Model-based Prediction of Progression-Free Survival for Combination Therapies in Oncology

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Introduction

Progression-free survival (PFS) is a clinical metric for comparing similar oncology treatments. Using RECIST v1.1 tumor lesions are classified as target or non-target lesions [1]. A patient's PFS time is set by target progression (TP) if there is at least a 20% and 5 mm increase of the sum of the largest target lesions' diameters (SLD) compared to the nadir or by non-target progression (NTP) if the non-target lesions are qualitatively proliferating. Patients are right censored if neither event occur prior trial departure. We present a nonlinear mixed effects joint modeling approach for predicting PFS for combination therapies building upon the model by Yu *et al* [2]. The model links the risk of progression events, such as tumor metastasis or death, with the rate of change of SLD. We calibrate the model with data (ProjectDataSphere) from a clinical study comparing FOLFOX (N=127) to panitumumab (pani) every 2 weeks + FOLFOX (N=121) in WT RAS mutated mCRC patients [3,4].

Clinical Data

We obtained SLD time series and event data for FOLFOX and FOLFOX + pani from the PRIME study [3]. A PFS-curve for pani given as a monotherapy was used from the ASPECCT study [5]. The sample size and available data for each treatment arm are summarized in Table 1.

Panitumumab was given every 2 weeks with a does of 6 mg/kg. FOLFOX was administered by the following regimen: Oxaliplatin 85 mg/m^2 intravenous (IV) infusion and leucovorin 200 mg/m^2 IV followed by fluorouracil (5-FU) 400 mg/m^2 IV bolus followed by 5-FU 600 mg/m^2 IV.

	panitumumab	FOLFOX	FOLFOX + panitumumab
Sample size	164	127	121
SLD Time-series		x	x
Event data		x	x
PFS curve	x	x	x

Table 1. Used data for each treatment arm

Tumor Growth Inhibition Modeling

$$\frac{dSLD}{dt} = (k_g - k_{s,Pani})\, SLD - k_{s,FOLFOX}\, SLD,$$

$$k_{s,i} = a_i\, D_i\, e^{-\gamma\, t}$$

$$SLD(0) = SLD_0,$$

SLD_0 : Initial SLD
k_g : Net tumor growth rate
a_i : Potency of drug i, $i \in \{Pani, FOLFOX\}$
D : Dose of drug i, $i \in \{Pani, FOLFOX\}$
γ : Aquired resistance rate

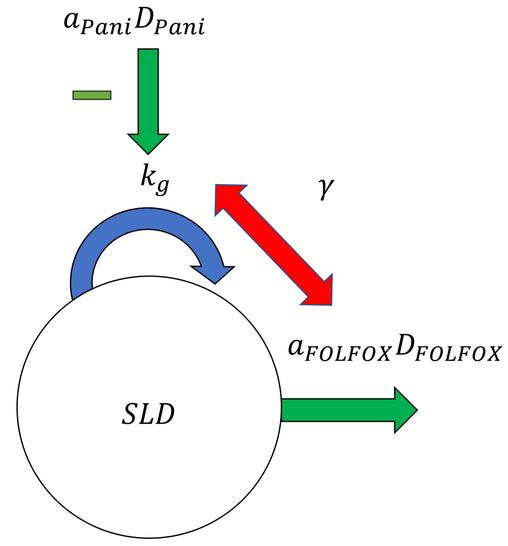

Fig. 1 The tumor growth inhibition model. Pani is an EGFR inhibitor and is modeled as reducing the growth rate. FOLFOX is modeled as an exponentially decaying chemotherapy.

Time-To-Event Modeling

The risk that a NTP event occur is larger the faster the tumor cells proliferate. We model this using a hazard function, h_1, proportional to the rate of change of SLD.

Dropout is assumed to be independent of patient response and is modeled separately using the Weibull survival model, with hazard function given by h_2.

$$h_1(t) = \max\left(\alpha \frac{dSLD(t)}{dt} + \beta, 0\right)$$

$$h_2(t) = \frac{k}{\lambda} \cdot \left(\frac{t}{\lambda}\right)^{k-1}$$

α : Treatment-dependent hazard coefficient
β : Baseline hazard
k : Shape parameter
λ : Scale parameter

Validation of the PFS Model

After the models were calibrated in Monolix [6] they were combined to make predictions of PFS. Predictions were made in the following manner.

1. Generate virtual patients mirroring the study's design
2. Estimated time for TP and sample times for NTP/dropout for each individual
3. Pick event that occur first for each individual and construct PFS curve
4. Repeat 1-3 1000 times to obtain a confidence interval for the prediction

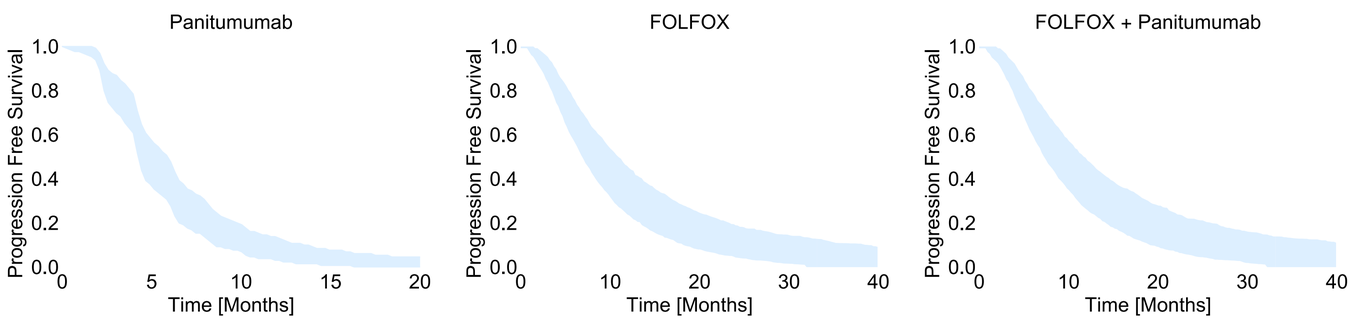

Fig. 2 PFS predictions. Black lines are the observed PFS, grey lines the median prediction, and the blue areas 95% confidence interval of the prediction.

PFS Predictions

To test the model's predictive capabilities, we first predicted the PFS for pani given as a monotherapy (Fig. 2) and then recalibrated the model with truncated data and made forward predictions (Fig. 3).

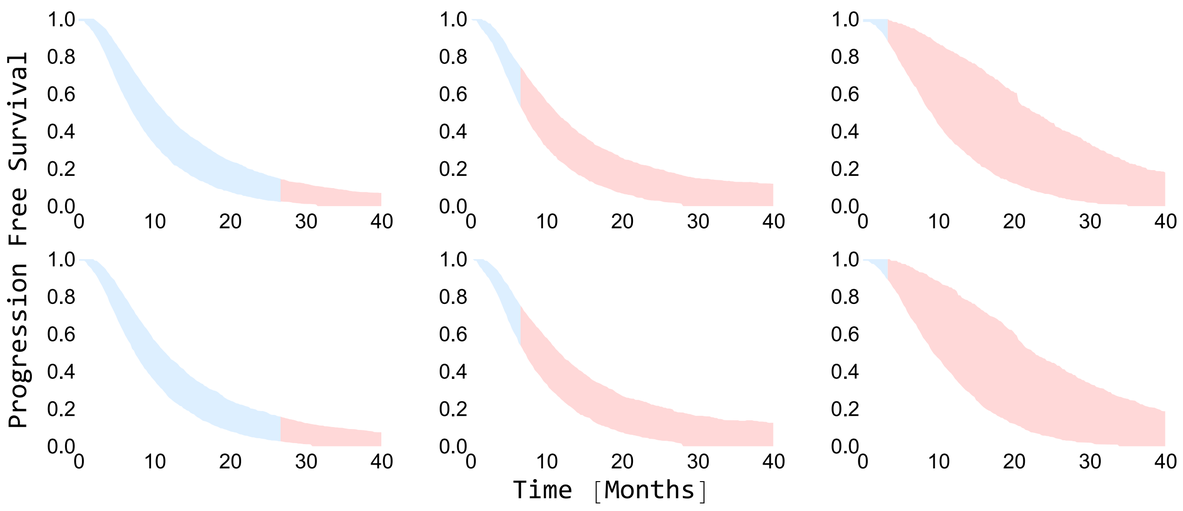

Fig. 3 PFS predictions for FOLFOX (upper row) and FOLFOX + pani (lower row) using truncated data. Red indicates data truncation. Black lines represent observed PFS, grey lines the median prediction, and the colored areas 95% confidence intervals for the prediction.

Conclusions

- A joint model was successfully calibrated with clinical data from a combination trial.
- By combining it with a parametric dropout model it could describe the observed PFS.
- Two external validations were performed and the model was shown to have good predictive capabilities.
- This modeling approach can potentially provide early insights into the efficacy of new drug combinations and be used to support decision-making

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