Model-Based Approach for Dose Optimization of HSP90 Inhibitor Luminespib

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Objectives: To optimize the once weekly via 1-hr intravenous infusion dosing regimens of luminespib in patients with advanced non-small cell lung cancer (NSCLC) using a model-based approach. The hypothesis we proposed was that a longer infusion time at its current efficacious doses 40 mg/m$^2$ and above would likely improve the benefit and risk ratio of luminespib by blunting its $C_{\text{max}}$ and prolonging its exposure in the systemic circulation.

Methods: The population PK analysis of luminespib was conducted in two-stages. First, the red blood cells (RBC)-plasma distribution model was developed to describe luminespib nonlinear capacity-limited specific binding and linear non-specific binding to RBC. Second, the systemic model parameters in plasma were estimated by fixing the apparent dissociation constant ($k_d$) to the value determined in the first stage. The relationship between the steady-state luminespib maximum blood concentration ($C_{\text{max}}$) and safety endpoints (G2+ diarrhea and G2+ eye disorders) were described by sigmoidal $E_{\text{max}}$ logistic regression models. Model-based simulations were performed to determine the longer infusion dosing regimens for luminespib that could keep its $C_{\text{max}}$ below the threshold level determined from the exposure-safety analyses.

Results: Luminespib PK in plasma was described by a linear three-compartment model with zero-order infusion. Luminespib PK in blood was nonlinear and was attributed to the concentration-dependent RBC binding. Luminespib $C_{\text{max}}$ was found to be a significant predictor of G2+ diarrhea and eye disorders ($p<0.001$). The $C_{\text{max}}$ producing the 50% maximum effect ($EC_{50}$) was 443 ng/mL for G2+ diarrhea and 574 ng/mL for G2+ eye disorders. The model-based simulation indicated luminespib 1-hr infusion at 40 mg/m$^2$ and above could produce $C_{\text{max}}>$443 ng/mL in >90% patients, while 4-hr infusion at 40 and 54 mg/m$^2$ could cap $C_{\text{max}}$ at 443 ng/mL in >80% patients (Figure 1).

Figure 1. Distribution of simulated luminespib blood $C_{\text{max}}$ at series of dosing regimens (28, 40, 54, 70 mg/m$^2$ with the infusion time of 1, 3, 4, 6, 8, 12 hrs)

Conclusions: An integrated population PK model adequately described luminespib PK in blood and plasma. The higher luminespib $C_{\text{max}}$ was associated with increased probability of G2+ diarrhea and eye disorders. The model-based approach was utilized to optimize luminespib dosing regimens that could keep drug exposure below the pre-determined threshold level.

References: