Poster
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Population pharmacokinetics of MYL-1401O (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer

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BACKGROUND

- Mylan trastuzumab (MYL-1401O) is a biosimilar to trastuzumab (Herceptin®)
- A multicenter, double-blind, randomized phase 3 study (HERITAGE) compared the efficacy, safety, population pharmacokinetics (Pop PK) and immunogenicity of MYL-1401O and Herceptin® in patients with HER2-positive metastatic breast cancer (MBC)
- In the HERITAGE trial, patients were randomized 1:1 to receive either MYL-1401O or Herceptin®, in combination with taxane, every 3 weeks for 24 weeks (8 cycles) followed by monotherapy until unacceptable toxicity, disease progression, or early discontinuation
- Results of the Pop PK analysis of the HERITAGE trial are presented here.

Study Objectives

- The primary objectives of the Pop PK analysis were:
  - To compare the Pop PK–derived area under the curve (AUC), maximum serum concentration (C_{max}), clearance (CL), volume of distribution (V_d), and terminal elimination half-life ($t_{1/2}$) profiles of MYL-1401O and Herceptin®
  - To perform an exploratory assessment of the impact of shed extracellular domain (ECD) fragments of the HER2 receptor (HER2/ECD) on PK parameters.

METHODS

PK Sample Collection

- PK samples were collected from all patients at cycles 1, 2, 4, 6, 8, and 9 to assess MYL-1401O/Herceptin® minimum serum concentrations (C_{min}; preinfusion trough samples)
- At Cycle 1 and Cycle 6, 1 sample at the end of infusion (C_{max}) was collected from all patients
- Additional samples were collected from patients enrolled in the Pop PK subset (MYL-1401O: 45; Herceptin®: 37) in the first dosing interval (any time on Day 2 and Day 8) and at subsequent times (2 unscheduled visits in cycles 2 through 8; end of infusion C_{max} sample in Cycle 4)

PK Analyses

- Pop PK modeling was performed using nonlinear mixed effects modeling. A Pop PK model was developed in consideration of previously published population analyses using a 2-compartment linear model.[1-3] Model development included assessment of covariate effects on the inter-individual variability in PK parameters. A bootstrap analysis and goodness-of-fit plots, including visual predictive checks, were performed to evaluate the robustness of the final model
- An analysis of C_{min} values was performed using observed trough samples at the end of Cycle 1 and at Cycle 6 without Pop PK modeling assumptions, using the 2 one-sided *t*-tests statistical approach for bioequivalence
- PK measures reflecting exposure to drug were generated for each patient in the PK population based on model-derived empirical Bayesian estimates of Pop PK parameters, including AUC, C_{max}, CL, V_d, $t_{1/2}$; PK measures were compared qualitatively between treatments
- The impacts of HER2/ECD and antidrug antibodies (ADAs) on trastuzumab CL were evaluated as part of the primary covariate analysis.

RESULTS

Study Population

- Of the 485 patients included in the PK population, 245 received MYL-1401O and 240 received Herceptin®; of them, 482 were included in the Pop PK analysis dataset. Excluding data with missing covariate values or concentrations below the limit of quantification, the final analysis dataset included 213 patients in the MYL-1401O group and 202 patients in the Herceptin® group
- In the Pop PK analysis, 3172 concentration records with sufficient information were included.

Demographics

- There were no notable demographic differences between the treatment groups (**Table 1**).

Table 1. Demographic Characteristics of the PK Population

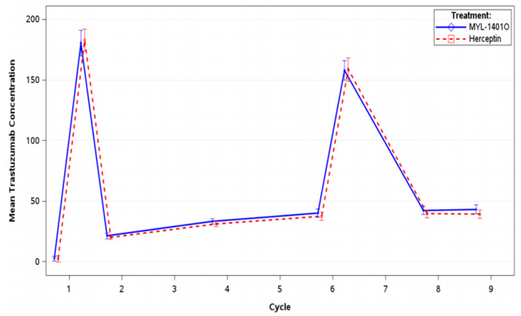
Parameter	MYL-1401O (n = 245)	Herceptin® (n = 240)	Total (N = 485)
Age (years), mean (SD)	54.9 (11.17)	53.7 (11.35)	54.3 (11.26)
Race, n			
White	170 (69.4%)	163 (67.9%)	333 (68.7%)
African American	1 (0.4%)	2 (0.8%)	3 (0.6%)
Asian	73 (29.8%)	74 (30.8%)	147 (30.3%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Weight (kg), mean (SD)	68.53 (14.83)	69.29 (16.36)	68.91 (15.60)
Creatinine clearance (mL/min), mean (SD)	90.27 (29.36)	92.95 (28.42)	91.59 (28.30)
AST (U/L), mean (SD)	35.54 (24.09)	35.54 (32.05)	35.54 (24.09)
ALT (U/L), mean (SD)	28.22 (16.88)	32.57 (25.68)	30.37 (21.77)
Albumin (g/L), mean (SD)	40.90 (5.09)	40.90 (4.74)	40.90 (4.92)
Alkaline phosphatase (U/L), mean (SD)	136.17 (95.45)	139.04 (102.18)	137.59 (98.74)
Bilirubin (µmol/L), mean (SD)	9.46 (4.22)	10.08 (5.63)	9.77 (4.97)
Lactate dehydrogenase (U/L), mean (SD)	364.60 (255.76)	378.11 (504.08)	371.32 (398.60)
HER2 overexpression			
Yes	201 (82.0%)	213 (88.8%)	414 (85.4%)
No	43 (17.6%)	27 (11.3%)	70 (14.4%)

ALT, alanine aminotransferase; AST, aspartate transaminase; PK, pharmacokinetic; SD, standard deviation.

Concentration Data

- Trastuzumab concentrations were similar between the 2 treatments; the mean (standard error) concentration plot is presented in **Figure 1**.

Figure 1. Mean (Standard Error) Concentration Plot



Covariate Analysis

- Treatment was not a significant covariate of CL (P = .177) or volume of the central compartment (P = .584) using the likelihood ratio chi-square test
- The HER2/ECD concentrations were a significant covariate of trastuzumab CL, and CL was similar between treatments
- Weight was also a significant covariate of CL and volume of the central compartment.

Trough Concentration Analysis

- The observed trough C_{min} was comparable between treatment arms at both the end of cycles 1 and 6 (**Table 2**).

Table 2. C_{min} Comparison Between Treatments on Cycle 1 and Cycle 6

C_{min}	Geometric LS means		Ratio (%)	90% confidence interval	
	MYL-1401O (n = 245)	Herceptin® (n = 240)		Lower bound	Upper bound
Cycle 1	17.225	16.706	103.11	90.61	117.33
Cycle 6	34.098	32.735	104.16	94.00	115.42

C_{min}, minimum serum concentration; LS, least squares.

PK Exposure Summary

- Bayesian parameter-based exposure estimates at or near steady-state dosing were comparable between treatments (**Table 3**).

Table 3. Bayesian Parameter-Based Exposure Estimates at Cycle 6 (Final Model)

		MYL-1401O (n = 245)	Herceptin® (n = 240)	Total (N = 485)
Parameter	n*	213	202	415
Dose (mg)	Mean (SD)	420.70 (90.46)	421.25 (97.67)	420.97 (93.92)
Clearance (L/day)		0.27 (0.10)	0.28 (0.08)	0.27 (0.09)
Volume of central compartment (L)		3.16 (0.60)	3.20 (0.60)	3.18 (0.60)
Volume at steady state (L)		6.36 (1.19)	6.33 (1.14)	6.34 (1.16)
AUC (µg*day/mL)		40501.40 (13037.04)	38816.90 (11966.26)	39681.40 (12540.58)
Dose-normalized AUC (µg*day/mL/mg)		98.50 (30.56)	94.41 (28.90)	96.51 (29.80)
$C_{max, ss}$ (µg/mL)		177.00 (37.76)	171.52 (34.61)	174.34 (36.32)
Dose-normalized $C_{max, ss}$ (µg/mL/mg)		0.43 (0.10)	0.42 (0.09)	0.43 (0.10)
Half-life (day)	Median (SD)	25.12 (7.50)	24.34 (6.89)	24.74 (7.21)

AUC, area under the curve; C_{max}, maximum serum concentration; ss, steady state.
*Concentrations below lower limit of quantification and samples before first dose with values >0 were excluded from Pop PK analysis, as were some patients with incomplete information for covariates significant in the final model.

Assessment of ADAs on Clearance

- The low frequency of ADAs was similar between treatments (N = 14 and N = 21 on the MYL-1401O vs Herceptin® products, respectively). A model-based assessment of ADA as a covariate of clearance was inconclusive due to the small sample size.

CONCLUSIONS

- Pop PK profiles of MYL-1401O versus Herceptin® were similar in patients with HER2-positive MBC; model-based exposure measures were similar between treatments
- The model describing the PK of MYL-1401O versus Herceptin® is similar to the model previously published by Fukushima et al, and was considered robust, with the exception that HER2+3 overexpression was not demonstrated to be a significant covariate of the volume of the peripheral compartment.

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