Population Pharmacokinetics and Pharmacodynamics Analysis of Selumetinib and its Metabolite in Phase 1 Subjects and Patients with Non-small Cell Lung Cancer

Xiao Tong1, Hongmei Xu1, David Carlile2, Helen Tomkinson2, Nidal Al-Huniti1, Diansong Zhou1

1 AstraZeneca, Waltham, MA; 2 AstraZeneca, Cambridge, UK

Objectives: Selumetinib (AZD6244, ARRAY-142886) is a MEK-inhibitor that’s been tested for treatment of non-small cell lung cancer (NSCLC). This analysis aimed to develop a population pharmacokinetic (popPK) model for selumetinib and its active metabolite N-desmethyl selumetinib in phase 1 subjects and in patient with NSCLC to investigate potential exposure-response for efficacy and safety endpoints.

Methods: The popPK model for selumetinib and its metabolite was first developed using 7 phase 1 studies (NCT 01974349, NCT02056392, NCT02322749, NCT02238782, NCT02063204, NCT02093728, NCT02046850); the popPK model in patients was then developed with two patient datasets (NCT01750281, NCT01933932) using the phase 1 popPK model as informative prior. Individual selumetinib exposure metrics at steady-state were simulated based on the final patient PK model to investigate the correlation between exposure and efficacy or safety endpoints observed in NSCLC patient studies. PopPK modeling was performed using NONMEM 7.3.0.

Results: A two-compartment model with zero-first order absorption and first order elimination reasonably described the selumetinib PK. A portion of total selumetinib elimination was converted to metabolite and the disposition of its metabolite was described by a one compartment model with first order elimination. The body weight on the central volume of distribution was the only significant covariate identified. The final PK parameter estimates were similar between phase 1 and patient population. The estimated typical clearance and central volume of distribution of selumetinib was 11.9 L/h and 32.1 L in patients. The estimated exposure (AUCss) of selumetinib and N-desmethyl selumetinib in patients were in similar range as those predicted in phase 1 subjects. No significant correlation between the exposure and varies of efficacy or safety endpoints was observed.

Conclusions: Population PK models developed reasonably described the selumetinib and its metabolite PK in both phase 1 and patients with NSCLC. There was no significant correlation between the selumetinib exposure and efficacy or safety endpoints at 75 mg studied dosing level.