

Risk score based on survival multivariate analysis of baseline patients’ characteristics reduces variability in a PKPD model of tumor growth inhibition

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Background

- Covariates search in PKPD modeling aims at reducing parameter variability, improving models predictions, and increasing understanding of the studied system.
- Covariate selection** can be **challenging** due to the large set of initial covariates to be tested, the correlations between them and the large number of combinations and alternative models that can be considered.

Objectives

Explore benefit of combining survival multivariate analysis with PKPD modeling to reduce variability and improve PKPD model predictions for dose selection and drug development support

Conclusion

- Survival **multivariate analysis** resulted in three **baseline predictive factors** of time to progression → Derivation of a **composite risk score**
- A **PKPD tumor response model** was developed with a **parameterization** estimating **dose for stasis**
- The **risk score** was found highly **significant** as a covariate on the **PKPD model resistance parameter** with **~25% reduction** of the variability
- The developed model was used to **support dose selection in drug development** for given patient populations using a simulation tool
- The proposed methodology can be applied for **other efficacy** and **safety endpoints**

4-steps approach

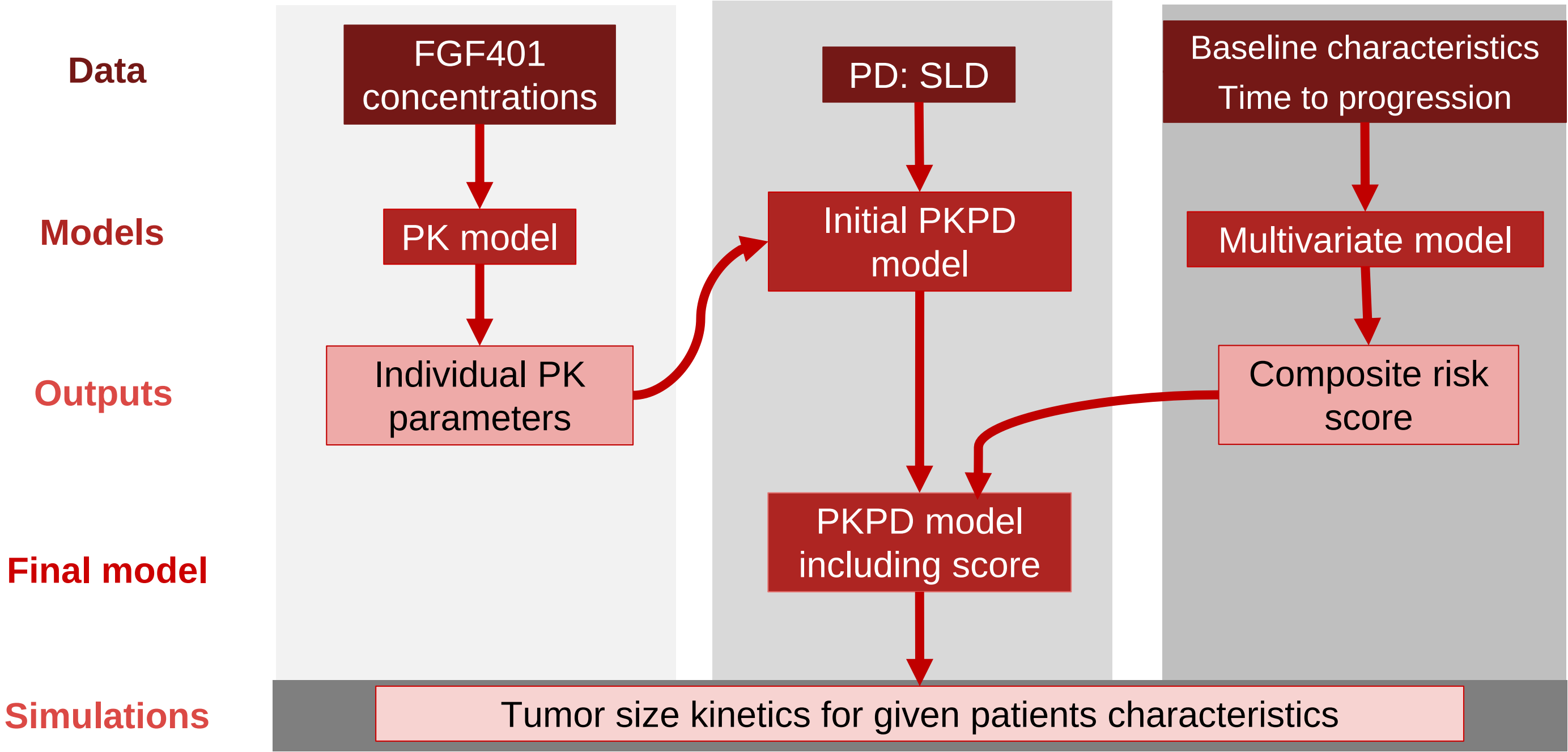
- Identification of clinical baseline characteristics** and derivation of a **continuous composite risk score** predictive of time to progression (TTP) using robust multivariate analysis with cross-validation methodology [1] in R-3.2.3
- Development of a sequential PKPD model** with PK parameters fixed at an individual level using non-linear mixed-effects modeling implemented in Monolix 2016R1
- Evaluation of the risk score as a covariate** on key PKPD model parameters
- Simulations of tumor response** for different patients characteristics to support dose selection for future studies using a Shiny simulation tool [2, 3]

Methods

Data summary

Description	Data
Study	Phase I/II study: NCT02325739
Compound	FGF401: oral FGFR4 kinase inhibitor
Patients	71 patients with hepatocellular carcinoma (HCC)
Doses	Once-daily doses from 50 mg to 150 mg
PK	Plasma concentrations time course (n=2188)
PD	Longitudinal sum of the longest diameters (SLD) (n=273)
Patient characteristics	82 individual baseline characteristics

Integration of multivariate analysis with a PKPD model



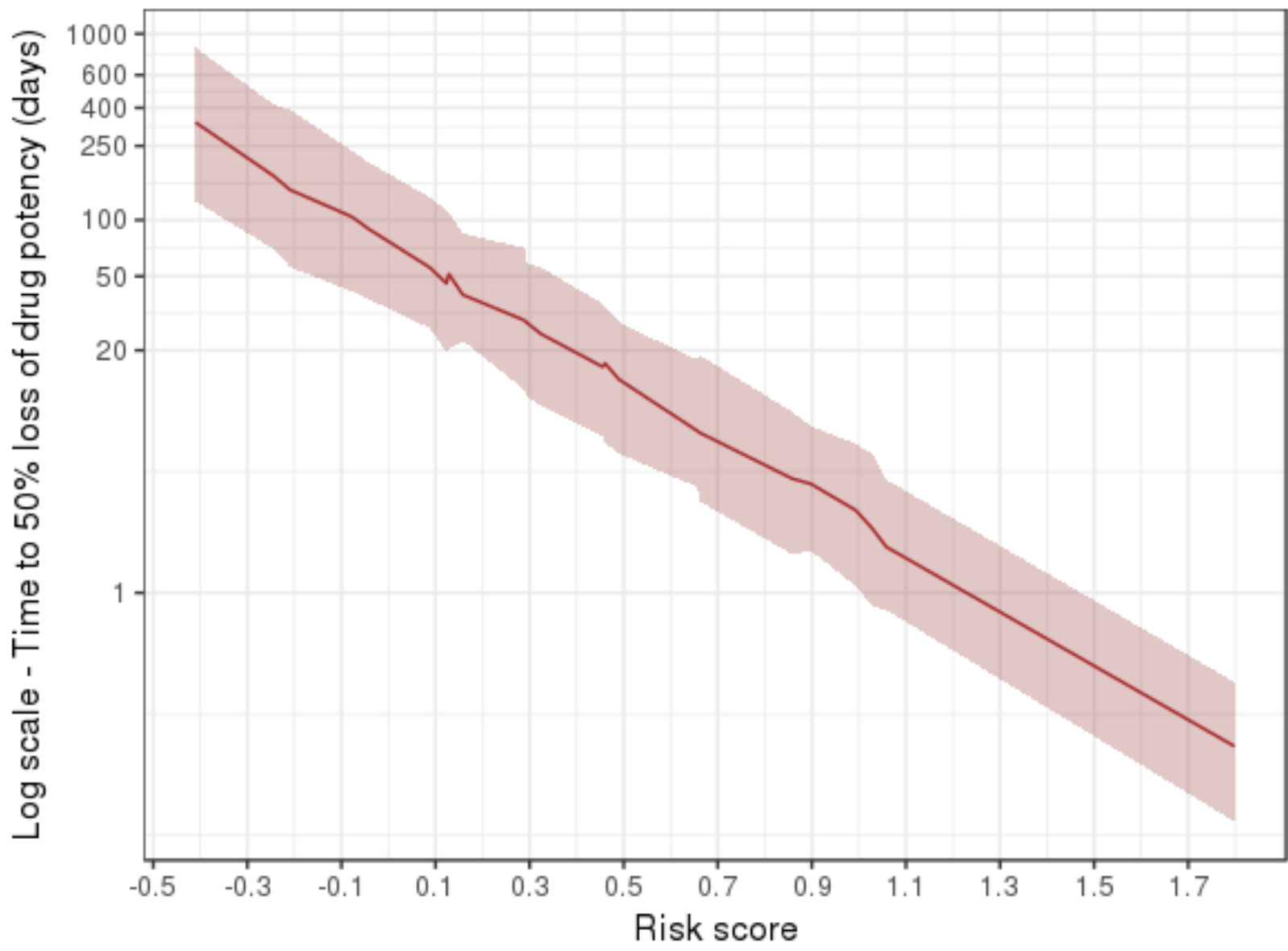
Composite risk score from multivariate analysis

- Three baseline predictive factors of time to progression (TTP) selected:
 - Adjacent organ invasion (e.g. gallbladder and peritoneum) - *adoinv*
 - Number of target lesions - *nbtarget*
 - Number of metastatic sites - *nbmeta*
- $$Score = 0.11 + 0.33 \cdot (0.56 \cdot adoinv + 0.59 \cdot nbmeta + 0.57 \cdot nbtarget)$$
- Dose** also found as a predictive factor of TTP, but excluded from the score used in the PKPD model
 - Patients can be **categorized** in two clusters:
 - **low risk** if *Score* < 0
 - **high risk** if *Score* ≥ 0

Results

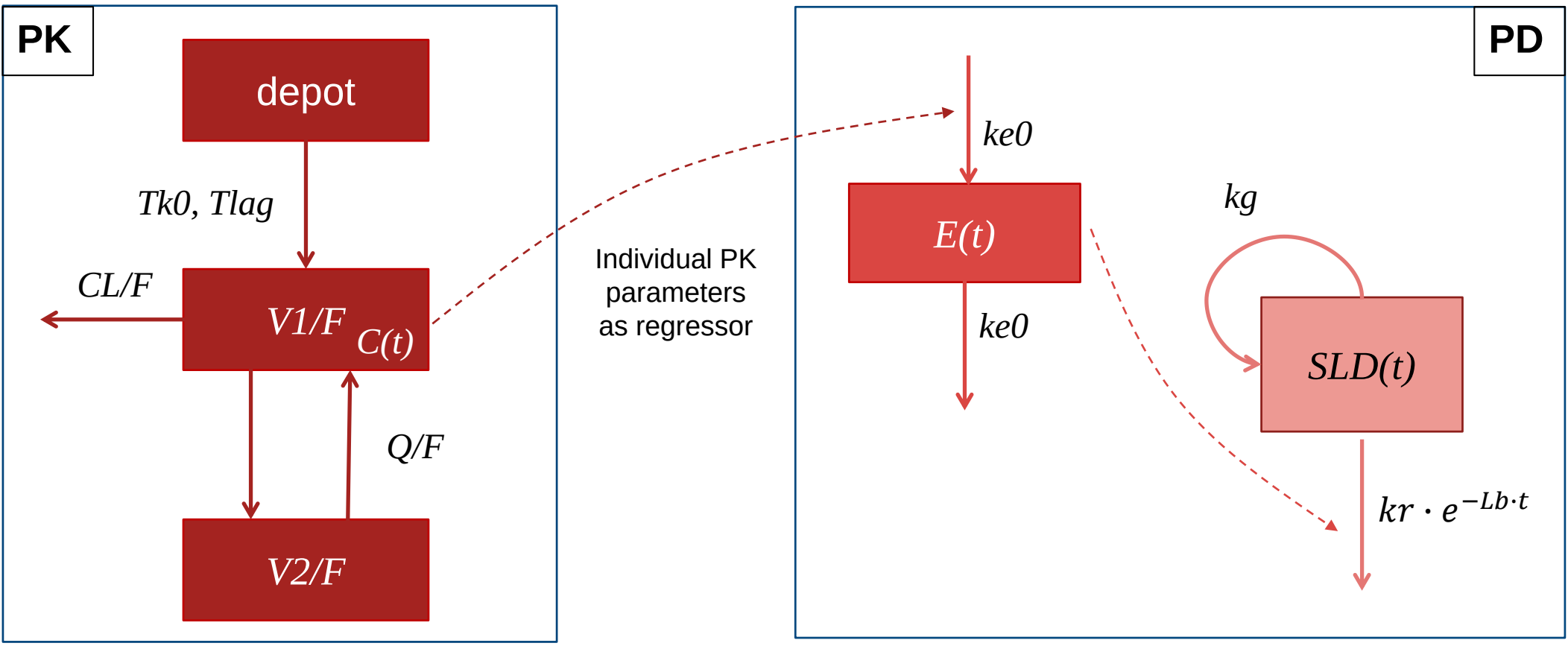
Simulations of time to 50% loss of drug potency vs. risk score

Median and percentiles (10th and 90th) time to 50% loss of drug potency (*T50*) for the observed range of *Score*:



$$T50 = \frac{\log(2)}{Lb_{pop} \cdot Score^{Lb}}$$

PKPD tumor growth inhibition model



Model equations [4]:

$$\frac{dE}{dt} = ke0 \cdot C(t) - ke0 \cdot E(t) \quad E(0) = 0$$
$$\frac{dSLD}{dt} = kg \cdot SLD(t) - kr \cdot SLD(t) \cdot e^{-Lb \cdot t} \quad SLD(0) = SLD0$$

Exponential growth Drug killing rate Resistance

$$kr = \frac{E(t) \cdot Cl \cdot kg \cdot \tau}{AvDstasis}$$

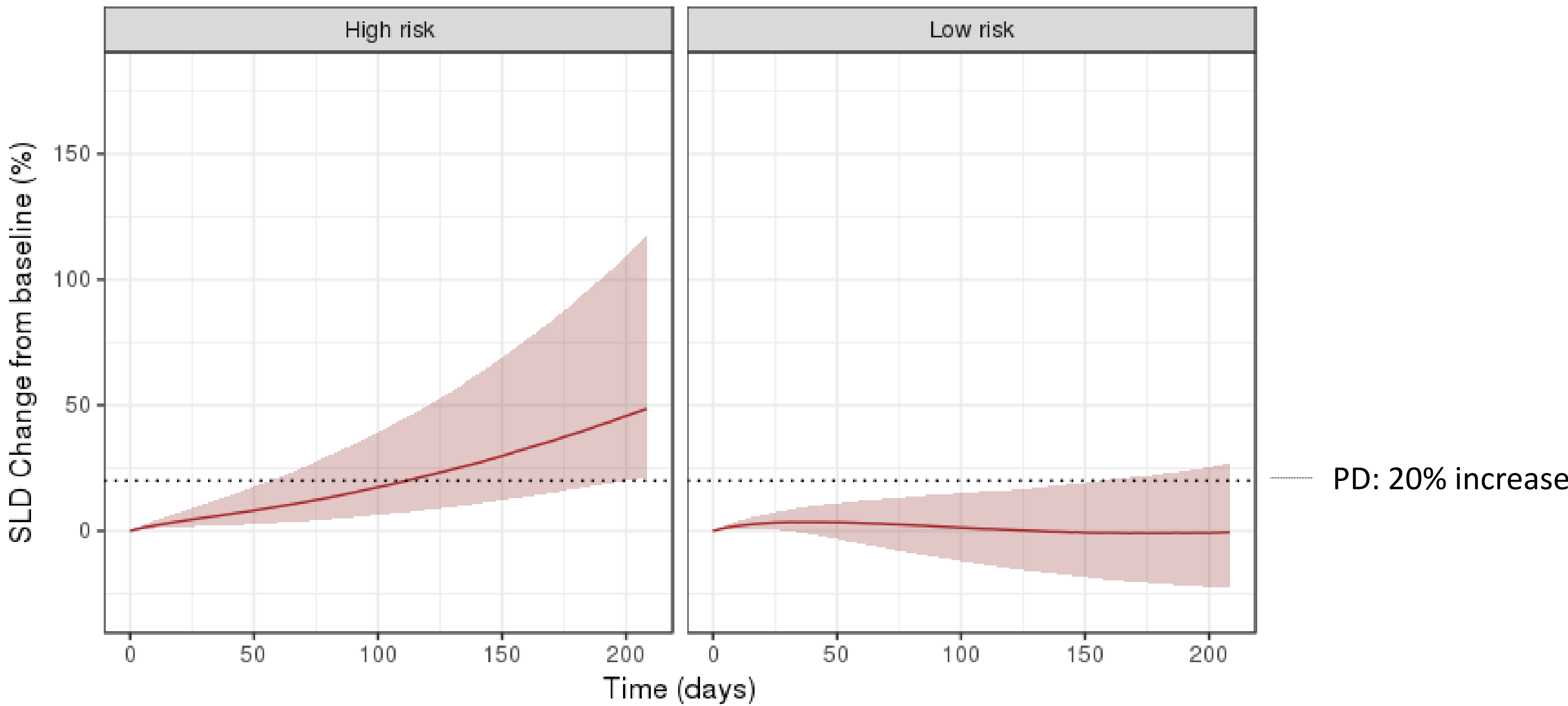
Continuous score significant on key PKPD model parameters: **resistance parameter *Lb*** and ***SLD0*** with **~25% reduction of inter-individual variability on *Lb* parameter**

Comparison of parameter estimates of the initial and final PKPD models

Parameter	Unit	Fixed effect (% RSE)		% IIV (% RSE)		p-value
Model		No score	With score	No score	With score	With score
<i>ke0</i>	<i>h</i> ⁻¹	0.00054 (34)	0.00063 (40)	130 (15)	146 (16)	-
<i>SLD0</i>	<i>mm</i>	107 (7)	97.7 (6)	55 (8)	47 (9)	-
<i>β_{SLD0}</i> : Score effect on <i>SLD0</i>	-	-	0.64 (20)	-	-	6e-07
<i>Lb</i>	-	0.00024 (28)	0.00028 (28)	70 (21)	53 (23)	-
<i>β_{Lb}</i> : Score effect on <i>Lb</i>	-	-	2.53 (24)	-	-	5e-05
<i>kg</i>	<i>h</i> ⁻¹	0.00013 (16)	0.00013 (15)	94 (14)	83 (14)	-
<i>AvDstasis</i>	<i>mg</i>	47.3 (18)	45.9 (21)	10 FIX	10 FIX	-
Combined residual error: additive / proportional	<i>mm</i> / %	0.18 (NA) / 5.4 (9)	3.42 (23) / 4.2 (15)	-	-	-

Support in drug development

Median and quartiles (25th and 75th) of simulated tumor response in high and low risk patients receiving a dose of 120 mg QD:



[1] Bøvelstad HM et al. Predicting survival from microarray data—a comparative study. Bioinformatics. 2007.
[2] <https://CRAN.R-project.org/package=shiny>. [3] <https://CRAN.R-project.org/package=mlxR>
[4] Claret L et al. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. J Clin Oncol. 2009.