Population Pharmacokinetic Meta-Analysis of Ramucirumab in Cancer Patients

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Objectives: Ramucirumab (Ram) is a monoclonal antibody that binds vascular endothelial growth factor receptor 2. The aims of this analysis were to characterize the pharmacokinetics (PK) of Ram in cancer patients, characterize the inter-patient variability (IIV), and investigate patient factors that influence Ram disposition.

Methods: The dataset consisted of 1639 patients with 6427 observations from 11 studies (Phase 1/1b, 2 and 3). Several disease states were represented: colorectal cancer (26.8%), gastric cancer (24.4%), non-small cell lung cancer (26.8%), hepatocellular carcinoma (19.0%), and other tumor types (3%). Ram was administered as an IV infusion over 1 hour, at either 8 mg/kg every 2 weeks or 10 mg/kg every 3 weeks. PK sampling varied across studies.

A pharmacostatistical base model was first developed to describe the concentration data. Demographics, cancer indication, dose, renal function, hepatic status, and other laboratory values were assessed as covariates using forward selection and backward elimination. Covariates were considered significant if they decreased IIV in the relevant parameter by ≥5% and reduced the objective function by ≥6.635 (p<0.01) in forward selection and ≥10.828 (p<0.001) in backward elimination. The model was evaluated using bootstrap and visual predictive check. All analyses were performed using NONMEM 7.3.

Results: The PK of Ram were well characterized by a 2-compartment model with IIV estimated on all parameters and covariance between CL and V1. A combined additive/proportional error model was used. No covariates were found to satisfy the predefined criteria, and no relationship was found between dose level and Ram PK. Mean (CV%) PK parameters derived from post-hoc parameter estimates were: CL 0.0147 L/hr (30.0%), Vss 5.38L (15.0%), and terminal half-life 14.2 days (20.0%).

Conclusions: The final model adequately described the time-concentration profile of Ram in patients with a range of cancer indications. The PK parameters were consistent with those obtained from non-compartmental analyses of Phase 1 and 2 studies, with the exception of half-life. Simulation using the model confirmed the appropriateness of weight-based dosing.