



Joint Modeling Of Longitudinal Circulating Tumor DNA And Survival In Metastatic Colorectal Cancer: A Promise Of Early Prediction Of Response In Oncology?

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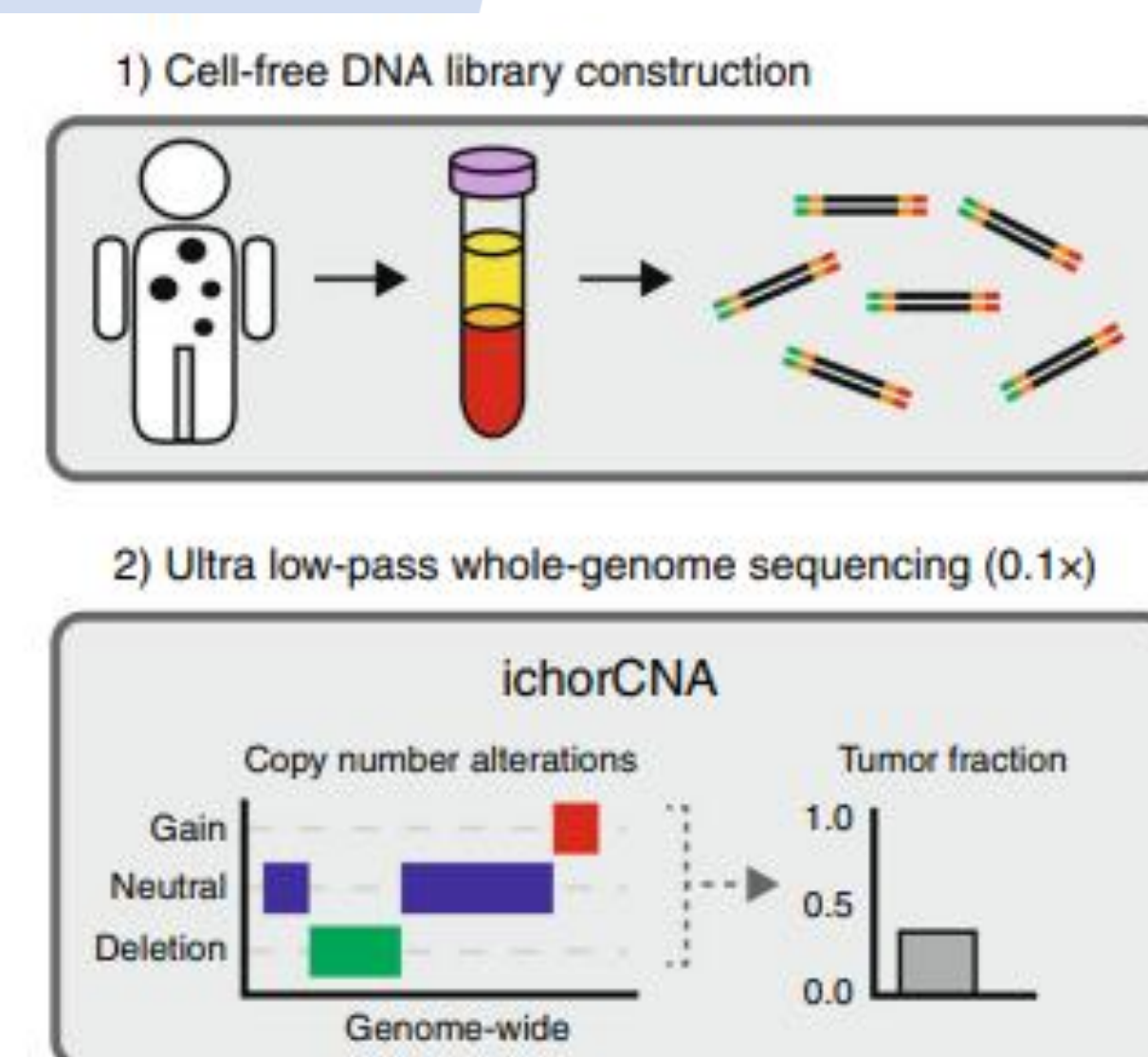
Background

- Circulating tumor DNA (ctDNA) is released by tumor tissues and can be present in plasma and serum of cancer patients. Therefore, ctDNA is collected through minimally invasive blood samples (i.e. liquid biopsies), which can be repeated frequently.
- Published data [1, 2] suggest that ctDNA levels are prognostic of survival. Moreover, ctDNA level changes can be used as a predictive marker of the response to treatments.
- Data integration of ctDNA is emerging and provides significant opportunities to study tumor growth dynamics, to monitor tumor response to therapy, and to detect emerging resistance mechanisms through the appearance of mutant clones.

Objectives: This work aims at exploring through joint modeling the link between the dynamics in longitudinal ctDNA data and the survival of patients with metastatic colorectal cancer receiving various therapies.

ctDNA and Clinical Data

- Plasma samples and associated clinical data were collected retrospectively from 21 patients with colorectal metastatic cancer, undergoing their third line or more of treatment (including VEGF, EGFR or Checkpoint inhibitors).
- For each patient, 4-6 plasma longitudinal samples were available, as well as time to progression (for Progression-Free Survival (PFS) analysis) and time to death (for Overall Survival (OS) analysis).
- Cell free DNA (cfDNA) was extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (QIAGEN). cfDNA libraries were constructed and sequenced on a NextSeq 550 or NovaSeq 6000 (Illumina) for Ultra Low-Pass Whole-Genome Sequencing (ULP-WGS).
- The ctDNA tumor fraction (TF) was determined using the ichorCNA algorithm, a probabilistic aneuploidy-based model for estimating the TF in cfDNA from ULP-WGS [3] with a limit of detection (LOD) of 3% and a limit of quantification (LOQ) of 5%.
- For TF between 3% and 5%, the ichorCNA profiles of individual patients were visually examined and if copy number alterations were consistent across samples, the observed TF was kept and the LOQ was set to 3%.
- Finally, ctDNA TF was converted, using the total concentration of cfDNA, into a concentration in ng/mL of plasma.



Joint ctDNA-Survival Modeling Framework

- Non-linear mixed effects modeling was performed using Monolix Suite 2021R2 to capture and quantify the link between ctDNA dynamics and survival.
- The joint models describing the PFS and OS data were developed in three steps. For each step, the best model was selected according to BICc.
 - 1/ a dynamic model of ctDNA concentrations was selected among standard empirical models describing Tumor Growth Inhibition.
 - 2/ a baseline hazard model of PFS/OS was selected among standard parametric functions (e.g., Gompertz, Weibull, Logistic...).
 - 3/ a link function between ctDNA and PFS/OS was selected among time-dependent (current value or slope of predicted ctDNA levels) or time-independent metrics (parameters of the dynamic ctDNA model).

Results

- A total of 108 ctDNA longitudinal observations were available over a range of 84 to 231 days, with 58 observations below the LOQ. Out of 21 patients, 12 progressions and 7 deaths were observed.

- ctDNA was best described by a two-exponential model with interpatient variability on all parameters:

$$ctDNA(t) = ctDNA_0 * e^{-k_{kill} * t} - 1 + e^{kg * t}$$

- A Weibull model was used to describe the hazard function of PFS and OS and the model predicted current ctDNA levels were found linked to PFS :

$$h(t) = \frac{p}{Te} * \left(\frac{t}{Te}\right)^{p-1} * e^{\beta * ctDNA(t)}$$

- Other link functions (using the slope of ctDNA(t) or kg) were associated with PFS, but with a lower drop in BICc.

- No link function was identified with OS, as only a small improvement in the log-likelihood was observed for some link functions.

Figure 1: Individual predictions (median and 95% prediction interval) of the ctDNA dynamics (green) and the probability of experiencing progression (blue)

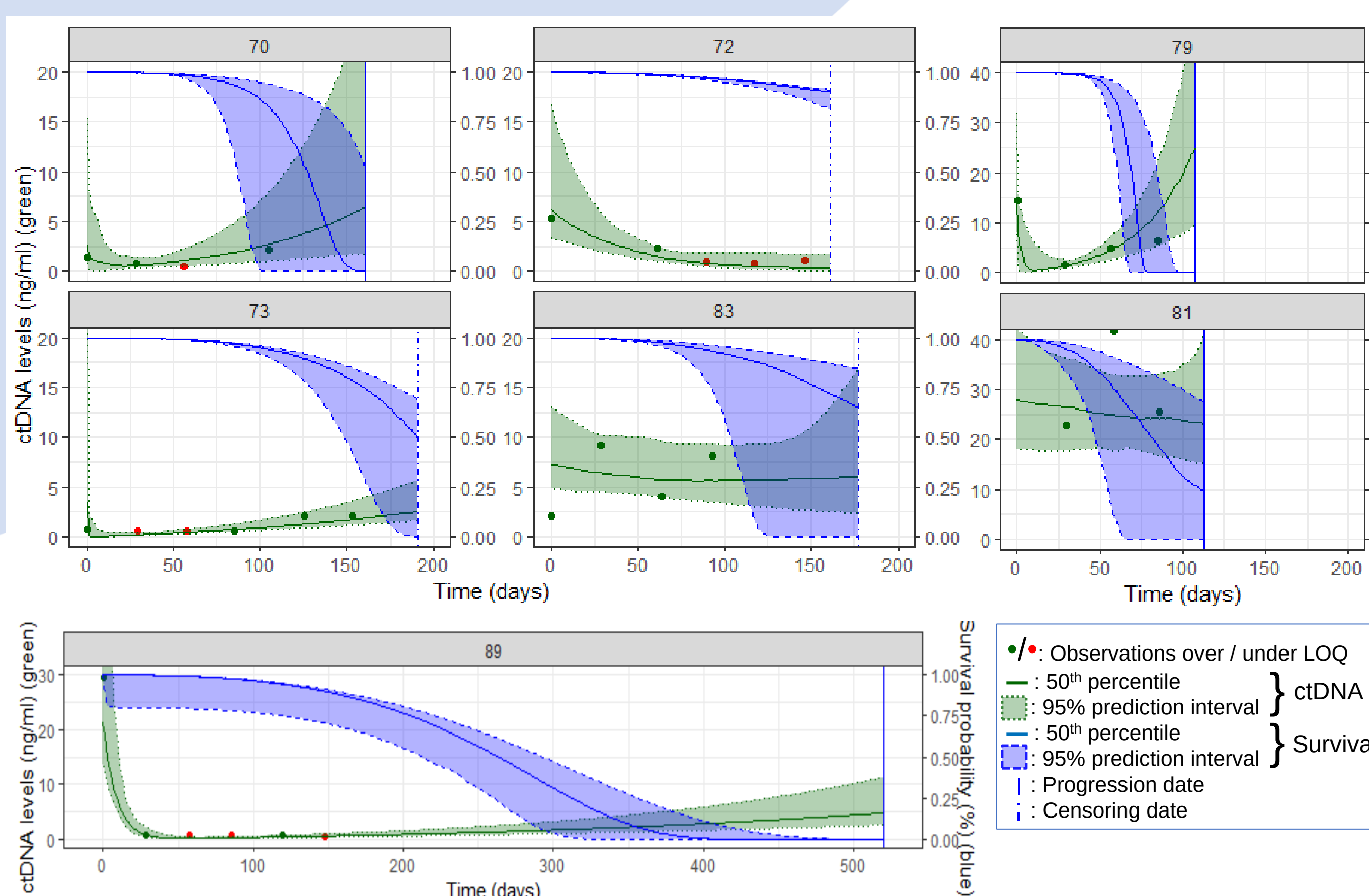
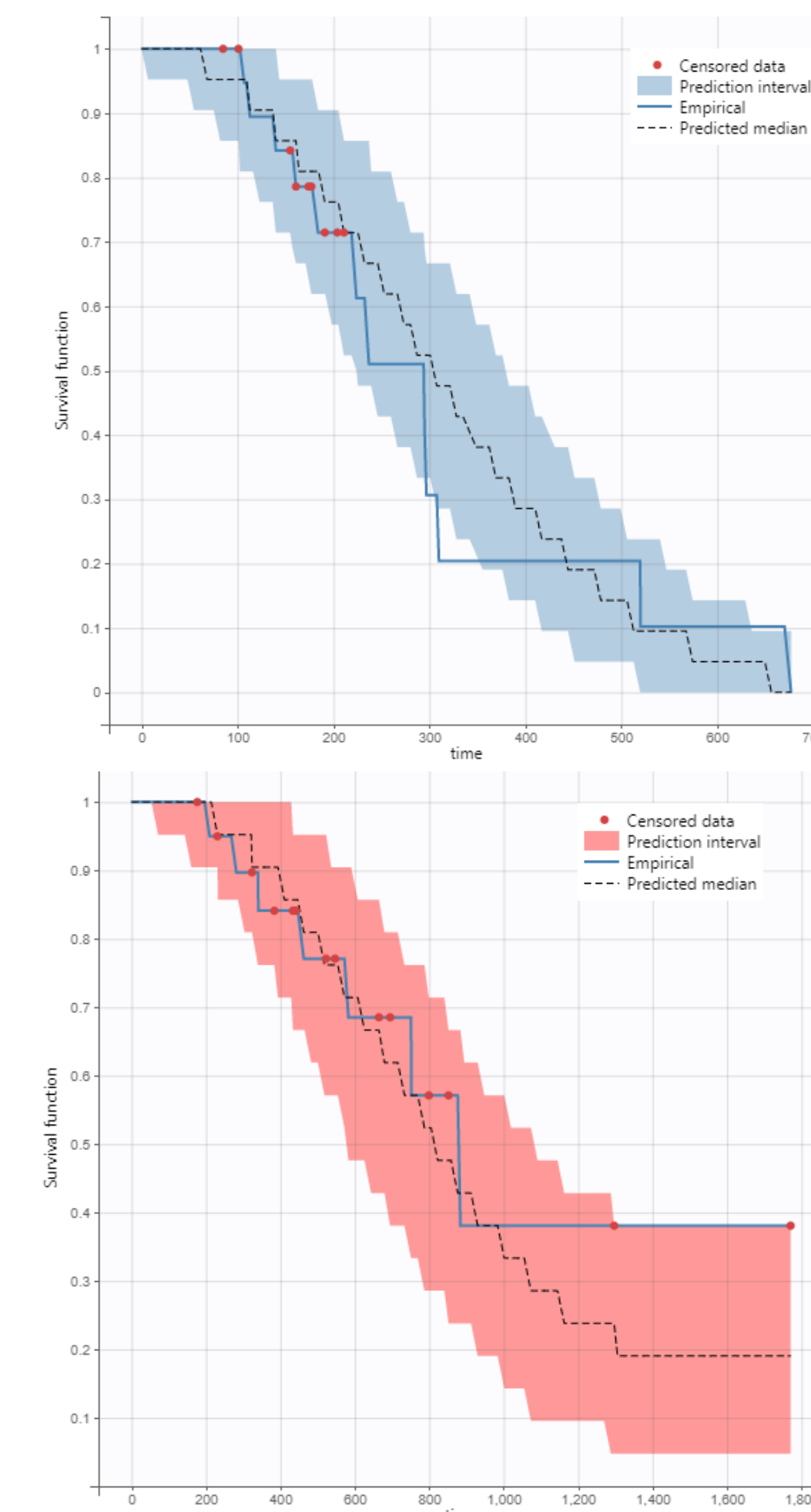


Figure 2: PFS (blue) and OS (red) survival curves by the Kaplan-Meier method with predicted median survival and 95% prediction interval



Conclusion

- The developed joint-modeling framework based on longitudinal ctDNA and survival data showed an association between ctDNA dynamics and PFS.
- PFS is based on the change in tumor size. Therefore, such association confirms the interest in ctDNA levels as a proxy of the tumor burden.
- No association was observed between ctDNA dynamics and OS, that may be due to the limited number of patients and the multifactorial nature of OS. In addition, the time between the last ctDNA observation and the date of death ranged from 125 to 800 days.
- This work shows that the use of minimally invasive blood samples and a cost-effective technology such as low-pass sequencing, when combined with joint modeling, is promising for the early prediction of response in oncology.
- This first exploration of the association between ctDNA and survival through pharmacometrics modeling, that could be refined in the future by integrating information on the exposure to treatments in order to evaluate the impact of various dosing regimens through simulations.

References

- [1] Osumi H et al. Sci Rep. 2019 Nov 22;9(1):17358. doi: 10.1038/s41598-019-53711-3.
- [2] Khan KH et al. Cancer Discov. 2018 Oct;8(10):1270-1285. doi: 10.1158/2159-8290.CD-17-0891
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