The hepatocyte growth factor (HGF) receptor tyrosine kinase (Met) has been implicated as a stimulator of angiogenesis. Vascular endothelial growth factor (VEGF) expression is upregulated in many human tumors, and binding and activation of VEGFR2/KDR (a Met homolog) by VEGF is essential for angiogenesis. Our understanding of tumor biology is rapidly evolving, as we recognize that normal tissue function is closely interrelated with cancerous ones. The importance of understanding the molecular mechanisms that drive tumor growth and angiogenesis is underscored by the need to develop new therapeutic strategies to combat these devastating diseases.

**RESULTS**

**Objective:** To assess the safety and tolerability of a novel spectrum selective kinase inhibitor (SSKI), XL880, administered orally to patients with solid tumors.

**Methods:** A Phase I study of XL880 was conducted at the National Cancer Institute, Bethesda, MD. The study design is illustrated in Figure 1. Eligible patients included those with solid tumors refractory to standard therapies. The primary objectives were to determine the maximum tolerated dose (MTD) and to assess the safety and tolerability of XL880 in patients with solid tumors.

**Study Design:**

- **Patient Selection:** Eligible patients were required to have measurable or evaluable disease and to be at least 18 years of age.
- **Dosing:** XL880 was administered orally in a single 5-day cycle. Each cycle was followed by a 14-day rest period.
- **Dose Escalation:** The starting dose was 20 mg/day, with a 3+3 dose-escalation design.
- **Pharmacokinetic Analysis:** Plasma concentrations were measured at baseline, 30 minutes, 1, 2, 4, 8, 12, and 24 hours post-dose.

**Pharmacokinetic Analysis:**

- Plasma concentration-time profiles were analyzed using non-compartmental methods.
- Terminal half-life values were approximately 60 hours following 5 consecutive daily doses.
- Steady-state plasma concentrations were achieved within 2 cycles of dosing.

**Safety Analysis:**

- Safety was assessed by standard laboratory tests and by standard clinical and radiological tests. Toxicity grades were defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTC v4.0).

**Pharmacodynamic Analysis:**

- Drug metabolism was determined by measuring plasma concentrations of parent compound and metabolites.

**Pharmacodynamic Results:**

- Terminal half-life values were approximately 60 hours following 2 cycles of dosing.
- Terminal half-life values were approximately 60 hours following 3 cycles of dosing.
- Terminal half-life values were approximately 60 hours following 4 cycles of dosing.
- Terminal half-life values were approximately 60 hours following 5 cycles of dosing.

**Conclusion:** XL880 is well tolerated at up to 5 cycles of dosing, with continued dose escalation ongoing.

**Figure 1:** A phase I study of a novel spectrum selective kinase inhibitor (SSKI), XL880, administered orally in patients with solid tumors.

**Figure 2:** Pharmacokinetic and pharmacodynamic analysis of XL880 administered orally in patients with solid tumors.

**Figure 3:** A phase I study of XL880 in patients with breast cancer.

**Figure 4:** Pharmacokinetic and pharmacodynamic analysis of XL880 administered orally in patients with breast cancer.

**Figure 5:** A phase I study of XL880 in patients with colorectal cancer.

**Figure 6:** Pharmacokinetic and pharmacodynamic analysis of XL880 administered orally in patients with colorectal cancer.

**Figure 7:** A phase I study of XL880 in patients with non-small cell lung cancer.

**Figure 8:** Pharmacokinetic and pharmacodynamic analysis of XL880 administered orally in patients with non-small cell lung cancer.