Pharmacokinetics (PK) and exposure-response (E-R) analysis of Kadcyla (K) as a single agent or in combination with Perjeta (P) in patients with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC) who have not received prior chemotherapy for their metastatic disease

Dan Lu[1], Chunze Li[1], Daniel Polhamus[2], Jonathan French[2], Matthew Riggs[2], Priya Agarwal[1], Shang-Chiung Chen[1], Xin Wang[1], Melanie Smitt[1], Monika Patre[3], Alexander Strasak[3], Nataliya Chernyukhin[1], Angelica Quartino[1], Jin Yan Jin[1], Sandhya Girish[1]

[1]Genentech [2]Metrum Research Group [3] F.Hoffmann La Roche

Objectives: PK and E-R analysis for K and P was performed in a Phase III study to assess the efficacy and safety of K as a single agent or in combination with P as compared to Herceptin with taxane in first-line HER2+ MBC patients.

Methods: Post-hoc analysis using historical population PK models for K and P were performed to assess if there is any potential of drug interactions. Correlation of exposure with progression free survival (PFS), incidence of grade 3+ hepatotoxicity, thrombocytopenia and any adverse events were assessed by cox-regression, case matching or chi-square tests.

Results: Mean (± SD) trough concentrations of K conjugate at Cycle 1 day 21 was 1.36 ± 0.832 μg/mL (n=186) and 1.33 ± 0.772 μg/mL (n=189) for K alone and in combination with P. Mean (± SD) trough concentration at Cycle 1 day 21 for P was 64.89 ± 17.78 μg/mL (n=188). The PFS hazard ratio (HR) of patients in quartile 1, 2, 3 and 4 of K conjugate trough concentrations versus control is shown in Figure 1. There was no positive correlation between K exposure with safety endpoints, and no correlation between P exposure with efficacy and safety endpoints.

Conclusion: In conclusion, PK of K and P in first-line HER2+ MBC patients are similar to historical data. No impact of P on K PK and vice versa. Patients with K conjugate trough concentrations in Q1 have a trend of higher HR than others with overlapping confidence intervals.
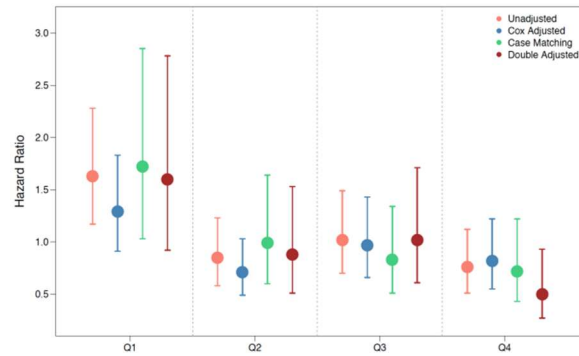

Figure 1: PFS HR of patients in quartile 1, 2, 3, 4 of K conjugate trough concentrations versus control