



# Translational modeling of tumor growth inhibition of an antibody-drug conjugate in oncology

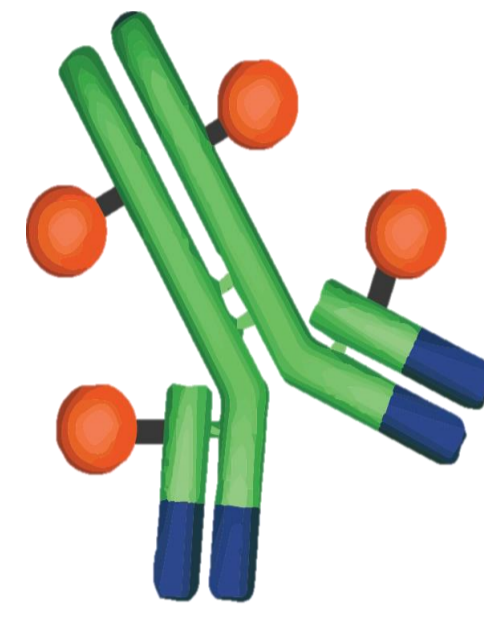


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## Background

- Pharmacometric modeling plays a pivotal role in bridging preclinical findings with clinical decision-making in drug development
- An ADC is currently in early oncology development, targeting the apoptosis pathway
- Early studies :
  - PK in huFcRn (humanized FcRn) mice
  - Tumor Growth Inhibition (TGI) in xenografted mice



## Objectives

- Characterize PK in huFcRn mice
- Characterize PK/PD relationship in xenografted mice
- Extrapolate the dose-efficacy relationship in human

Support design of the First-In-Human study

## Materials & Methods

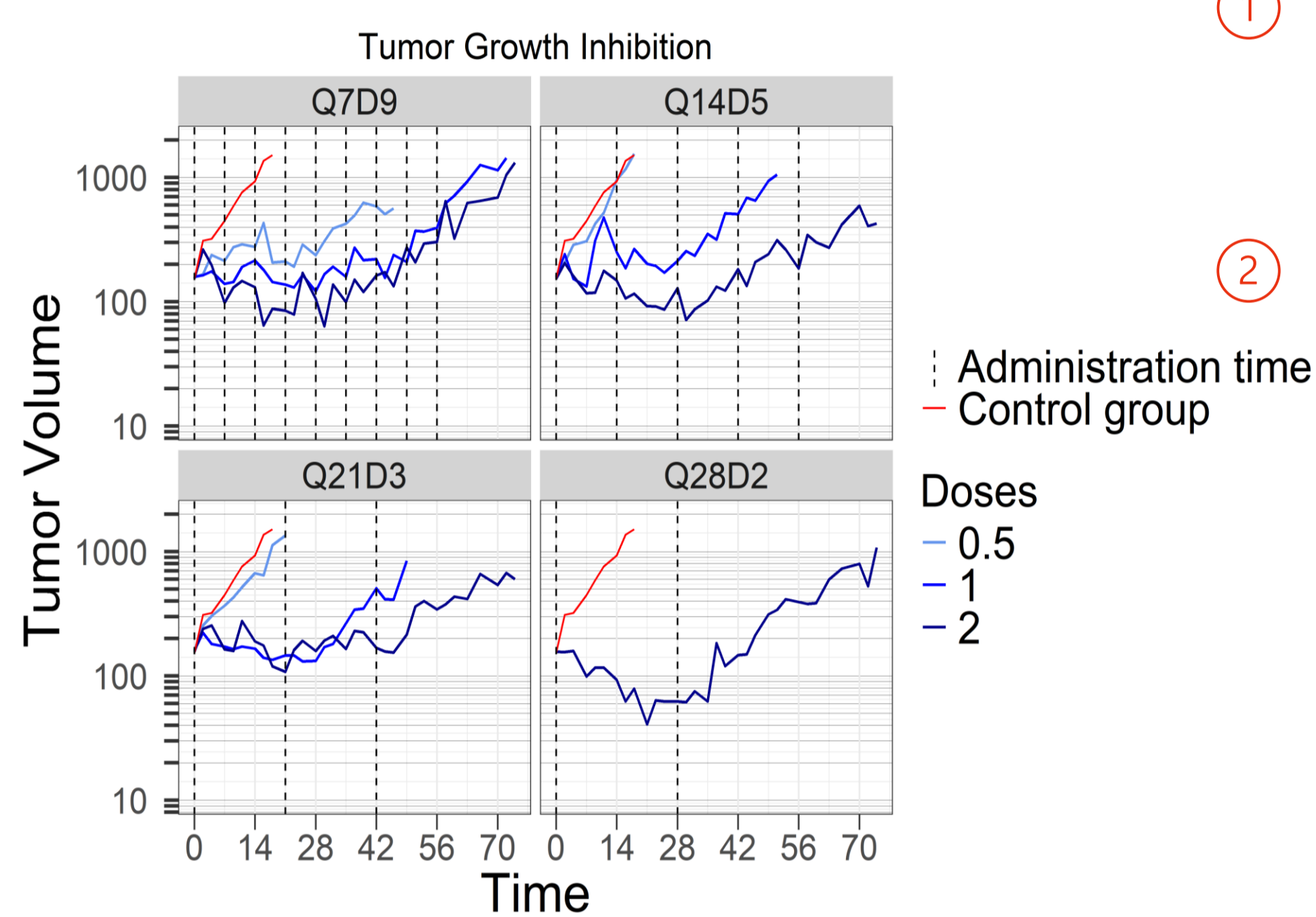
### Data

#### PK in huFcRn mice

- IV at dose 10
- 8 mice
- PK : 2 samples/mouse

#### PK/PD (TGI)

- IV at dose 0.5, 1, 2
- 4 dosing schedules
- 66 mice
- PK : 2 samples/mouse
- PD : ~25 tumor volume measurements/mouse



### Model development

#### ① PK in huFcRn mice

- Population approach

#### ② PKPD modeling with TGI data

- Tumor growth : Exponential / exponential-linear [1]
- Resistance : innate / acquired
- Effect :
  - Concentration / Time above threshold / AUC above threshold
  - Linear / exponential / emax / power

→ Monolix 2023 R1

### Simulations

#### ③ PKPD extrapolation to human

- PK extrapolation from huFcRn mice using allometry [2]
- PKPD relationship extrapolation from TGI model in mice
  - Hypothesis of the same PKPD relationship between mice and humans
- Simulations :
  - Dose/efficacy relationship
  - Dosing schedules from once a week to once a month

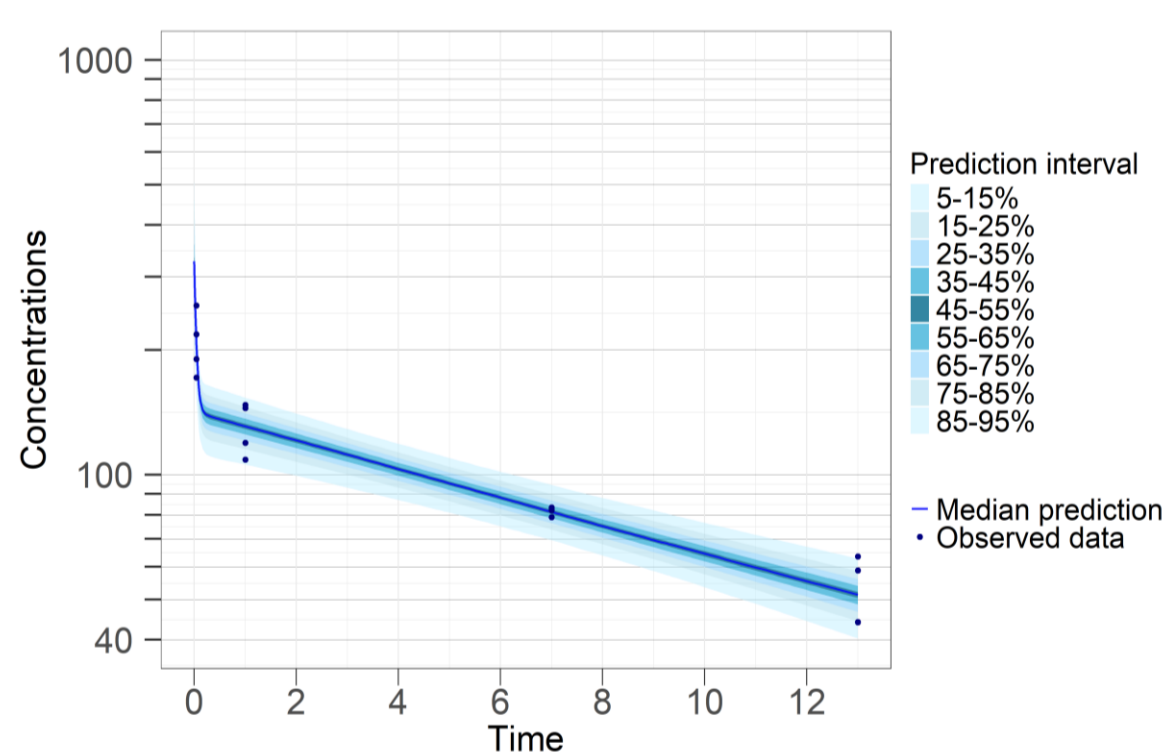
→ SimulX 2023 R1

## Results

### ① PK in huFcRn mice

- 2-compartment model, linear elimination

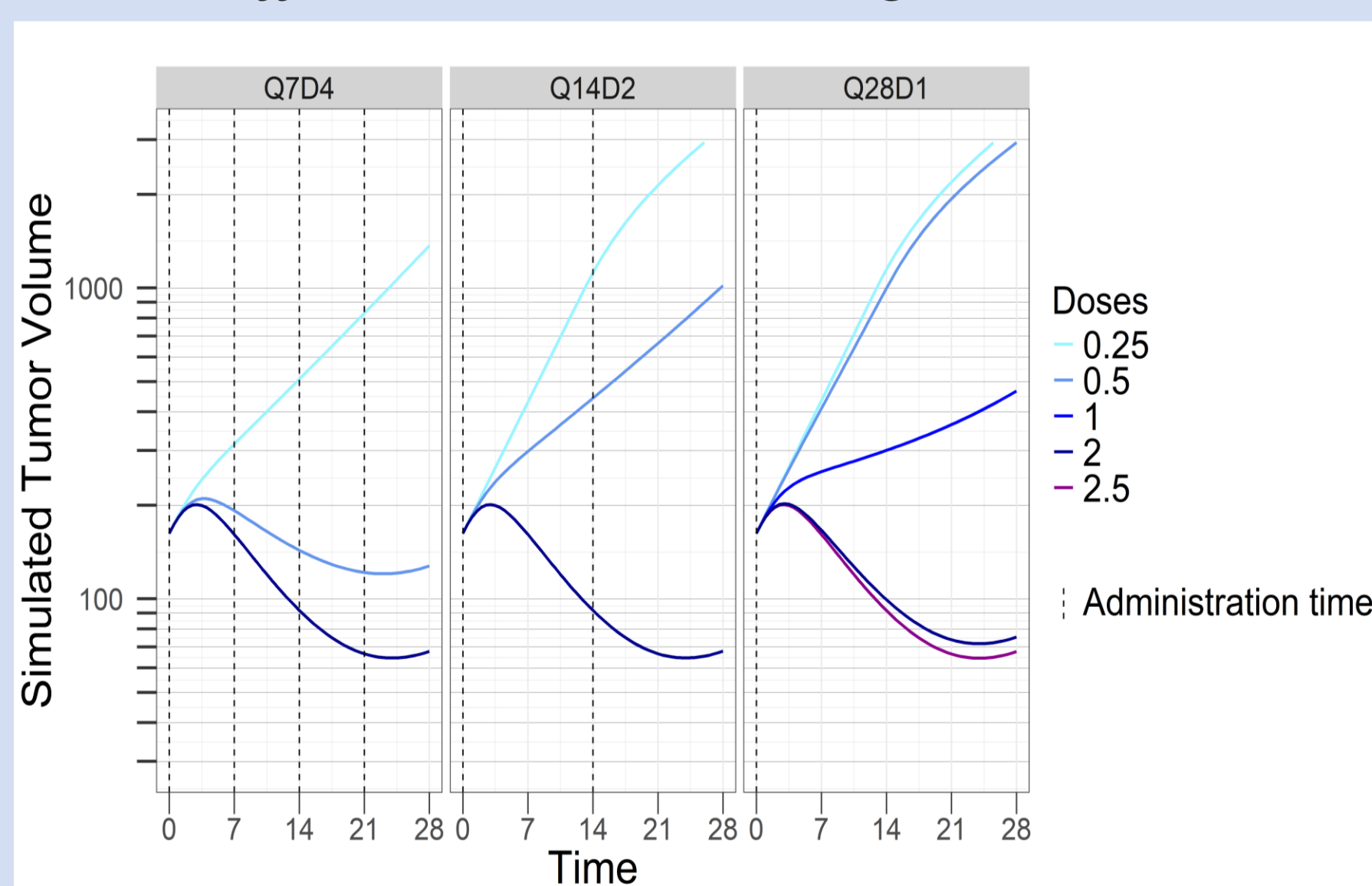
PK model – Prediction distribution plot



### ③ PKPD extrapolation to human

- Predicted half-life in human : 13 days

Tumor growth inhibition simulations in human at different doses and dosing schedules

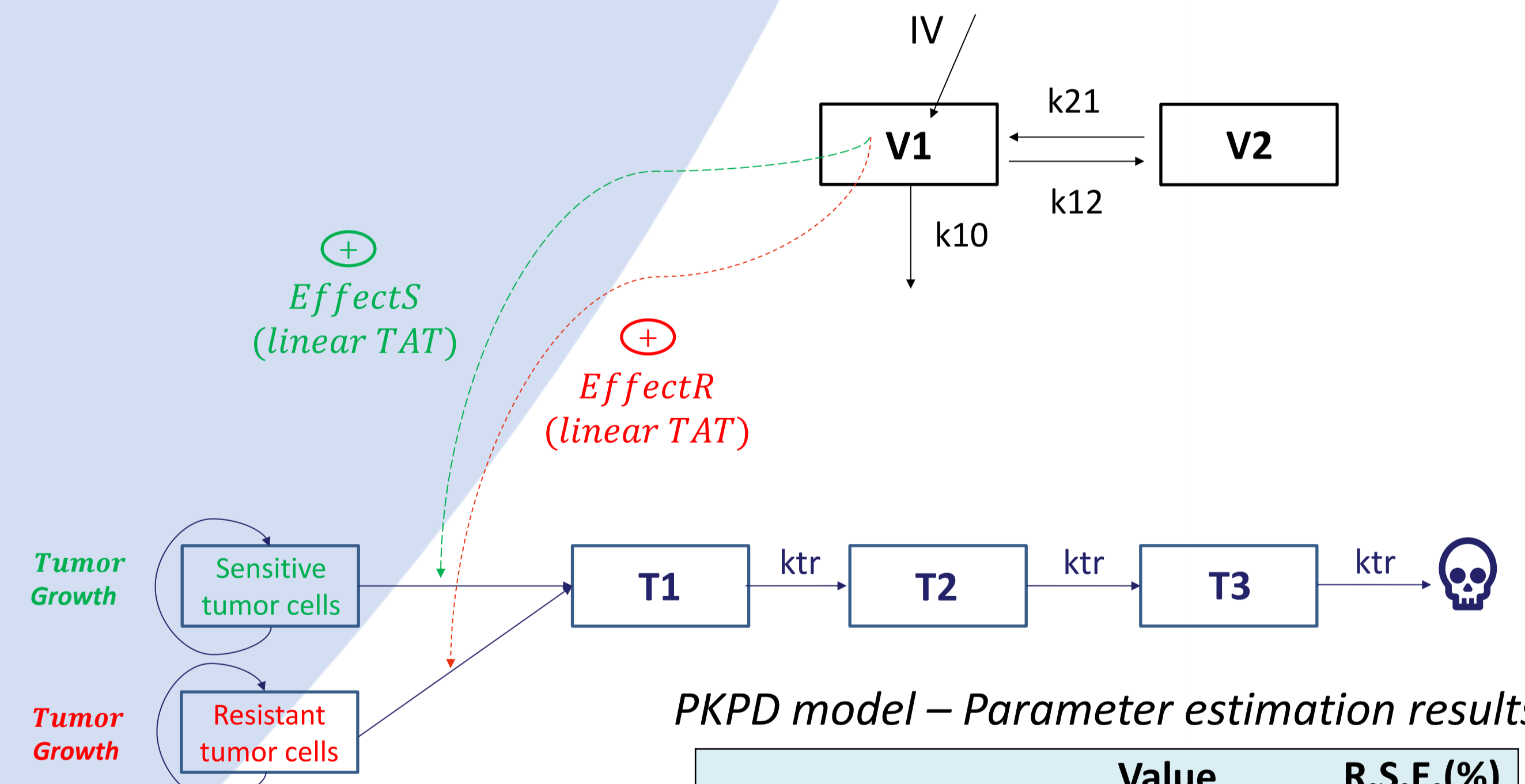


→ Around maximal effect achieved with only one administration/month at a dose of 2

### ② PKPD modeling with TGI data

- Exponential-linear tumor growth [1]
- Innate resistance : resistance does not depend on treatment exposure, but is instead represented as a part of the tumor originally resistant to treatment
- Time Above Threshold (TAT)** is used as a linear relation with PD
- Linear effect for both sensitive and resistant tumor cells

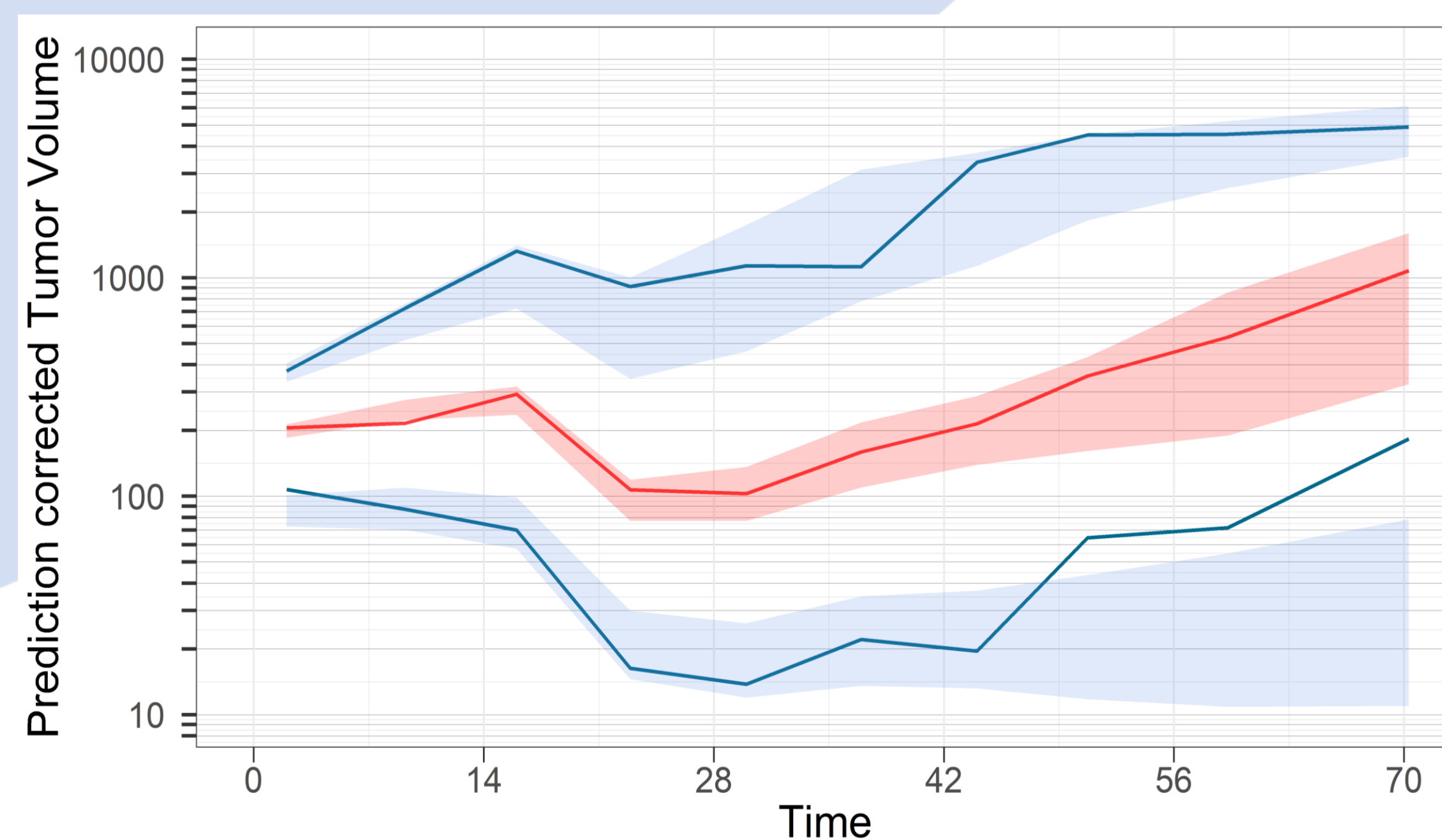
Representation of the PKPD model of TGI including innate resistance



PKPD model – Parameter estimation results

	Value	R.S.E.(%)
<b>Fixed Effects</b>		
TS0 (tumor volume baseline)	160.39	3.57
kge (growth)	0.0057	3.41
F (fraction of resistant cells)	0.053	9.47
kgl (growth)	8.13	6.29
kkill (effect on sensitive cells)	0.000015	5.54
kkill_r (effect on resistant cells)	0.0000046	2.92
KTR (transit rate)	0.032	14.0
<b>Standard Deviation of the Random Effects</b>		
<b>Value</b>		
omega_TS0	0.23	12.5
omega_kge	0.26	12.2
omega_kkill	0.31	11.4
<b>Error Model Parameters</b>		
Proportional error	0.32	2.22

Prediction-Corrected Visual Predictive Check of the model



## Conclusion

PK and PKPD models, incorporating a resistance mechanism for ADC, were successfully developed in mice

- PK and PKPD translation in human : early dose-efficacy relationship in human
- First step in a model informed drug development approach in order to support early development of ADC
- Some mechanistic components such as payload release and target-mediated drug disposition (TMDD) still needs to be assessed for definitive extrapolation to human

## References

[1] Simeoni M, et al.. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res, 2004

[2] Betts A, et al.. Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: A comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach. Mabs, 2018