

# MODELLING TUMOUR GROWTH AND SURVIVAL OF PATIENTS WITH PANCREATIC CANCER RECEIVING GEMCITABINE

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## BACKGROUND

**Gemcitabine** is a nucleoside antimetabolite anticancer pro-drug that shows activity against several solid tumours. Its main indication given as a single agent is to treat **pancreatic cancer**. Gemcitabine has been chosen as model drug to build a translational approach from early to advanced (clinical) stages in drug development as a part of pillar 3 of working package I (models in oncology) within the IMI7 founded project, Drug Disease Models Resource (DDMoRe).

The aim of this evaluation was: 1) To build a **joint tumour size and survival pharmacokinetic-pharmacodynamic model of Gemcitabine in patients with advanced pancreatic cancer**  
2) To investigate the potential **relationship between the risk of development new metastasis and the overall survival**.

## METHODS

Information related to tumour size and survival was obtained from a clinical phase II and a phase III studies where Gemcitabine was given on standard treatment (1500 mg/kg over 30 min i.v infusion) to patients (n=287) with unresectable pancreatic cancer (locally advanced or metastatic).

Drug exposure of Gemcitabine active metabolite (dFdC-TP) was calculated for each patient using a pharmacokinetic model previously developed.

Tumour size, Survival and Metastasis development versus time data were linked and described using the population approach with NONMEM 7.2. Model evaluation was performed through predictive checks.

Table I. Data summary.

|                          |                                                                                                                                                                                                                              |                    |                            |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------|
| Patients                 | N=287. Advanced, metastatic and unresectable pancreatic cancer.                                                                                                                                                              |                    |                            |
| Dosing Schedule          | STUDY 1: Gemcitabine i.v infusion (30 min) 1000mg/m <sup>2</sup> given once a week x3 + 1week rest per cycle<br>STUDY 2: Gemcitabine i.v infusion (30 min) 1500mg/m <sup>2</sup> given once a week x2 + 1week rest per cycle |                    |                            |
| Lesion Location          | Pancreas= 227 Patients                                                                                                                                                                                                       | Liver=159 Patients | Other location=94 Patients |
| Overall Survival (weeks) | Max= 120.4                                                                                                                                                                                                                   | Mean=45.96         | Median=41.40               |
| New Lesion appearance    | 49 Patients                                                                                                                                                                                                                  |                    |                            |

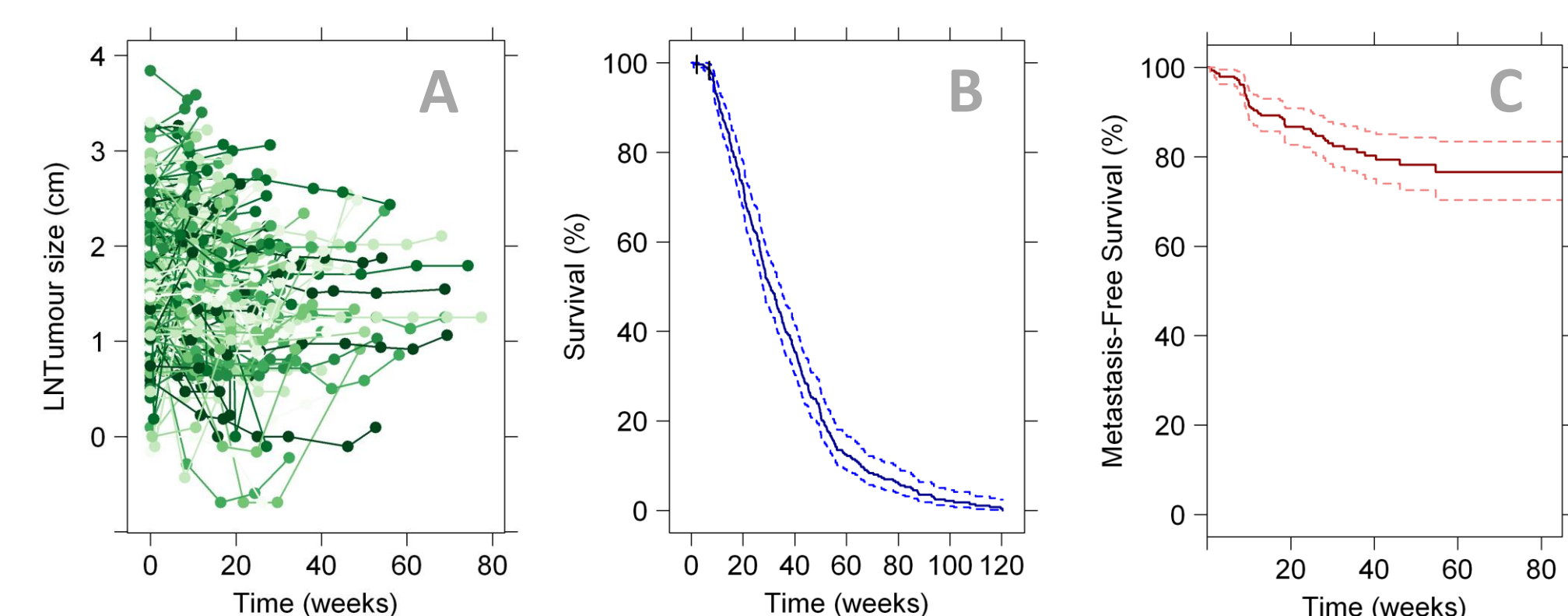


Figure I. Raw data. A) Tumour growth. B) Kaplan Meier Overall Survival. C) Kaplan Meier Metastasis Free Survival

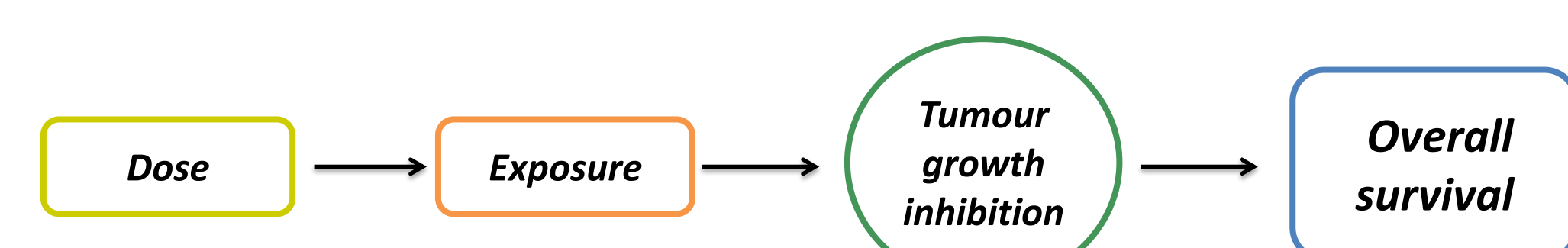


Figure II. Drug-disease framework for clinical oncology drug development.[1] Modelling strategy followed for our analysis

## RESULTS

The model [2] used to describe the tumour mass over time incorporates a disease progression component modelled as an exponential growth, a drug efficacy part dependent of drug exposure represented by the metabolite AUC, together with resistance development. Predicted tumour changes over time were linked to probability of survival as an argument for the hazard, which are described using a Weibull model. Regarding the metastasis analysis, the model was developed taking into account only the first new lesion development and was described with the Weibull model. The study of a possible link between the risk of metastasis development and survival is currently ongoing.

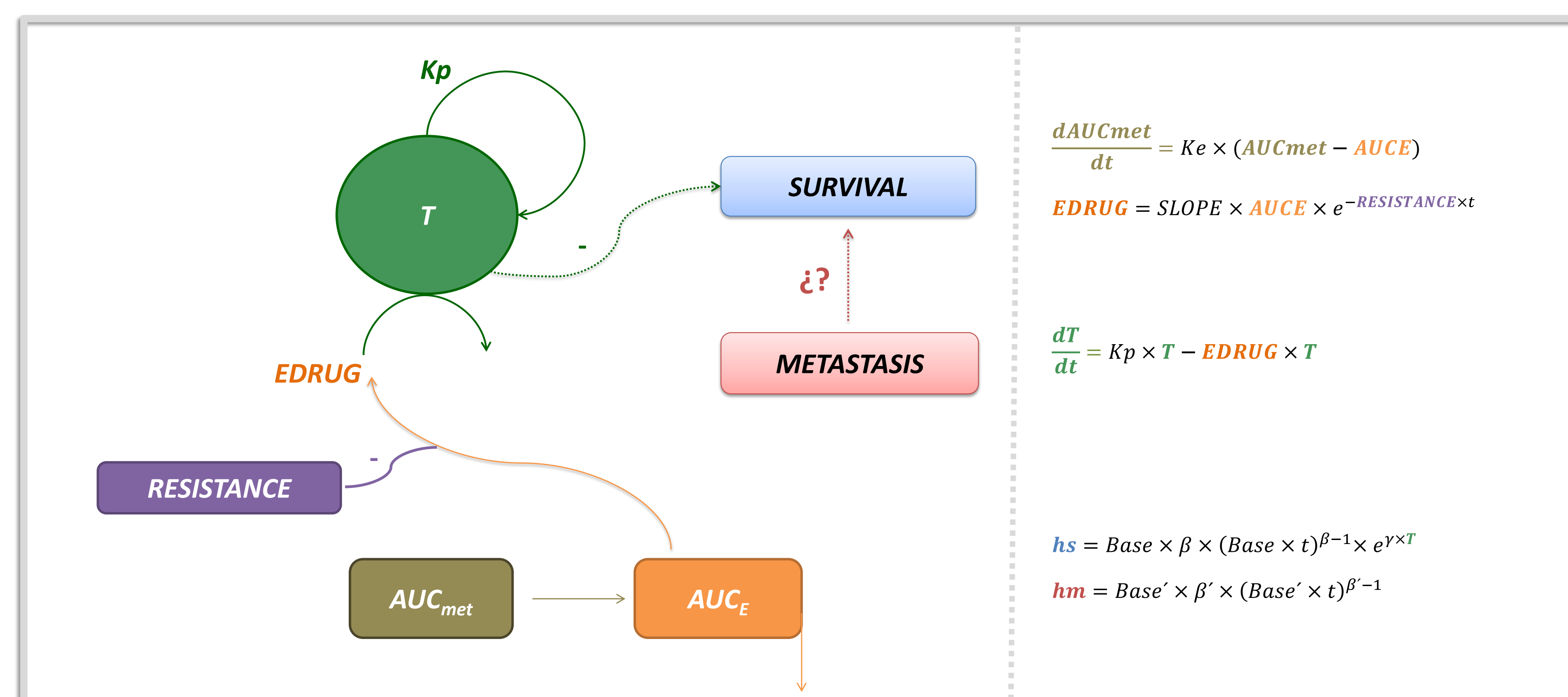


Figure III. Tumour growth PKPD model.

AUCmet, Gemcitabine metabolite exposure, calculated from a pharmacokinetic model. Ke, effect compartment rate constant. AUCe, effective Gemcitabine metabolite exposure. RESISTANCE, drug resistance development. EDRUG, drug effect. T, tumour volume. Kp tumour proliferation rate. SLOPE, drug effect constant. Base & Weibull parameters for survival model. , link tumour-survival rate constant. Base' & Weibull parameters for metastasis model. hs, survival hazard, hm, metastasis hazard.

Table II. Estimated model parameters.

| Parameters                 | Typical estimate      | Variability | Shrinkage (%) |
|----------------------------|-----------------------|-------------|---------------|
| T <sub>0</sub> (cm)        | 5.9                   | 66%         | 6.8           |
| Kp (wk <sup>-1</sup> )     | 1.87x10 <sup>-2</sup> | 90%         | 23.8          |
| Kd (wk <sup>-1</sup> xAUC) | 7.71x10 <sup>-3</sup> | 105%        | 29.7          |
| Ke (wk <sup>-1</sup> xAUC) | 6.24x10 <sup>-3</sup> | -           | -             |
| RES (wk <sup>-1</sup> )    | 1.64x10 <sup>-1</sup> | 64%         | 47.3          |
| Error [log(cm)]            | 1.76x10 <sup>-1</sup> | -           | 19.7          |
| Base                       | 4.47x10 <sup>-3</sup> | -           | -             |
| β (wk <sup>-1</sup> )      | 2.34                  | -           | -             |
| γ (cm <sup>-1</sup> )      | 1.64                  | -           | -             |
| Base'                      | 3.06x10 <sup>-3</sup> | -           | -             |
| β' (wk <sup>-1</sup> )     | 8.31x10 <sup>-1</sup> | -           | -             |

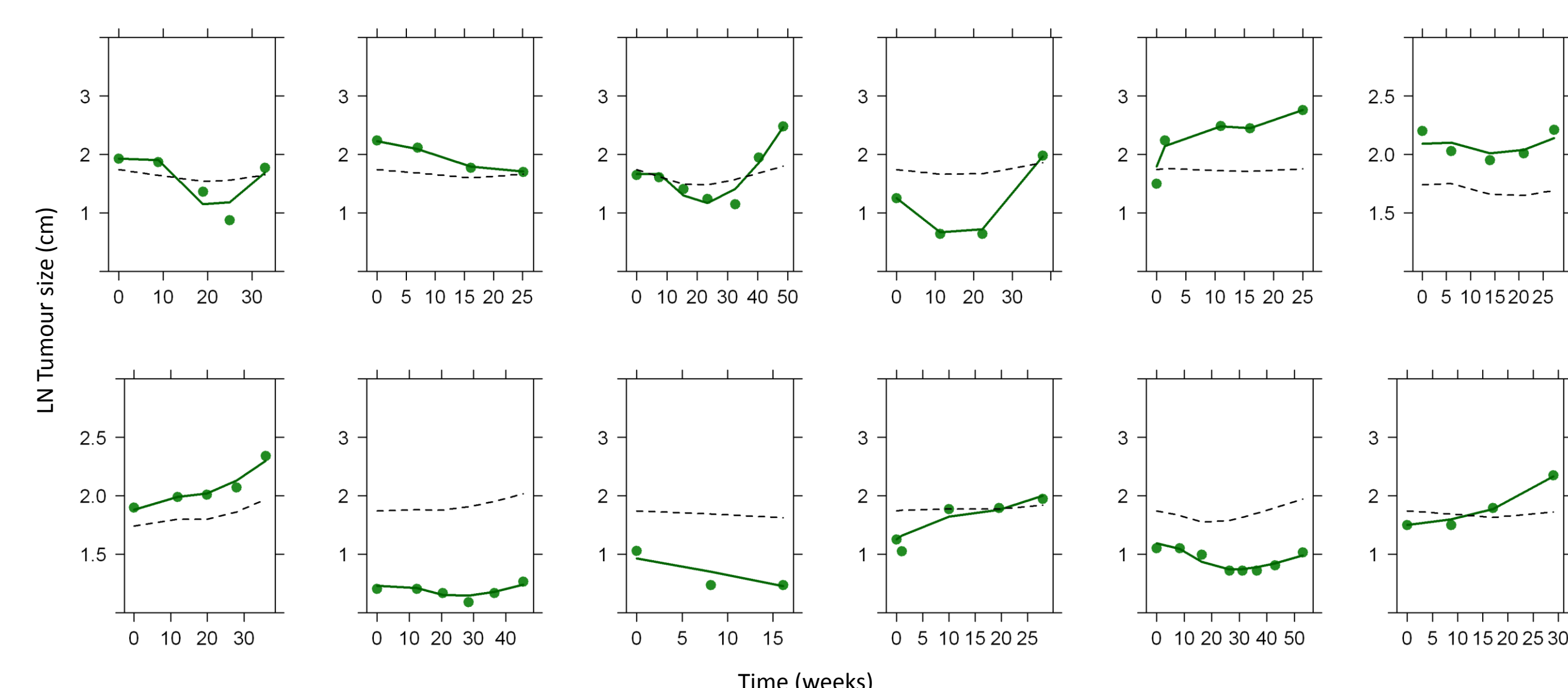


Figure IV. Individual Tumour growth profile. Observation VS Prediction. Points, Individual tumour size observations. Straight line, individual prediction. Dashed line, population prediction.

## CONCLUSIONS & FUTURE PERSPECTIVES

The modelling exercise predicts the efficacy of Gemcitabine in terms of tumour growth inhibition and survival of patients with pancreatic cancer. It is expected to have a potential impact on the development of new anticancer drugs as well as optimizing the standard treatment of patients receiving Gemcitabine, predicting the likelihood of the treatment success and assisting with the dosing regimen selection.

Preliminary modelling work does not show a significant link between the appearance of the first new lesion and survival. Next step will be focus on modelling the risk of development metastasis, as repeated time to event, and evaluate its impact on survival.

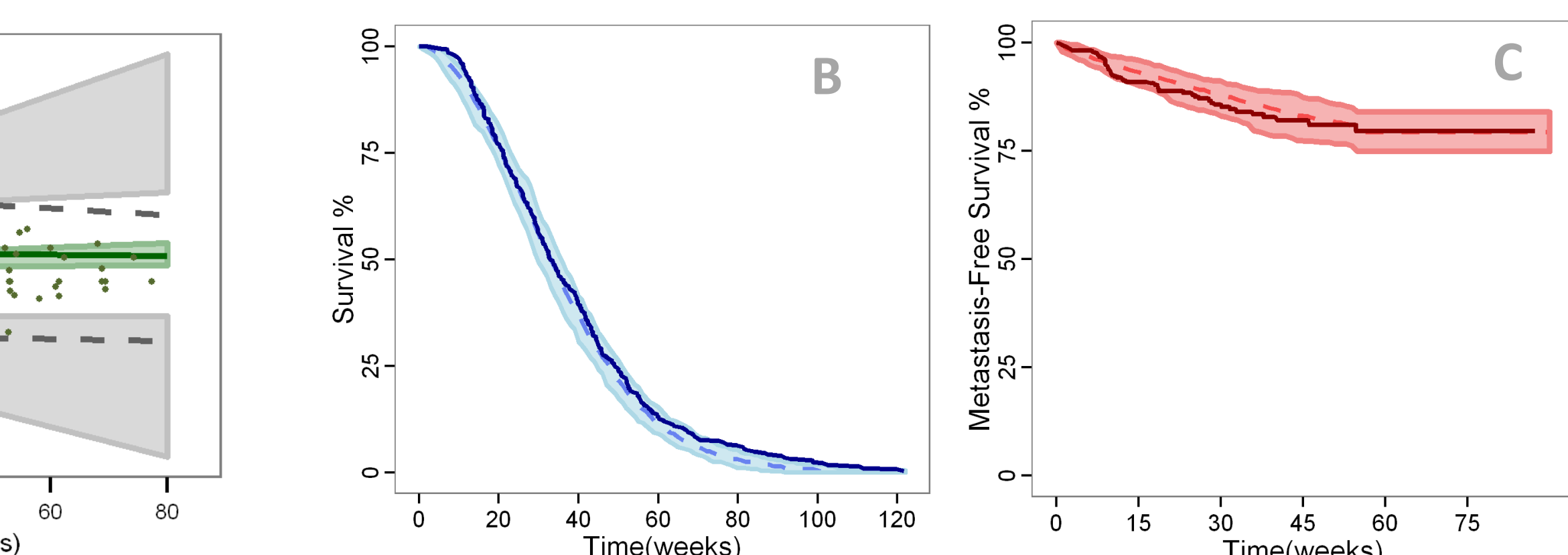


Figure V. Model evaluation. Prediction Visual Predictive Check. A) Tumour growth; Median (solid green line), 5th and 95th percentiles (dashed grey line) of the observed data. 95% confidence intervals for median (shaded green area), 5th and 95th percentiles (shaded green areas) of the simulated data. B) Kaplan meier Overall Survival. C) Kaplan Meier Metastasis Free Survival; Kaplan Meier of observed data (solid line), Kaplan Meier of simulated data at 95% confidence interval (shaded areas).

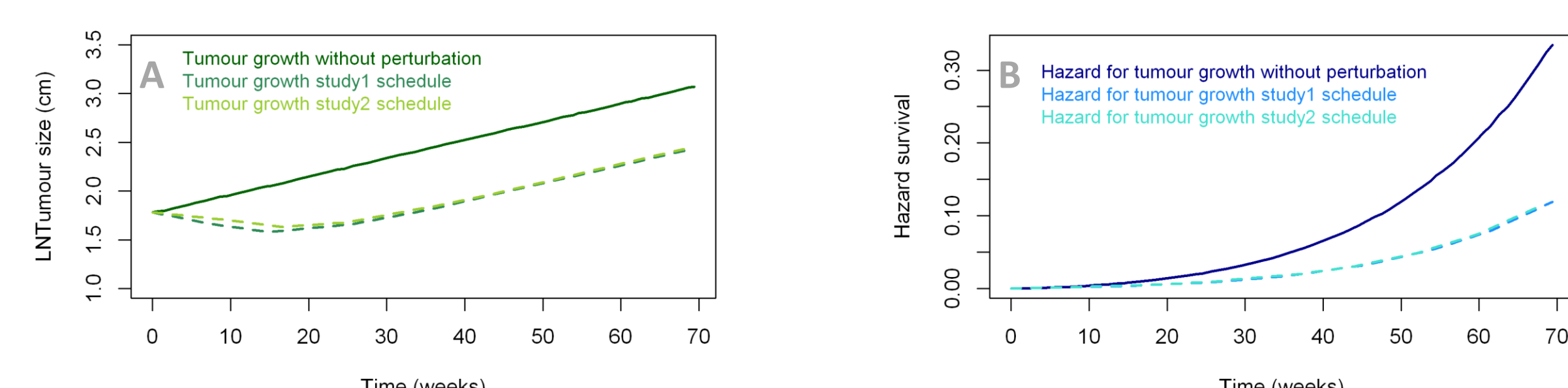


Figure VI. Simulation of Tumour growth (A) and Survival hazard (B). Typical profile without perturbation and after receiving Study1 and Study2 dosing schedule.

## References

- [1] Bruno R. et al. Clin Pharmacol Ther. 86:136-138
- [2] Claret et al. J Clin Oncol 27:4103-4108