Prediction of PD-L1 receptor occupancy in the tumor with PBPK/RO model of PD-L1 inhibitors

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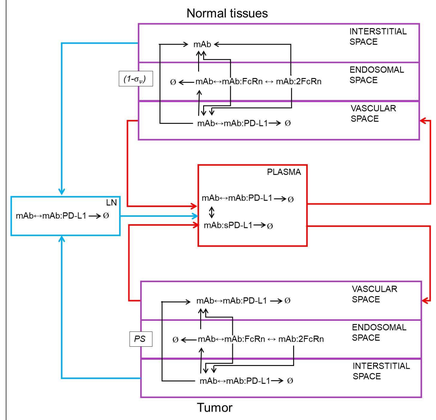
INTRODUCTION AND AIMS

Measurements of receptor occupancy (RO) are believed to provide the necessary information on the pharmacodynamics of immune checkpoint inhibitors. Testing for target receptor occupancy in the blood can be assessed in clinical studies. However, it is difficult to sample tumor tissues in patients to assess RO.

The aim of this work is to develop physiologically based pharmacokinetic (PBPK) and RO model of anti-PD-L1 therapeutic antibodies that will be capable to describe clinical pharmacokinetic (PK) and RO data available for the anti-PD-L1 antibodies and use the model for prediction of PD-L1 RO in the tumor for various regimens and doses of PD-L1 inhibitors.

MODEL DESCRIPTION



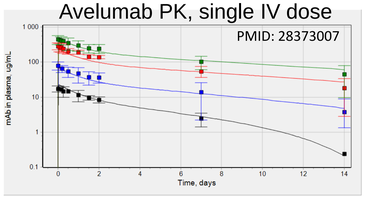
Key features of the model:

- surface binding of anti-PD-L1 antibodies with membrane bound receptor, i.e., number of target receptor per cell, number of cell expressing target receptor and valency of therapeutic antibodies were taken into account;
- internalization of target receptor bound with anti-PD-L1 antibody;
- uptake of therapeutic antibodies by endothelial cells, their binding with FcRn and recycling, degradation of free anti-PD-L1 antibodies;
- binding of anti-PD-L1 antibodies with soluble PD-L1 in plasma;
- competition of anti-PD-L1 antibodies with endogenous IgG. Physiological parameters were taken from published literature; other parameters were identified on the basis of in vitro and in vivo data. Clinical data on anti-PD-L1 monoclonal antibodies were used for model validation.

MODEL VALIDATION: PK IN PLASMA

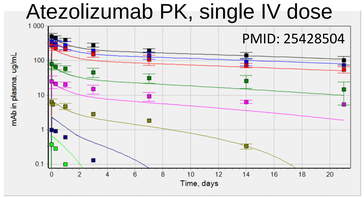
Developed PBPK model was tested on a set of four anti-PD-L1 monoclonal antibodies: atezolizumab, durvalumab, avelumab, and BMS-936559. The model adequately described the PK profile of all tested drugs, as well as target RO in the blood, without any additional parameter fitting. PDL1 expression by endothelial cells was very important (as the most numerous population which uptakes therapeutic antibodies) and was taken 4.5% [PMID: 29628925] PDL1 positive cells for all antibodies excluding Avelumab (25%)

Avelumab PK, single IV dose



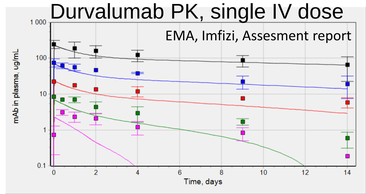
1mg/kg, 3mg/kg, 10mg/kg, 20mg/kg

Atezolizumab PK, single IV dose



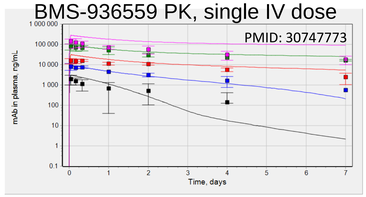
0.03mg/kg, 0.1mg/kg, 0.3mg/kg, 1mg/kg, 3mg/kg 10mg/kg, 15mg/kg, 20mg/kg

Durvalumab PK, single IV dose



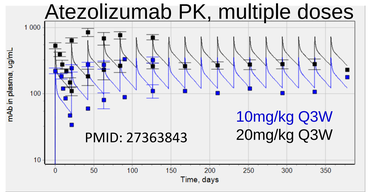
10mg/kg, 3mg/kg, 1mg/kg, 0.3mg/kg , 0.1mg/kg

BMS-936559 PK, single IV dose

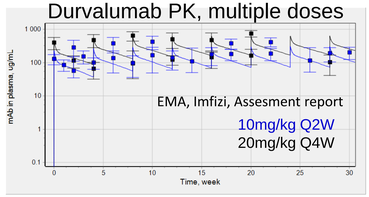


10mg, 30mg, 100mg, 300mg, 900mg

Atezolizumab PK, multiple doses

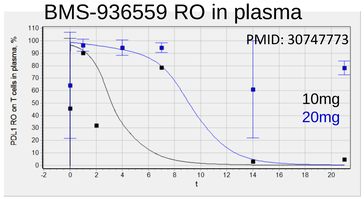


Durvalumab PK, multiple doses

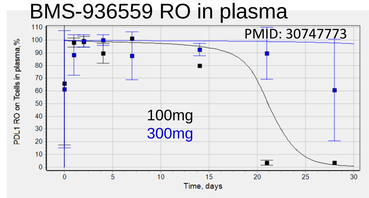


MODEL VALIDATION: RO IN PLASMA

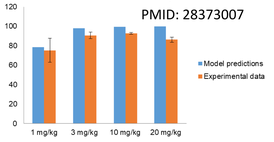
BMS-936559 RO in plasma



BMS-936559 RO in plasma



Avelumab RO on T cell in plasma, %



Model describes dynamic RO data and through RO on T cells in plasma on 14 day for Avelumab. Data on RO in tumor or other data on T cell in plasma were absent in published literature.

PREDICTIONS: RO IN TUMOR

Model predicts RO in tumor for approved drugs and new anti-PDL1 mAbs. All Kd and koff values for approved drugs were taken from FDA, EMA reports.

	Atezolizumab			Durvalumab	Avelumab
Dose regimen	840mg Q2W	1200mg Q3W	1640mg Q4W	10mg/kg Q2W	800mg Q2W
RO on T cells in tumor	99.74	99.795	99.82	99.99	98.63
RO on cancer cells	99.68	99.76	99.795	99.98	97.76

The results can be explained by almost similar Kd values (0.4 nM for atezolizumab[1], 0.02 nM for durvalumab[2], 0.7 nM for avelumab[3]) and applied doses of these three approved anti-PD-L1 antibodies.

Because PD-L1 is mainly expressed and functioning on antigen presenting cells and tumor cells, it is more important to predict RO on tumor cells.

	JS003			TBQ2450			Sugemalimab		
Dose regimen	1mg/kg Q2W	3mg/kg Q2W	10mg/kg Q2W	800mg Q2W	1200mg Q3W	1600mg Q4W	800mg Q2W	1200mg Q3W	1600mg Q4W
RO on T cells in tumor	21.24	95.48	99.73	99.876	99.82	99.82	98.87	99.32	99.03
RO on cancer cells	0.12	76.25	99.65	99.85	99.78	99.78	98.56	99.2	98.8

PK of JS003, TBQ2450 and Sugemalimab was assumed the same as for other anti-PD-L1 antibodies in accordance with type of immunoglobulin.

In accordance with model predictions new anti-PDL1 mabs in dose higher than 10 mg/kg (800 mg total dose) result to through RO 98% and higher on T and cancer cells in the tumor tissue. In the model PD-L1 expression in the tumor was 62.2 %[4].

	Atezolizumab		Avelumab	
Dose regimen	240mg Q2W	1200mg Q3W	800mg Q2W	240mg Q2W
Trough RO (%) on cancer cell in tumor	94.21	99.795	97.76	5.67
Trough RO (%) with on cancer cell in tumor PDL1 expression 10 fold lower	99.24	99.85	99.15	96.37

Expression of PD-L1 on tumor cells is important for low doses of antibodies and is not sensitive for doses 800mg and higher.

RO on cancer cell was predicted in high PD-L1(62.2.%) and low (10 fold lower percent of positive cells).

[1] Tiffany K. Ricks, FDA Pharmacology review of Atezolizumab
[2] EMA Assessment report of Imfinzi
[3] FDA Pharmacology review of Avelumab
[4] PMID: 31132649

CONCLUSIONS

- Developed model successfully described clinical PK & RO anti-PDL1mAbs data.
- Similar doses of three approved anti-PD-L1 monoclonal antibodies showed almost equal PD-L1 RO in the tumor
- Developed model could be used for prediction of anti-PDL1mAbs RO in tumor.

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