Population Pharmacokinetics of Trametinib in Combination with Continuous or Intermittent Dosing of a PI3K inhibitor, GSK2126458 in Patients with Advanced Solid Tumors

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Objective: To characterize the pharmacokinetics (PK) of MEK1/2 inhibitor trametinib and dual pan-PI3K/mTOR inhibitor GSK2126458 administered together in patients with advanced solid tumors and to identify potential covariates influencing their PK.

Methods: Population PK analysis was performed using NONMEM version 7.1.2 (ICON, Ellicott City, MD). Subjects (n=65) received escalating doses of GSK2126458 (BID, continuous or intermittent) and trametinib (QD). Covariates were included in the base model based on improvement in objective function value using the likelihood ratio. Final model selection was based on evaluation of goodness-of-fit plots, biological plausibility and precision of parameter estimates. Visual predictive checks (VPC) were implemented for final model evaluation.

Results: A two-compartment model with first order absorption and linear elimination described the GSK2126458 PK with CL/F and Q/F of 3.25 and 2.71 L/h, Vc/F and Vp/F of 8.95 and 38.4 L. WT and ALT levels were predictors of CL/F. WT and age were predictors of Vc/F. The inter-individual variability (IIV) on CL/F and Vc/F was 53% and 97%. For trametinib, a two-compartment model with rapid and slow absorption components (with MTIME) and first order elimination described PK with CL/F and Q/F of 5.46 and 85.3 L/h, Vc/F and Vp/F of 107 and 348 L respectively. The population estimates of slow and rapid absorption rates and MTIME were 0.135, 0.906 h⁻¹ and 0.42 h, respectively. The IIV on CL/F, Q/F, Vc/F, Vp/F, KA1 were 29.6%, 84%, 84%, 72%, and 34%. WT and gender were predictors of CL/F. WT was predictor of Q/F. The VPC plots suggested that the model adequately predicted the concentrations of both agents in this patient population.

Conclusions: The two-compartment model with linear elimination adequately described the PK of both trametinib and GSK2126458. There was no significant difference in the PK estimates of both agents when coadministered as compared to the estimates when administered alone.