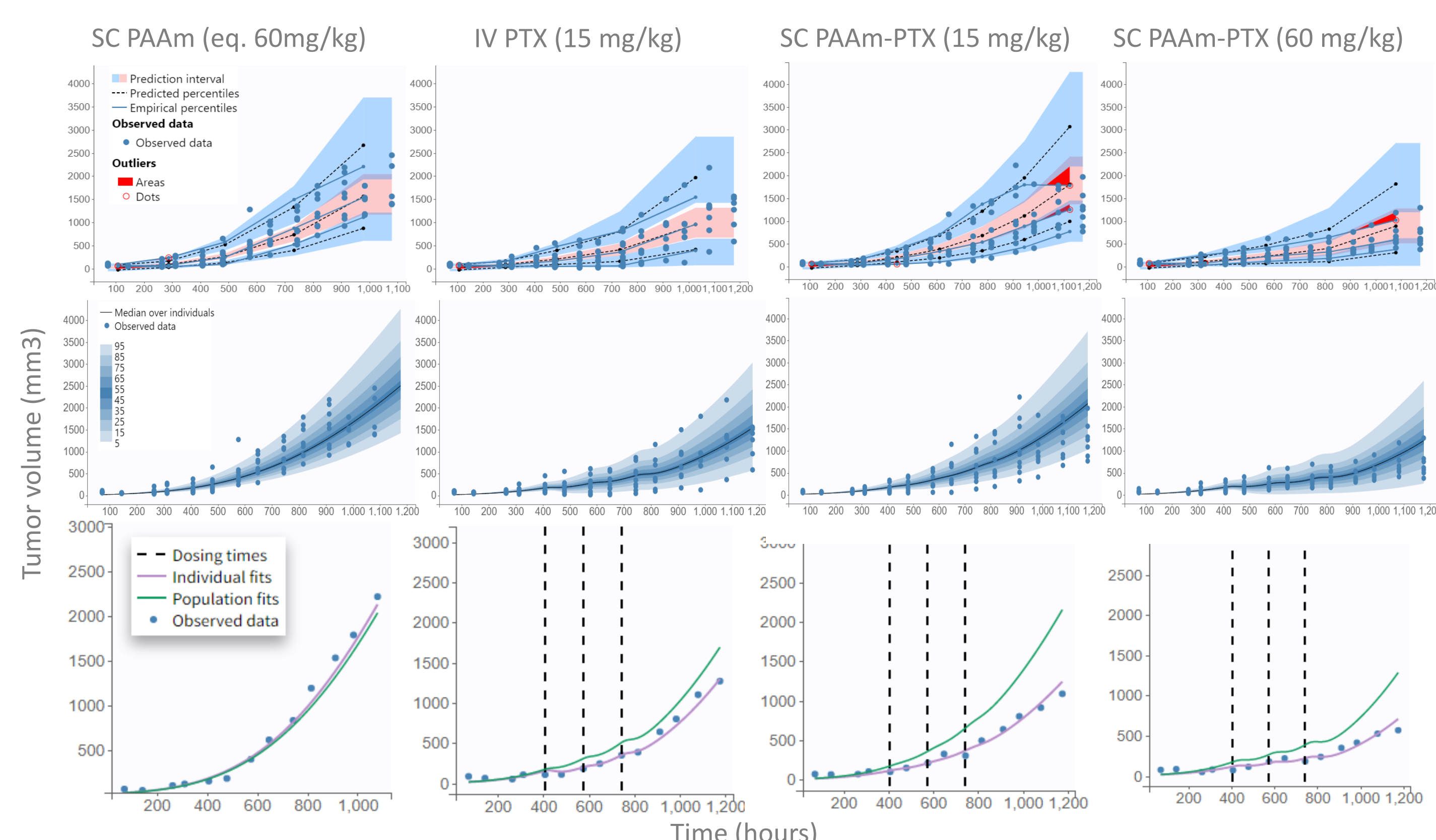


Model estimates and prediction power

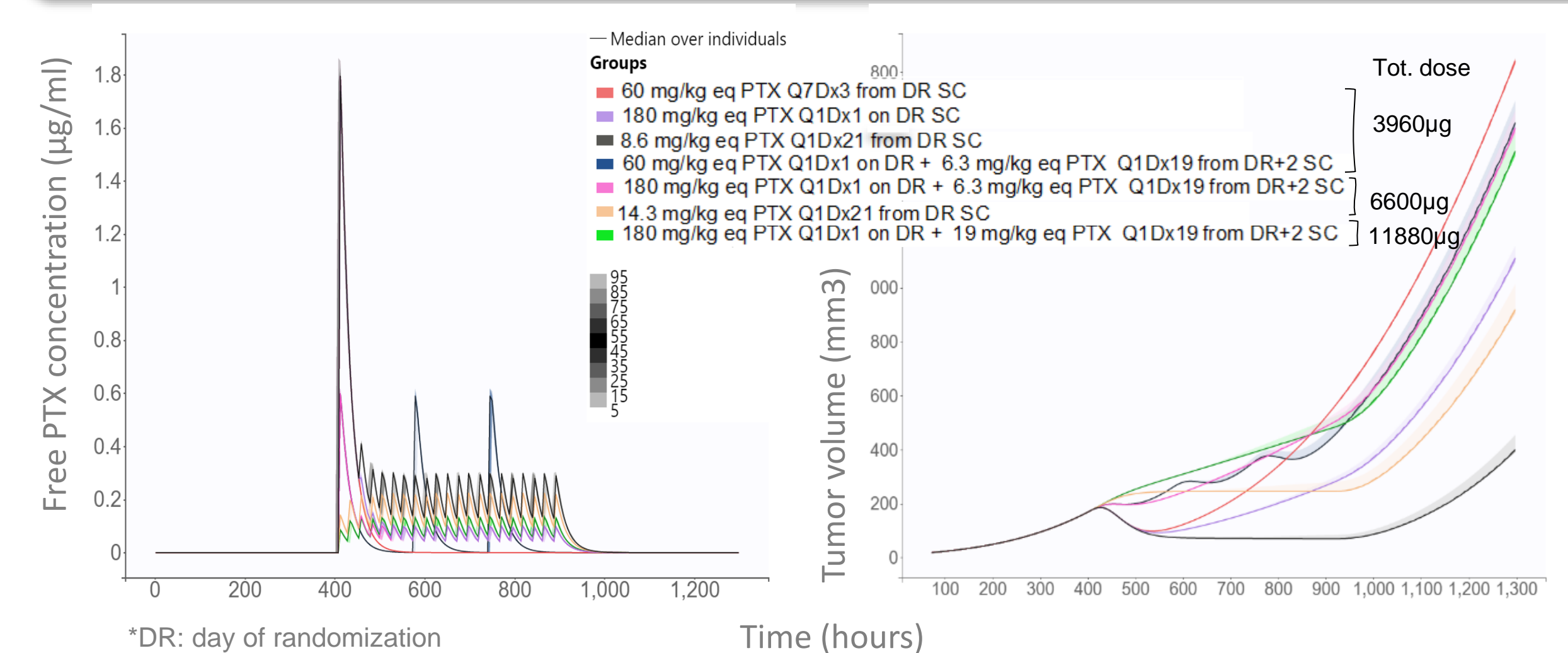
| PARAMETER | ESTIMATE | RSE % |
|---|----------|-------|
| FIXED EFFECT | | |
| V1 (ml) | 10.73 | 5.82 |
| k ₁₂ | 0.65 | 12.8 |
| k ₂₁ | 0.51 | 0.852 |
| k _e | 2.76 | 0.134 |
| k _b | 0.047 | 13.5 |
| γ | 7.17 | 5.25 |
| β | 0.0013 | 10.3 |
| k _{tran} | 0.05 | 0.402 |
| Emax1 | 15.48 | 40.1 |
| Emax2 | 13.8 | 3.51 |
| EC50 | 462.7 | 1.16 |
| STANDARD DEVIATION OF THE RANDOM EFFECT | | |
| ΩV1 | 0.26 | 19.4 |
| Ωk ₁₂ | 0.21 | 37 |
| Ωk _e | 0.57 | 19.9 |
| ΩK _β | 1.15 | 24.5 |
| ΩEmax1 | 1.23 | 25.4 |



Goodness of fit



TREATMENT SIMULATIONS



ACKNOWLEDGMENTS

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Bordat A, Boissenot T, Ibrahim N, Ferrere M, Levêque M, Denis S, et al. A Polymer Prodrug Strategy to Switch from Intravenous to Subcutaneous Cancer Therapy for Irritant/Vesicant Drugs. J. Am. Chem. Soc. 2022, 144, 18844

Vaghi C, Rodallec A, Fanciullino R, Ciccolini J, Mochel JP, Mastro M, Poignard C, Ebos JML, Benzekry S. Population modeling of tumor growth curves and the reduced Gompertz model improve prediction of the age of experimental tumors. PLoS Comput Biol. 2020 Feb 25;16(2):e1007178.

