PK-PD MODELLING OF AN ANTI-PD-L1 MONOCLONAL ANTIBODY

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BACKGROUND AND AIM

Programmed death-1 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-inhibitory activity, and therefore anti-tumor activity **[1]**. PD-1/PD-L1 binding is able to enhance lymphocyte apoptosis (effector T cells) and tumor proliferation by inhibition of cytokines production such as interleukin (IL)-2 and interferon gamma (IFN-Ɣ) **[1, 2]**.

Therefore, although overexpression of PD-L1 in tumor cells allows the use of this pathway as a mechanism to escape from immune response **[1, 2]**. This PDL-1 pathway had been also proposed as a novel anti-tumor strategy, being possible to block the PD-1/PD-L1 interaction by a targeted molecule in order to increase tumor specific T-cell response **[1, 2]**.

Nowadays, the development of anti-PD-L1 monoclonal antibodies (mAbs) arises as an effective approach for specific tumor immunotherapy **[3]**, so that its pharmacokinetics and pharmacodynamics characterizations are essential.

Hence, the aim of this work was to develop a mAb targeted to PD-L1 PK/PD model able to characterize its anti-tumor effect based on different initial tumor sizes (Ts).

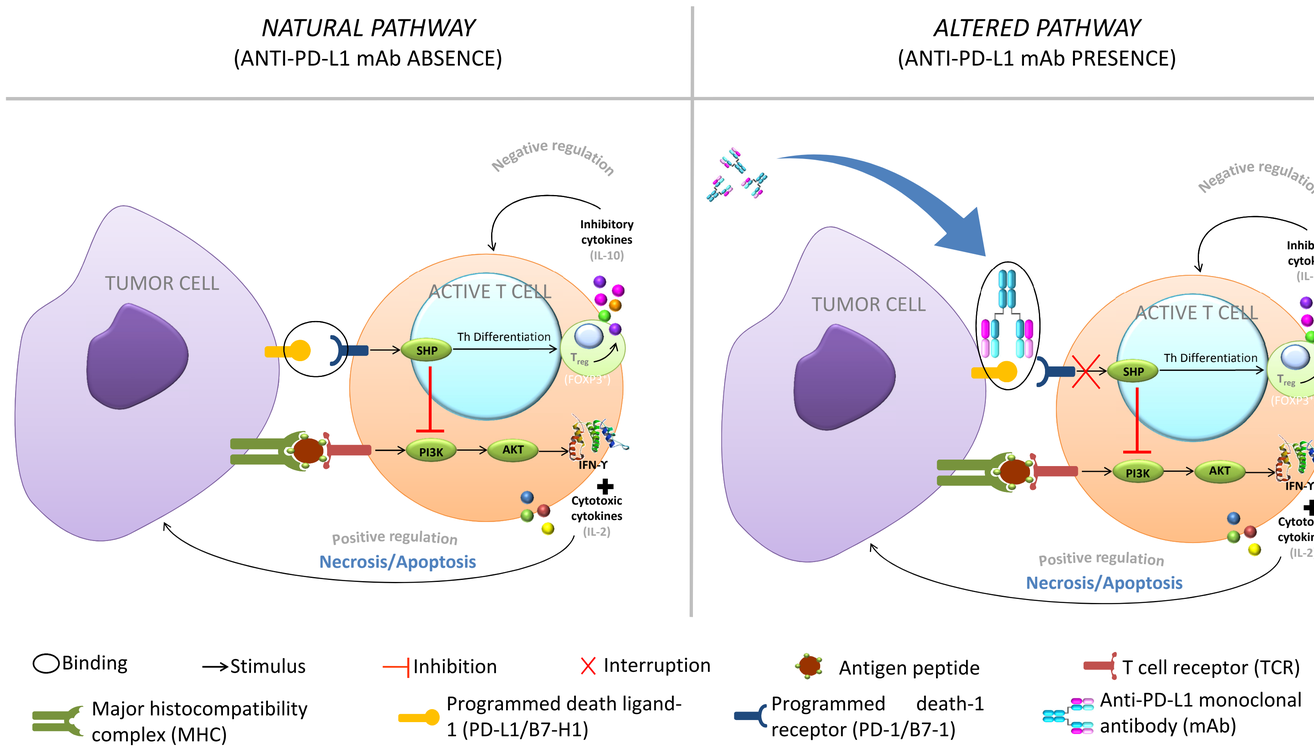

Figure 1. **Mechanism of tumor evasion from host immunity and anti-PD-L1 mAb strategy**

MATERIALS AND METOHODS

Drug administration: 100µg/mouse, I.V. single dose.

Animals and samples: 6 female C57BL/6 mice, were administrated with the drug and serum samples were taken at specific times based on several extraction windows for every animal.

Data analysis: One compartmental model was used to describe plasma concentrations of mAb in mice.

Animal model: B16-OVA melanoma cell line, PD-L1 positive.

Animals: C57BL/6 mice, were randomly divided into four groups (n = 7/group): G1) small Ts, G2) medium Ts, G3) large Ts and G4) control group.

Tumor cells inoculation: $2x10^5$ (CN_1) and $5x10^5$ (CN_2) B16-OVA cells/100µL/mouse were S.C. inoculated on day 0 in one flank of every mouse.

Treatment regimen: 100µg/mouse, I.V. Q3D x 4 administrations.

Data analysis: Time profiles of tumor volume (mm^3) data were fit using the Hahnfeldt´s model **[4].**

For PK/PD modelling, all data were log transformed and the analysis was done using NONMEM 7.2. and R program for graphs.

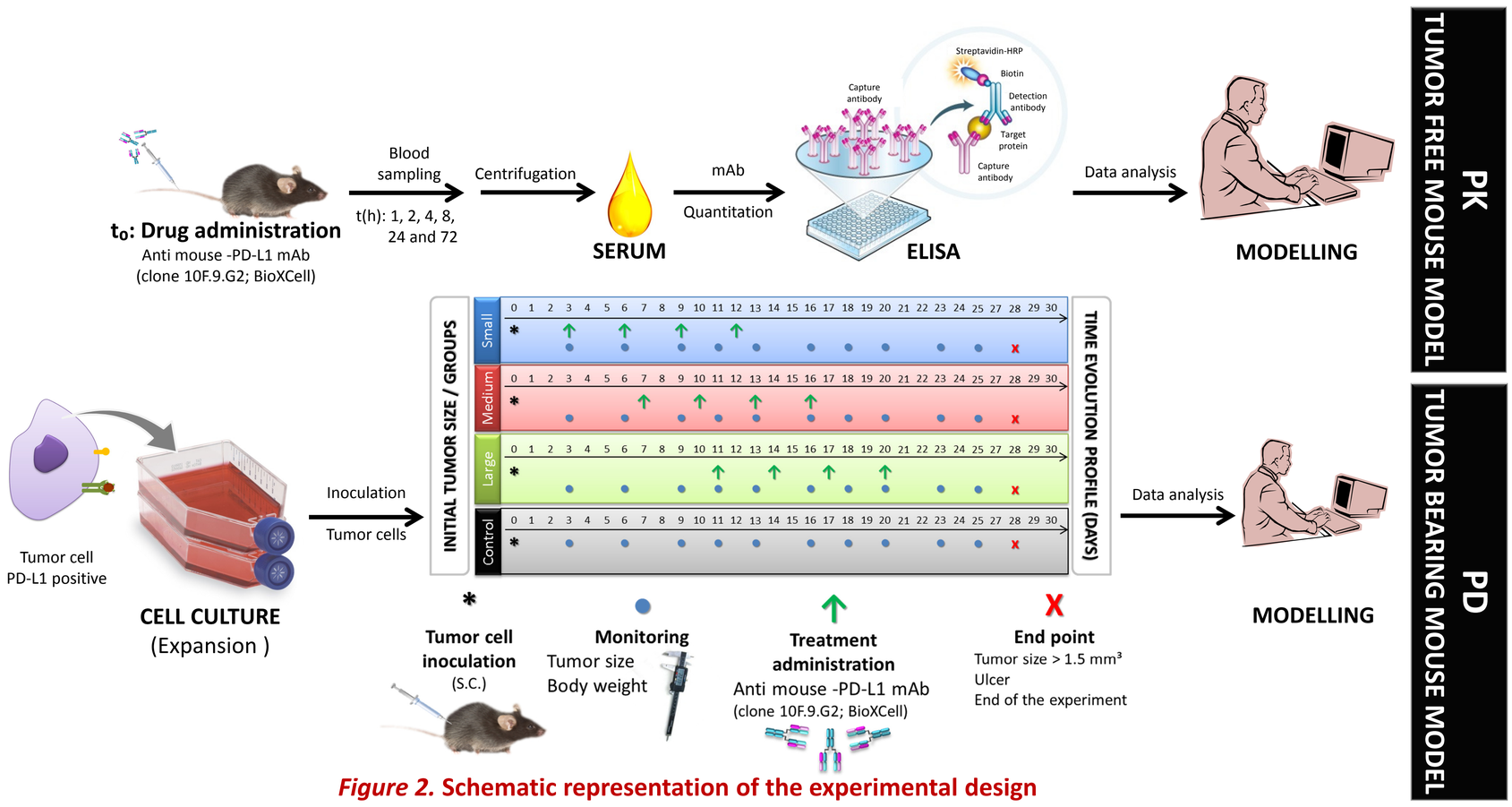

Figure 2. **Schematic representation of the experimental design**

RESULTS

PK MONOCOMPARTIMENTAL MODEL

Table 1. **PK model parameters**

Parameter	Estimates	RSE (%)
CL (mL/h)	0.088	17.7
V (mL)	3.88	10.3
Res. error (µg/mL)	0.449	6.9
IIV_CL (%)	35.4	15.7

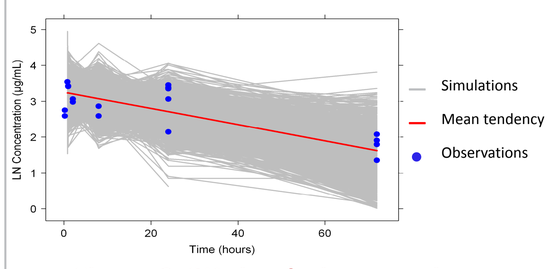

Figure 3. **PK simulation exercise**

*Table 2. PK/*PD model parameters

Parameter	Estimates	RSE (%)
α_1 ($days^{-1}$)	0.596	48.7
CN_1 (mm^3)	20.7	30.2
CN_2 (mm^3)	5.35	49
k (mm^3)	0.504	67.7
b ($days^{-1}$)	0.503	8.5
d ($days^{-1}(mm^3)^{-⅔}$)	0.00044	56.4
Res. error (mm^3)	0.416	6.6
SLOPE (µg/mL)	0.0119	2
γ	0.216	28.7
IIV_α_1 (%)	80.4	37.6
IIV_CN_1 (%)	87.4	25.6
IIV_CN_2 (%)	86.8	96.3

***α_1**: tumor proliferation. **CN_1:** initial tumor size for control population 1. **CN_2:** initial tumor size for control population 2. **k:** carrying capacity or vasculature. **b:** stimulatory capacity of the tumor upon the inducible vasculature. **d:** endogenous inhibition of previously generated vasculature. **w:** residual error. **SLOPE:** drug effect constant. **γ:** shape parameter*

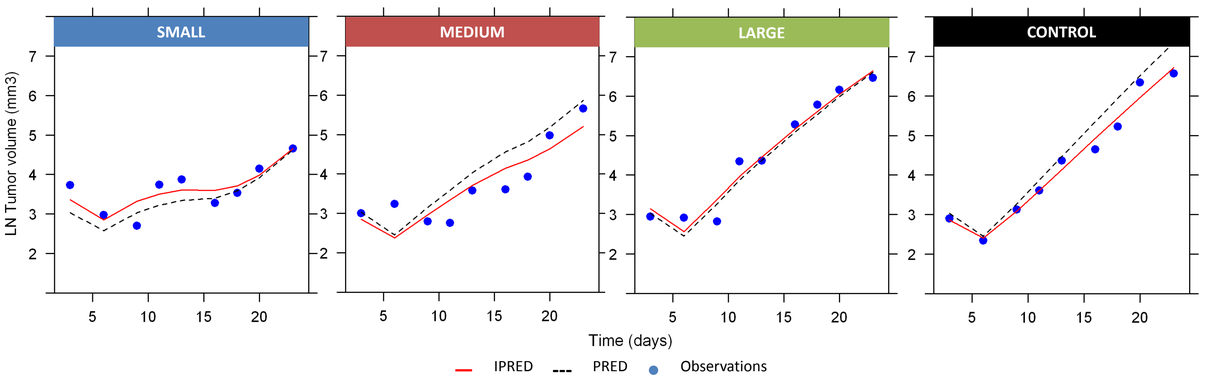

Figure 5. **Individual PK/PD predictions of the model for each group**

$$\frac{dT}{dt} = -\alpha_1 \times (1 - E_{DRUG}) \times T \times Log\left(\frac{T}{K}\right)$$

$$\frac{dK}{dt} = -\alpha_2 \times K + b \times T - d \times K \times T^{2/3}$$

$$E_{DRUG} = SLOPE \times Cs \times \left(\frac{T_0}{T}\right)^{\gamma}$$

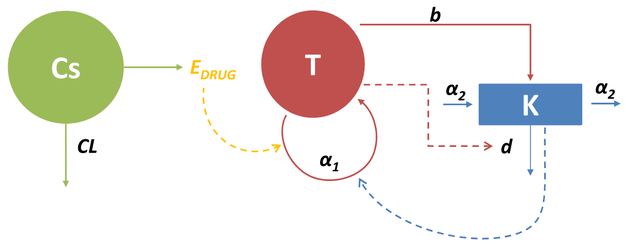

Figure 4. **Schematic representation of the PK/PD model for and anti-PD-L1 mAb**

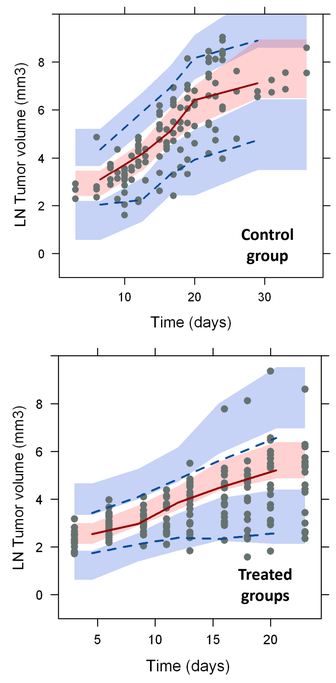

Figure 6. PRED corrected VPC

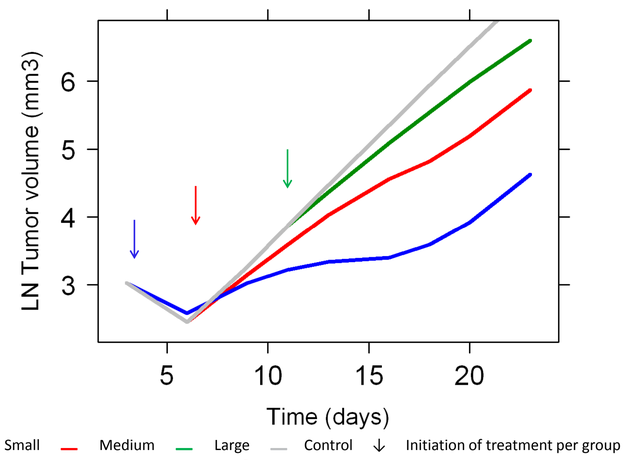

Figure 7. Population PK/PD predictions of the model for each group

CONCLUSIONS

1. The body disposition of the anti-PD-L1 mAb (clone 10F.9.G2) was described by a mono-compartimental model
2. The tumor growth of a B16-OVA mouse model was described by the Hanhfeldt model.
3. The proliferation rate of B16-OVA cells was affected by the anti-PD-L1 mAb (clone 10F.9.G2) inducing a delay on the tumor growth and that effect was dependent on the initial tumor size.

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