



Background

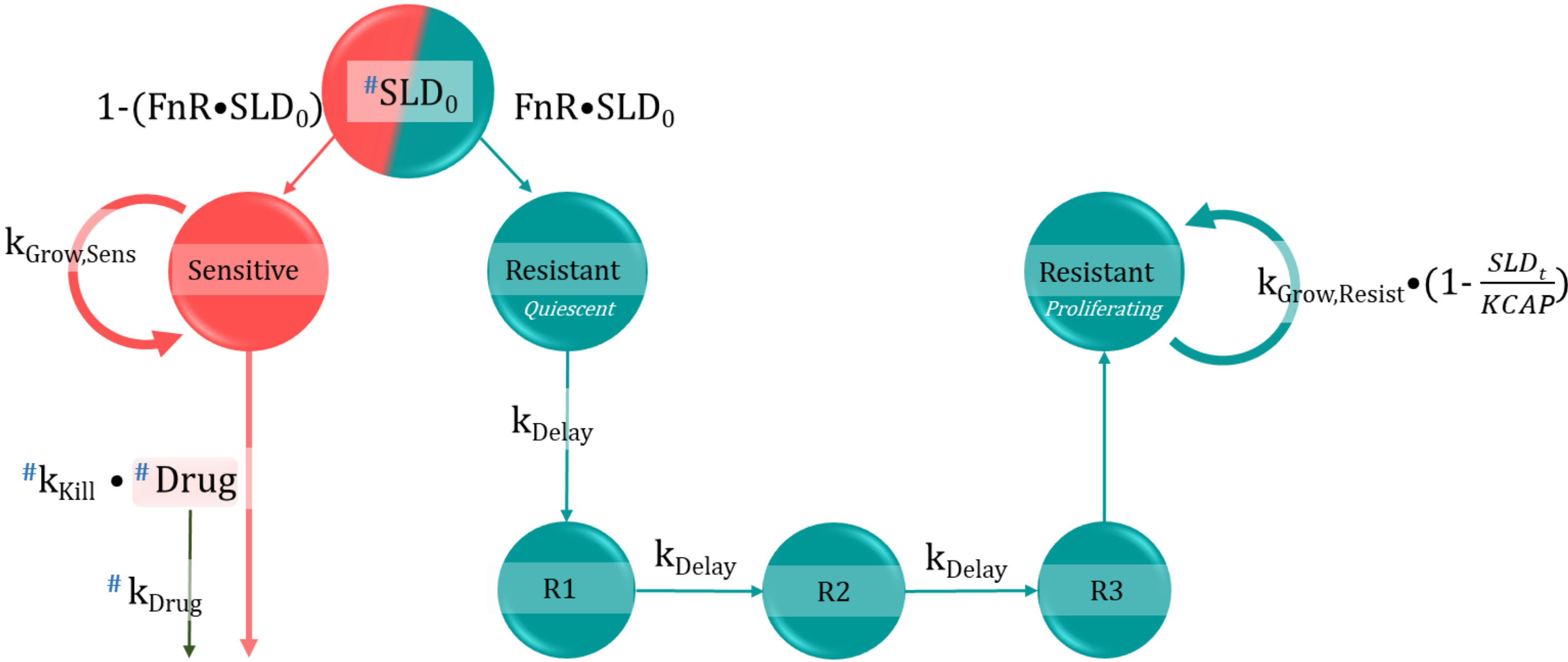
- Bender et al. [1] developed a mechanism–based kinetic–pharmacodynamic (KPD) model to characterize tumor growth in HER2–negative metastatic breast cancer patients receiving either docetaxel or paclitaxel treatment.

Aim

- To evaluate a capacity limiting function in the model proposed by Bender et al. [1]
- To evaluate the sharing of model parameters using a combined dataset for docetaxel and paclitaxel treatments in HER2- metastatic breast cancer patients
- To investigate predictors of overall survival (OS), including time-dependent covariates, such as tumor time-courses and relative change from baseline

Tumor model

- A logistic growth function with a maximum tumor carrying capacity (KCAP = 925 mm) was incorporated into the drug resistant tumor growth compartment



Schematic representation of the tumor size model. Observed SLD is the sum of Sensitive (red) and Resistant (quiescent, R1, R2, R3, proliferating) tumor (cyan) compartments. # treatment-related parameters.

Parameter estimates and their uncertainty

Parameter	Description	Estimate (RSE %)	95% CI	IIV (CV) (RSE %)	95% CI
Treatment-related parameters					
k_{kill_doce} (mg ⁻¹ •week ⁻¹)	Docetaxel tumor kill rate constant	0.000583 (42)	0.000238 - 0.00118	69 (3)	67-70
k_{kill_pacli} (mg ⁻¹ •week ⁻¹)	Paclitaxel tumor kill rate constant	0.000342 (26)	0.000194 - 0.000545		
k_{drug_doce} (week ⁻¹)	Docetaxel elimination rate constant in KPD-model	0.259 (59)	0.0136 - 0.587	73 (6)	68-78
k_{drug_pacli} (week ⁻¹)	Paclitaxel elimination rate constant in KPD-model	0.718 (30)	0.337 - 1.19		
SLD_{0_doce} (mm)	Docetaxel baseline SLD	62.7 (13)	49.4 - 81.3	86 (7)	82 – 93
SLD_{0_pacli} (mm)	Paclitaxel baseline SLD	70.3 (9)	57.8 - 83.5		
RUV^a_{doce}	Residual error docetaxel	24% (9)	0.200 - 0.28	-	-
RUV^a_{pacli}	Residual error paclitaxel	13% (7)	0.119 - 0.155	-	-
Shared tumor-growth related parameters					
$k_{Grow,Sens}$ (week ⁻¹)	Growth rate constant of sensitive tumor fraction	0.00484 (47)	0.00115 - 0.009	-	-
$k_{Grow,resist}$ (week ⁻¹)	Growth rate constant of resistant tumor fraction	15.7 (62)	0.0532 - 0.429	53 (52)	26 - 80
k_{Delay_pop1} (week ⁻¹)	Transit delay rate constant population 1	0 FIX	-	-	-
k_{Delay_pop2} (week ⁻¹)	Transit delay rate constant population 2	0.0425 (63)	0.0112 - 0.113	73 (7)	69 - 78
$FN R_{logit}$	Logit transformed FnR	-0.0929 (126)	-0.291 - 0.178	0.9 ^b (2)	0.95 - 1.02
$FN R^c$	Fraction tumor resistant	0.47	0.43 – 0.54	-	-
$1-FN R^c$	Fraction tumor sensitive	0.53	0.57 – 0.46	-	-
KCAP (mm)	Maximum tumor carrying capacity	925 (26)	418 - 1371	-	-
P_{pop1}	K_{Delay_pop1} probability	0.83 (9)	0.65 - 0.943	-	-

IIV = inter-individual variability; RSE = relative standard error; CI = confidence interval, SLD= sum of longest diameters
^a additive residual error model, ^b standard deviation, ^c Derived parameter $FN R = \exp(FN R_{logit}) / (1 + \exp(FN R_{logit}))$.

Results

- A shared model for HER2- breast cancer patients receiving taxane treatment was developed; tumor-growth related parameters were shared between docetaxel and paclitaxel treatment groups, while treatment-related parameters were specific to the taxane arm
- The results from the OS analysis indicated that a large tumor baseline ($HR_{SLD0} = 1.0039$) and higher derivative of TS(t) at dropout from study ($HR_{TSderivative} = 1.0113$) were associated with lower survival.
- The developed modeling approach provides a flexible tool to 1) describe tumor responses where resistance to therapy exhibits high variability and 2) evaluate model-predicted time varying tumor metrics as predictors of OS

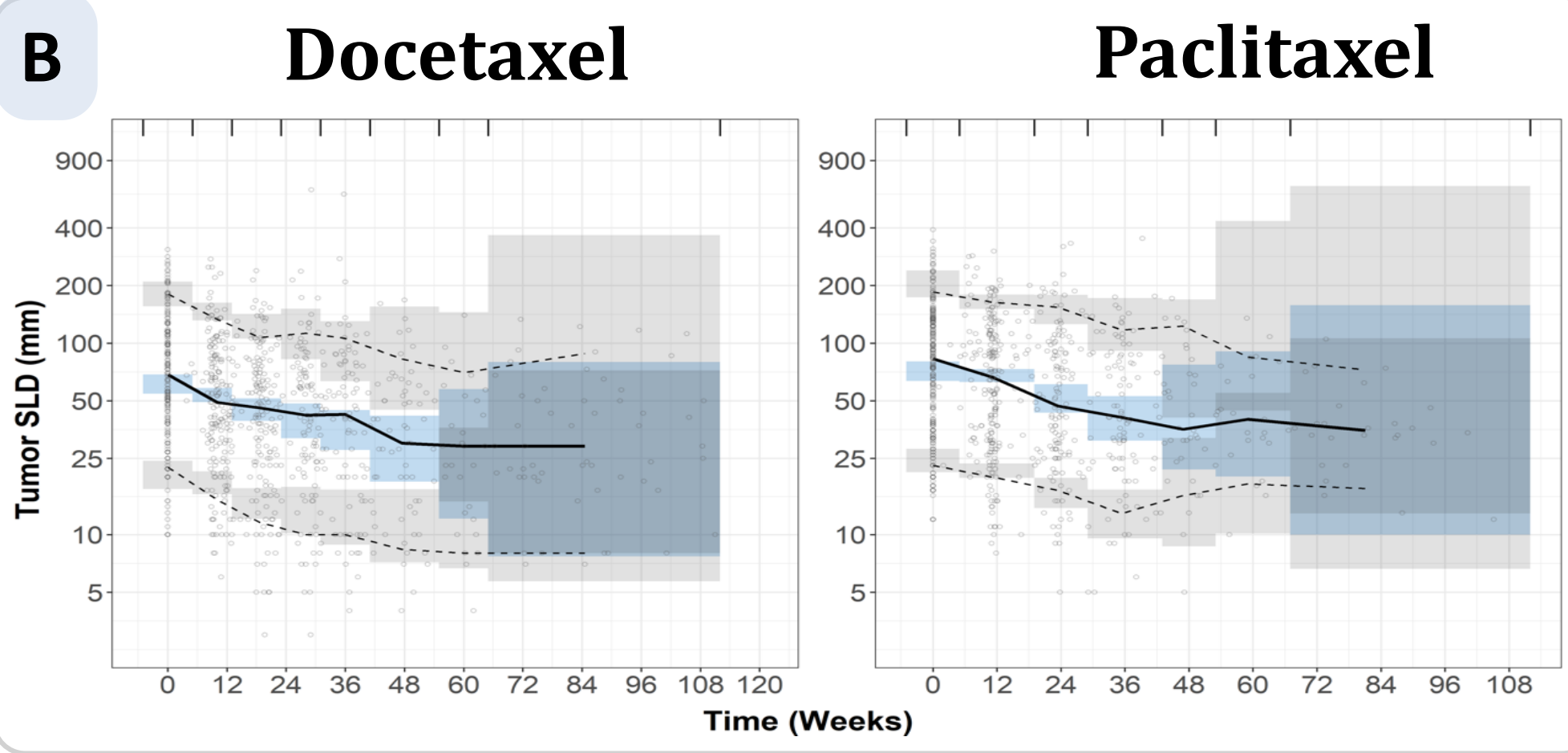
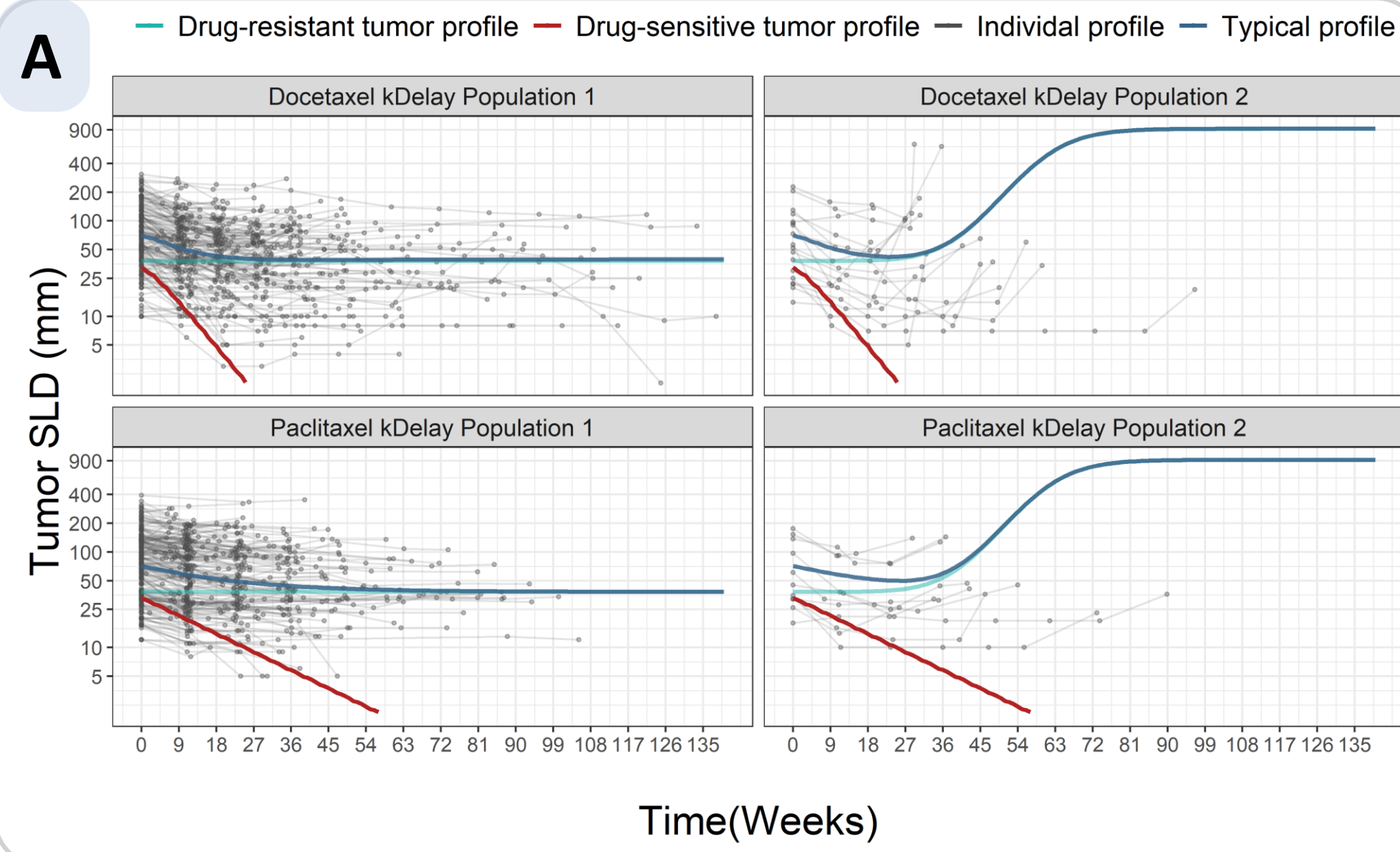
A: Model predictions for the two typical tumor patient responses ($k_{Delay, pop1}$ and $k_{Delay, pop2}$) receiving docetaxel (top panel) and paclitaxel (lower panel) treatment.

B: Visual predictive checks of final tumor model of docetaxel (left panel) and paclitaxel (right panel).

OS model

- OS model: Weibull distribution
- Univariate analysis: Baseline tumor size, derivative of TS(t), tumor time-course (log transformed), TSRw6, and TTG.
- After the best predictor, baseline tumor size, was included, the derivative of TS(t) was the most significant predictor and included in the final OS model.

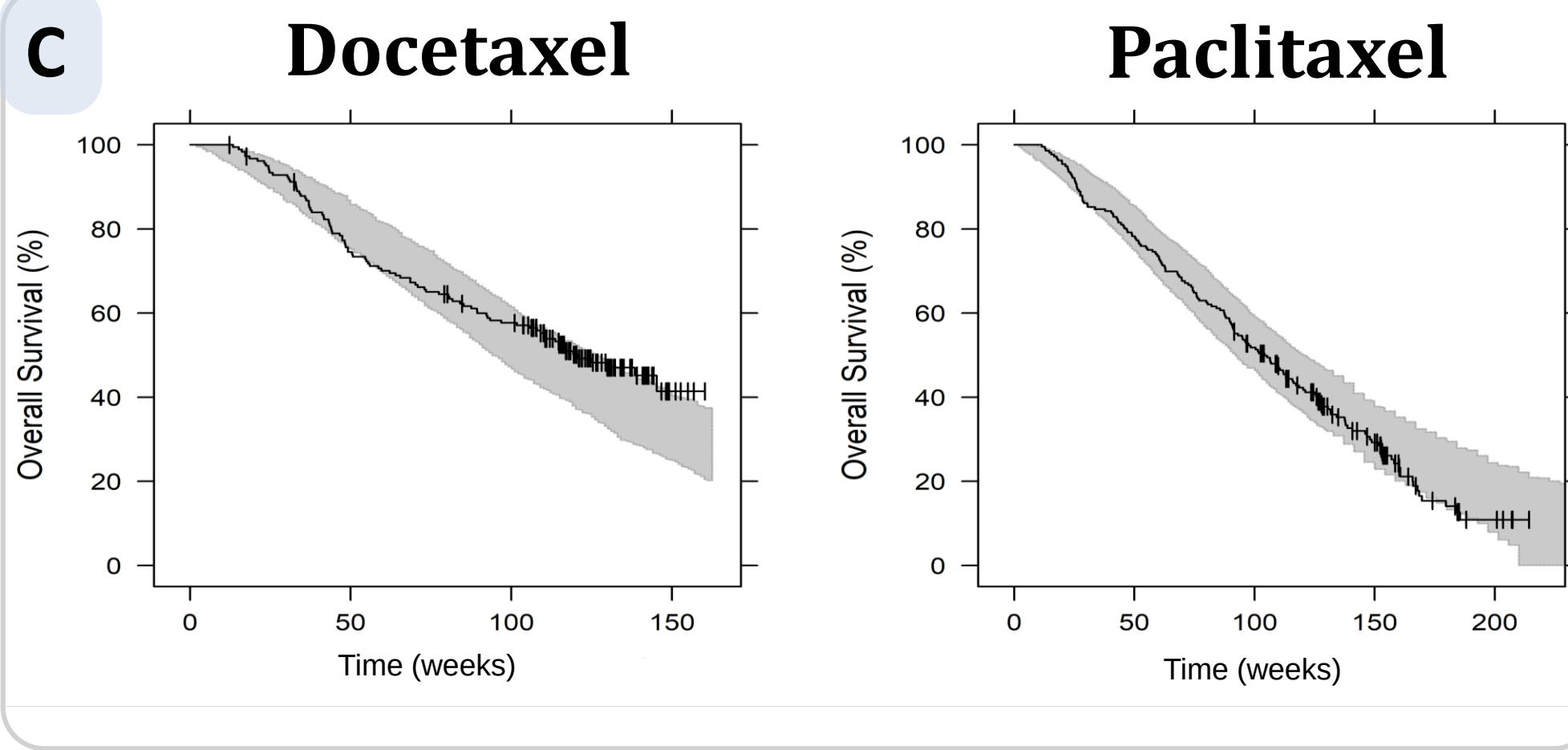
C: Kaplan–Meier visual predictive checks for the final overall survival model of docetaxel (left) and paclitaxel (right).



Parameter estimates and their uncertainty

Parameter	Description	Estimate (RSE %)	95% CI
λ_{OS}	scale parameter	5.75 (1)	5.60 – 5.90
α_{OS}	shape parameter	1.53 (22)	0.087 – 2.18
β_{SLD0}	coefficient of the effect of baseline SLD	0.0039 (39)	0.00095 – 0.0067
$\beta_{Tumor\_derivative}$	coefficient of the effect of tumor derivative until disease progression	0.0113 (9)	0.0093 – 0.0133

RSE = relative standard error; CI = confidence interval



Methods

Tumor data and modeling

- The tumor dataset included 879 tumor SLD measurements collected from 185 patients receiving docetaxel and 784 tumor SLD measurements from 219 patients treated with paclitaxel
- Tumor growth-related parameters were evaluated as being shared between the two drugs while treatment-related parameters were allowed to differ
- Model development and evaluations were performed using NONMEM v 7.4.3.

References

1. Bender et al. PAGE 26 (2017) Abstr 7344 [www.page-meeting.org/?abstract=7344]
2. Zhang et. Al., J Pharmacokinet Pharmacodyn (2003).

Acknowledgement

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Contact: sreenath.krishnan@farmbio.uu.se