A PHASE I DOSE-ESCALATION AND PHARMACOKINETIC (PK) STUDY OF A NOVEL SPECTRUM SELECTIVE KINASE INHIBITOR (SSKI), XL999, IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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OBJECTIVES

The primary objective of the study was to determine the maximum tolerated dose (MTD) and to evaluate the safety profile of XL999 administered as a single dose (CD) to healthy human volunteers in 3 dose cohorts: 300 mg, 450 mg, and 600 mg. Secondary objectives were to evaluate plasma pharmacokinetics of XL999 administered as a single dose (CD) to patients with solid tumors. Tumor response rate was also included as a exploratory objective.

INTRODUCTION

A variety of growth factors are known to be intimately involved in the growth, invasion, and metastasis of cancer cells.1,6,25-27 They drive the proliferation of cancer cells through autocrine or paracrine signaling (7) and may contribute to poor therapeutic efficacy of standard-of-care antineoplastic regimens (8). Hence, the discovery of small molecule inhibitors of pathways that drive cancer cell growth, proliferation, and survival is an active area of research.11,13,23-25 Several pharmaceutical companies have adopted strategies to develop selective kinase inhibitors to address the need for improved therapies with less toxicity and better efficacy.6,7,12,13 The aim of our study is to identify and characterize novel selective kinase inhibitors that may be applicable to clinical settings.

C82 shows a single-dose of XL999 at 1.0 mg/kg was generally well tolerated. Tumor response was assessed using RECIST, and no objective responses were observed. The study was conducted on 21 patients on day 1. Preliminary pharmacokinetic analyses show dose-proportionality across all levels but with wide variability. The mean exposure (Cmax and AUC) at the recommended dose (0.75 mg/kg) was significantly lower than that at 0.80 mg/kg.

11Cytotoxic chemotherapy is frequently used in combination with antitumor agents and exhibits broad antitumor activity in xenograft models.11-13 A PHASE I DOSE-ESCALATION AND PHARMACOKINETIC (PK) STUDY OF A NOVEL SPECTRUM SELECTIVE KINASE INHIBITOR (SSKI), XL999, IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES 1

RESULTS

1. Preliminary Pharmacokinetic Analyses

1.1 Pharmacokinetics

1.2 Dose-Proportionality

1.3 Exposure-Related Toxicity

1.4 Tumor Response

1.5 Safety

1.6 Pharmacodynamics

1.7 Pharmacokinetics

1.8 Dose-Proportionality

1.9 Exposure-Related Toxicity

1.10 Tumor Response

1.11 Safety

1.12 Pharmacodynamics

1.13 Pharmacokinetics