Machine Learning and Mechanistic Modeling for the prediction of Overall Survival on the basis of 1st line Tumor Dynamics in Head and Neck Squamous Cell Carcinoma

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BACKGROUND

- Prediction of **Overall Survival** and **Response to 2nd line** is a **major challenge** in treatment of HNSCC
- **Tumor kinetics during first line** may provide interesting **predictive metrics** for Overall Survival

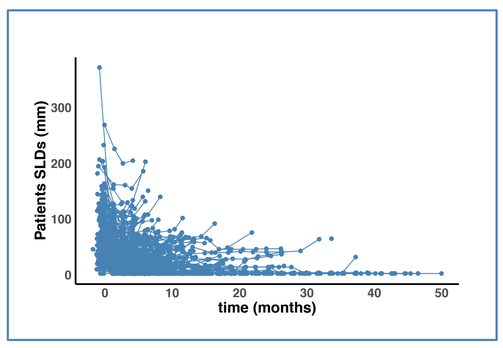
OBJECTIVES

- Propose the best **mathematical model** for the description of the longitudinal measurement of the patients individual SLDs (Sum of the Largest Diameters)
- Predict the **Overall Survival** using the kinetic data of first line and some baseline data

MATERIAL AND METHODS [1]

Clinical data

- EXTREME (cetuximab, 5-FU, platinum) vs TPEx (cetuximab, docetaxel, platinum) **Phase 2 clinical trial**
- **528 patients** enrolled (263 (TPEx) and 265 (EXTREME)).



Tumor Growth Inhibition (TGI) models [2]:

Tumor Growth model with treatment effect

$$SLD(t) = SLD_0 e^{-KS/\lambda(1-e^{-\lambda t})+KGt}$$

Biexponential model with resistant cells

$$SLD(t) = SLD_0\left(\alpha e^{KGt} + (1-\alpha)e^{-KSt} - 1\right)$$

Biexponential model

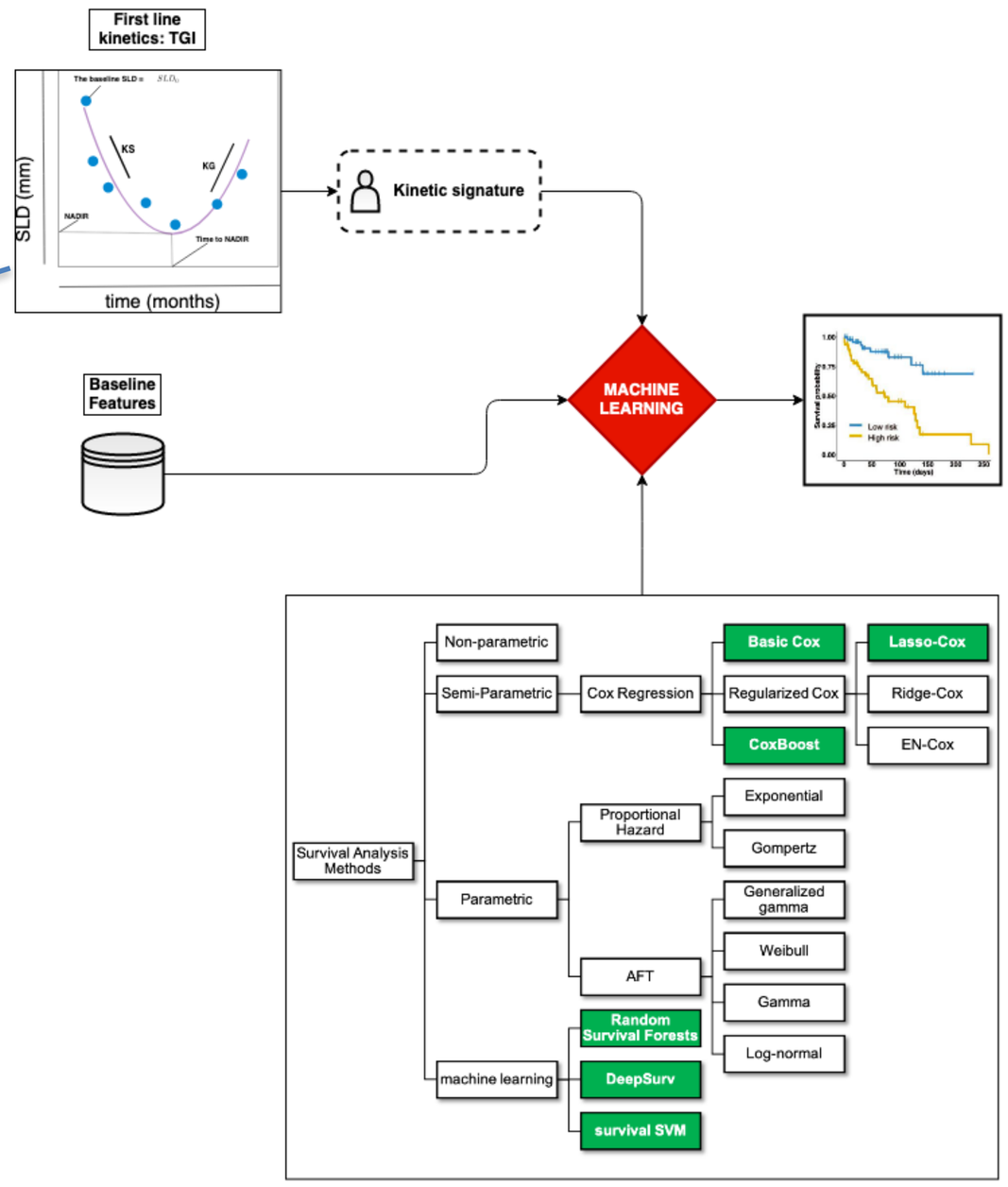
$$SLD(t) = SLD_0\left(e^{KGt} + e^{-KSt} - 1\right)$$

Nonlinear Mixed Effects Modeling (NLMEM)

$$\underbrace{y_j^i}_{\substack{\text{observation}\\ \text{of individual } i\\ \text{at time } t_j^i}} = \underbrace{f(t_j^i;\theta^i)}_{\text{structural model}} + \underbrace{e_j^i}_{\text{error model}}$$

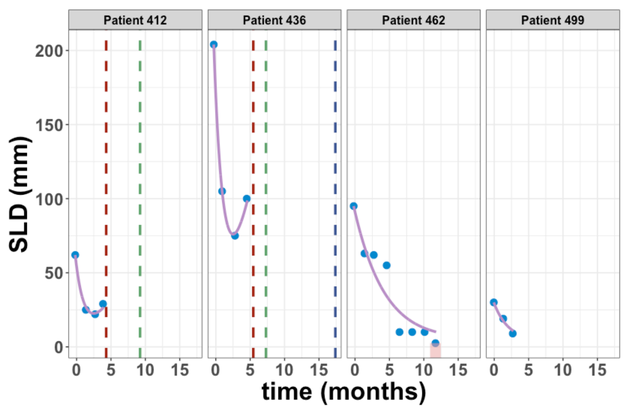
$$\theta^i = \mu\exp(\eta^i) \qquad \eta^i \sim \mathcal{N}(0,\omega) \qquad \mu \text{ fixed effects, } \eta^i \text{ random effects}$$

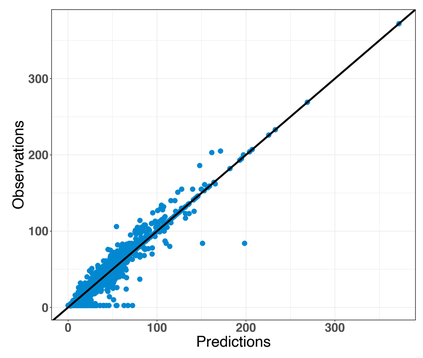
$$e_j^i = (\sigma_1 + \sigma_2 f(t_j^i;\theta^i))\epsilon_j^i \qquad \epsilon_j^i \sim \mathcal{N}(0,1) \qquad \text{combined error model}$$



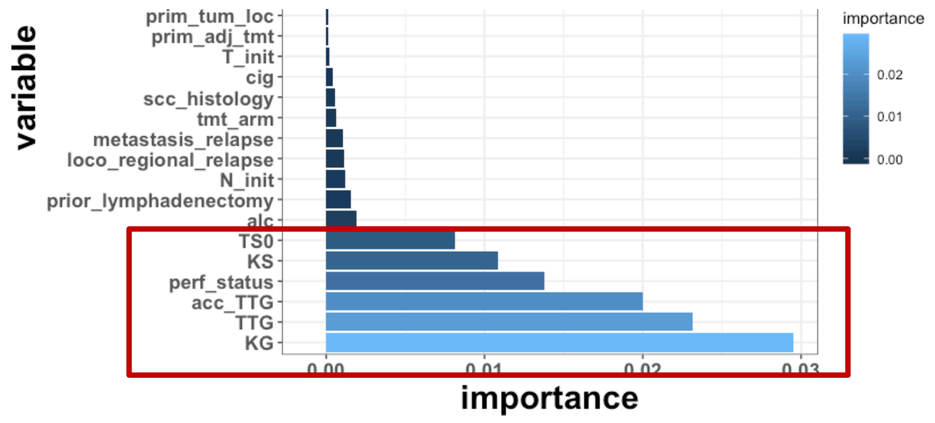
RESULTS

The Biexponential model provides the best Fit (AIC and identifiability) [3]





KG is the most important parameter for predicting OS

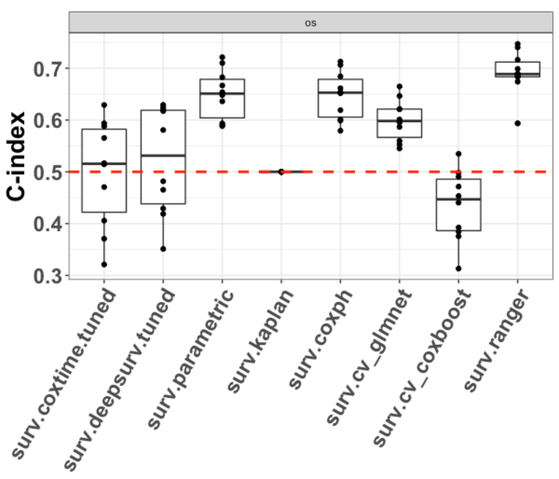


Tumor Kinetic Parameters Outperform All Others

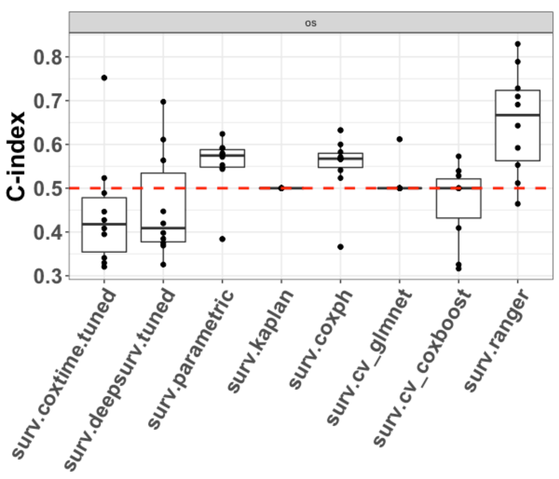
Prediction of the Overall Survival

Best performance for Random Survival Forest (C-index= 0.7)

On the training set: 0.7



On the test set: 0.67



CONCLUSION AND PERSPECTIVES

- A **mechanistic** mathematical model was able to fit the **clinical data** of SLD measurements in a HNSCC clinical trial
- Mechanistic modeling and Machine learning algorithms were combined to predict **Overall Survival**
- Predictive power is **only modest so far** but only the SLD measurements was considered

==> include **more features** and model **individual lesions kinetics**

References

1. S. Benzekry, Artificial Intelligence and Mechanistic Modeling for clinical Decision Making in Oncology, Clinical Pharmacology and Therapeutics (2020)
2. R. Bruno, F. Mercier, L. Claret, Evaluation of Tumor size Response Metrics to predict Survival in Oncology Clinical Trials, Clinical Pharmacology and Therapeutics (2014)
3. Monolix Version 2018R2. Lixoft SAS (2018)