

TOWARDS A PLATFORM PK/PD MODEL FOR AN ANTI-PD-L1 MONOCLONAL ANTIBODY THROUGH A PRECLINICAL SYNGENEIC MELANOMA MOUSE MODEL

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BACKGROUND

Programmed death ligand-1 (PD-L1 or B7-H1) is a co-stimulatory molecule which is expressed at higher levels in tumor cells [1]. PD-L1 and its receptor PD-1 at the activated lymphocytes, play a critical role in T-cell regulation to enhance immune activity and therefore anti-tumor activity [1]. Recently, PD-L1 pathway has been proposed as a novel anti-tumor strategy. The blockage of the PD-1/PD-L1 interaction by a targeted molecule is able to increase tumor-specific cytotoxic T cell (TCT) response [1, 2]. Therefore, the development of anti-PD-L1 monoclonal antibodies (mAbs) arises as an effective approach for specific tumor immunotherapy [3]. Hence, pharmacokinetic and pharmacodynamic characterizations of these mAbs are essential. In that sense, infiltration level and functionality of TCT seem to be critical factors to enhance anti-tumor effect [4]. This suggests that TCT might be used as biomarkers for efficacy.

HYPOTHESIS AND OBJECTIVE

Hypothesis: Anti-PD-L1 immunotherapy enhances anti-tumor effect thought the activation of tumor-specific lymphocytes able to promote tumor cell death.
Objective: To develop a semi-mechanistic PK/PD model to describe the anti-tumor effect induced by an anti-PD-L1 mAb administered to melanoma tumor bearing mice.

MATERIAL AND METHODS

Cell line: B16-OVA syngeneic melanoma cell line, PD-L1⁺ (characterized by flow cytometry).
Treatment regimen: 100µg/mouse, I.V. Q3D x 4 administrations (one cycle).
Animals and samples: Female C57BL/6 mice (6-8 weeks of age) inoculated S.C. with 5x10⁵ cells/100µL/mouse in right flank (figure 2).
• **mAb Serum PK and OVA-CD8⁺ expression:** At different time points (10 min - 72h), 3 animals were sacrificed to measure mAb's serum concentrations by ELISA and OVA-CD8⁺ cell's population in tumor by flow cytometry.
• **PD:** A total of 48 animals randomized in 4 groups (12 animals/groups) were used to evaluate the anti-tumor activity of the mAb. The groups were: G1 – control (not treated) and G2- small, G3 – medium and G4 – large, corresponding to different initial tumor size at the day of treatment (3, 7 and 11 after tumor cell inoculation, respectively).
Data analysis and model development: The preliminary semi-mechanistic PK/PD model has been developed using Berkeley Madonna software. Model parameters listed in table 1 were obtained to describe mAb's serum concentrations, OVA-CD8⁺ time profile and the tumor growth kinetic (data Log-transformed) of the different groups. R software was used to simulate the different profiles shown in figures 3 and 5.

RESULTS

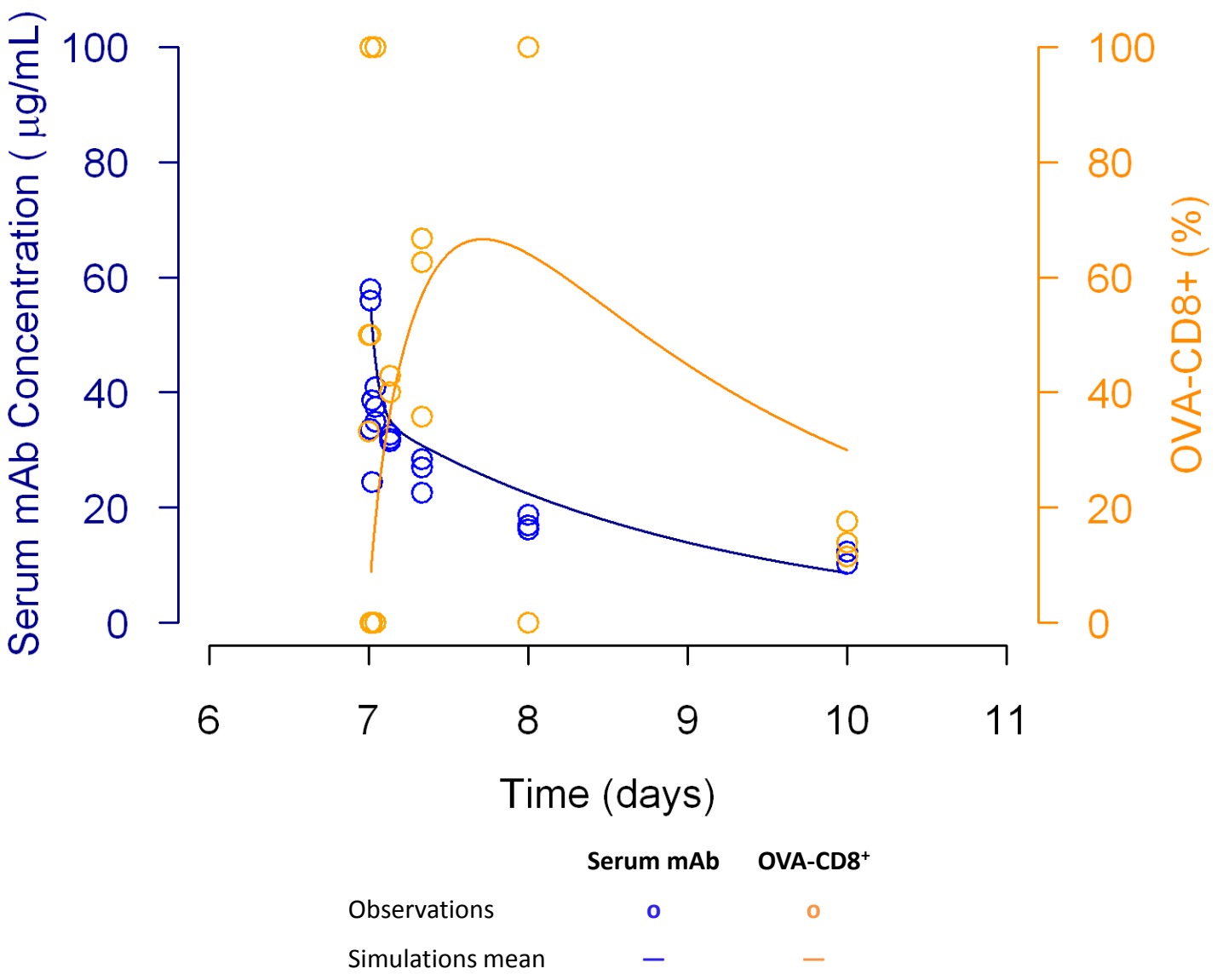


Figure 3. Simulated time profiles of mAb's serum concentrations and OVA-CD8⁺ tumor expression

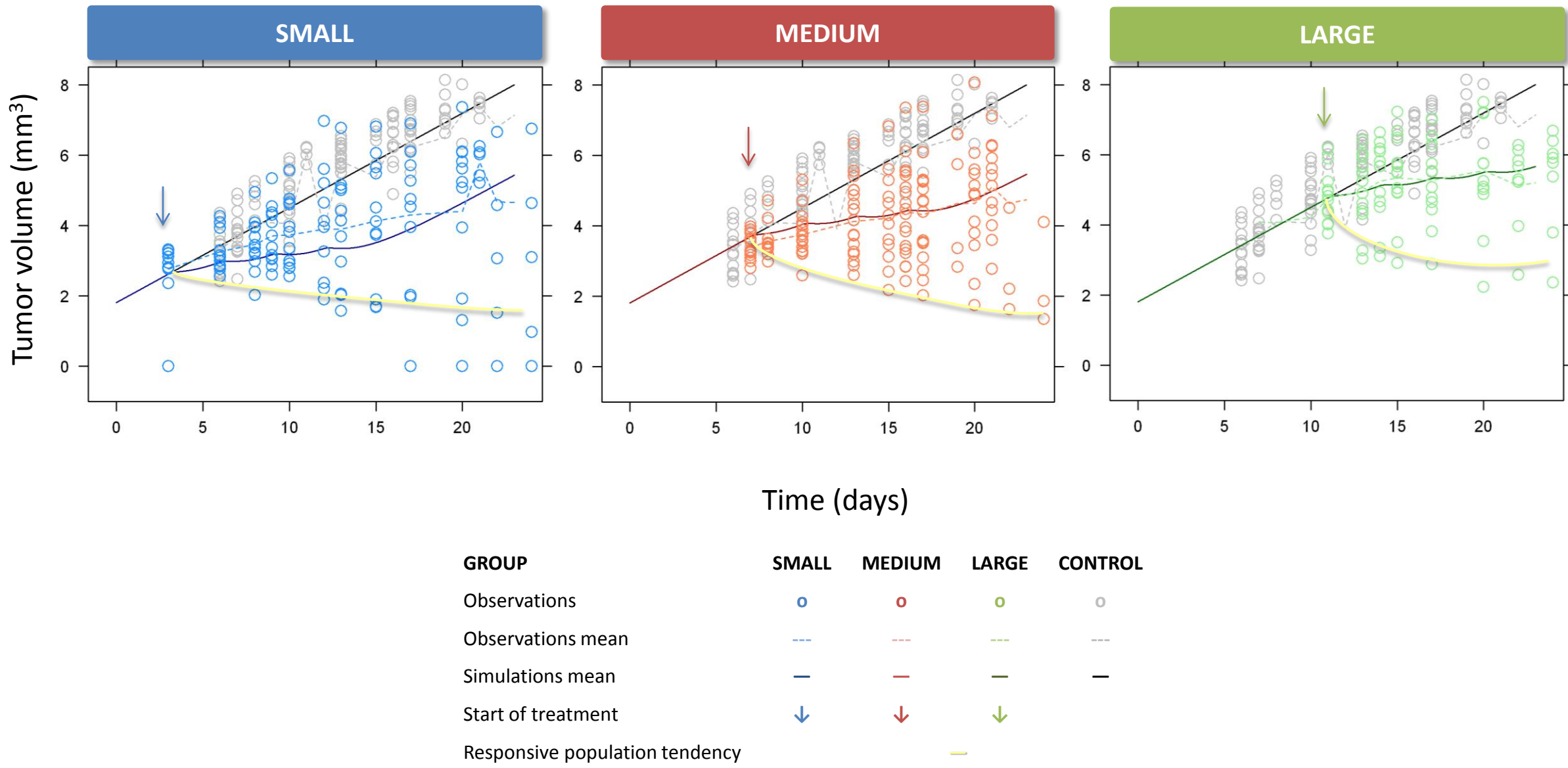


Figure 4. Simulated time profiles of tumor growth for the different treated groups

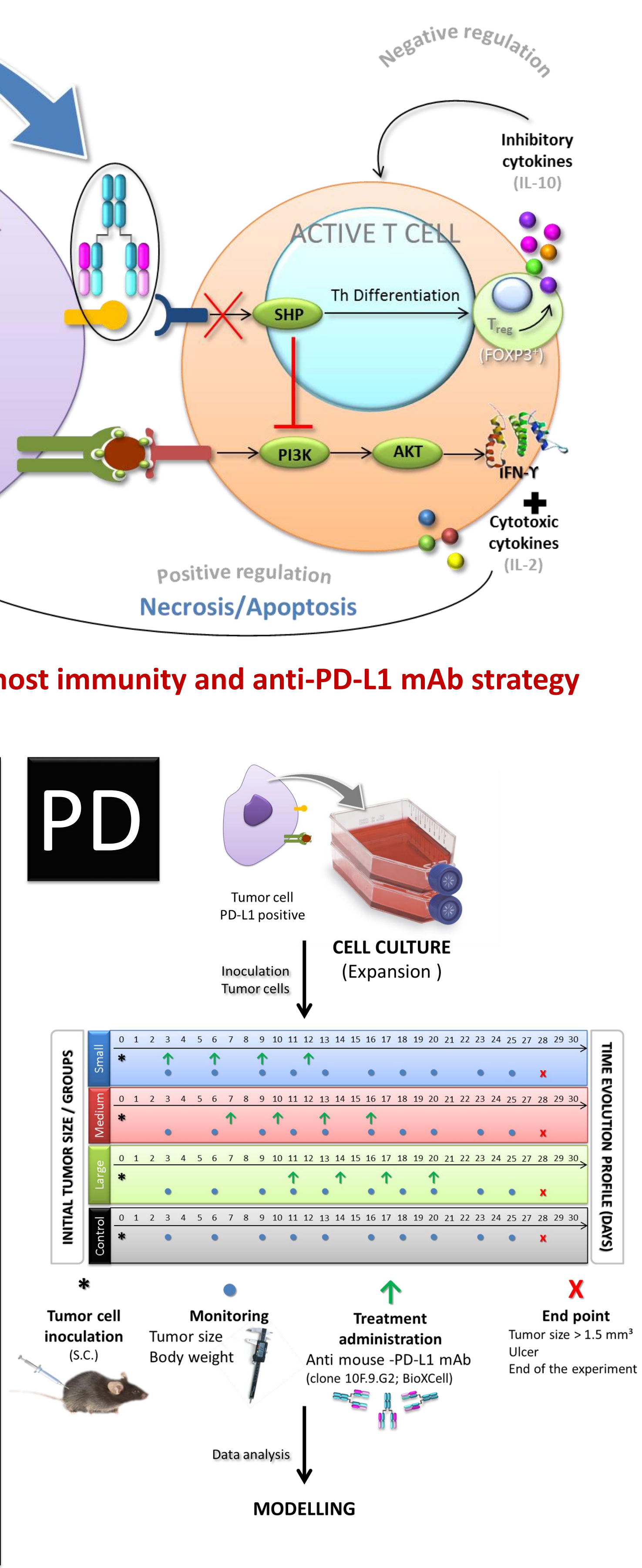


Figure 5. Kaplan Meier survival curve for all the groups of the study

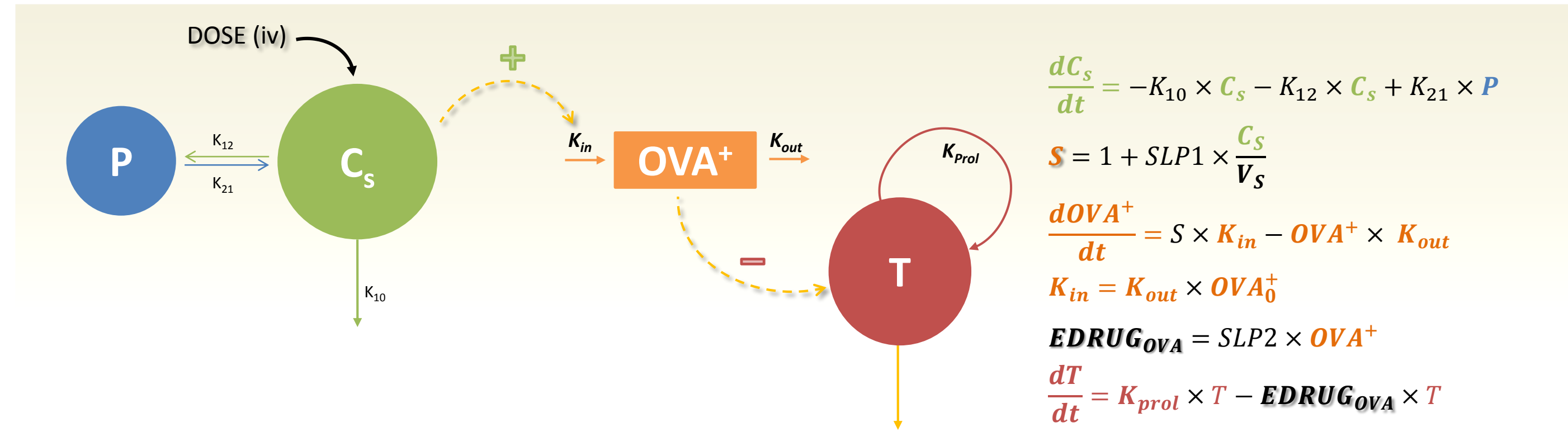


Figure 6. Schematic and mathematical representation of the PK/PD model proposed for an anti-PD-L1 mAb. P: Peripheral compartment, K₁₂ and K₂₁: First order of rate constant of inter-compartmental equilibrium, C_s: mAb amount in central compartment (serum), K₁₀: First order rate constant of drug elimination, K_{in} and K_{out}: First order rate constant of synthesis and degradation of OVA⁺ (OVA-CD8⁺), OVA⁺: Tumor-specific lymphocytes in transit compartment, K_{prol}: First order rate constant of tumor growth, T: Tumor, +: Up-regulation, -: Down-regulation.

CONCLUSIONS

- Anti-PD-L1 mAb treatment promotes an increase in the level of expression of infiltrated tumor-specific lymphocytes (OVA-CD8⁺). This seems to be responsible of the enhanced anti-tumor effect shown in figures 3 and 6.
- The survival reached at day 40 by the three treated groups was 20% (figure 5). This suggests that the survival due to the treatment does not dependent on the initial tumor size.

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FUTURE APPROACHES

- To refine the current proposed model:
- To assess the relationship between OVA-CD8⁺ levels of expression and the anti-tumor activity.
 - To study the OVA-CD8⁺ levels of expression during one cycle of treatment.
 - To characterize the PK of the mAb within the tumor.

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