

# Unveiling a “predator/prey” interplay of anti-CD19 CAR T-Cells and their targets in Relapsed/refractory DLBCL patients

David TERNANT<sup>1</sup>, Sylain LAMURE<sup>2</sup>, Olivier LE TILLY<sup>1</sup>, Caroline BRET<sup>3</sup>, Yassine ALTABAA<sup>4</sup>, Guillaume CARTRON<sup>2</sup>

<sup>1</sup>Université de Tours, EA 4245 T2I, Tours, France. <sup>2</sup>CHU de Montpellier, Département d'hématologie Clinique, Montpellier, France; Institut de Génétique Moléculaire de Montpellier UMR 5535 CNRS Université de Montpellier. <sup>3</sup>CHU de Montpellier, Département d'hématologie biologique, Montpellier, France; Institut de Génétique Humaine UMR 9002 CNRS Université de Montpellier, Montpellier, France. <sup>4</sup>Centre de Médecine Nucléaire Scintidoc, Montpellier, France.

## INTRODUCTION

- **Context.** CD19-targeted Chimeric Antigen Receptor (CAR) T-cells are recombinant receptors for CD19 antigen that redirect patients' T-lymphocytes toward CD19+ cell recognition and elimination. CAR T-cell kinetics:
  - presents two phases of expansion/contraction and engraftment/persistence;
  - was previously described using over-simplistic models and/or based on strong mechanistic hypotheses [1-3].
- **Objectives.** to describe the pharmacokinetic interindividual variability of CD19-targeted CART-cells in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients

## METHODS

- **Prospective cohort of 64 patients** with DLBCL treated with anti-CD19 CAR T-cells (Axicabtagene Ciloleucel or tisagenlecleucel) in University Hospital of Montpellier, France.
- 1 single dose of 2,000,000 cells/kg
- CAR T-cell counts measured using flow cytometry (LLOQ = 0.005 G/L)
- Transit (Friberg) models [4] were used to describe:
  - CAR T-cell pharmacokinetics
  - Target (latent) B-cell kinetics over time
  - «predator/prey» interplay between CAR T-cells and targets using second-order rate constants:
    - **Target kill rate** increased with both **circulating CAR T-cell** and **target** counts;
    - **CAR T-cell proliferation rate** increased with both **deep CAR T-cell** and **circulating target** counts
- Relationship between CAR T-cell kinetics and progression-free survival (PFS) was made using parametric modeling
- Covariate analysis was made on kinetic and PFS models
- Modeling was carried out using nonlinear mixed-effect modeling software **Monolix Suite 2023** and **Simulx** (Lixoft®, Antony, France)

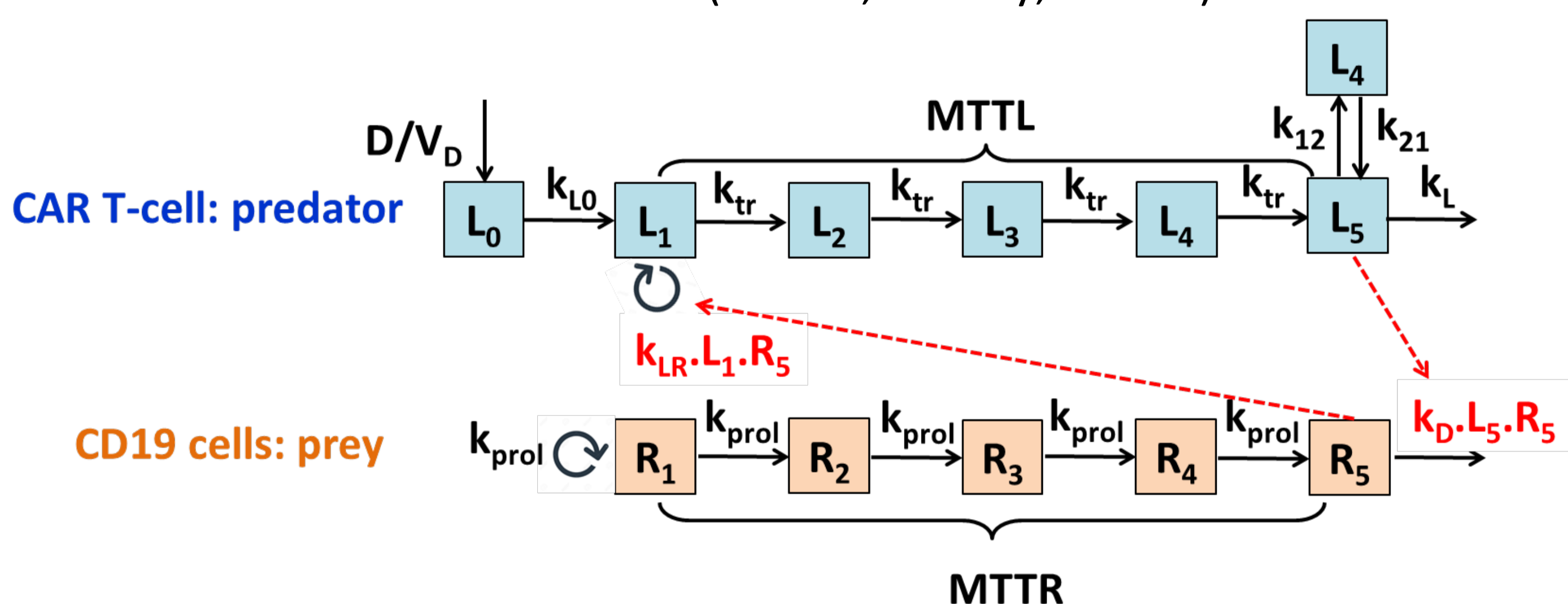


Figure 1: CAR T-cell – target interaction kinetic model

**Legends.** Kinetic models consisted in a first proliferating compartment, three maturation compartments and a fifth compartment of circulating cells. For each transit model, parameters to be estimated were CART-cell first-order absorption ( $k_{L0}$ ), proliferation (resp.  $k_{LR}$  and  $k_{prol}$ ), death (resp.  $k_L$  and  $k_D$ ) and transit rate constants, the last being estimated as mean transit time (resp. MTTL and MTTR). A peripheral compartment for circulating CAR-T cells with first-order intercompartmental rate constants ( $k_{12}$  and  $k_{21}$ ) improved description. CART-cell proliferation and CART-cell-induced target elimination were assumed to depend on both circulating target ( $k_{LR} \cdot L_1 \cdot R_5$ ) and CAR T-cell counts ( $k_D \cdot L_5 \cdot R_5$ ).

## CONCLUSION

- First model to describe both expansion and persistence phases with limited mechanistic assumptions
- The model explained CAR T-cell long-term residence by death-and-rebirth phenomenon, which may be due to repeated target-induced reactivation of memory CAR T-cells
- higher CD4 CAR T-cell peak may be associated with decreased hazard to progression

## RESULTS

- 531 CAR T-cell counts assessed in 61 patients
- Satisfactory description of count-time data with coupled transit models and second-order recursive interactions

Table 1: Kinetic parameter estimates

Parameter	Unit	Base model		Final model	
		Estimate	RSE%	Estimate	RSE%
$V_D$	L	7.6	18	6.7	23
$LYM_{J0} \cdot V_D$	—	—	—	-1.2	11
$R_0$	G/L	0.63	6.8	1	1.6
MTTL	days	4.6	4.0	4.8	3.0
AGE_MTTT	—	—	—	-0.62	5.7
TMTV_MTTT	—	—	—	0.073	13
MTTR	days	17.3	12	12.8	8.5
$k_{L0}$	day <sup>-1</sup>	0.029	13	0.032	8.6
$k_L$	day <sup>-1</sup>	2.9	14	4.8	12
DIAG_ $k_L$	—	—	—	0.38	12
$k_{LR}$	day <sup>-1</sup>	2.5	14	1.9	23
AGE_ $k_{LR}$	—	—	—	0.44	19
$k_D$	day <sup>-1</sup>	129	16	135	23
TMTV_ $k_{LR}$	—	—	—	0.14	29
$k_{12}$	day <sup>-1</sup>	2.4	12	3.7	12
$k_{21}$	day <sup>-1</sup>	0.14	5.0	0.13	7.7
$\omega_{VD}$	—	2.2	7.2	2.0	5.4
$\omega_{MTTL}$	—	0.16	14	0.12	18
$\omega_{KL}$	—	1.4	11	1.2	5.3
$\omega_{KLR}$	—	0.24	6.8	0.23	6.7
$\omega_{KD}$	—	0.64	4.5	0.60	4.1
$\sigma_{prop}$	—	0.45	3.4	0.43	2.7

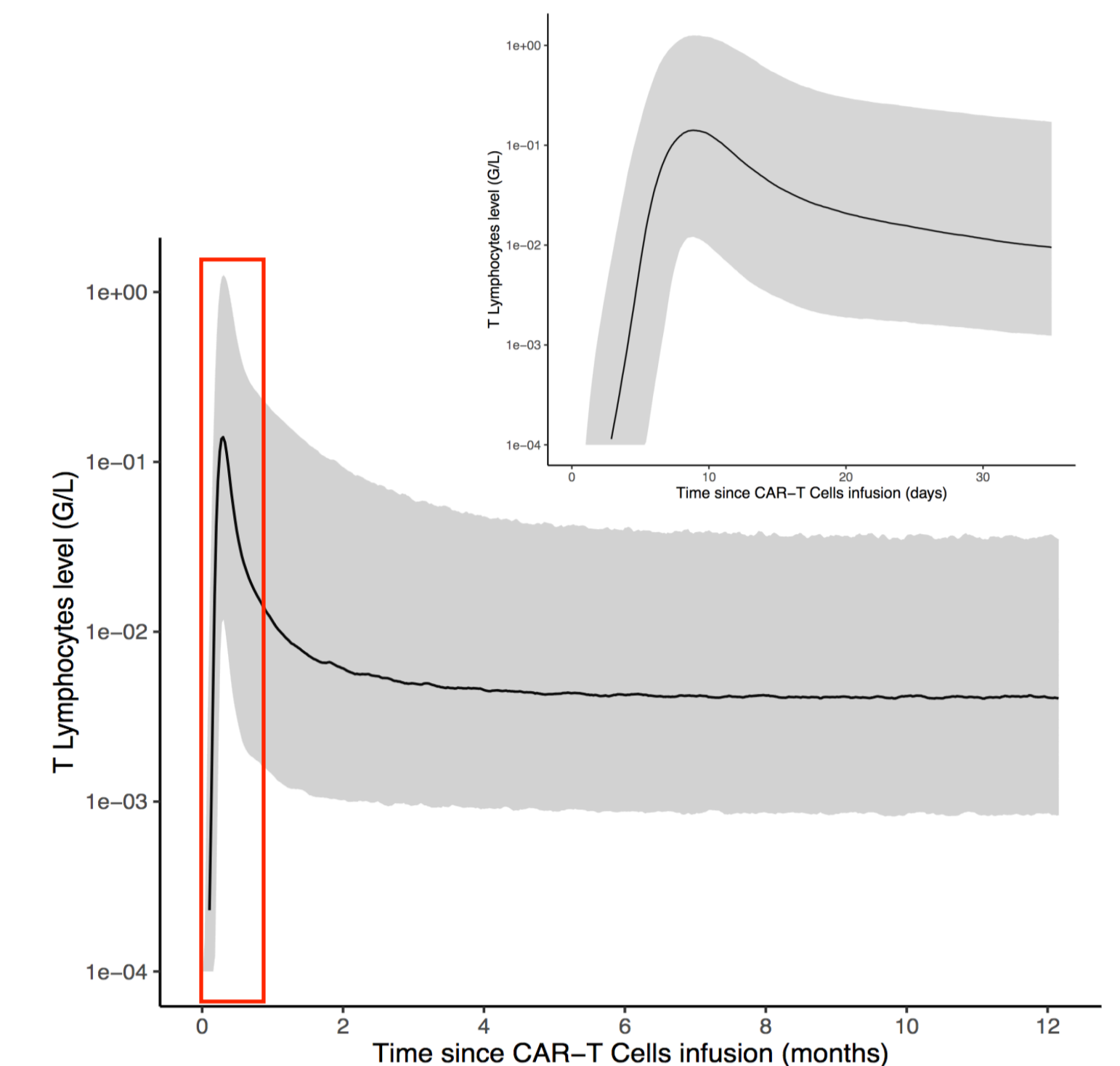


Figure 2: Diagnostic plots of final model

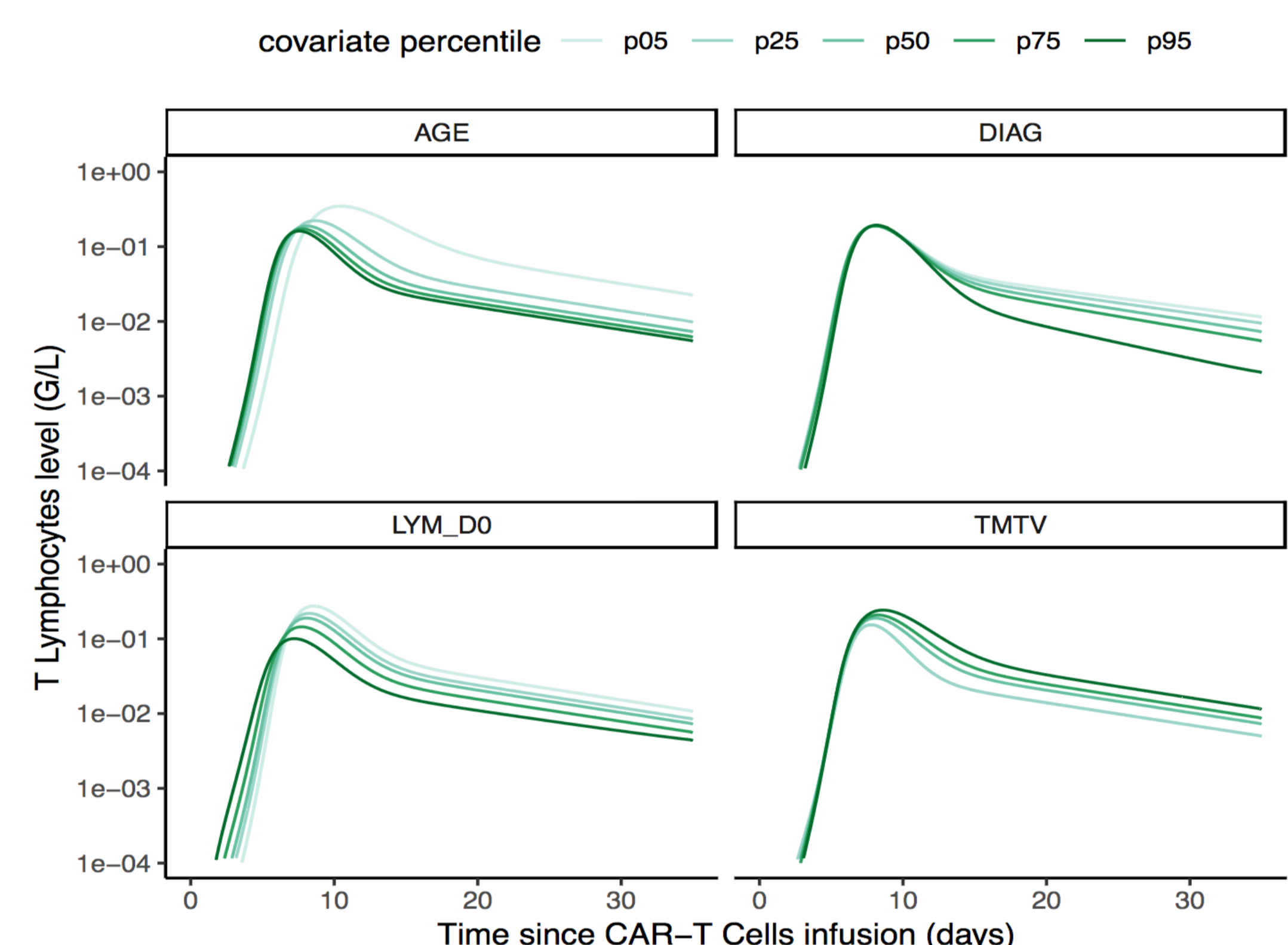


Figure 3: Influence of covariates on CAR-T cell kinetics

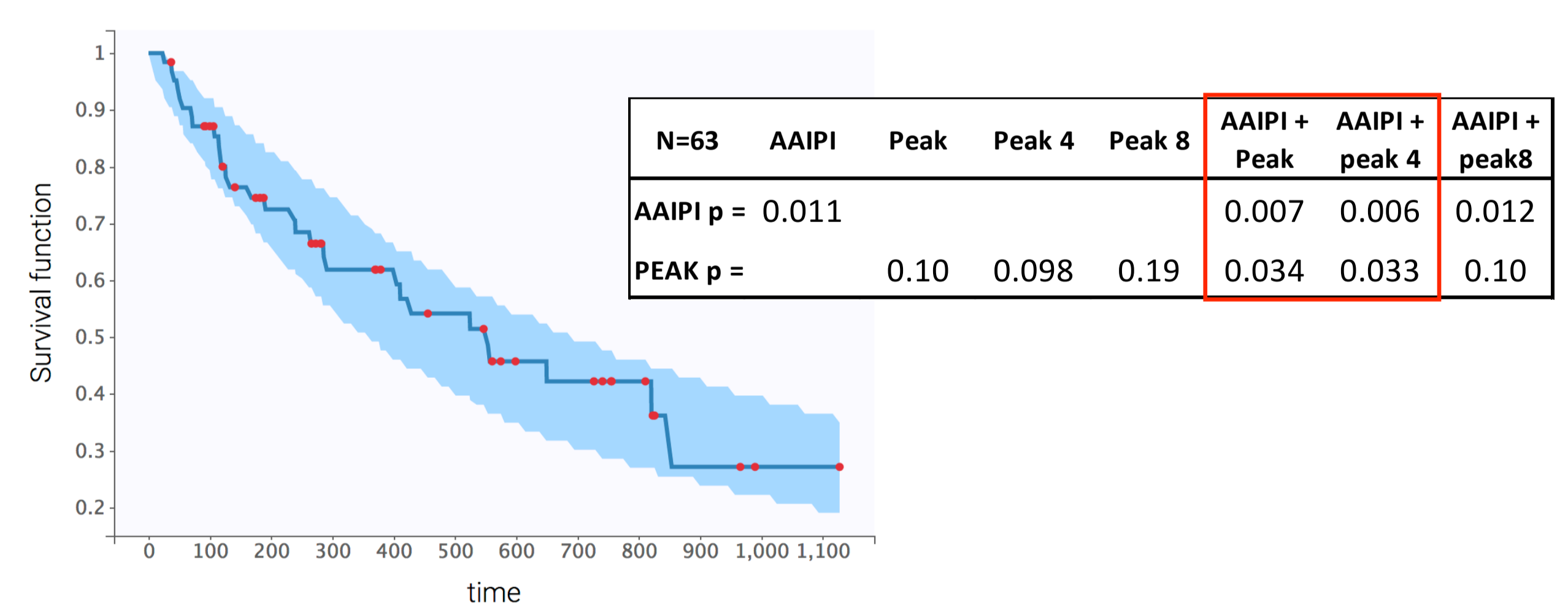


Figure 4: Influence of covariates on CAR-T cell kinetics

## Legends

**Table 1.**  $V_1$  central volume of distribution,  $k_{L0}$  CART-cell first-order absorption, proliferation (resp.  $k_{LR}$  and  $k_{prol}$ ), death (resp.  $k_L$  and  $k_D$ ) rate constants of CAR T-cell and targets, respectively, and transit rate constants, the last being estimated as mean transit time (resp. MTTL and MTTR),  $k_{12}$  and  $k_{21}$  resp. central to peripheral and peripheral to central transfer rate constants, TMTV total metabolic tumor volume, DIAG time since DLBCL diagnosis, RSE relative standard ratio,  $\omega$  interindividual standard deviation,  $\sigma_{prop}$  proportional residual standard deviation.

**Figure 2.** Line and grey area are median and 90% interval predicted CAR T-cell kinetics.

**Figure 3.** AGE age, DIAG time since DLBCL diagnosis, LYM J0 lymphocyte count at CAR T-cell administration, TMTV total metabolic tumor volume.

**Figure 4.** Progression-free survival. Observed vs. simulated 90% prediction interval. PFS was increased with decreasing age-adjusted international prognostic index (aaiPI) and increasing peak CD4 count.

## REFERENCES

- [1] Stein AM, et al.. CPT Pharmacometrics Syst Pharmacol. 2019;8:285-295.
- [2] Liu C, et al. Clin Pharmacol Ther 2021;109:716-727
- [3] Paixão EA, et al. Cancers (Basel). 2022;14:5576
- [4] Friberg LE, et al. J Clin Oncol. 2002;20:4713-21.