Prediction of intratumoral TIGIT receptor occupancy after the treatment with anti-TIGIT antibodies

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Abstract:

Background:

T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain (TIGIT) is a co-inhibitory immune checkpoint receptor expressed on several types of immune cells, which can suppress T-cell activation, promote T-cell exhaustion, and suppress natural killer cell mediated cytotoxicity. Recent clinical data with anti-TIGIT monoclonal antibodies (mAbs) indicate that TIGIT blockade is a highly promising therapy when combined with PD-1/PD-L1 blockade. However, unlike PD-1 receptor occupancy (RO), there is a lack of information regarding RO in peripheral blood and tumors at different dose regimens with anti-TIGIT therapies. This study aims to predict intratumoral RO for a series of anti-TIGIT antibodies with known pharmacokinetic (PK) and binding characteristics (ociperlimab [BGB-A1217], vibostolimab, domvanalimab, etigilimab, tiragolumab) utilizing a physiologically-based PK (PBPK)/RO model.

Methods:

The PBPK/RO model describes biodistribution of mAbs within bodily fluids, detailed transport across the endothelial barrier, two-step binding with the membrane-bound TIGIT receptor (taking into account target expression level, number of cells expressing target receptor and internalization process), linear and non-linear clearance of mAbs (via uptake by endothelium and internalization of mAb:TIGIT complexes, respectively). Physiological parameters were taken from the literature, while other parameters were identified based on available *in vitro* and *in vivo* data. Clinical PK data of anti-TIGIT mAbs were used for model calibration.

Results:

The model-predicted results for RO in peripheral blood demonstrated almost complete occupancy, which is supported by clinical data available for ociperlimab and domvanalimab (predicted 99.9% vs observed 100%). A similar tendency was observed for all studied cell types (CD8, CD4, regulatory T cells) despite the significant differences in TIGIT expression on different cell types. According to model predictions, the intratumoral RO was close to the values reported for blood over a range of doses close to the recommended Phase 2 dose (e.g. ociperlimab 900 mg Q3W median trough RO with 95% CI: blood 99.96% [99.89, 99.98] vs tumor 99.75% [98.88, 99.94]). The direct comparison of extended dosing regimens (e.g. ociperlimab 150/200/300 mg per week regimens) demonstrated a sustainable level of TIGIT blockade and comparable values of trough RO.

Conclusions:

The PBPK/RO model accurately predicted the RO in peripheral blood and tumors for different anti-TIGIT mAbs by taking into account their PK and binding properties. Moreover, the model allowed a direct comparison of RO across different regimens and different anti-TIGIT mAbs. The predicted TIGIT receptor occupancy within the tumor may be useful for future dose selection or optimization in clinical trials.