Predicting tumor volume doubling time and progression-free survival curves in cancer patients from patient-derived-xenograft (PDX) models: a translational model-based population approach

E.M.Tosca[1], D. Ronchi[1], M. Cossali[1], M. Zavettieri[1], M. Rocchetti[2], P. Magni[1]

1. Department of Electrical, Computer and Biomedical Engineering - University of Pavia, 2. Consultant, Milan

BACKGROUND

Tumor volume doubling time (TVDT):

- time required by a tumor to doubling its volume;
- computed from at least 2 subsequent tumor volume measurements

$$\mathbf{TVDT} = \frac{(\boldsymbol{t}_2 - \boldsymbol{t}_1)\ln(2)}{\ln(\boldsymbol{TV}_2/\boldsymbol{TV}_1)};$$

- essential in clinical cancer management for many medical decisions;
- correlated with response to therapy, tumor progression and patient survival.

Progression-free-survival (PFS):

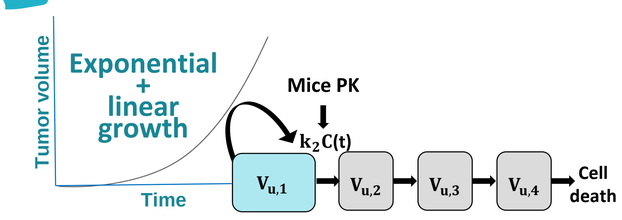
- timeframe between study randomization and tumor progression or death, whichever occurs first;
- inherently linked to tumor growth (TG) dynamics;
- summarized through Kaplan-Meier (KM) curves;
- primary endpoint in early clinical studies: in absence of placebo-controlled arm, quantification of investigated treatment benefit in terms of PFS timespan increment respect to standard therapies.

OBJECTIVE: Developing a translational modeling framework to predict TVDTs and PFS curves in an untreated cancer patient population from TG data in patient-derived xenograft (PDX) mice [1]. Extending the translational population approach to predict PFS curves in pancreatic (PA) and liver (LI) cancer patients treated with Gemcitabine and Sorafenib, respectively.

METHODS

Modeling PDX data

Simeoni TGI model [2]

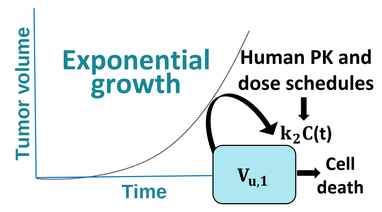


- non-linear mixed effect approach to account for inter-PDX variability
- Identification of log-normal distributions of:
  - exponential growth rate, $\boldsymbol{\lambda}_{\mathrm{Mice}}$
    - 11 cancer types
    - 25 PDX models for cancer type (n_{tot}=265)
  - anticancer drug potency, $\mathbf{k}_{2,\mathrm{Mice}}$
    - Gemcitabine on PA PDX models (n=27)
    - Sorafenib on LI PDX models (n=24)

CROWN BIOSCIENCE

Scaling from PDX mice to humans

TGI model in humans



- Exponential growth model with direct killing effect
- Allometric scaling

$$\boldsymbol{\lambda}_{Human} = \boldsymbol{\lambda}_{\mathrm{Mice}}\left(\frac{\mathbf{BW}_{Human}}{\mathbf{BW}_{Mice}}\right)^{-1/3}$$

$$\boldsymbol{k}_{2,Human} = \mathbf{k}_{2,\mathrm{Mice}}\left(\frac{\mathbf{BW}_{Human}}{\mathbf{BW}_{Mice}}\right)^{-1/3}$$

- Log-normal distributions where inter-patient variability = inter-PDX variability

Predictions in cancer patients

Under exponential tumor growth assumption

$$\mathbf{TVDT}_{\mathbf{Human}} = \frac{\ln(2)}{\boldsymbol{\lambda}_{Human}}$$

Considering

- a single spherical mass
- only progression event

20% increase of tumor diameter ⟷ 72.8% increase of tumor volume

- KM-visual predict check (VPC) plots from 1000 studies, each with 200 patients

RESULTS

Comparison with clinical TVDTs from literature:

- 91% of predicted TVDT medians within the 2-fold of observations; RMSE=0.9244 (Fig.2).
- 83.59% of individual-PDX TVDTs predictions within clinical 80%CI ranges (Fig.2).
- Predicted 80%CI TVDT ranges fell within the observed ranges, with a general underestimation of the clinically observed inter-patient variability .

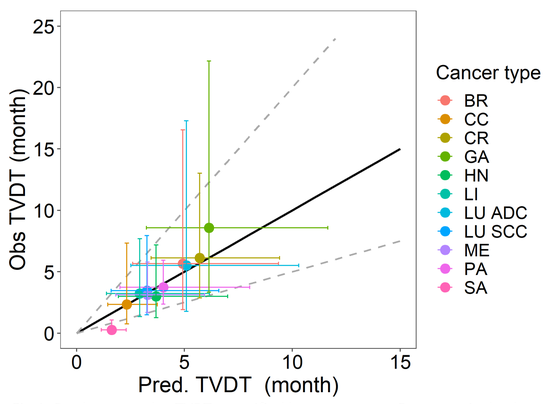


Fig 1: Pred. versus obs. TVDTs stratified by cancer type. Dots = typical values. Bars = 80% CI. Solid line=Identity. Dashed lines=2-fold area.

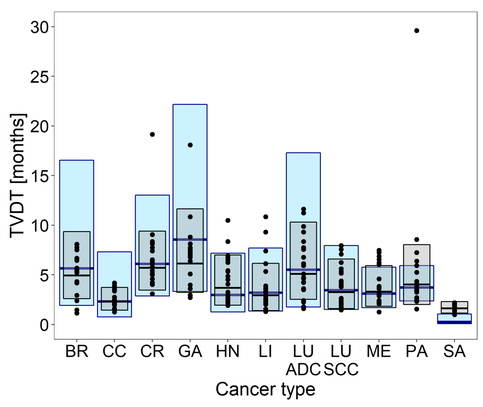
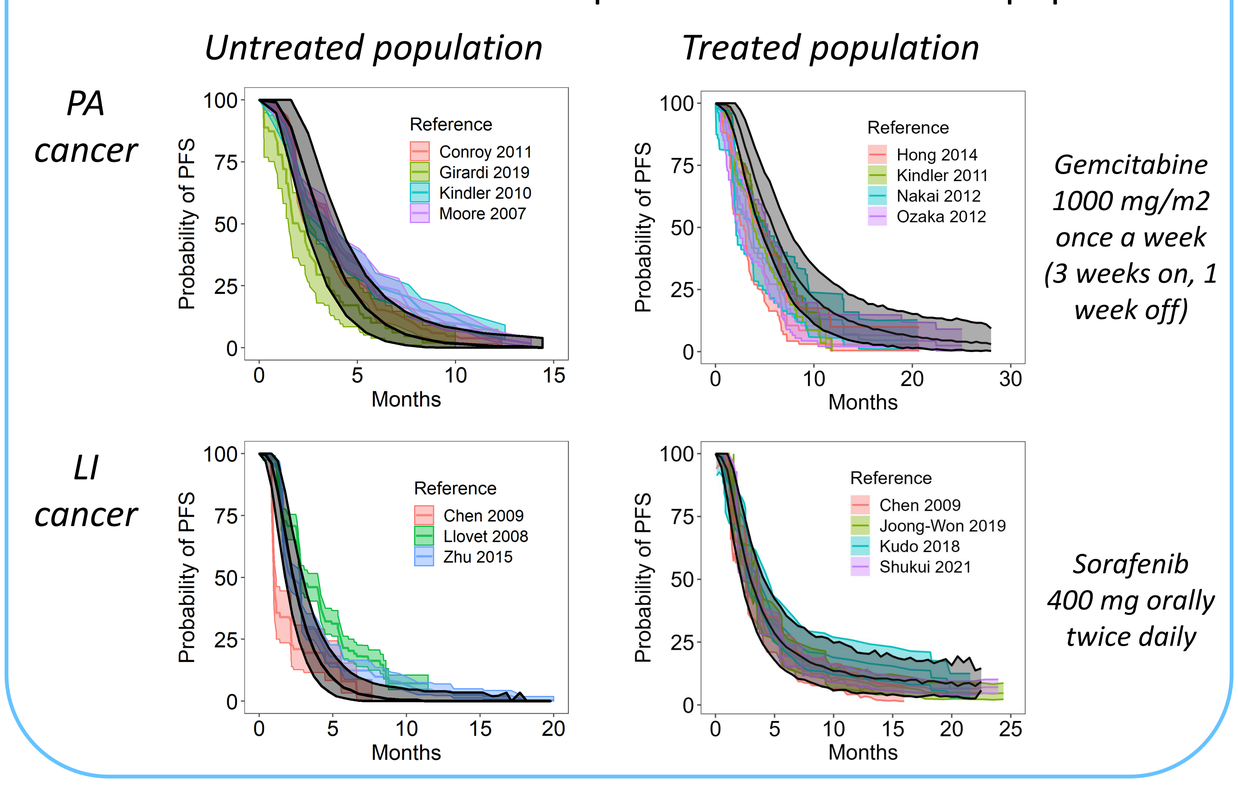


Fig 2: Box plots (medians and 80% CI) of obs (lightblue) and pred (grey) TVDTs. Dots=individual TVDTs predicted from the analysed PDX models.

Comparison with published PFS data from different clinical trials; patient cohorts receiving placebo or active treatments exerting little to no effect were used for comparison with untreated population



CONCLUSIONS: The proposed model-based translational framework provides a powerful tool to i) increase the knowledge on TVDT without the need of further tumor volume measurements; ii) early predict the treatment effect on PFS starting from a panel of TGI studies in PDX mice.

REFERENCES

[1] HuBase database, Crownbio Bioscience Inc., https://www.crownbio.com/).

[2] Simeoni M, et al. Predictive pharmacokinetic- pharmacodynamic modeling of tumor growth kinetics in xenograft model after administration of anticancer agents. Cancer Res. 2004; 64:1094–101.