II-60

Pharmacokinetic interspecies extrapolation of a fully human mAb from animal to human

Wenyuan Xiong,[1] Andrea Paoletti,[2] Anna Bernhardt,[3] Pascal Girard,[1] Barbara Testa[2]

[1]Merck Serono S.A. – Geneva, Switzerland*; [2]Merck Serono – Ivrea Italy; [3]EMD Serono – Rockland USA

Introduction

Anti-LX is a fully human monoclonal antibody directed against ligand X, which is expressed on a wide variety of cell types and has a key role in down-regulating immune responses. Its anti-tumor effect relies on a dual mode of action :

1) Blocking the interaction of ligand X with receptor X on T cells can release T cells from immunosuppression, and lead to elimination of tumor cells;
2) 2) Bridging ligand X that is highly expressed on tumor cells and FCGR on leukocytes triggers tumor-directed ADCC.

Blocking ligand X has shown promising results in mouse oncology models. One of the key translational challenges is the prediction of the human pharmacokinetics and thus the selection of the (expected) optimum dose and dosing regimen.

Objectives

- Describe PK of anti-LX in mouse and monkey.
- Extrapolate the human exposure from the animal profile.
- Support the selection of dosing regimen in first-in-human trial based on target occupancy data from mouse.

Methods

- Algorithm: FOCE in NONMEM 7.2
- PK and TK data from 48 mice and 21 monkeys were fitted simultaneously.
- PK parameters were scaled between animal species and then to human by allometric relationships to simulate human exposure and its variability.
- EC95 derived from mouse target occupancy data was defined as the efficacy threshold.
- Dosing regimen of achieving at least 95% target occupancy in 70% of population was recommended as a reference for dose escalation in the first-in-human trial.

Results

- Anti-LX demonstrated pronounced non-linear PK characteristics in mouse and monkey, which was speculated to be target-mediated clearance related.
- Limited data impeded the development of a full mechanistic target-mediated drug disposition (TMDD) model [1].
- A simplification of TMDD model [2], consisting in two-compartment distribution and mixed elimination, well characterized the PK profiles of mice and monkeys (Figure 1, Figure 2).
- Inter-species variability of Km(f(target affinity)) plus IIV in linear CL, Vmax(f (target density)) and Km_monkey.
- Vc, Vp, Q, CLlin, Vmax for human were scaled up allometrically by body weight with power factor of 1, 1, 0.75, 0.75, 0.75, respectively.

$$Vc_i = V1 * (weight/3500)$$
$$Vp_i = V2 * (weight/3500)$$
$$Q_i = Q * (weight/3500)^{0.75}$$
$$CL_i = CLlin_i + CLnonlin_i$$
$$= CLL * (weight/3500)^{0.75} * exp(IIV_{CLL}) + \frac{V\,max * (weight/3500)^{0.75} * exp(IIV_{Vmax})}{Km * exp(IIV_{Km}) + c}$$

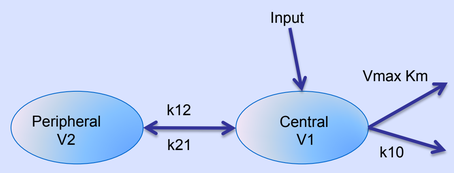


Table 1. Population PK Parameter Estimation of Mouse and Monkey

First Order Conditional Estimation with Interaction

Objective function value: -468.558

	Theta	Estimate	SE	RSE	[lower,	init,	upper]
1	CLL - linear clearance [L/h]	**1.08**	0.0879	8.1%	0	1	+Inf
2	V1 - central volume of distribution [L]	**145**	5.44	3.8%	0	150	+Inf
3	Q - intercompartmenal clearance [L/h]	**4.03**	0.467	11.6%	0	4	+Inf
4	V2 - peripheral volume of distribution [L]	**175**	11.9	6.8%	0	100	+Inf
5	VMAX – maximal TMDD clearance [ug/h]	**12.2**	3.6	29.5%	0	17	+Inf
6	KM_ Monkey - Concentration yielding half maximal TMDD clearance [ug/ml]	**0.35**	0.195	55.7%	0	1	+Inf
7	KM_ Mouse - Concentration yielding half maximal TMDD clearance [ug/ml]	**3.75**	1.47	39.2%	0	10	+Inf
8	Additive residual error	**0 FIX**	0	%	0	0	0
9	Proportional residual error	**0.276**	0.0255	9.2%	0	0.2	+Inf

Omega	1	2	6	Etabar (SE)	p val	Shrinkage
1.IIV/CLL	0.311			0.008 (0.059)	0.8941	10.9%
2.IIV/VMAX	0	1.02		0.033 (0.06)	0.5823	50.3%
6.IIV/KM_Monkey	0	0	1.19	0.002 (0.039)	0.9565	45.4%

Omega (on SD scale)	1	2	6
1.IIV/CLL	55.8%		
2.IIV/VMAX	0%	101%	
6.IIV/KM_Monkey	0%	0%	109.1%

Sigma	Shrinkage
1 SIs as TH	8.5%

Figure 1. Basic Goodness-of-Fit Plots of the Pooled PK Model

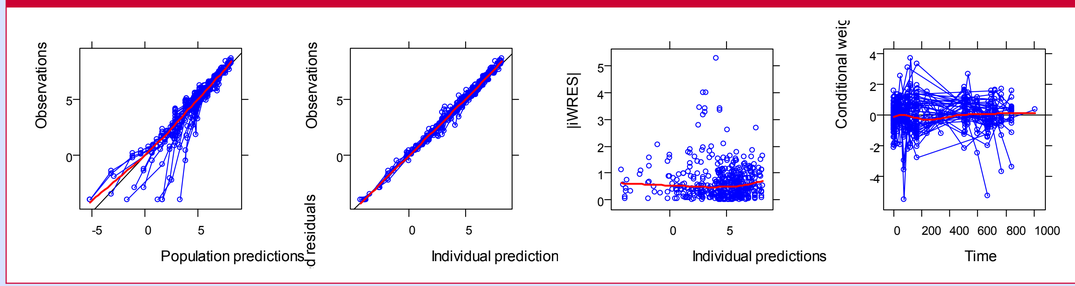
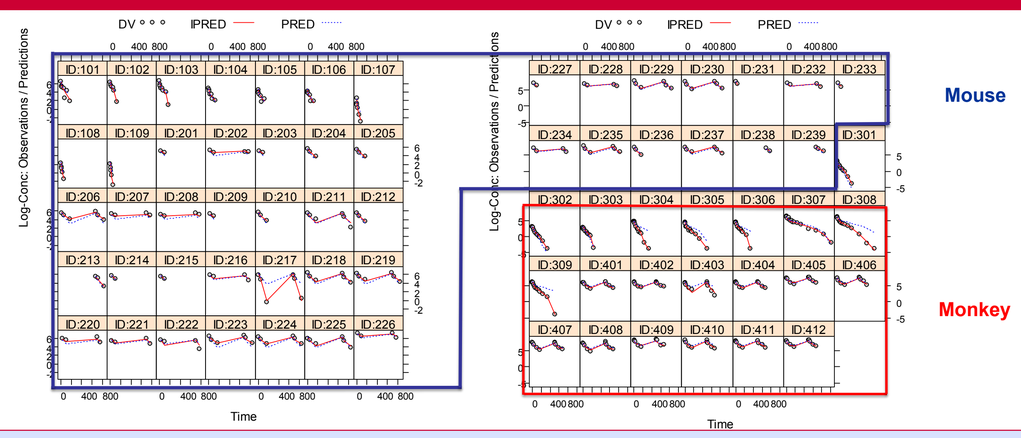


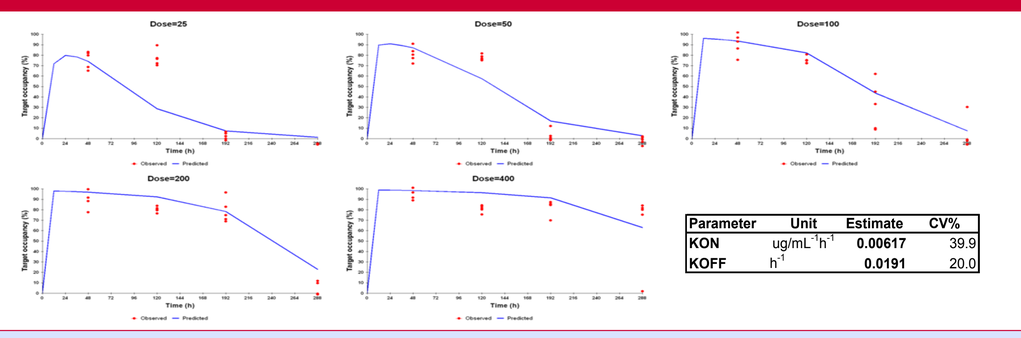
Figure 2. Individual Plots: Observations, Individual Predictions and Population Predications



- Target occupancy data from mouse were fitted using a receptor binding model (Figure 3).

$$[C] + [R] \underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}} [RC] \qquad Binding = \frac{B_{max} \cdot [C]}{[C] + K_d}$$

Figure 3. Target Occupancy in Mouse: Observations and Predictions



Parameter	Unit	Estimate	CV%
KON	$ug/mL^{-1}h^{-1}$	**0.00617**	39.9
KOFF	h^{-1}	**0.0191**	20.0

- The target effective concentration was defined as EC95 (58.8 µg/ml) derived from the target occupancy model.
- Assuming the same target affinity (Km) in human and monkey, human exposure was simulated, incorporating variability associated with clearance.
- Time above target effective concentration in the predicted human profile was considered to be an important reference when selecting the dose range to be tested in FIM study. Simulation suggested that, in human a dose of 7 mg/kg infused in 90 min can be administered every other week, to maintain a trough plasma level above the target in 70% of the population (Figure 4).
- Sensitivity analysis: 1) As Km << Conc in both monkey and mouse, minor impact of Km to the simulated human exposure was expected; 2) Up to 2 fold alteration of the assumed Vm value had small impact to the simulated trough concentration (Figure 5).

Figure 4. Simulation of Human Population Exposure with 7mg/kg Biweekly Regimen

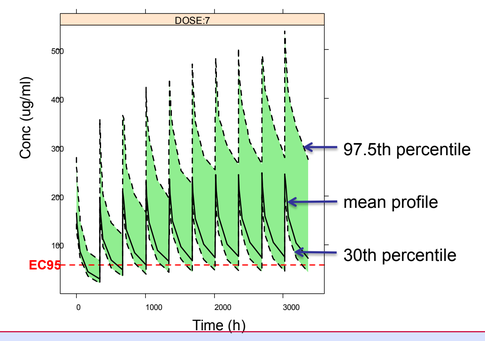
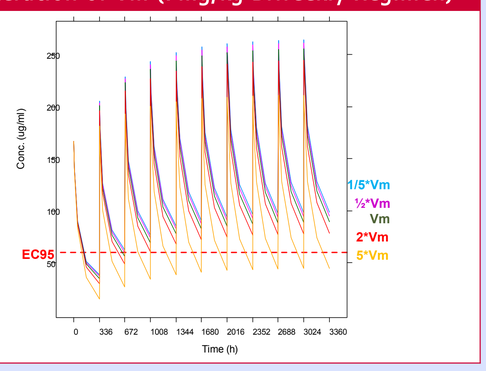


Figure 5. Sensitivity Analysis: Alteration of Vm (7mg/kg Biweekly Regimen)



Conclusion / Discussion

- Two-compartment model with mixed elimination, a simplification of TMDD model, well described the PK profiles of anti-LX both in mouse and monkey.
- Linear clearance is dominant at high concentration when TM pathway is saturated; target-mediated clearance is more visible at low concentration resulting in faster elimination.
- In addition to the time independent linear and nonlinear components of the clearance, a time dependency associated with the binding to the anti-drug antibody developed during the late stage of treatment is taken into account for the human extrapolation (working in progress by incorporating SCID mice data).
- Simulations suggested that for maintaining at least 95% target occupancy in human in 70% of the population, a dose of 7 mg/kg can be administered every other week as a 90 min infusion. This supports the selection of the dose range and frequency to be tested in the FIM study, to maintain a trough plasma level for an expected clinical relevant PD response. It is however compounded by uncertainties in the assumptions and importantly so, in allometric scaling, and caution will be exercised with respect to the selection of the starting dose and escalation.

References

[1] Gibiansky L. etc., Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic–pharmacodynamic modeling of biologics., *Expert Opin Drug Metab Toxicol.* 2009 Jul;5(7):803-12.

[2] Yan X. etc., Selection between Michaelis-Menten and target-mediated drug disposition pharmacokinetic models., *J Pharmacokinet Pharmacodyn.* 2010 Feb;37(1):25-47.

Acknowledgments

These studies were supported by Merck KGaA. The authors thank Sandra Berric-Millet for editorial support.
*A branch of Merck Serono S.A., Coinsins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

Merck Serono
Living science, transforming lives

MERCK