



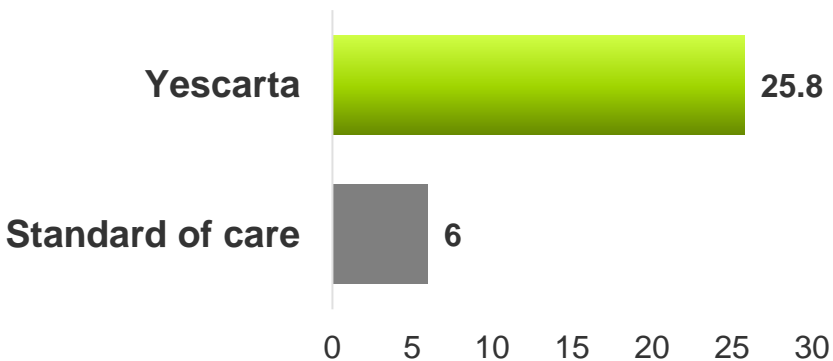
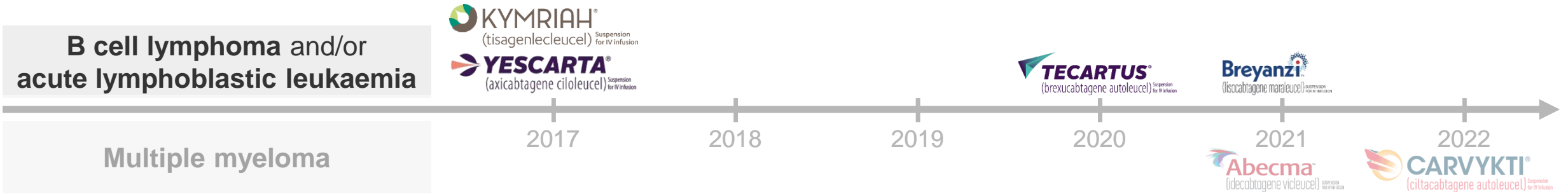
Early survival prediction framework for autologous CAR-T cells using PK/PD modelling

Fenja Klima

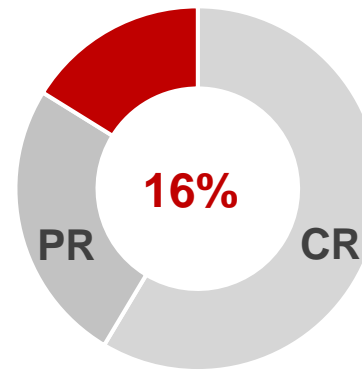
Dept. of Clinical Pharmacy & Biochemistry
Institute of Pharmacy, Freie Universität Berlin

XIXes Journées du Groupe de Pharmacologie Clinique Oncologique
16 - 17 November 2023

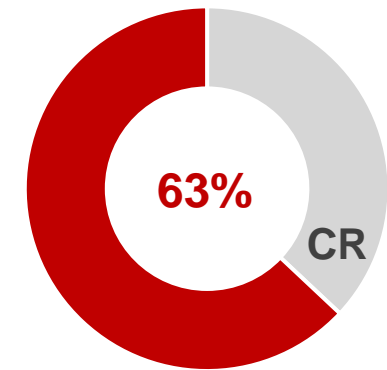
CAR-T cell therapy




Median overall survival [months]^{1,2}



No response³

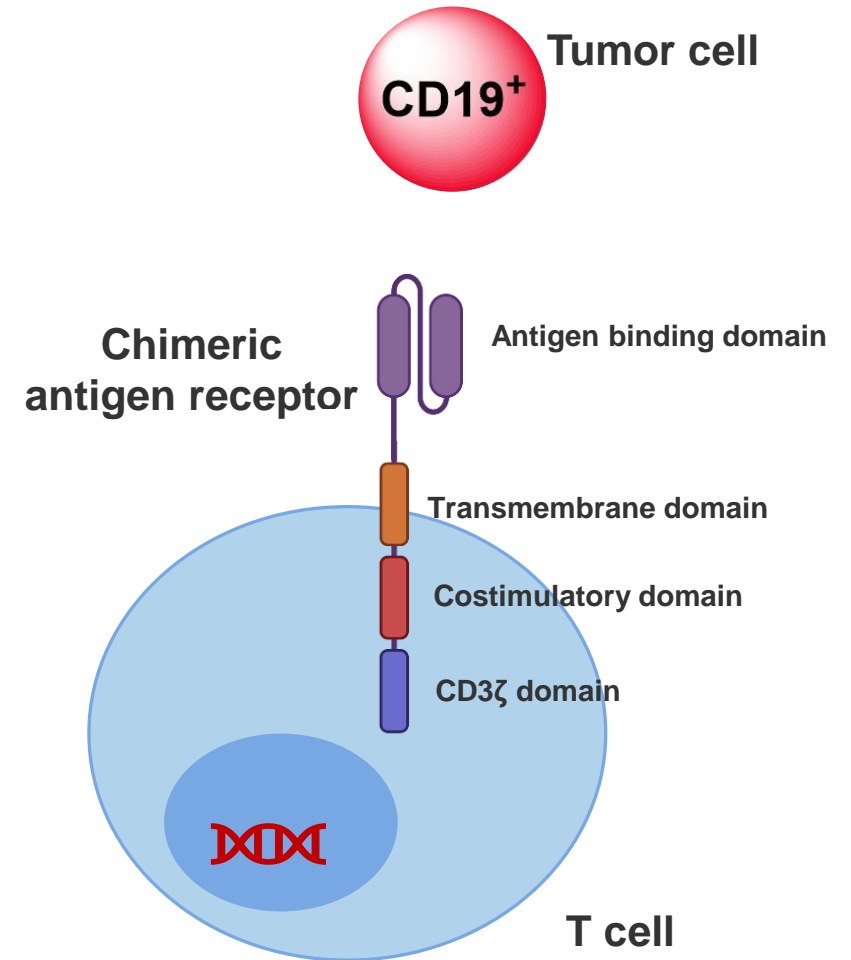
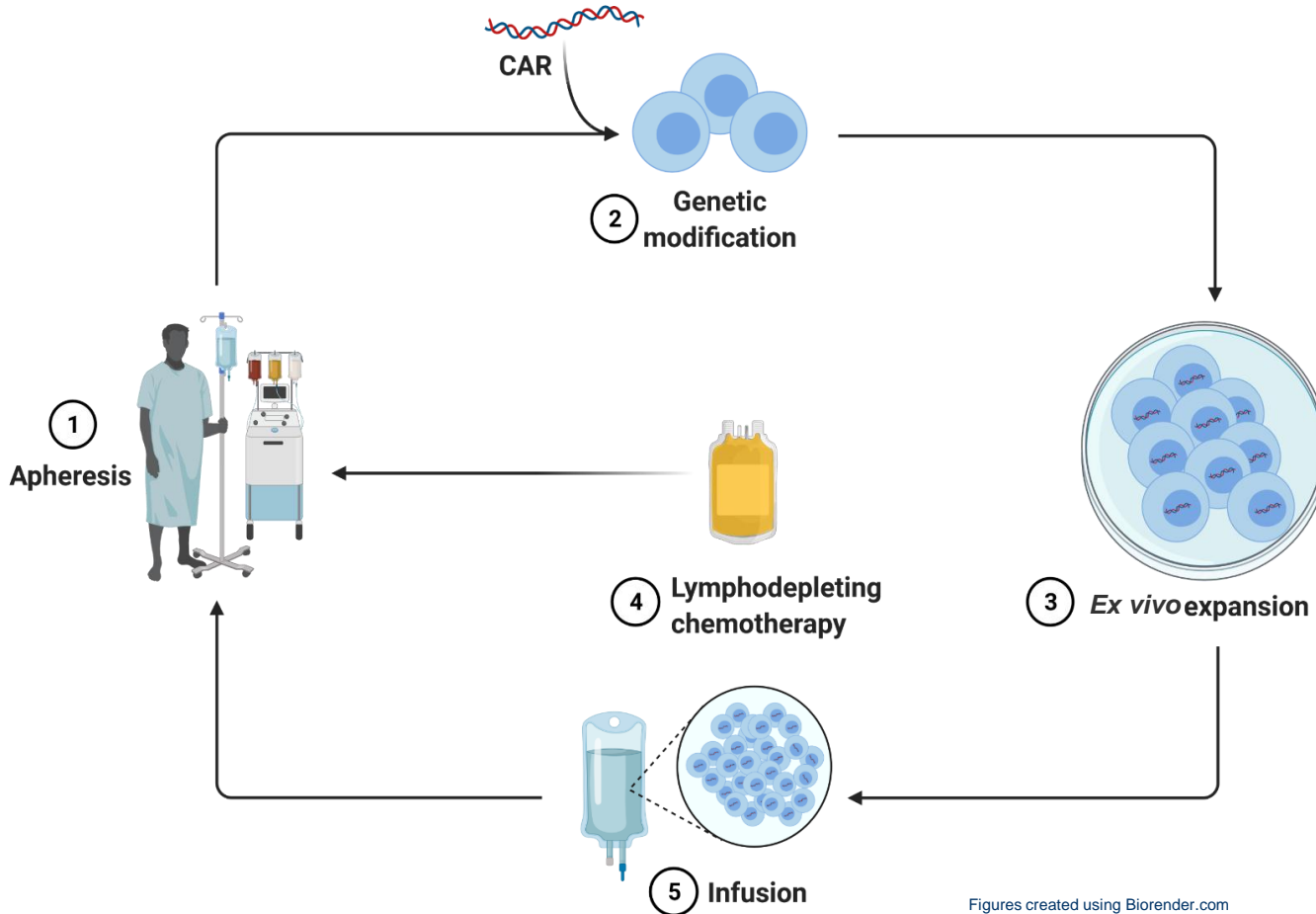


Relapse after complete response³

 **Early prediction of response and survival?**
Better understanding of underlying processes needed

¹Neelapu et al. *Blood* 2023
²Crump et al. *Blood* 2017
³Locke et al. *Lancet Oncol.* 2019

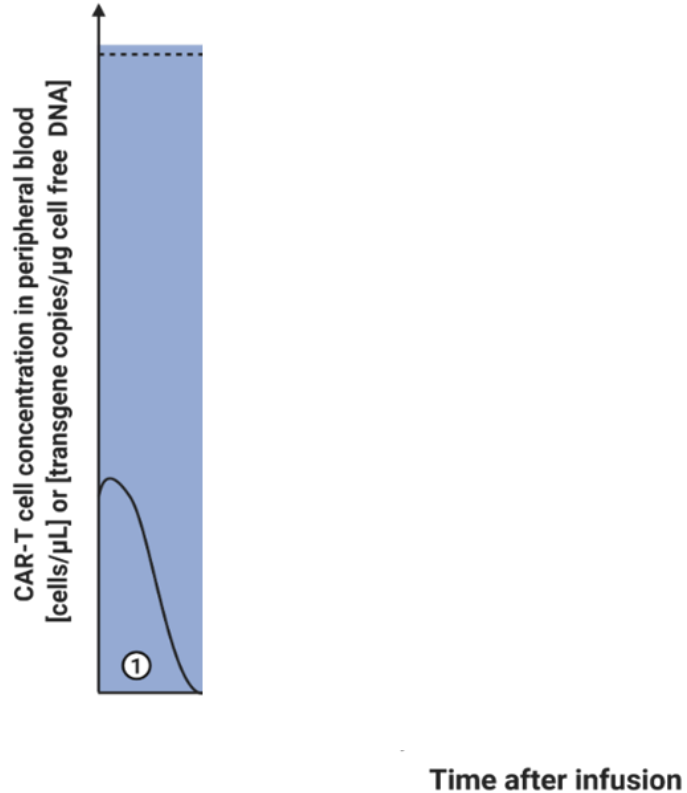
What are CAR-T cells?



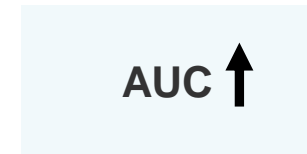
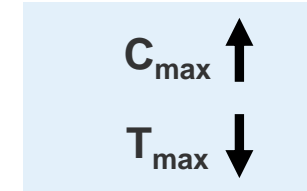
Figures created using Biorender.com

Understanding of CAR-T cell kinetics and product composition

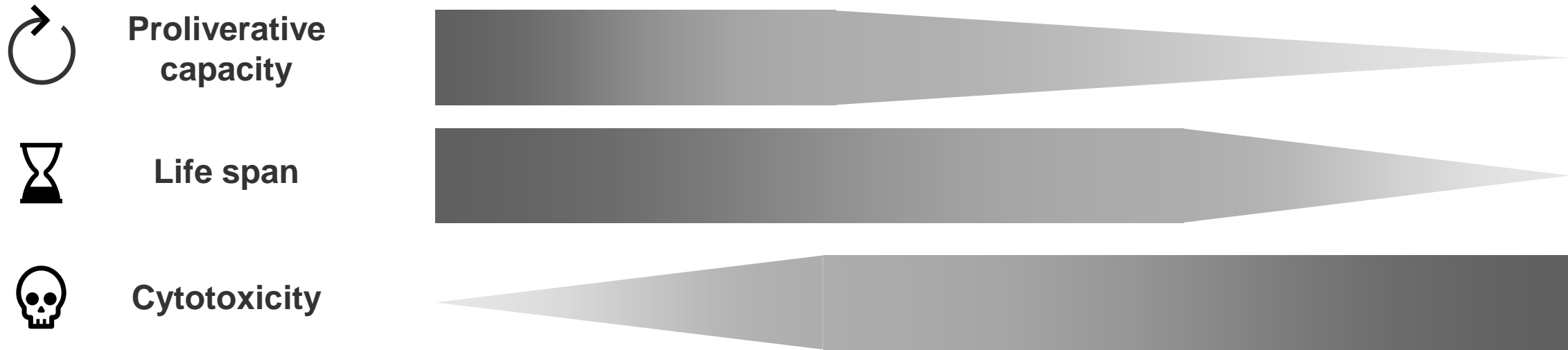
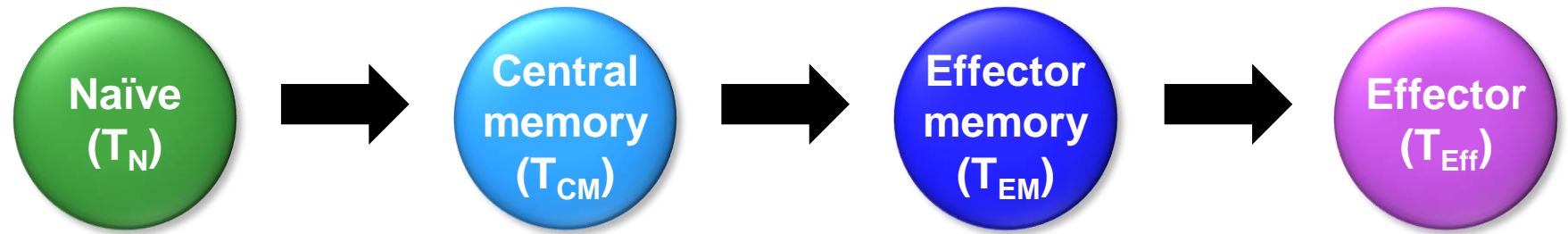
Clinical CAR-T cell kinetics



- 1 Distribution
- 2 Expansion
- 3 Contraction



Role of CAR-T cell phenotypes



Less differentiated CAR-T cells in infusion product

CAR-T cell clinical data

Early response and survival prediction?

⚙️ Characterise cell kinetics and dynamics

⚙️ Responders vs. non-responders

⚙️ Predictors for long-term response & survival

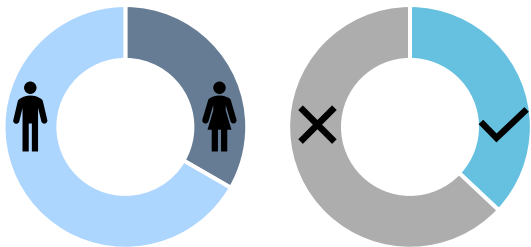


'Real-world' observational study



- r/r Non-Hodgkin lymphoma
- Follow-up ≤ 24 months

19 patients



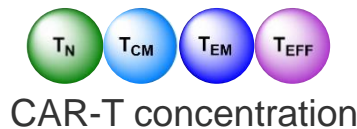
Autologous stem cell transplantation



16 months median overall survival



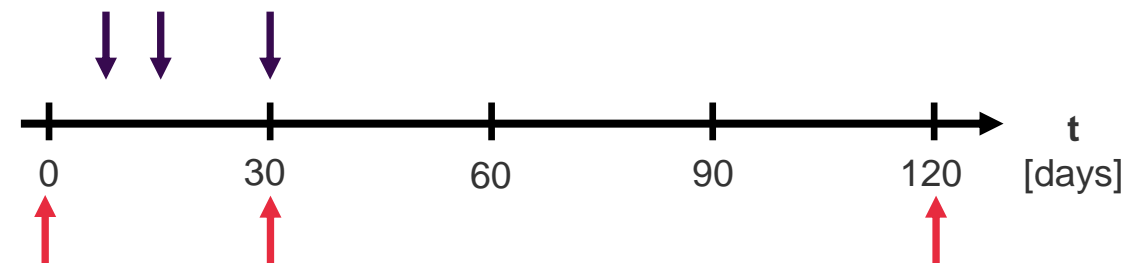
- Single dose
- Phenotypes measured by flow cytometry



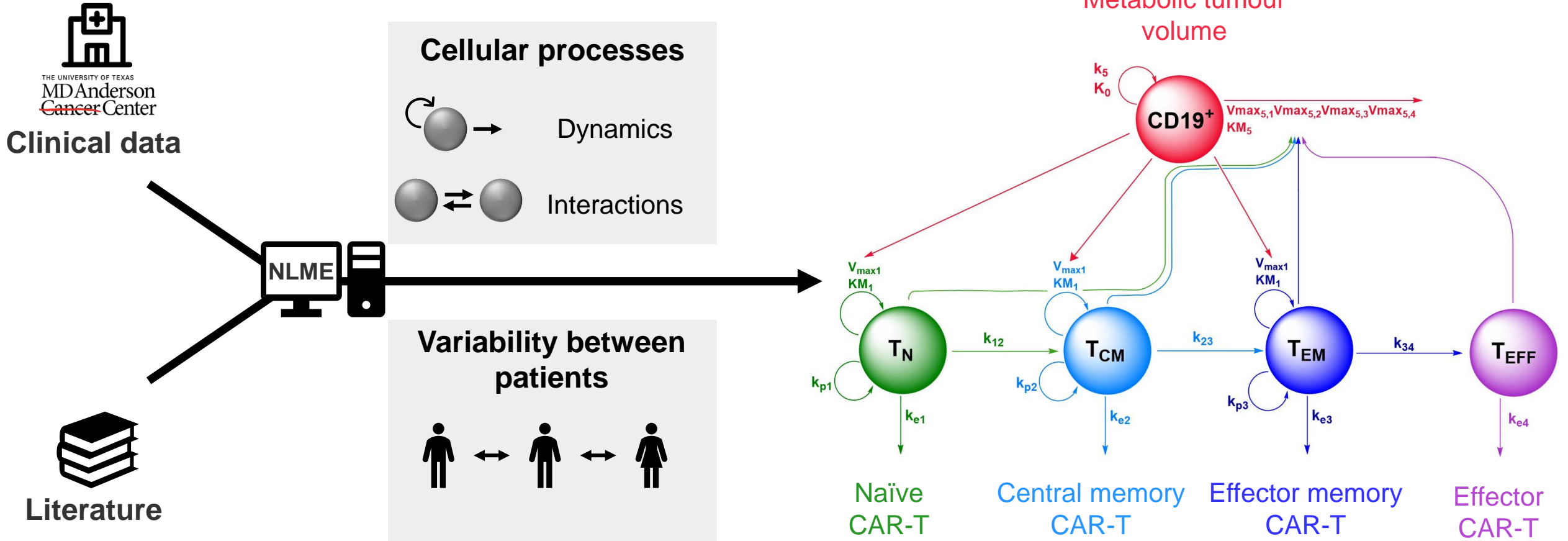
CAR-T concentration



Tumor burden



CAR-T cell model



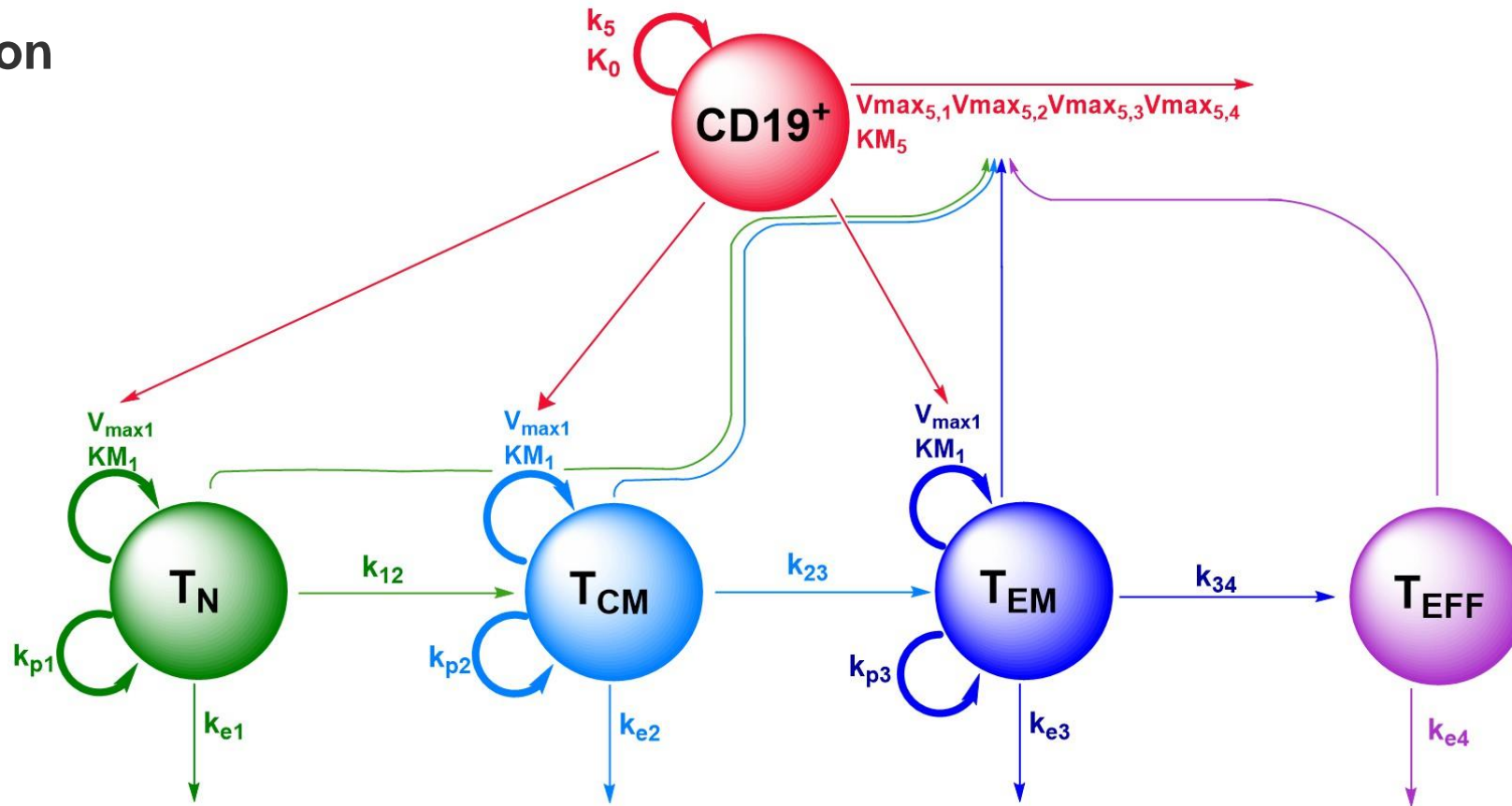
CD19⁺: CD19⁺ metabolic tumour volume
 NLME: Nonlinear mixed-effects model
 T_N: Naïve CAR-T cells

T_{CM}: Central memory CAR-T cells
 T_{EM}: Effector memory CAR-T cells
 T_{EFF}: Effector CAR-T cells

Mueller-Schoell et al. *Cancers* 2021

CAR-T cell model

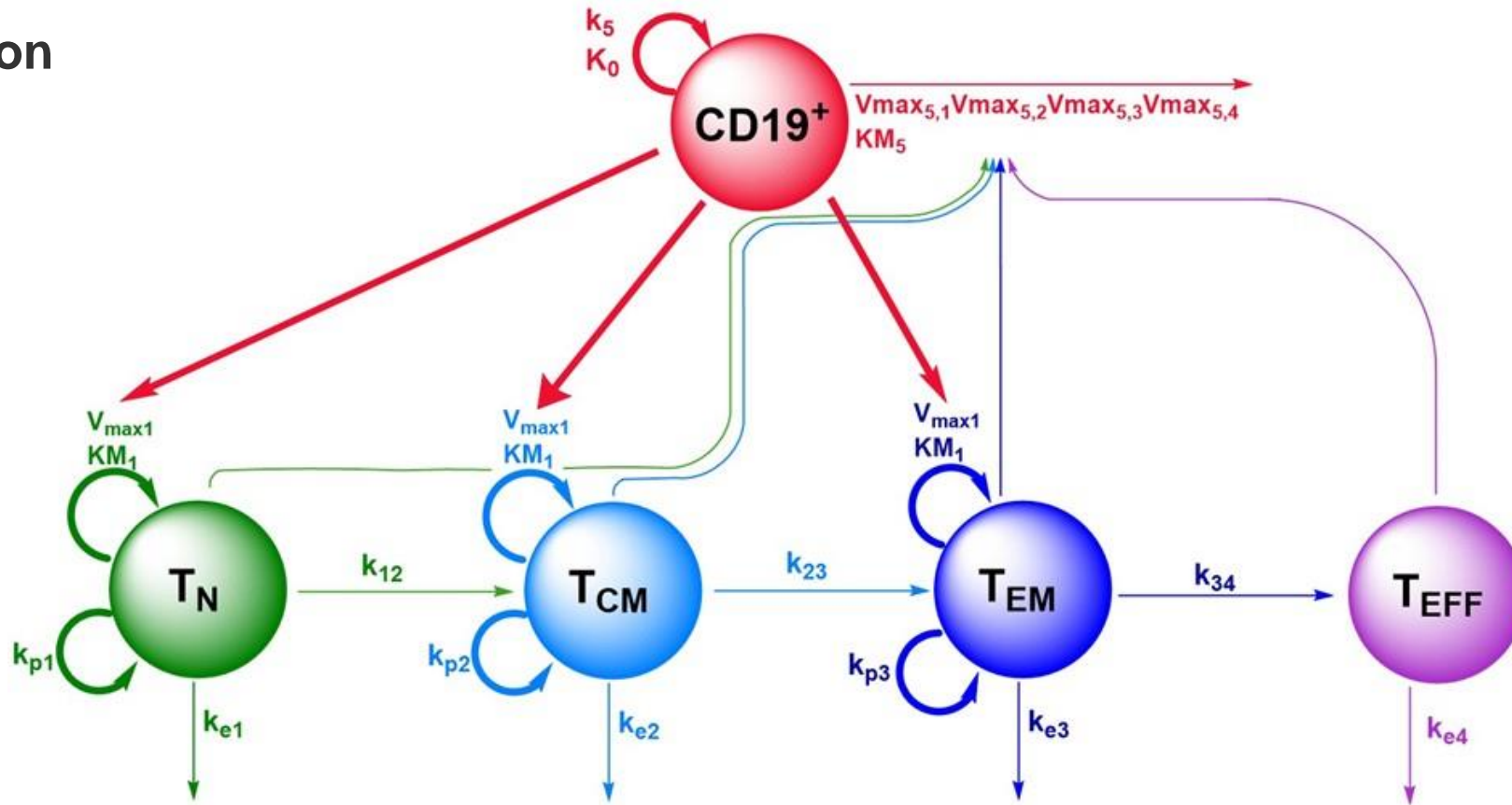
1 Proliferation



T_N : Naïve CAR-T cells
 T_{CM} : Central memory CAR-T cells
 T_{EM} : Effector memory CAR-T cells
 T_{EFF} : Effector CAR-T cells
 $CD19^+$: $CD19^+$ metabolic tumour volume

CAR-T cell model

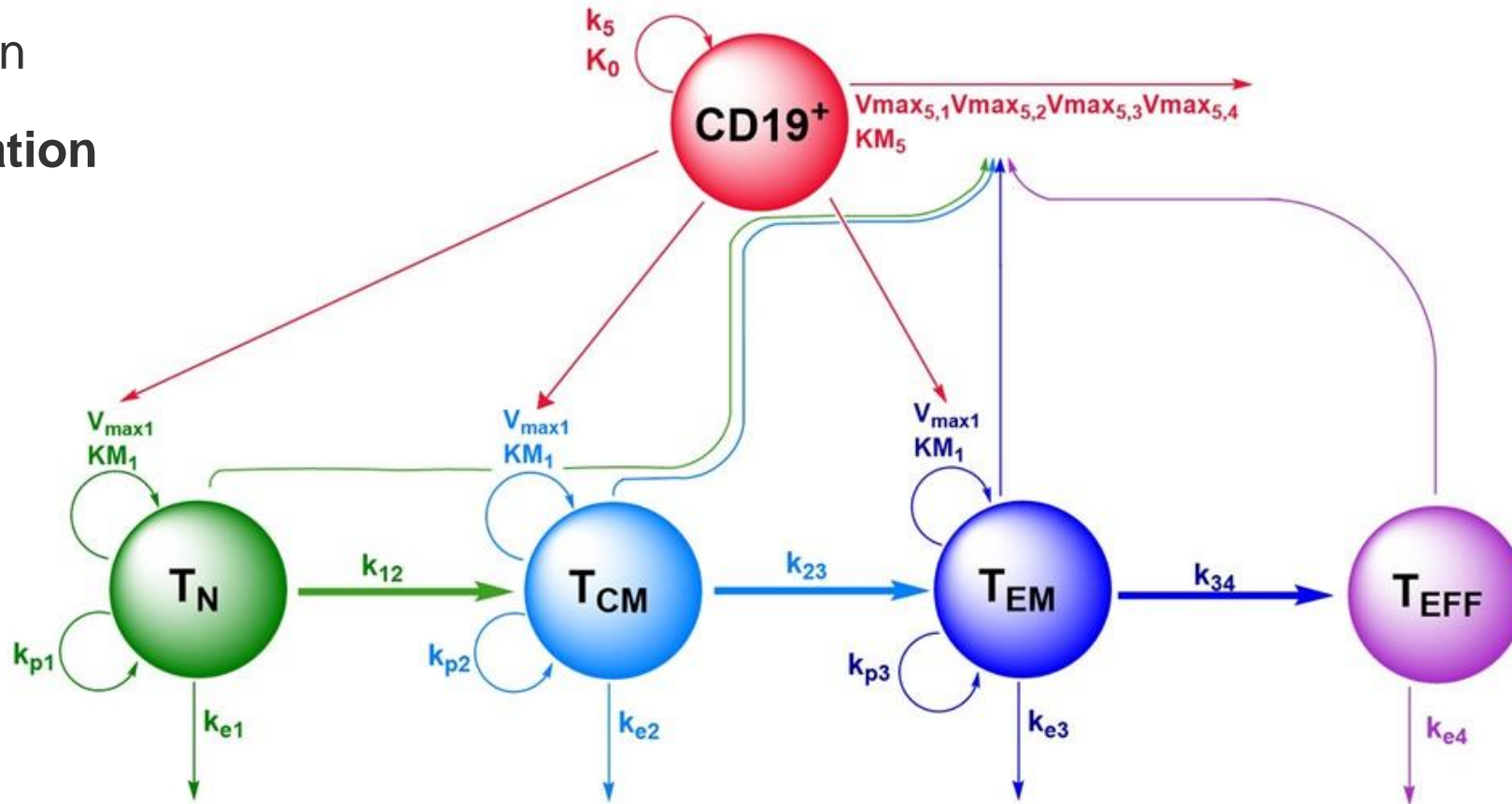
1 Proliferation



T_N : Naïve CAR-T cells
 T_{CM} : Central memory CAR-T cells
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 T_{EFF} : Effector CAR-T cells
 $CD19^+$: $CD19^+$ metabolic tumour volume

CAR-T cell model

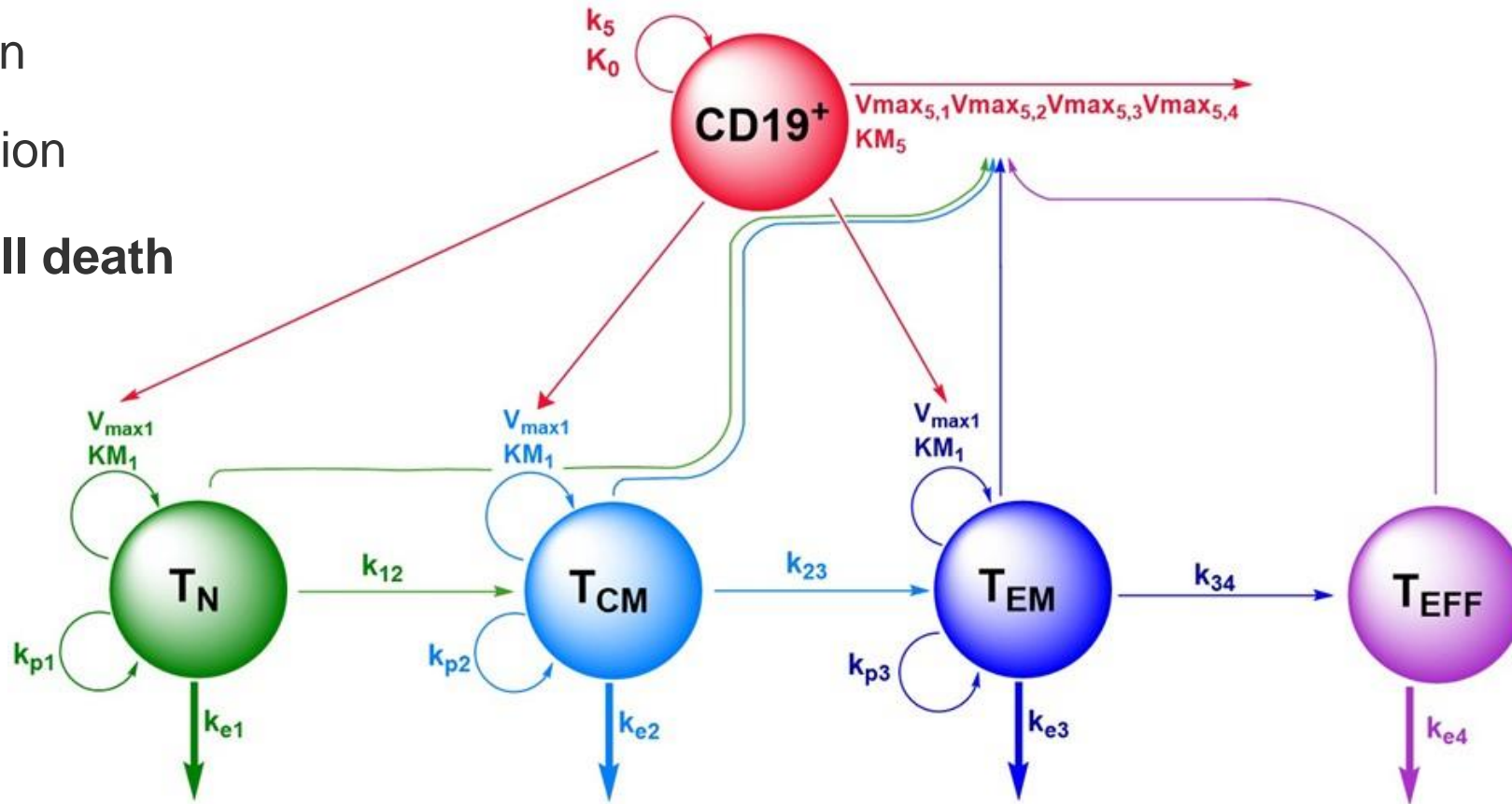
- 1 Proliferation
- 2 Differentiation



T_N : Naïve CAR-T cells
 T_{CM} : Central memory CAR-T cells
 T_{EM} : Effector memory CAR-T cells
 T_{EFF} : Effector CAR-T cells
 $CD19^+$: $CD19^+$ metabolic tumour volume

CAR-T cell model

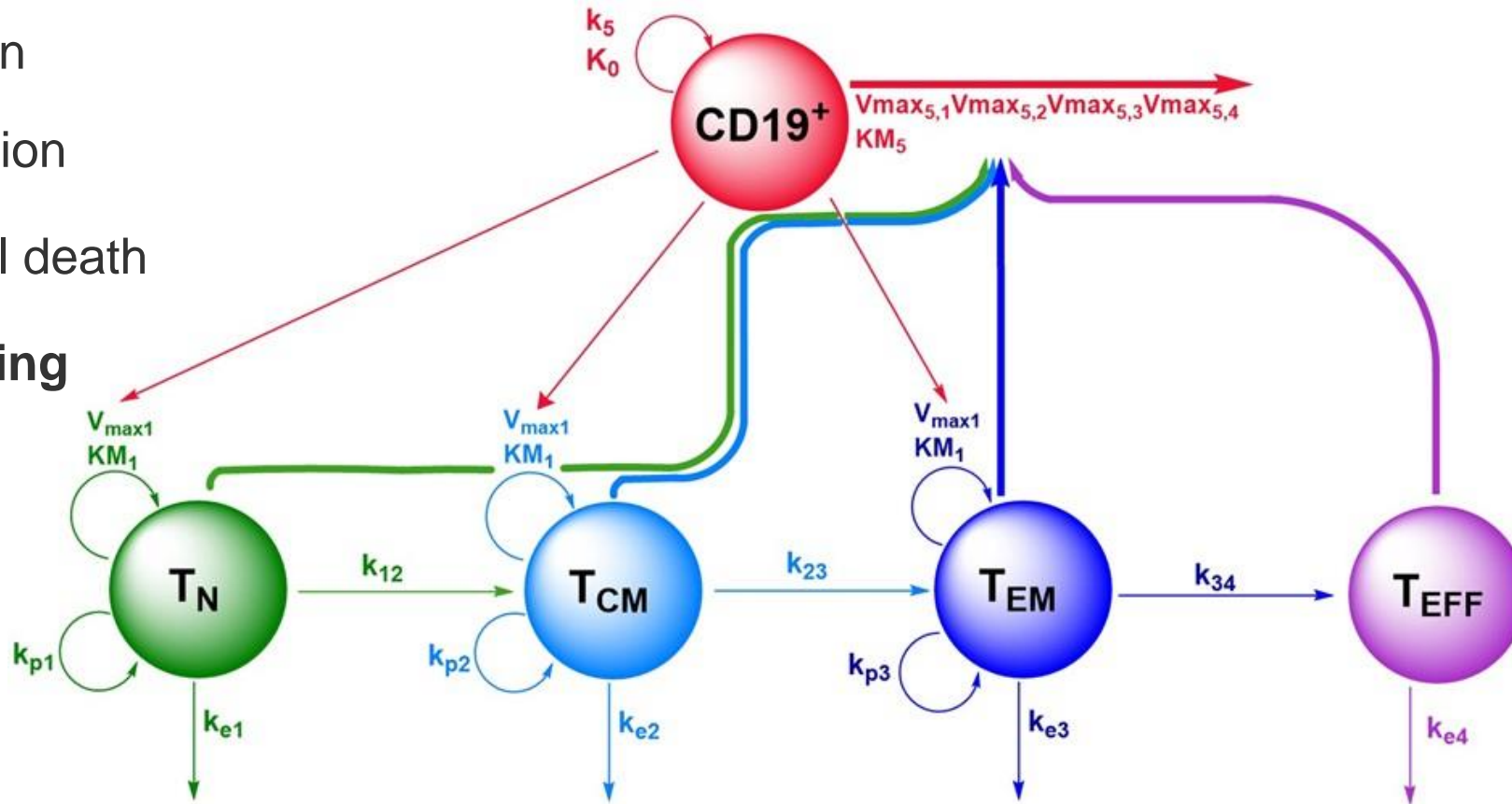
- 1 Proliferation
- 2 Differentiation
- 3 Natural cell death



T_N : Naïve CAR-T cells
 T_{CM} : Central memory CAR-T cells
 T_{EM} : Effector memory CAR-T cells
 T_{EFF} : Effector CAR-T cells
 $CD19^+$: $CD19^+$ metabolic tumour volume

CAR-T cell model

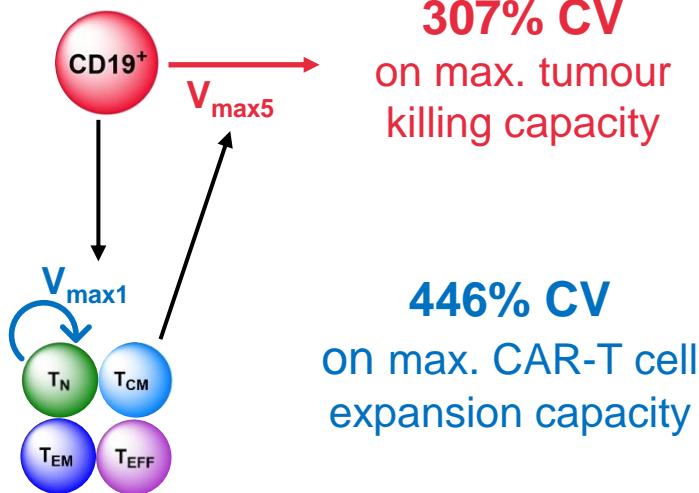
- 1 Proliferation
- 2 Differentiation
- 3 Natural cell death
- 4 Tumor killing**



T_N : Naive CAR-T cells
 T_{CM} : Central memory CAR-T cells
 T_{EM} : Effector memory CAR-T cells
 T_{EFF} : Effector CAR-T cells
 $CD19^+$: $CD19^+$ metabolic tumour volume

Assessing between-patient variability

High between-patient variability



Subpopulations with
different V_{max1}



Reference
expansion
(n=15)

$\geq 10x$



Low
expansion
(n=4)



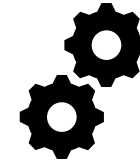
Factors increasing V_{max1}

Previous
ASCT

CD4+/CD8+
ratio 



2/3 of variability on
 V_{max1} explained

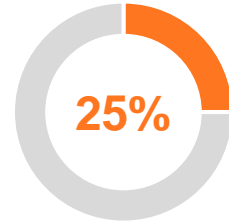


Translation to
treatment outcome?

Overall survival in different subpopulations



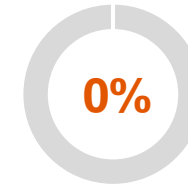
Low CAR-T cell expansion (n=4)



1 out of 4 patients still alive



No previous ASCT (n=3)



0 out of 3 patients still alive



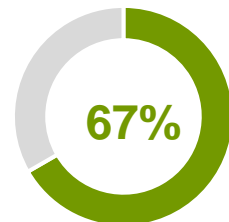
Previous ASCT (n=1)



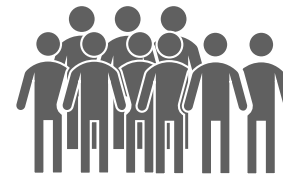
1 out of 1 patients still alive



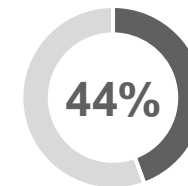
Reference CAR-T cell expansion (n=15)



10 out of 15 patients still alive



No previous ASCT (n=9)



4 out of 9 patients still alive



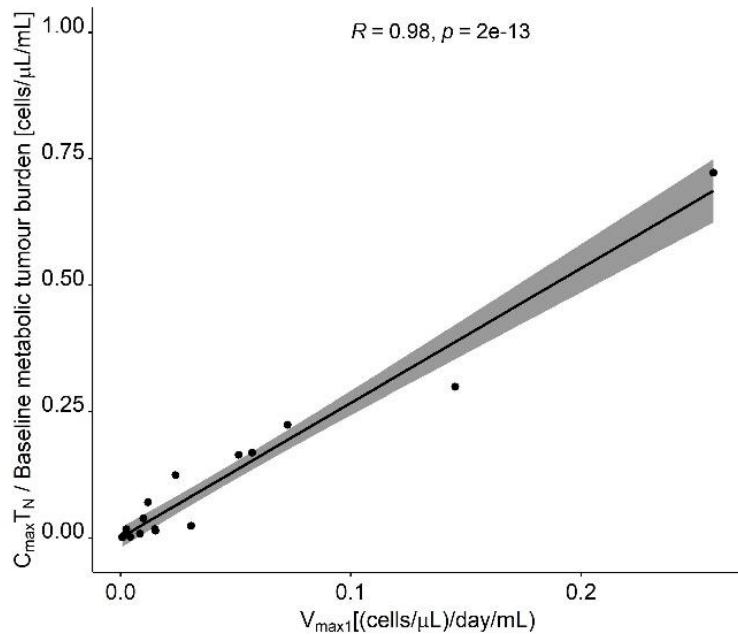
Previous ASCT (n=6)



6 out of 6 patients still alive

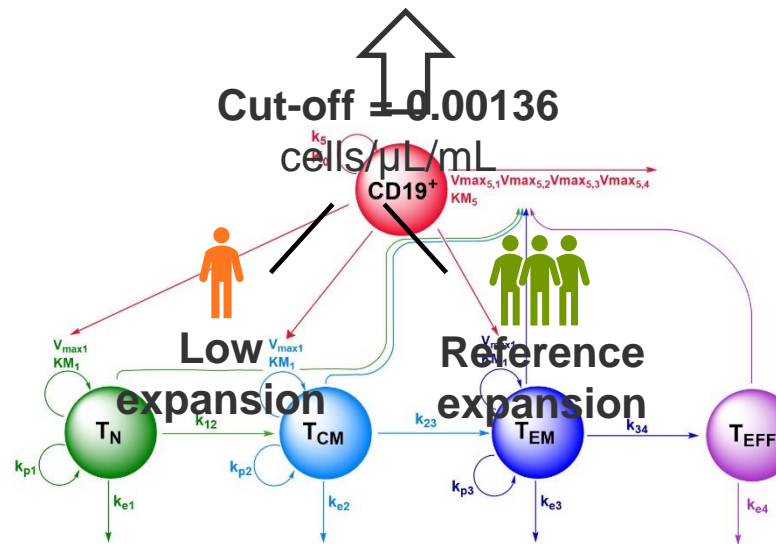
Clinical composite score (CCS_{TN}) for survival prediction

1 Correlation with CAR-T cell expansion capacity V_{max1}

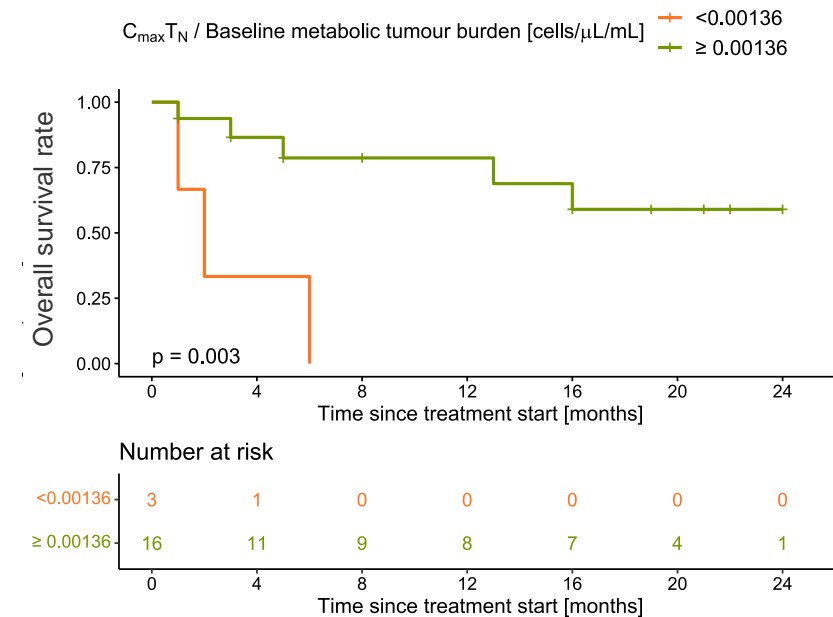


2 Determination of cut-off value

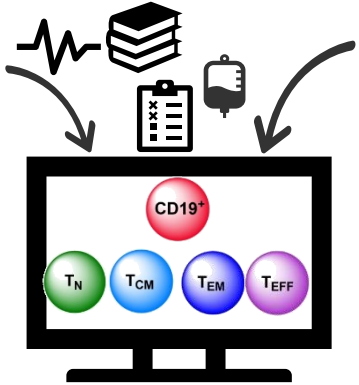
$$CCS_{TN} = \frac{\text{C}_{max} \text{ of } T_N \text{ [cells/}\mu\text{L]}}{\text{Tumor at baseline [mL]}}$$



3 Overall survival using CCS



Summary and perspective



- 💡 Pharmacometric model of CAR-T cell kinetics and dynamics
- 💡 Subgroups with different overall survival
- 💡 Clinical score for early survival prediction



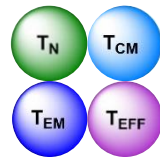
Evaluation in larger patient cohort required

⚠️ Typically small sample size

Multicenter data analysis




Comparability and standardisation of multicenter data?




CAR-T cell quantification using flow cytometry

Analysis of multi-center CAR-T cell data

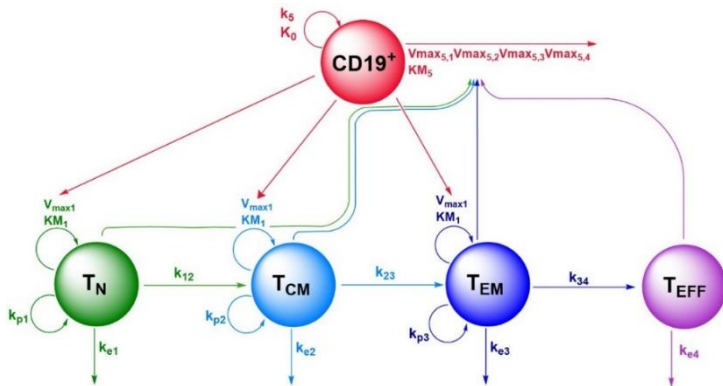
 Patient characteristics
 Tumor burden
 CAR-T cell concentration
 Treatment outcome



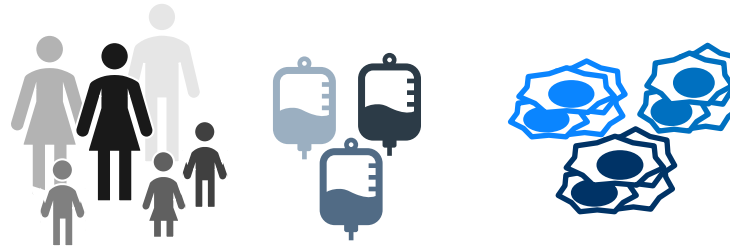
Standardisation of
 flow cytometry assays



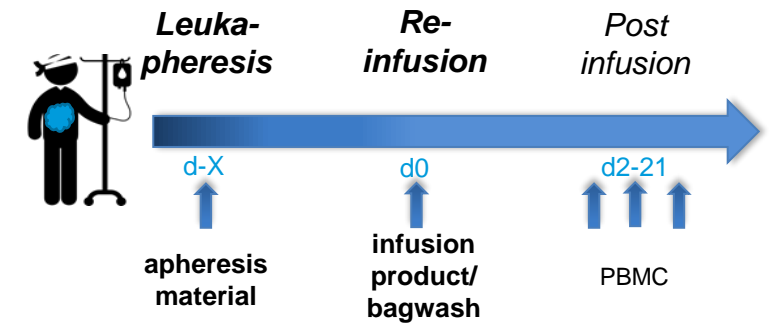

Integration of multi-center data in developed CAR-T cell model



Evaluation of CAR-T cell model and clinical composite score



Extension of CAR-T cell model for
Age groups **CAR-T cell constructs** **Tumor type**



Extension with data from leukapheresate infusion product

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Universität Potsdam Universität Navarra Humboldt Research Fellow Universität Hamburg Humboldt Research Fellow

Backup

CAR-T cell products and indications

Table 1 | Targets of CAR T cell therapies with clinical evidence of efficacy

Target	Disease	Response rate ^a	Survival	Comments	Date of FDA approval	Refs.
Haematological malignancies						
CD19	B-ALL	CR or CRi: 81%,	EFS: 50% OS: 76% at 12 months	Tis-cel approved for R/R B-ALL (≤25 yr of age)	Aug 2017	⁵
CD19	LBCL	CR: 58%,	PFS: 44% at 12 months OS: 52% at 18 months	Axi-cel approved as 3rd line treatment for LBCL (>18 yr of age)	Oct 2017	³
CD19	LBCL	CR: 40%	RFS: 65% OS: 49% at 12 months	Tis-cel approved as 3rd line treatment for LBCL (>18 yr of age)	May 2018	⁴
CD19	MCL	CR: 67%	PFS: 61% OS: 83% at 12 months	Brex-cel approved for R/R MCL (>18 yr of age)	July 2020	⁸
CD19	FL	CR: 74%	PFS: 65% OS: 87% at 18 months	Axi-cel approved as 3rd line treatment for R/R FL (>18 yr of age)	Mar 2021	²²²
CD19	LBCL	CR: 53%	PFS: 44% OS: 58% at 12 months	Liso-cel approved for 3rd line LBCL (>18 yr of age)	Feb 2021	¹
BCMA	MM	CR: 33%	Median PFS: 8.8 months OS: 78% at 12 months	Ide-cel approved for 5th line treatment for MM (>18 yr of age)	Mar 2021	¹³
CD19	B-ALL	CR: 56%	RFS: 58% at 6 months OS: 71% at 12 months	Brex-cel approved for R/R B-ALL (>18 yr of age)	Oct 2021	²²³
BCMA	MM	sCR: 67%	PFS: 77% OS: 89% at 12 months	Cilta-cel approved for 5th line MM (>18 yr of age)	Feb 2022	¹⁴
CD19	FL	CR: 69%	PFS: 67% at 12 months	Tis-cel approved for 3rd line treatment of FL (>18 yr of age)	May 2022	⁹
CD19	LBCL	(Axi-cel vs SOC) CR: 65% vs 32%	(Axi-cel vs SOC) EFS: 41% vs 16% OS: 61% vs 52% at 24 months	Axi-cel approved as 2nd line treatment for LBCL (>18 yr of age)	April 2022	¹⁰
CD19	LBCL	(Liso-cel vs SOC) CR: 66% vs 39%	(Liso-cel vs SOC) EFS: 45% vs 24% OS: 79% vs 64% at 12 months	Liso-cel approved as 2nd line treatment for LBCL (>18 yr of age)	June 2022	¹¹

Model parameters I

Table 1. Final parameter estimates for the CD19-specific CAR-T cell quantitative systems pharmacology model.

Parameter (Unit)	Description	Estimate	RSE or Literature Source
$V_{\max1,base,ref}$ [(cells· μL^{-1}) ·day $^{-1}$ ·mL $^{-1}$]	Maximum expansion rate per mL tumor volume of T_N , T_{CM} , and T_{EM} for the reference expansion population without previous ASCT and a CD4 $^+$ /CD8 $^+$ CAR-T cell ratio at day seven of 1	0.00846	36%
$V_{\max1,base,low}$ [(cells· μL^{-1}) ·day $^{-1}$ ·mL $^{-1}$]	Maximum expansion rate per mL tumor volume of T_N , T_{CM} , and T_{EM} for the low expansion subpopulation without previous ASCT	0.000700	17%
ASCT $V_{\max1}$ § (-)	Fractional change in $V_{\max1,base,ref}$ or $V_{\max1,base,low}$ due to a previous ASCT	2.53	31%
CD4/CD8 $_{exp}$ † (-)	Fractional change in $V_{\max1,base,ref}$ due to a change of the CD4 $^+$ /CD8 $^+$ CAR-T cell ratio on day seven from a value of 1	-0.385	45%
KM_1 (cells· μL^{-1})	T_N , T_{CM} , or T_{EM} concentration at half-maximum expansion of T_N , T_{CM} , or T_{EM}	1.13	22%
kp_1 (day $^{-1}$)	Homeostatic proliferation rate constant for T_N	0.0005	[47]
kp_2 (day $^{-1}$)	Homeostatic proliferation rate constant for T_{CM}	0.007	[47]
kp_3 (day $^{-1}$)	Homeostatic proliferation rate constant for T_{EM}	0.007	[47]
k_{12} (day $^{-1}$)	Rate constant for differentiation of T_N to T_{CM}	0.140	9%
k_{23} (day $^{-1}$)	Rate constant for differentiation of T_{CM} to T_{EM}	0.191	11%
k_{34} (day $^{-1}$)	Rate constant for differentiation of T_{EM} to T_{Eff}	0.355	13%
ke_1 (day $^{-1}$)	Death rate constant for T_N	0.0104 ‡	13%
ke_2 (day $^{-1}$)	Death rate constant for T_{CM}	0.0104 ‡	13%
ke_3 (day $^{-1}$)	Death rate constant for T_{EM}	0.0104 ‡	13%
ke_4 (day $^{-1}$)	Death rate constant for T_{Eff}	0.518	13%



Model parameters II

$V_{\max 5,1}$ [mL·day ⁻¹ ·(cells·μL ⁻¹) ⁻¹]	Maximum killing rate of metabolic tumor volume by T _N	2.57 *	39%
$V_{\max 5,2}$ [mL·day ⁻¹ ·(cells·μL ⁻¹) ⁻¹]	Maximum killing rate of metabolic tumor volume by T _{CM}	4.04	39%
$V_{\max 5,3}$ [mL·day ⁻¹ ·(cells·μL ⁻¹) ⁻¹]	Maximum killing rate of metabolic tumor volume by T _{EM}	3.78 *	39%
$V_{\max 5,4}$ [mL·day ⁻¹ ·(cells·μL ⁻¹) ⁻¹]	Maximum killing rate of metabolic tumor volume by T _{Eff}	4.24 *	39%
KM ₅ (mL)	Metabolic tumor volume at half-maximum killing rate	276	33%
K ₀ (mL)	Maximum tumor volume observable (tumor carrying capacity)	5000	-
k ₅ (day ⁻¹)	Proliferation rate constant of metabolic tumor volume	0.0023	-
MIXP (-)	Estimated proportion of patients in the reference population using the mixture model	0.803	11%
IIV V _{max1,base,ref}	Interindividual variability in V _{max1,base,ref}	150% CV	19%
IIV V _{max 5,2}	Interindividual variability in V _{max 5,2}	307% CV	19%
RUV T _N	Residual unexplained variability in observed T _N concentrations	59.1% CV	11%
RUV T _{CM}	Residual unexplained variability in observed T _{CM} concentrations	85.9% CV	9%
RUV T _{EM}	Residual unexplained variability in observed T _{EM} concentrations	120% CV	9%
RUV T _{Eff}	Residual unexplained variability in observed T _{Eff} concentrations	70.6% CV	10%
RUV CD19 ⁺ tumor	Residual unexplained variability in observed metabolic tumor volumes	115% CV	12%

IIV: interindividual variability; RSE: relative standard error, % = (standard error/estimate)·100; §: implemented as fractional change covariate model, †: implemented as power covariate model; ‡ derived using the estimated death rate constant for effector T cells ke_4 and the relationship between death rate constants of short- and long-lived T cells in the publication by Stein et al. [21]; * derived using the estimated maximum killing rate of metabolic tumor volume by T_{CM} and the digitized relationships of tumor cell killing rates in the publication by Schmueck-Henneresse et al. [49].

