

Semi-mechanistic PK Model Development of Sabestomig for Dose Selection

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Introduction

- Bispecific antibodies, targeting two distinct antigens simultaneously, are an emerging biologic format. A good understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) relationships for both targets is required to optimise the dose for a given indication¹.
- Sabestomig, a monovalent, bispecific, humanised IgG1 antibody targeting PD1 and TIM3 is being evaluated for safety and efficacy in Phase 1 dose escalation studies in solid and lymphatic tumour indications.
- The goal was to:
 - Implement one model for both solid and lymphatic tumour indications.
 - Describe the non-linear plasma PK of sabestomig.
 - Describe the total concentration kinetics of peripheral sTIM3.
 - Predict peripheral and tumoral receptor occupancy.

Methods

- A semi-mechanistic PK model (Figure 1) like the one implemented by Cao et al² was applied to gain insight into sabestomig concentration kinetics in the central, lymph and solid tumour compartments, and to fit to plasma PK sample data for 25 lymphatic and 53 solid tumour patients.

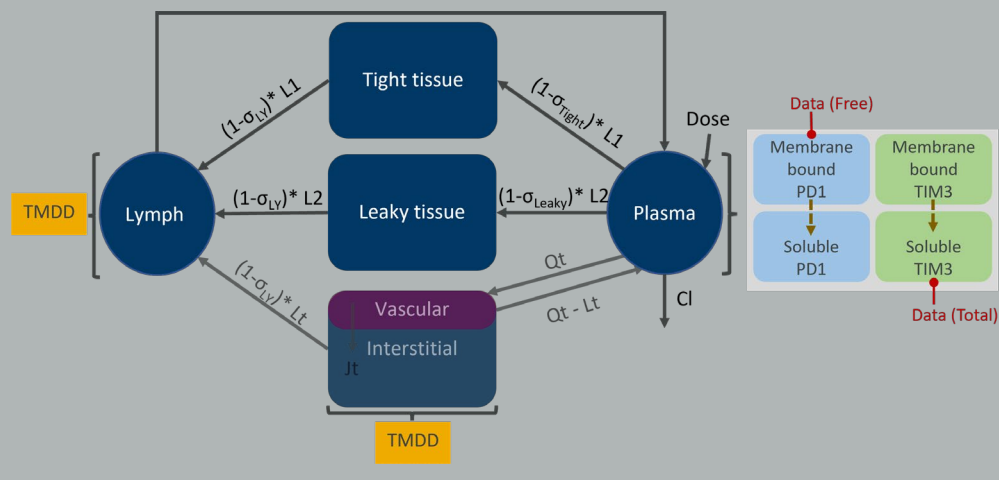
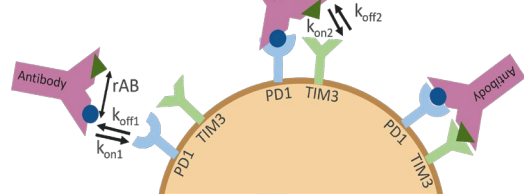


Figure 1: Semi-mechanistic PK model with plasma, tight tissue, leaky tissue, tumour and lymph compartment.

- Target-mediated drug disposition was included at the site of the tumour with consideration for the receptor-expressing phenotypes and avidity.

Avidity



- Bispecific binds to PD1 with an affinity
- If TIM3 is located sufficiently closely, binding to PD1 increases apparent affinity for binding TIM3
- This can delay the bispecific's clearance on dual target expressing cells

- Total concentration data for the lower-affinity soluble receptor (sTIM3) in the periphery was described by a sub-model with target-mediated drug disposition for both the membrane-bound and soluble receptors.

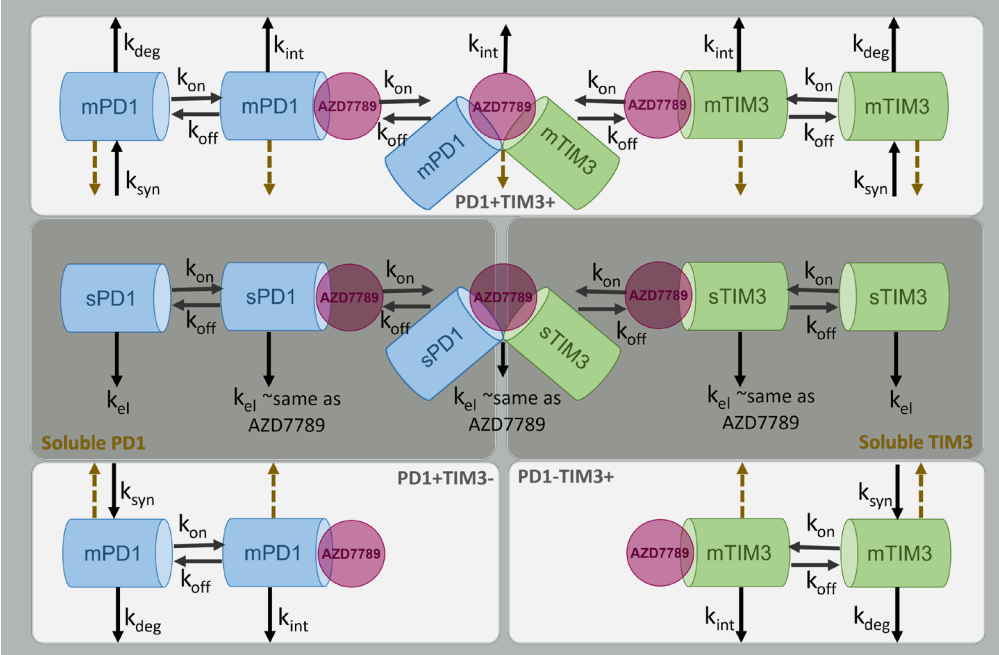


Figure 2: Target-mediated drug disposition for membrane bound and soluble receptors.

- The model was used to simulate intra-tumoural target engagement predictions for both targets on single and dual-expressing cells, as well as steady-state exposure metrics for each patient in exposure response and exposure safety analysis.

Results

- The model described the plasma PK data and the peripheral soluble target exposure in the clinical dose range for both the solid and lymphatic tumour indications.

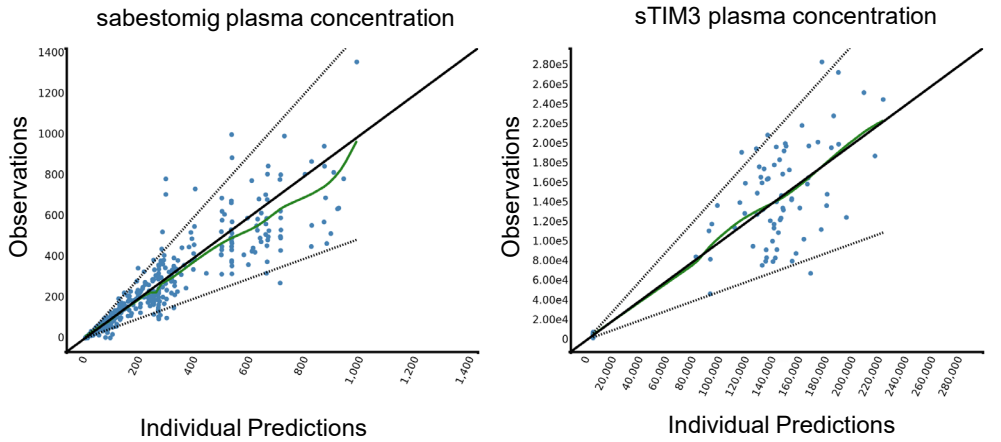


Figure 3: Observations vs individual predictions plots for sabestomig plasma concentration (left) and peripheral soluble Tim3 receptor (right). The solid black line represents $y=x$, the dashed black line represents the 90% prediction interval, and the green line represents a spline interpolation. The observed data is shown as blue dots.

- Simulated total receptor occupancy at steady state trough concentrations at the tumour site for both targets is shown in Figure 4.
- Tim3 on PD1-TIM3+ cell indicates the target engagement on the myeloid population.
- Steady state Ctrough below 12.2 mg/L resulted in TIM3 target engagement below 90% on PD1-TIM3+ cells.

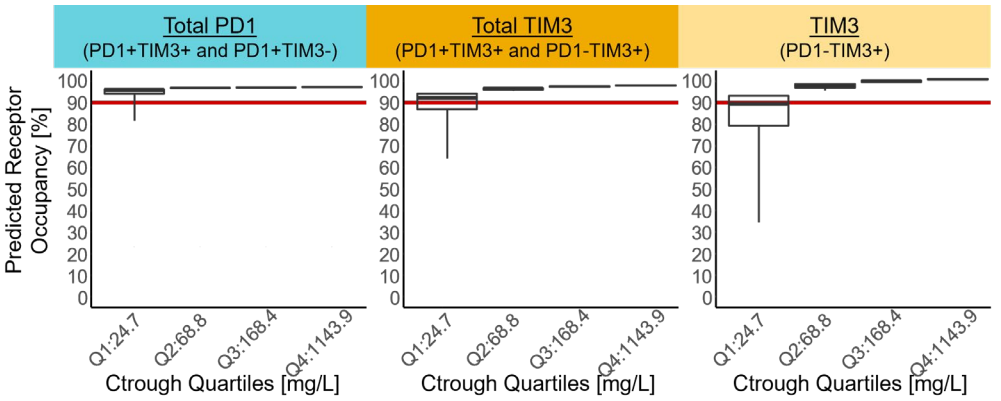


Figure 4: Boxplots of simulated receptor occupancy [%] on single and dual expressing cells for sabestomig plasma Ctrough_{ss} concentration Quartiles. Red line represents 90%.

Serious Adverse Events

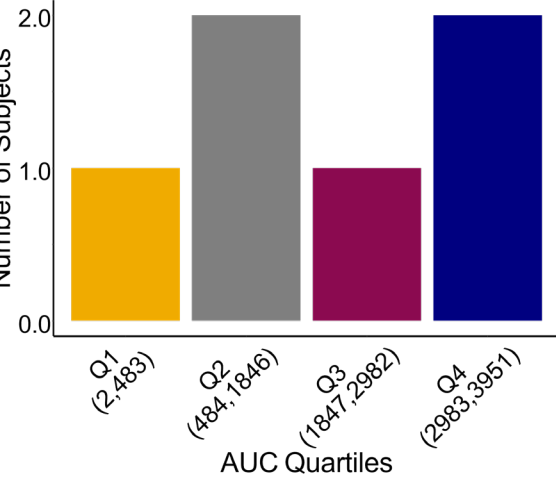


Figure 5: Bar chart of serious adverse events for sabestomig plasma AUC Quartiles.

- The simulated exposure metrics, $AUC_{0-21days}$, C_{min} , and C_{max} , were incorporated into exposure response and exposure safety analysis to inform dose selection.
- The lymphatic tumour indication had 17, 33, 17, and 33% serious adverse events in the ascending quartiles of simulated $AUC_{0-21days}$ with a range of 2-3951 mg.day/L.
- Efficacy of 28.5% was observed in the simulated steady state C_{min} range of 0 to 196.9 mg/L.

Conclusions

- A dose selection decision following a dose-escalation study was informed by intra-tumoural target engagement and PK exposure predictions.
- The development of a semi-mechanistic PK model for both a solid and lymphatic tumour indications describing sabestomig plasma PK and peripheral soluble target kinetics supported the predictions.

References

- Gibbs, J.P., Yuraszek, T., Biesdorf, C., Xu, Y. and Kasichayanula, S. Informing Development of Bispecific Antibodies Using Physiologically Based Pharmacokinetic-Pharmacodynamic Models: Current Capabilities and Future Opportunities. The Journal of Clinical Pharmacology. 2020. 60: S132-S146.
- Cao Y, Balthasar JP, Jusko WJ. Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn. 2013. 40(5):597-607.