Semi-mechanistic PK and target-occupancy modeling to support dose justification for anti-PD-L1 clinical candidate CK-301 (cosibelimab) in oncology patients

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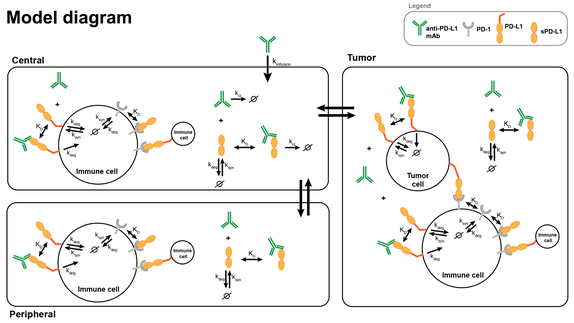
Background

A semi-mechanistic pharmacokinetic/target-occupancy (PKTO) model was developed with in vitro, preclinical and clinical data to facilitate dose selection of CK-301 (also known as TG-1501, cosibelimab), an anti-PD-L1 monoclonal antibody (mAb), for ongoing and future clinical trials in oncology patients. The model was used to compare the PK and tumor target occupancy (TO) at steady state under various dosing regimens with cosibelimab to those with three marketed anti-PD-L1 mAbs (i.e. atezolizumab, durvalumab and avelumab)

Model Development

Model diagram



Ø indicates degradation/elimination of the indicated species in the model

Model descriptions:

The main reactions included in model (in all three compartments unless otherwise indicated):

- PD-L1, sPD-L1 and PD1 are constantly synthesized and degraded, and the equilibrium has been reached before dosing
- PD-1 binds to both PD-L1 and sPD-L1 reversibly
- Drug binds to both PD-L1 and sPD-L1 reversibly
- Drug-PD-L1 complex is degraded with the same rate constant as PD-L1
- Drug and drug-sPD-L1 complex are eliminated in central compartment
- Drug, sPD-L1 and drug-sPD-L1 complex transport across the compartments

Main model assumptions:

- PK parameters of drug-sPD-L1 complex are the same as free drug for individual drug
- Drug-PD-L1 complex has the same degradation rate as PD-L1
- sPD-L1 production and degradation rates are the same in all three compartments.
- Drug binds to PD-L1 and sPD-L1 with the same affinity
- PD1 binds to PD-L1 and sPD-L1 with the same affinity
- PD-L1 related parameters (e.g. PD-L1 burden) are assumed to be the same regardless of treatment, while drug-related PK parameters (e.g., 1st order elimination half-life for drug) are different for different drugs (cosibelimab, atezolizumab, durvalumab, avelumab)

Experimentally determined PD-L1 binding affinities(Internal data)

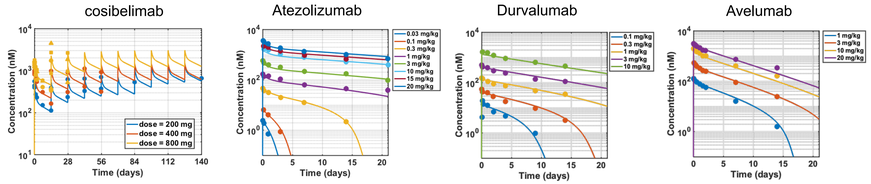
	kon (1/nM/s)	koff (1/s)	Kd (nM)
Cosibelimab	1.89E-03	3.79E-04	0.207
Atezolizumab	1.99E-03	6.58E-04	0.343
Durvalumab	1.42E-03	7.70E-04	0.544
Avelumab	9.08E-04	2.72E-04	0.299

Model Calibration and Prediction

PK datasets used for model calibration of cosibelimab, atezolizumab, durvalumab and avelumab

Molecule	Cosibelimab	Atezolizumab	Durvalumab	Avelumab
Study Design	Multi-dose PK study	Single-dose PK study	Single-dose PK study	Single-dose PK study
Data	Individual patient data (internal)	Group mean from digitizing literature data (Herbst et al, 2014)	Group mean from digitizing literature data (BLA)	Group mean from digitizing literature data (Heery et al, 2017)
Doses	200, 400, 800 mg q2w	0.03, 0.1, 0.3, 1, 3, 10, 15, 20 mg/kg	0.1, 0.3, 1, 3, 10, 15, 20 mg/kg	1, 3, 10, 20 mg/kg

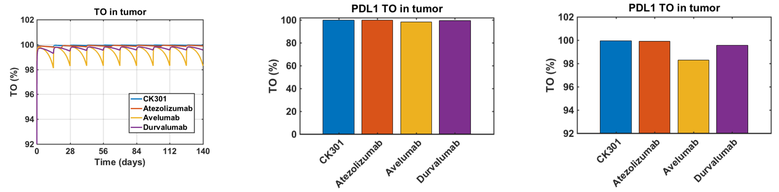
Model fitted to PK data from clinical studies for cosibelimab, atezolizumab, durvalumab and avelumab



Model predicted tumor TO(%) for cosibelimab and the approved anti-PD-L1 mAbs at their marketed doses

Cosibelimab is dosed at 800 mg q2w, and the three approved mAbs are simulated with their approved doses (Atezolizumab:1200 mg q3w, Durvalumab: 10 mg/kg q2w, Avelumab 10 mg/kg q2w)

TO(%) in time | Trough TO(%) at steady state | Trough TO(%) – zoomed in

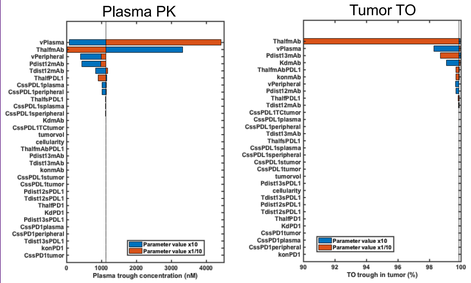


Model predicted tumor TO at steady-state C_{trough} for cosibelimab and three approved anti-PD-L1 mAbs for patients with nominal PD-L1 and 10-fold higher PD-L1 burden in tumor

	Cosibelimab				Atezolizumab	Durvalumab	Avelumab
Dose regimen	800 mg q2w	800 mg q3w	1200 mg q2w	1200 mg q3w	1200 mg q3w	10 mg/kg q2w	10 mg/kg q2w
Trough TO (%) with **nominal** PD-L1 burden	99.9	99.8	99.9	99.9	99.9	99.6	98.2
Trough TO (%) with **10x nominal** PD-L1 burden	99.9	99.8	99.9	99.9	99.8	99.4	58.7

Model Prediction and Analysis

Sensitivity analysis for PK and tumor TO (%) - use 800 mg q2w as an example



Approach:
Vary one parameter at a time by 10-fold increase or decrease from the nominal value, simulate steady-state trough drug concentration in plasma and TO in tumor. Parameters are sorted from most sensitive to least sensitive.

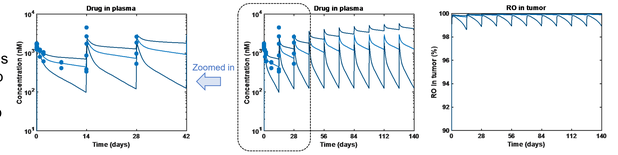
Key findings:
Parameters that are not sensitive for PK but are sensitive for TO lead to uncertainty in model prediction: binding affinity, tumor penetration ratio, & **PD-L1 burden in tumor** (known to vary significantly between patients)

Assessment of PK variability and its impact on tumor TO prediction

- Adjust the variability of plasma volume and drug half-life, two most sensitive parameters for PK, in the model so that the simulated variability in C_{trough} matches the observed variability in C_{trough} for approved anti-PD-L1 (i.e. coefficient of variation (CV) reported in BLA)
- Assume the similar variability of C_{trough} for cosibelimab as approved mAbs (atezolizumab & durvalumab)
- Simulate #1000 virtual patients for approved mAbs and cosibelimab, simulate RO in tumor at steady state

Here use cosibelimab 800 mg q2w as an example. Similar simulations are done for atezolizumab and durvalumab.

CV% for C_{trough} after 1st dose from simulation is 50.0% (similar to reported values for atezolizumab & durvalumab)



With PK variability, the model predicted trough TO (%) for cosibelimab and the approved anti-PD-L1 mAbs at different levels of PD-L1 expression in tumor

PD-L1 Burden in Tumor		Atezolizumab 1200 mg q3w	Durvalumab 10 mg/kg q2w	Cosibelimab			
				800 mg q2w	800 mg q3w	1200 mg q2w	1200 mg q3w
Nominal	Mean TO at C_{trough}	99.4%	99.0%	99.4%	99.4%	99.6%	99.7%
	% of patients with TO_{trough}>99%	94.0%	83.9%	94.5%	93.0%	96.4%	96.2%
10x Nominal	Mean TO at C_{trough}	97.6%	96.1%	96.5%	95.6%	97.4%	97.0%
	% of patients with TO_{trough}>99%	89.6%	67.1%	86.0%	80.1%	91.6%	89.5%

Conclusions

- With cosibelimab (also known as CK-301) IV dosing of 800 and 1200 mg q2w or q3w, a >99% TO is expected throughout the dosing interval, comparable to TO achieved with atezolizumab at 1200 mg q3w, and durvalumab at 10 mg/kg q2w
- Relative to atezolizumab and durvalumab treatments, similar percentages of patients would possibly benefit from cosibelimab treatment, under the assumption that cosibelimab has similar PK variability