A PHASE I DOSE-ESCALATION AND PHARMACOKINETIC (PK) STUDY OF A NOVEL SPECTRUM-SELECTIVE KINASE INHIBITOR, XL647, IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES (ASM)

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INTRODUCTION

XL647 is a novel, orally available small molecule inhibitor of multiple receptor tyrosine kinases involved in tumor growth, angiogenesis, and metastasis, including EGFR (ErbB1), ErbB2 (HER2), VEGFR2 (KDR), and EphB4.

Methods:

Screening assessments were conducted within 21 days of the first dose of XL647. Treatment cohorts were dosed in escalating order. Dose escalation was allowed only after the safety of the previous cohort had been established, based on the absence of any drug-related adverse events of 

A total of 40 patients are evaluable for safety, of whom 36 are also evaluable for response. Baseline staging assessments were conducted prior to entering the study. During each cycle, blood samples were collected at the following timepoints (Figure 2):

Study treatment

- On Day 1 of each cycle, patients received a single oral dose of XL647.
- On Days 1 and 8 of Cycle 1, patients received a single oral dose of XL647.

Figure 3 Panel (A) shows mean plasma concentrations of XL647 from Cohort 1 following oral administration of single 4.68 mg/kg and 0.39 mg/kg liquid formulations. The 4.68 mg/kg dose was selected for further study.

Figure 3 Panel (B) shows the mean plasma concentration-time profiles following single oral doses of XL647 in Cohort 1.

Pharmacokinetics

- XL647 shows approximately dose-proportional exposure, a mean time to maximal concentration (tmax) of 1.04 hours following 4.68 mg/kg and 1.56 mg/kg doses, and a terminal half-life (t1/2) of approximately 70.4 ±13.4 hours following five doses and did not change with repeated dosing.

Figure 4: Pharmacokinetic profiles of XL647 in Cohort 1 following single oral doses of XL647. Terminal half-life (t1/2) was measured in Cohort 1 following five oral doses of XL647.

CONCLUSIONS

- XL647, a novel, spectrum-selective kinase inhibitor, was well tolerated with a manageable safety profile in patients with advanced solid malignancies.

References


Figure 5: Pharmacokinetic profiles of XL647 in Cohort 1 following single oral doses of XL647. Terminal half-life (t1/2) was measured in Cohort 1 following five oral doses of XL647.