Population pharmacokinetics of trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced gastric cancer (AGC)

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Objectives: A population pharmacokinetic (PK) analysis was performed to characterize T-DM1 pharmacokinetics in previously treated patients with HER2-positive advanced gastric cancer (AGC), and to quantify effects of baseline demographic, laboratory, and disease characteristics on T-DM1 PK.

Methods: 789 T-DM1 serum concentration-time data points from 137 T-DM1 treated patients were fitted using NONMEM® software. Relevant and plausible covariates likely to have an effect on T-DM1 systemic exposure were explored for possible correlation with the key T-DM1 PK parameters of linear clearance (CL) and central volume of distribution (Vc).

Results: T-DM1 PK in HER2 positive AGC patients was best described by a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination from the central compartment. The final population PK model estimated linear CL of 0.79 L/day, Vc of 4.48 L, Q of 0.62 L/day, Vp of 1.49 L, non-linear CL of 2.06 L/day, and KM of 1.63 μg/mL. Parameter uncertainty was low to moderate for fixed effects except for KM, which was estimated with poor precision. Patients with higher body weight and lower baseline trastuzumab concentrations had statistically significant faster CL. Patients with higher body weight also have statistically significant larger Vc. Incorporation of these covariates (P<0.001 by likelihood ratio test) decreased IIV of CL and Vc to 26% and 21%, respectively. The model sensitivity analysis suggests <35% PK variability (as represented by T-DM1 AUC) when statistically significant PK covariates were between 5th and 95th percentile of the population.

Conclusions: In HER2-positive AGC population, T-DM1 PK was best described by a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination. Baseline body weight and trastuzumab concentrations were identified as statistically significant covariates influencing the PK in HER2-positive AGC patients. Predicted PK exposure was lower than previously reported for HER2-positive metastatic breast cancer.