Optimal design for informative protocols in xenograft tumor growth inhibition models

Giulia Lestini[1,2], France Mentré[1], Paolo Magni[2]

(1) IAME, UMR 1137, INSERM, University Paris Diderot, Paris, France, (2) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Pavia, Italy

BACKGROUND. The in vivo evaluation of antitumor effect is an important step of the preclinical drug development. Xenograft experiments are performed, but tumor size measurements are usually taken only during treatment [1], preventing a correct identification of certain parameters of Tumor Growth Inhibition (TGI) models. Our aim was to use optimal design approach in TGI models to evaluate the importance of including measurements during the tumor regrowth phase in those studies.

MATERIALS AND METHODS. We considered the Simeoni TGI model [2]. Optimal design was performed for several examples of xenograft experiments in treated and control arms, reported in [2,3], involving different drugs, schedules and cell lines. Various scenarios were studied. Basic scenarios are those with same real settings as in [2,3]. In other scenarios, the parameter related to the cells death rate (k_1), was set larger than the reported value to assess the effect on the experimental design. Finally sampling design was optimized, for each selected experiment, with or without the constraint of not sampling during tumor regrowth, that we defined as "short" and "long" studies, respectively. In the long study, measurements could be taken up to six grams of tumor weight, for ethical reasons, whereas in the short study the experiment was stopped two or three days after the end of the period of treatment. Design optimization was performed using the determinant of the Fisher Information Matrix in PFIM 4.0 [4]. Predicted Relative Standard Errors (RSE) and D-optimal criterion were used to compare those scenarios.

$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 \cdot c(t) \cdot x_1(t) \quad x_1(0) = w_0$$, where w_0 is the tumor weight at inoculation time

$$\frac{dx_2(t)}{dt} = k_2 \cdot c(t) \cdot x_1(t) - k_1 \cdot x_2(t) \quad x_2(0) = 0$$

$$\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)] \quad x_3(0) = 0$$

$$\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)] \quad x_4(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

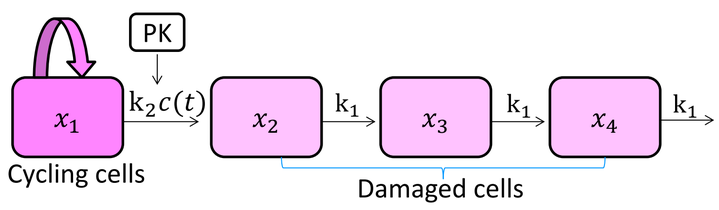

Figure 1: Scheme of the TGI model. k_1, first-order rate constant of transit; k_2, measure of drug potency; c(t), plasma concentration

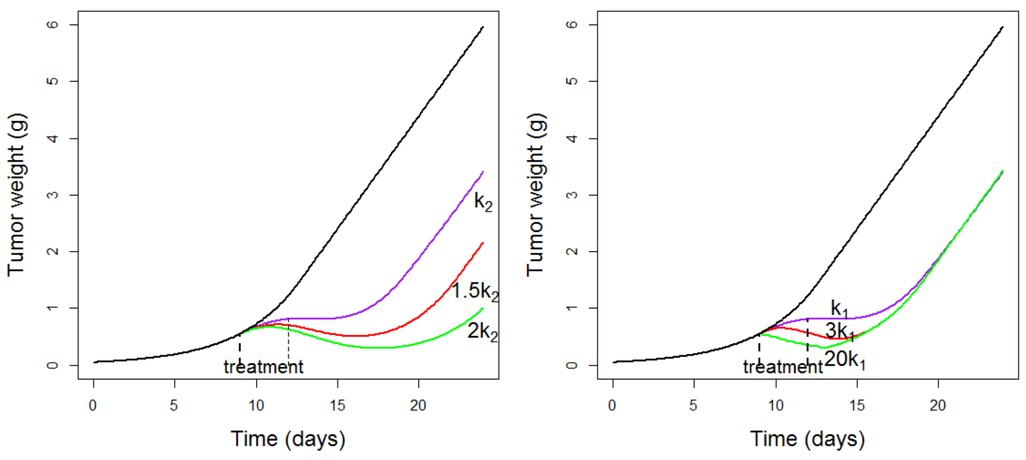

Figure 2: Simulated Simeoni model for control arm (black) and treated arms with different values for parameter k_2 (left) and k_1 (right)

Experiment	Drug administration regimen	Dose	Samipling window treated arm		Optimal designs in treated arm
Exp 1 ref[3], drug A	i.v. bolus – Since day 8, every 4 days, for 3 times. Treat. window: 8-16	30 mg/kg	Long study	8-68 days	8, 28, 63, 68 days
			Short study	8-19 days	8, 12, 18, 19 days
Exp 2 ref[3], drug B	i.v. bolus – Since day 9, twice a day, for 4 days. Treat. window: 9-12	60 mg/kg	Long study	9-29 days	9, 15, 23, 29 days
			Short study	8-15 days	8, 13, 14, 15 days
Exp 3 ref[2], table 2	i.v. bolus – Since day 13, every 4 days, for 3 times. Treat. window: 13-21	30 mg/kg	Long study	9-31 days	9, 15, 23, 27 days
			Short study	9-24 days	9, 16, 22, 24 days
Exp 4 ref[2], table 2	i.v. bolus – Since day 8, every 4 days, for 3 times . Treat. window: 8-16	30 mg/kg	Long study	8-30 days	14, 18, 26, 30 days
			Short study	8-19 days	8, 11, 12, 19 days
Exp 5* ref[2], table 3	i.v. bolus – Since day 8, every week, for 2 weeks. Treat. window: 8-15	50 mg/kg	Long study	8-26 days	8, 20, 24, 26 days
			Short study	8-18 days	8, 12, 17, 18 days
Exp 6* ref[2], table 3	i.v. bolus – Since day 8, every week, for 4 weeks. Treat. window: 8-29	50 mg/kg	Long study	8-44 days	11, 29, 35, 44 days
			Short study	8-31 days	12, 28, 30, 31 days
Exp 7 ref[2], table 5	i.v. bolus – Since day 13, twice a day, for 5 days. Treat. window: 13-17	15 mg/kg	Long study	9-23 days	9, 14, 20, 23 days
			Short study	9-20 days	9, 15, 19, 20 days
Exp 8 ref[2], table 5	Since day 9, 7 days of infusion. Treat. window: 9-15	83 mg/kg/day	Long study	8-32 days	8, 18, 22, 24 days
			Short study	8-17 days	8, 11, 16, 17 days
Exp1 Pop ref[3], drug A	i.v. bolus – Since day 8, every 4 days, for 3 times. Treat. window: 8-16	30 mg/kg	Long study	8-68 days	8, 23, 58, 63 days
			Short study	8-19 days	8, 12, 18, 19 days
Exp 2 Pop ref[3], drug B	i.v. bolus – Since day 9, twice a day, for 4 days. Treat. window: 9-12	60 mg/kg	Long study	9-29 days	9, 15, 23, 29 days
			Short study	8-15 days	8, 13, 14, 15 days

Table 1: Selected experiments from reference [2] and [3]. Those with (*) have parameter k_1 10 fold bigger than the reported value. Optimal times for Exp 1 Pop and Exp 2 Pop were obtained using the population Fisher information matrix, considering 4 or 7 mice, respectively, in both control and treated arms. For the other experiments only an individual was included in each arm

RESULTS As expected, predicted RSE and D-optimal criterion obtained in long studies were better compared to those obtained in the short study of the corresponding experiments. Indeed, some optimal times were located in the regrowth phase, highlighting the importance of continuing the experiment also after the end of the treatment.

Exp 1

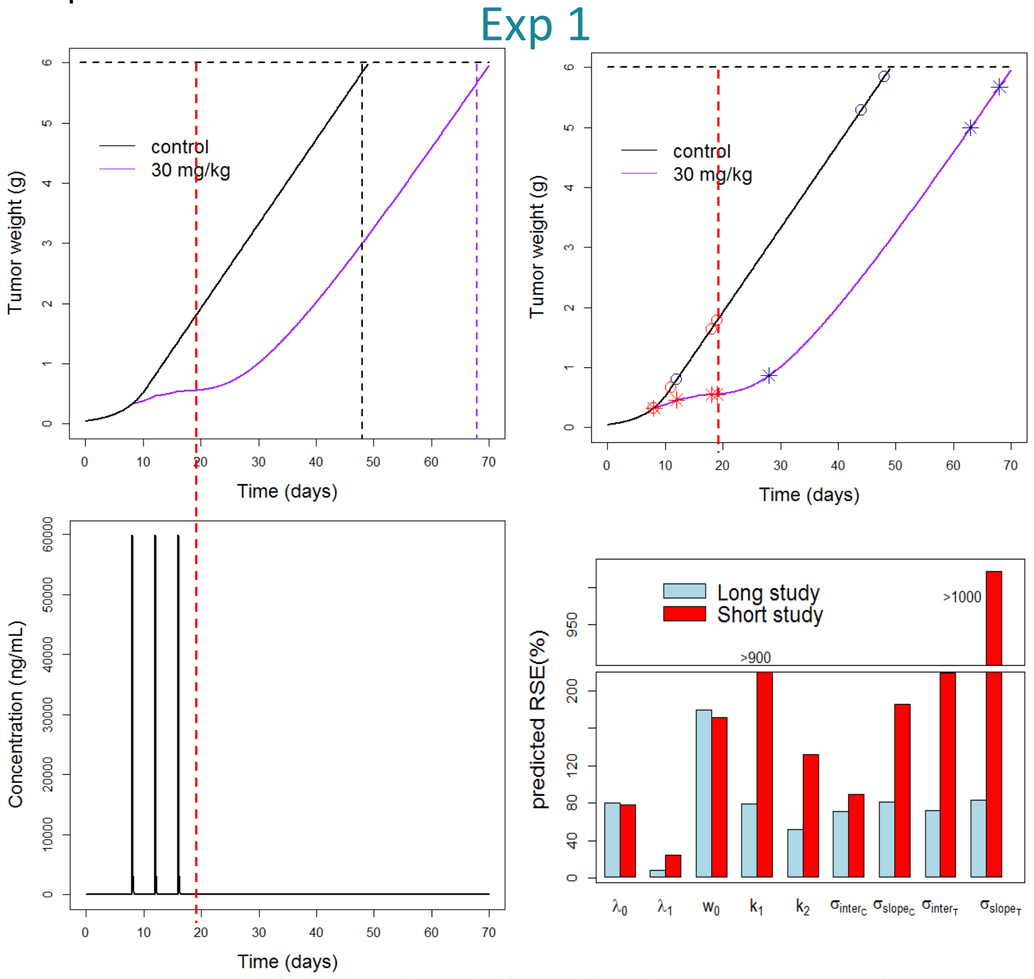

Figure 3: Simulated PK (bottom left) and PD (top left) for Exp 1; Optimal times (top right) in the long study (blue symbols) and short study (red symbols) and predictive RSE (%) in all parameters (bottom right). Red dashed lines define the time point where the short study ends, whereas dashed black and purple lines define the time points where long study ends for control and treated arm, respectively.

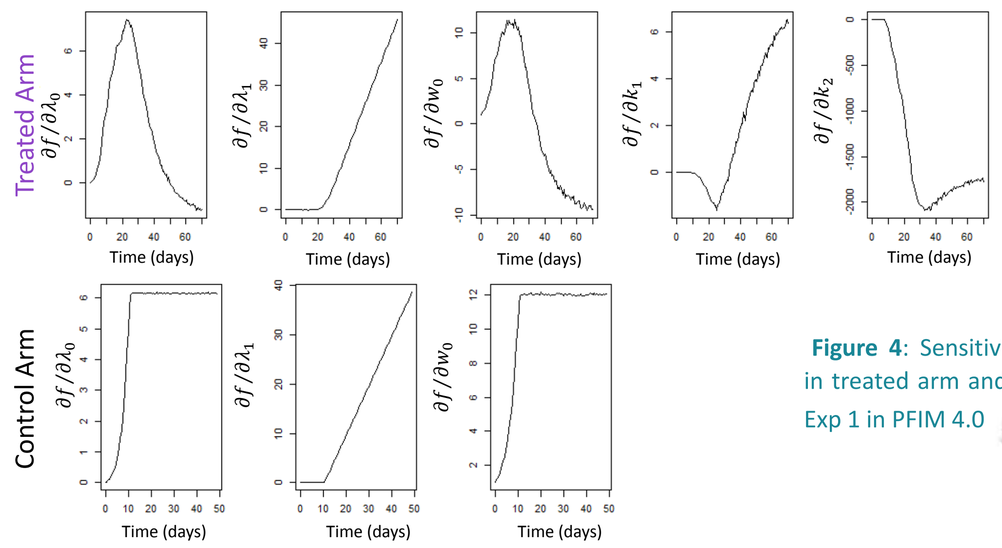

Figure 4: Sensitivity graphs for parameters in treated arm and control arm obtained for Exp 1 in PFIM 4.0

Summary

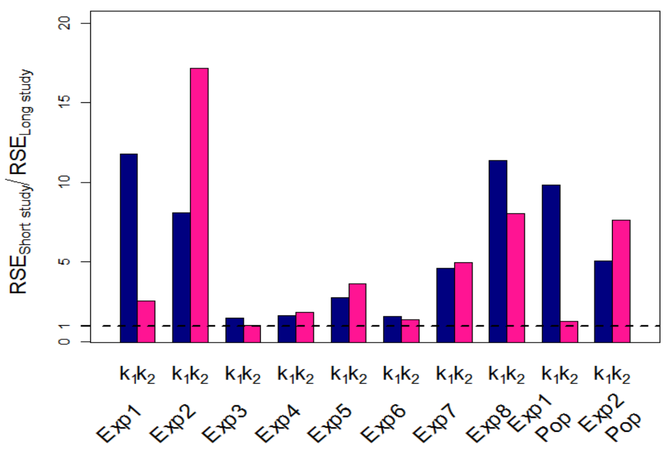

Figure 5: Ratio of predicted RSE of short study to long study for two parameters k_1 (blue bars) and k_2 (pink bars) for the selected experiments

CONCLUSIONS Based on results obtained here, making measurements during tumor regrowth should become a general rule for more informative preclinical studies in oncology.

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