Population Pharmacokinetic Analysis of Trastuzumab (Herceptin®) Based on Three Different Dosing Regimens

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Objective

Herceptin® (trastuzumab) is currently indicated for the treatment of HER2 overexpressed metastatic breast cancer (MBC) and HER2 positive early breast cancer (EBC) patients. The aim of the analysis is to establish a comprehensive population pharmacokinetic (PK) model for trastuzumab, taking data from three dosing regimens into account, which can be used as a reference for future PK analyses in other cancer populations.

Material and Methods

3979 exploitable concentrations from 265 patients were available from 5 Phase I – III studies involving the following 3 different regimens:

i) Weekly: a 4 mg/kg loading dose followed by 2 mg/kg maintenance (1Q)
ii) 3 weekly: a 8 mg/kg loading dose followed by 6 mg/kg maintenance (3Q)
iii) 6 mg/kg weekly for the first 3 weeks followed by 6mg/kg every 3 weeks as maintenance (Novel loading regimen)

A previously developed model for the 1Q and 3Q regimens was used as a reference [1]. Data of the novel loading regimen were combined, and used to refine the model.

- NONMEM VI with the FOCE INTER estimation method was used.
- The effects of the covariates age, body weight (WT), SGOT, SGPT, total bilirubin, alkaline phosphatase (ALKP), creatinine clearance, number of metastatic sites, HER2 overexpression (HER2) and shed antigen (ECD) were investigated on CL, V_c and V_p.
- Power and linear relations were applied to continuous and categorical covariates, respectively.
- Automated stepwise covariate model building and bootstrap (800 resamplings) were conducted using PsN (ver. 2.2.3).
- Nominal p values of 0.005 and 0.001 were used as statistically significant criteria for the forward and backward steps, respectively.
- The magnitude of the effect of continuous covariates was estimated as following:

$$\%Change = \left[\left(\frac{X_{5th\%}}{med(X)}\right)^{\theta} - 1\right] \times 100$$

Where $X_{5th\%}$ is the 5th percentile of covariate X, a change of 20% was used as clinically significant criteria in the covariate analysis.

Results

- The best structural population PK model in the current analysis was a two compartment model.
- Log normal Inter-Patient Variability: $CL_j = TVCL * \exp(\eta_j CL)$.
- Residual Variability was modeled as a proportional, assuming a constant CV over the range of measured concentrations.
- Covariate analysis: after forward selection and backward deletion, WT, ECD and ALKP effects on CL, WT on V_c and HER2 on V_p were considered statistically significant and clinically relevant, and therefore kept in the final model:

$$CL = 0.241 \times \left[\frac{ALKP}{107}\right]^{0.141} \times \left[\frac{ECD}{17.9}\right]^{0.102} \times \left[\frac{WT}{68}\right]^{0.557}$$

$$V_c = 3.02 \times \left[\frac{WT}{68}\right]^{0.484}$$

$V_p = 2.68$ (HER2=1: HER2 overexpression +3) or,

$V_p = 2.68 \times 1.518$ (HER2=0: HER2 overexpression +2 or others)

Table 1: Parameter Estimates of the Final Population Pharmacokinetic Model and bootstrap results

Parameters	NONMEM VI (FOCE INTER)			Bootstrap (800 resamplings)		
	Estimates	95% CI		Median	95% CI	
CL (L/day)	0.241	0.229	0.253	0.241	0.227	0.256
V_c (L)	3.02	2.91	3.13	3.01	2.92	3.13
V_p (L)	2.68	2.35	3.01	2.71	2.32	3.31
Q (L/day)	0.460	0.394	0.526	0.460	0.395	0.545
WT on CL	0.557	0.312	0.802	0.546	0.298	0.820
ALKP on CL	0.141	0.0548	0.227	0.138	0.0544	0.234
ECD on CL	0.102	0.0457	0.158	0.103	0.0389	0.162
WT on V_c	0.484	0.329	0.639	0.482	0.349	0.635
HER2 on V_p	0.518	0.179	0.857	0.500	0.0982	1.04

The estimates of ω_{CL}, ω_{Vc}, ω_{Vp} and σ were:38.6%, 21.4%, 72.6% and 20.9%, respectively.

Figure 1 : Goodness of Fit Plots

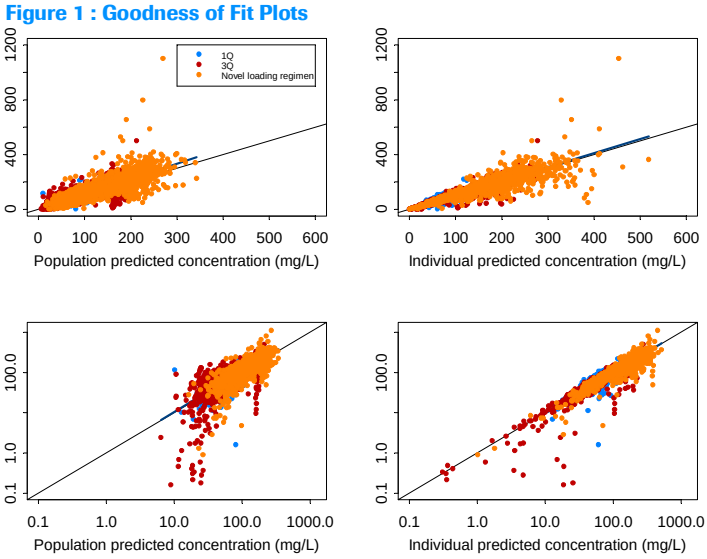


Figure 2: Body Weight Effect on ω_{CL}

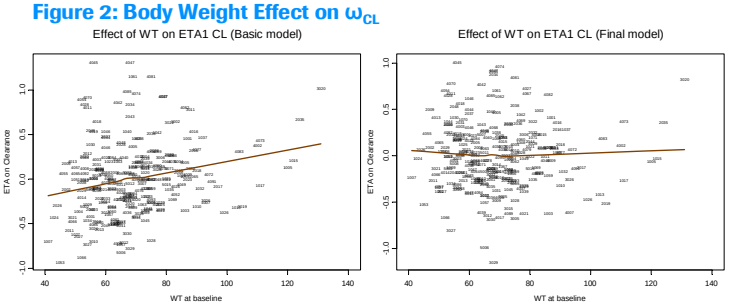
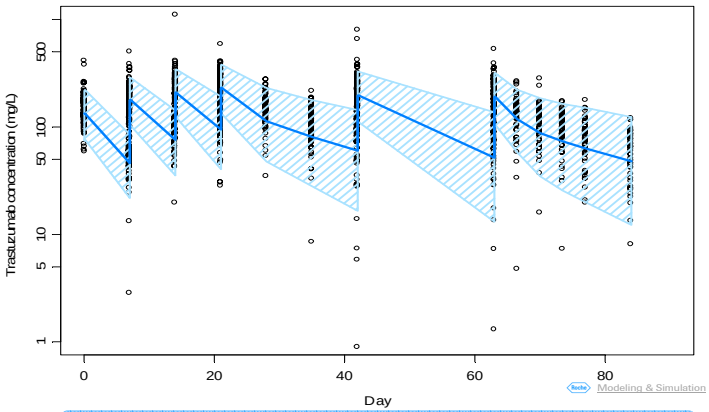


Figure 3: Visual Predictive Check with 90% PI (Novel loading regimen only)

Observations above 95% PI: 4.9%, Observations below 5% PI: 3.5%



Discussion and Conclusion

- The previous model was refined using NONMEM VI with FOCE INTER.
- PK parameterization was changed from TRANS1 to TRANS4 for the current analysis and estimates of CL and V_c were similar to the former model (CL: 0.226, V_c: 3.17) [1].
- PsN (ver. 2.2.3) enabled automated covariate analysis and selected WT, ECD and ALKP effects on CL, WT on V_c and HER2 on V_p , which is similar to previous reports [1,2].
- The PK parameter estimates and 95% CIs were in good agreement with the 800 resamplings of bootstrap results.
- The refinement of the PK model will allow Roche to prepare and support future filings with PK analyses (e.g. adjuvant breast cancer indication) and therefore fulfill regulatory needs.

References

[1] Charoin JE. et al. Population pharmacokinetic analysis of trastuzumab (Herceptin®) following long-term administration using different regimens. PAGE 2004.
[2] Bruno R. et al. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. Cancer Chemother Pharmacol (2005) 56: 361-369.