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

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Background

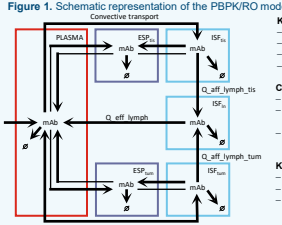
- T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain (TIGIT) is a co-inhibitory immune checkpoint receptor expressed on several types of immune cells, which can suppress T-cell activation, promote T-cell exhaustion, and suppress natural killer (NK) cell mediated cytotoxicity[1,2]
- Recent clinical data with anti-TIGIT monoclonal antibodies (mAbs) indicate that TIGIT blockade is a highly promising therapy when combined with programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade[3,4]
- 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
- The objectives of this modelling exercise were:
  - To develop physiologically-based pharmacokinetic (PBPK)/RO model describing anti-TIGIT antibody pharmacokinetics (PK) and target RO in blood and tumors
  - To predict intratumoral RO for anti-TIGIT mAbs (ociperlimab [BGB-A1217], tiragolumab, vibostolimab, domvanalimab, etigilimab) based on their PK and binding characteristics

Methods

PBPK/RO model

- The PBPK/RO model is shown in **Figure 1**. This model describes the following characteristics:[5]
  - Biodistribution of mAbs within bodily fluids
  - Detailed transport across the endothelial barrier (via convection, diffusion, and FcRn-mediated transport)
  - Two-step binding with the membrane-bound TIGIT receptor (considering 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 based on existing literature, while other parameters were identified based on available *in vitro and in vivo* data.[5,6] Clinical PK data of anti-TIGIT mAbs were used for model calibration
- Inter-patient variability was introduced into the model based on known variations of physiological parameters and TIGIT expression.[7,8] Simulations were conducted for 100 virtual patients

Figure 1. Schematic representation of the PBPK/RO model



Key cell types
- CD8 T cells
- CD4 T cells
- CD4 Tregs
- NK cells

Compartments
- Blood plasma
- Interstitial fluid of tissues, tumor, lymph nodes
- Endosomal space of endothelium in tissues and tumors

Key features
- Cell-type specific TIGIT expression
- Tissue-specific TIGIT expression
- All parameters of TIGIT receptor were gathered from the literature (i.e. not fitted against clinical RO data)

ESP, endosomal space; ISF, interstitial fluid; ln, lymph node; mAb, monoclonal antibody; NK, natural killer; PBPK, physiologically-based pharmacokinetic; Q_aff_lymph, afferent lymph flow; Q_eff_lymph, efferent lymph flow; RO, receptor occupancy; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain; tis, tissue; tum, tumor

Results

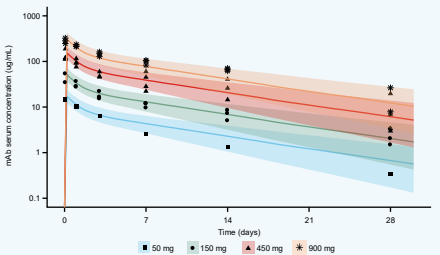
Model validation

- PK simulations following single administration of ociperlimab 50, 150, 450, and 900 mg were able to reproduce clinical PK data and capture the observed level of inter-patient variability (**Figure 2**). The model also described PK of other investigated anti-TIGIT mAbs with adequate precision (data not shown)
- Model simulations predicted almost complete TIGIT occupancy in peripheral blood following administration of ociperlimab 50 mg and 150 mg once every 3 weeks (Q3W) (**Figure 3**), which were in agreement with reported results from Phase 1 dose-escalation study of ociperlimab in combination with anti-PD-1 tislelizumab, in patients with advanced solid tumors[9]
- The model-predicted results for RO in peripheral blood for domvanalimab were close to 100% at dose levels starting from 0.5 mg/kg, which is supported by clinical data available for domvanalimab[3] (**Table 1**)

Conclusions

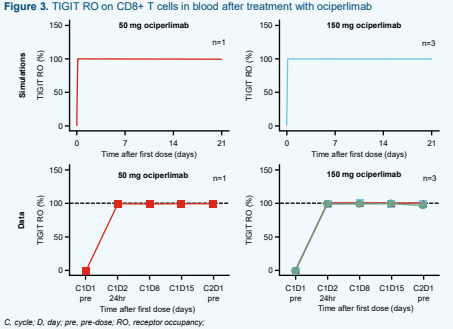
- The **PBPK/RO model accurately predicted the RO** in peripheral blood for different anti-TIGIT mAbs by taking into account their PK and binding properties
- The model allowed a direct comparison of **RO across different regimens** and different **anti-TIGIT mAbs**
- The **predicted TIGIT RO within the tumor in conjunction with clinical data** could help **support dose regimen selection** for anti-TIGIT antibodies

Figure 2. Predicted* vs observed† serum PK profiles of ociperlimab



**Predicted PK are presented as median (95% CI); †Observed PK are denoted by symbols for each dose of ociperlimab*
mAb, monoclonal antibody; PK, pharmacokinetic

Figure 3. TIGIT RO on CD8+ T cells in blood after treatment with ociperlimab



C, cycle; D, day; pre, pre-dose; RO, receptor occupancy;
TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain

Table 1. Predicted vs observed trough TIGIT RO in peripheral blood for domvanalimab

Dosing regimen	Observed RO% mean (SD)	Predicted RO% median (95% CI)
0.5 mg/kg Q2W	99.7 (0.3)	99.88 (99.8, 99.92)
1 mg/kg Q2W	100 (0)	99.94 (99.89, 99.96)
3 mg/kg Q2W	100 (0)	99.98 (99.96, 99.99)

CI, confidence interval; TIGIT, T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain; Q2W, once every 2 weeks; RO, receptor occupancy; SD, standard deviation

Model simulations

- High TIGIT RO was predicted for all studied cell types (CD8, CD4, Treg, NK) in both peripheral blood and tumor despite the significant differences in TIGIT expression on various cell types (**Table 2** and **Table 3**)
- According to model predictions for ociperlimab, the intratumoral RO was close to the values reported for blood over a range of doses close to the recommended Phase 2 dose 900 mg Q3W[3] (**Table 2** and **Table 3**)
- The direct comparison of extended dosing regimens (ociperlimab 150, 200, or 300 mg per week) demonstrated a sustainable level of TIGIT blockade and comparable values of trough RO in tumor (**Table 3**)
- The model-predicted trough RO in tumor for other drugs (tiragolumab, vibostolimab, domvanalimab, etigilimab) revealed comparable occupancy rates according to mAb PK and binding properties (**Table 4**)
- The relationship between RO and a clinical outcome is currently unknown and may be determined from ongoing studies with anti-TIGIT mAbs

Table 2. Predicted trough TIGIT RO in peripheral blood for ociperlimab*

Cell type	50 mg Q3W	150 mg Q3W	450 mg Q3W	900 mg Q3W
CD8 T cells	99.48 (98.77, 99.72)	99.80 (99.46, 99.9)	99.93 (99.79, 99.96)	99.96 (99.89, 99.98)
CD4 T cells	99.45 (98.48, 99.72)	99.79 (99.38, 99.9)	99.93 (99.77, 99.96)	99.96 (99.88, 99.98)
Tregs	99.48 (98.77, 99.73)	99.80 (99.46, 99.9)	99.93 (99.79, 99.97)	99.96 (99.89, 99.98)
NK cells	99.21 (98.44, 99.55)	99.65 (99.26, 99.82)	99.86 (99.66, 99.93)	99.93 (99.81, 99.97)

**Results are presented as median (95% CI)*
CI, confidence interval; NK, natural killer; Q3W, once every 3 weeks; RO, receptor occupancy;
TIGIT,T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain; Tregs, regulatory T cells

Table 3. Predicted trough TIGIT RO in tumor for extended regimens of ociperlimab*†

Dosing regimen		CD8 T cells	CD4 T cells	Tregs	NK cells
150 mg per week	450 mg Q3W	99.53 (98.07, 99.88)	99.54 (98.11, 99.88)	99.64 (98.78, 99.89)	99.51 (97.88, 99.87)
	600 mg Q4W	99.36 (97.35, 99.83)	99.37 (97.35, 99.83)	99.49 (98.34, 99.85)	99.30 (96.96, 99.83)
	900 mg Q6W	98.69 (94.51, 99.64)	98.73 (94.74, 99.66)	99.08 (96.68, 99.71)	98.61 (92.85, 99.64)
200 mg per week	600 Q3W	99.64 (98.41, 99.91)	99.64 (98.46, 99.91)	99.71 (98.98, 99.91)	99.62 (98.28, 99.91)
	800 Q4W	99.51 (98.14, 99.88)	99.53 (98.05, 99.88)	99.60 (98.73, 99.89)	99.49 (97.67, 99.88)
	1200 Q6W	98.94 (95.41, 99.72)	98.98 (95.57, 99.73)	99.24 (97.18, 99.77)	98.89 (94.01, 99.72)
300 mg per week	900 Q3W	99.75 (98.81, 99.94)	99.75 (98.85, 99.94)	99.79 (99.21, 99.94)	99.74 (98.74, 99.94)
	1200 Q4W	99.64 (98.29, 99.91)	99.64 (98.34, 99.91)	99.70 (98.91, 99.92)	99.62 (98.15, 99.91)
	1800 Q6W	99.22 (96.45, 99.81)	99.26 (96.54, 99.81)	99.42 (97.77, 99.83)	99.19 (95.37, 99.81)

**Results are presented as median (95% CI). †Trough RO in tumor was predicted using the PBPK/RO model. 'Trough RO' is RO at the end of dosing cycle prior to the next dose. Simulation results are presented at day 84 on treatment when both PK and RO reached a steady state. CI, confidence interval; NK, natural killer; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; Q3W, once every 3 weeks; Q4W, once every 4 weeks; Q6W, once every 6 weeks; RO, receptor occupancy; TIGIT,T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain; Tregs, regulatory T cells*

Table 4. Predicted trough TIGIT RO in tumor for different drugs*

Therapy	CD8 T cells	CD4 T cells	Tregs	NK cells
Tiragolumab 600 mg Q3W	99.58 (98.01, 99.89)	99.57 (98.07, 99.89)	99.62 (98.56, 99.89)	99.57 (97.94, 99.89)
Vibostolimab 200 mg Q3W	99.43 (97.68, 99.84)	99.42 (97.74, 99.84)	99.55 (98.5, 99.85)	99.41 (97.49, 99.84)
Domvanalimab 15 mg/kg Q3W	99.94 (99.73, 99.99)	99.94 (99.73, 99.99)	99.94 (99.76, 99.99)	99.94 (99.73, 99.99)
Etigilimab 10 mg/kg Q2W	99.24 (97.07, 99.80)	99.27 (96.97, 99.80)	99.36 (97.89, 99.81)	99.23 (96.59, 99.80)

**Results are presented as median (95% CI)*
CI, confidence interval; NK, natural killer; Q2W, once every 2 weeks; Q3W, once every 3 weeks; RO, receptor occupancy; TIGIT,T-cell immunoreceptor with immunoglobulin and tyrosine based inhibitory motif domain; Tregs, regulatory T cells

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