Setting a Safe Starting Dose for a First-in-Man trial of a Monoclonal Antibody Based on Population PK-PD Predictions.

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Aims

To guide in setting a safe starting dose for the First-in-Man trial of a monoclonal antibody (mAb) interacting with the innate immune system via a novel mechanism of action.

Background

Anti-KIR (1-7F9) is a novel, fully human monoclonal antibody being developed for cancer therapy, acting through facilitation of the NK-cell mediated lysis of cancer cells.

Conclusions

- A cautious starting dose for the Anti-KIR monoclonal antibody was suggested, based on a predicted human PK-PD model
- The suggested dose is 30x times lower than in any previous mAb First-in-Man trials

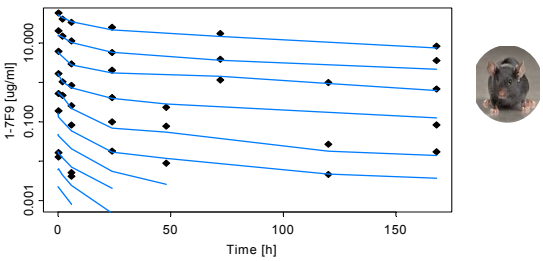
No direct preclinical toxicology testing possible ← **KIR target specific to humans** → **KIR occupancy by Anti-KIR used as marker of NK-cell activation** → **Cautious starting dose:** •Use highest affinity estimate for occupancy prediction •Avoid full KIR occupancy

Methods

- **Strategy:**
  - i. Develop PK-model for Anti-KIR in wild-type B6 and KIR-tg mice, a mouse strain transgenic for the human KIR.
  - ii. Develop PK/PD model in mice using %KIR occupancy as surrogate PD-measure
  - iii. Predict PK-profile of anti-KIR in humans assuming PK resembles that of endogenous IgG.
  - iv. Simulate KIR-occupancy in humans by substituting the PK in the mouse PK/PD model with the predicted human PK-profile
  - v. Suggest starting dose: 30% <KIR occupancy <95% for a short duration of time
- **Data source:** 5 PK samples/B6 mouse; two PK samples and one occupancy assessment/KIR-tg mouse. Dose range 0.0001 mg/kg-10 mg/k.g
- **Modelling:** PK and PD in mice was modelled sequentially using NONMEM V (FOCE method).

Results

Figure 1. **Mouse** PK model



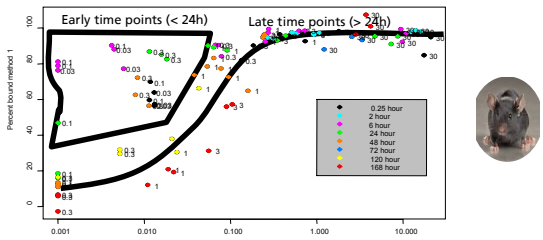
PK profiles in the KIR-transgenic mice for 10 dose levels (i.v.). Black dots: mean data, blue lines: model fit. Res. error 22%
The model structure was a 2-compartment model, combined with a 3rd saturable distribution compart-ment. A combined model for KIR-transgenic and B6 mice was developed (parameters in Table 1).

Table 1. Mouse PK parameters

V1	V2	CL	Q12	Bmax	kon	koff
ml/g	ml/g	ml/h	ml/h	ug mAb/g	1/h	1/h
0.068	0.063	0.027	0.127	0.066	0.094	0.003

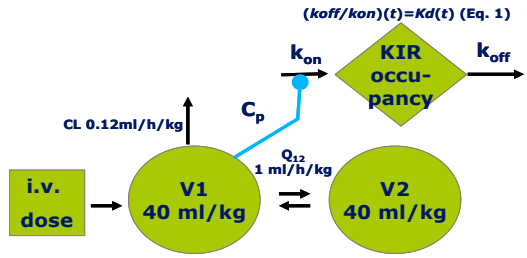
V1, V2: central & peripheral volume of distribution, Cl: clearance, Q12: intercompartmental cl, Bmax: max. binding in 3rd comp., kon and koff: rate constants for binding in 3rd compartment

Figure 2. PK-PD relationship in KIR-transgenic **mice**



KIR occupancy vs plasma concentration of Anti-KIR in KIR-transgenice mice. Colour coding according to time (h). Numbers are dose in ug/mouse.
Less Anti-KIR is needed to saturate the receptors at early time points compared to later time points; this was modelled as a decrease in affinity with time, cf. Figure 3, Eq.1.

Figure 3. Structure of **human** PK/PD model

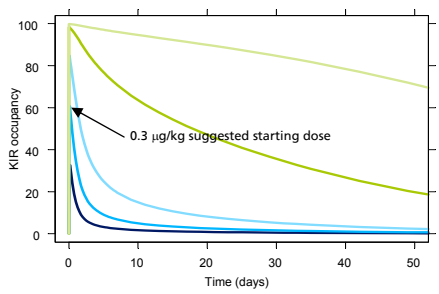


- Anti-KIR is a fully human IgG (Immunoglobulin G) and, hence most likely will display the same PK properties as endogenous IgGs.
  -Literature PK parameters were used to simulate human PK.
- The PD parameters driving KIR occupancy were obtained from the PK/PD model in KIR-transgenic mice .
- The change of Kd with time was modelled according to:

$$Kd(t) = e^{\log(Kd\,\min)+(\log(Kd\,\max)-\log(Kd\,\min))\frac{Time}{(Time+T50)}} \qquad \text{Eq.1}$$

Kdmin: 4 ng/ml. Kdmax: 100 ng/ml. T50:72 h.

Figure 4. Simulated **human** KIR occupancy profiles



Simulations of KIR-occupancy vs time based on the model in Figure 3. Doses 0.1 µg/kg, 0.3 µg/kg, 1 µg/kg, 3 µg/kg 10 µg/kg.