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A phase I dose-escalation study of the safety and pharmacokinetics (PK) of XL184, a VEGFR and MET kinase inhibitor, administered orally to patients (pts) with advanced malignancies

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Abstract

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Background: XL184 is a potent orally available small molecule inhibitor of MET and VEGFR2/KDR, and also inhibits KIT, RET, FLT3, and Tie-2. **Methods:** This is a ph 1 cohort dose escalation study. Pts with advanced malignancies are treated with 2 cycles of XL184 orally daily for 5 consecutive days every 2 weeks. Response is assessed every 8 wks by RECIST criteria and pts with SD or better receive maintenance therapy. Plasma markers of angiogenesis VEGF-A, sVEGFR2 and Ang2 are being analyzed. **Results:** A total of 25 pts with advanced malignancies have been treated across 7 dose levels: 0.08 to 5.12 mg/kg. A total of 10 pts have had SD lasting > 3 months. Three pts with medullary thyroid carcinoma (one of whom had a documented RET mutation) had substantial reductions in plasma calcitonin. Three pts have had stable disease for over 6 months, including 1 pt with carcinoid (20% decrease in liver metastases) and 1 pt with T- cell lymphoma (on treatment for >12 mos). One pt with papillary renal cell cancer, a disease that sometimes bears activating MET mutations, demonstrated 9% tumor reduction at first restaging. There have been no DLTs to date. Preliminary PK analysis (0.08–1.28 mg/kg) suggests linear PK with average Cmax values 34.2, 70, 198, 322 and 603 ng/mL following the fifth dose at 0.08, 0.16, 0.32, 0.64 and 1.28 mg/kg, respectively. The terminal half-life is 80–90 hrs, resulting in concentrations exceeding 200 ng/mL for 96 hours following the fifth dose at 1.28 mg/kg. **Conclusions:** XL184 appears generally well tolerated at doses tested to date. XL184 has a long terminal half-life. Early signs of antitumor activity have been observed, at doses not associated with toxicity, in patients with various cancers, including but not limited to those that may have RET (medullary thyroid) or MET (papillary renal) mutations.

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