Population PK-tumor size dynamic modeling and survival analysis of EGF816, a third generation, mutant-selective EGFR TKI, in patients with advanced NSCLC harboring T790M

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Objectives: To investigate the relationship between EGF816 exposure and tumor growth inhibition (TGI) in patients with advanced NSCLC harboring an EGFR T790M mutation. The predictability of progression free survival (PFS) using tumor size (TS) response metrics was also evaluated.

Methods: Data were obtained from a phase 1, dose escalation study (NCT02108964), in which patients were treated with oral EGF816 from 75 mg to 350 mg QD in either capsule or tablet formulations. The analyses were performed sequentially using NONMEM v7.2. First the population PK model was developed to estimate the individual daily AUC (AUCtau). A semi-mechanistic AUCtau-driven TGI model was then fit to the longitudinal TS data to predict individual TS metrics, namely TS ratio to baseline at week 8, time to tumor growth (TTG), and tumor growth rate (G). The risk of progression or death with TS metrics was assessed using a parametric survival model.

Results: EGF816 PK was described with a linear two-compartment disposition model and with an absorption process characterized by a transit model[1]. The TS data were best described by a TGI model which incorporated a first-order tumor growth rate, the drug effect on tumor cell killing, and resistance to drug effect [2]. The AUCtau producing 50% of maximal TGI was 1.94 mg·hr/L, which when converted to a daily average concentration (i.e., 81 ng/mL), was similar to the human equivalent tumor stasis concentration (99 ng/mL) determined using the H1975 xenograft model. The lower TTG corresponded to higher risk of progression or death.

Conclusions: Tumor growth inhibition was achieved at all dose levels and increased with EGF816 dose up to 300 mg QD. Further, TTG was a predictor of PFS in patients with EGFR T790M mutant NSCLC receiving EGF816.

References: