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

3097 exploitable concentrations from 285 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, Vc, and Vp.

Results

• The best structural population PK model in the current analysis was a two compartment model.

• Log normal Inter-Patient Variability: CLj=TVCL*exp(ωCL)

• The magnitude of the effect of continuous covariates was estimated as following:

%Change = \left( \frac{X_{\text{atives}}}{X_{\text{med}}(\text{med})} \right)^{\theta} - 1 \times 100

Where Xav is the 5th percentile of covariate X, a change of 20% was used as clinically significant criteria in the covariate analysis.

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 Vc were similar to the former model (CL: 0.226 Vc: 3.17) [1].

• PsN (ver. 2.2.3) enabled automated covariate analysis and selected WT, ECD and ALKP effects on CL, WT on Vc and HER2 on Vp were considered statistically significant and clinically relevant, and therefore kept in the final model:

\begin{align*}
\text{CL} &= 0.241 \times \text{ALKP}^{1.141} \\
\text{Vc} &= 0.30 \times \text{WT}^{0.102} \\
\text{Vp} &= 2.68 \times \text{HER2}_{\text{overexpression} +3} \quad \text{or,} \\
\text{Vp} &= 2.68 \times 1.518 \times \text{HER2}_{\text{overexpression} +2 \text{ othes}}
\end{align*}

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NONMEM VI (FOCE INTER)</th>
<th>Bootstrap (800 resamplings)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimates</td>
<td>95% CI</td>
</tr>
<tr>
<td>CL (L/day)</td>
<td>0.241</td>
<td>0.229, 0.253</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>3.22</td>
<td>2.91, 3.13</td>
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<tr>
<td>Vp (L)</td>
<td>2.68</td>
<td>2.35, 3.01</td>
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<tr>
<td>Q (L/day)</td>
<td>0.460</td>
<td>0.394, 0.526</td>
</tr>
<tr>
<td>WT on CL</td>
<td>0.557</td>
<td>0.512, 0.602</td>
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<tr>
<td>ALKP on CL</td>
<td>0.141</td>
<td>0.0548, 0.227</td>
</tr>
<tr>
<td>ECD on CL</td>
<td>0.102</td>
<td>0.0457, 0.158</td>
</tr>
<tr>
<td>WT on Vc</td>
<td>0.584</td>
<td>0.509, 0.659</td>
</tr>
<tr>
<td>HER2 on Vp</td>
<td>0.518</td>
<td>0.179, 0.857</td>
</tr>
</tbody>
</table>

The estimates of ωCL, ωVc, ωVp and n were 38.6%, 21.4%, 72.6% and 20.9%, respectively.

References
