A Phase I, open label, ascending dose study of the safety, tolerability, pharmacokinetics and pharmacodynamics of the endothelin B agonist, SPI-1620, in patients with recurrent or progressive carcinoma

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Introduction. Chemotherapy, one of the mainstays of solid tumor treatment, often fails because of poor drug delivery to tumors. Pharmacological agents that increase tumor blood flow could be utilized to promote the delivery of anti-cancer drugs to tumors. We developed a novel approach to target endothelin B receptors in the tumor vasculature with SPI-1620 to enhance tumor blood flow. SPI-1620 is an agonist of ET_B receptor. Preclinical studies have shown that SPI-1620 selectively and transiently increases blood flow to tumors and enhances the response of various chemotherapeutic agents in tumor bearing animals.

Objective. Primary objective of this study is to assess the safety and tolerability of SPI-1620 administered to patients with recurrent or progressive carcinoma who have failed all standard therapy. Secondary objectives of this study are to assess PK, PD profiles of SPI-1620 and to identify the optimum dose of SPI-1620 to be used in future Phase II studies.

Methods. This is a 2-part, open label, single arm, dose escalation study. Part 1 of the study is designed to define MTD, optimal dose of SPI-1620 and to measure PK/PD profiles. Patients with progressive or recurrent carcinoma who failed all standard therapies were eligible for the study. Patients with a history of CHF, stroke, symptomatic COPD, ventricular arrhythmia were excluded from the study. Eligible patients received SPI-1620 delivered intravenously over one minute on Days 1, 8 and 15. On Day 8 patients underwent a series of four $H_2{}^{15}O$ PET Blood Flow (BF) scans to assess alterations in BF induced by SPI-1620 in tumor and non-tumor regions. Fifteen minutes after receiving SPI-1620 on Day 15, patients received docetaxel, 60 mg/m^2, administered by infusion over 1 hour.

Part 2 of the study will focus on the safety and tolerability of docetaxel administered at a dose of 75 mg/m² following SPI-1620 at MTD and an additional dose in 2 groups. CT or MRI scans will be used to assess the patient's tumor size. A series of dynamic contrast enhancer pattern MRI scans will be used to measure any increases in blood flow induced by SPI-1620.

Results. In all 30 patients were enrolled in part 1 of the study. Patient characteristics-M/F: 14/16, median age 61 years (range 41-77), prostate cancer (9/30), breast cancer (3/30), female reproductive malignancies (4/30), GI 3/30, pancreatic 2/30 etc. SPI-1620 dose levels were 0.5 µg/m^2 (n=1), 1.0 µg/m^2 (n=1), 2.0 µg/m^2 (n=3), 2.8 µg/m^2 (n=3), 3.7 µg/m^2 (n=1), 3.9 µg/m^2 (n=4), 5.5 µg/m^2 (n=3), 7.7 µg/m^2 (n=3), 10.8 µg/m^2 (n=4), 15.1 µg/m^2 (n=3), 10.8 µg/m^2 (n=4). Docetaxel dose level was 60 mg/m^2. Dose limiting toxicities were observed at a dose of 15.1 µg/m^2 of SPI-1620. Maximum tolerated dose was defined as 11 µg/m^2. Drug related serious adverse events were (n; %): ischemic stroke (1, 0.03), dyspnoea (1, 0.03), pleural effusion (1, 0.03). Disease progression was the most common reason for the discontinuation of the study (84%). There were 5 cases of stable disease (16% SD). Prolonged clinical benefit was observed in 4 cases (13%) where patients stayed on the study for 20-74 weeks. A PSA response in previously docetaxel treated prostate cancer patient as well as a measurable decrease in metastatic prostate cancer. One notable case was of a patient with cholangiocarcinoma who achieved complete regression of lung metastasis within 3 months of treatment and stayed on the study for 41 weeks before eventually progressing. Treatment with SPI-1620 did not result in any measurable changes in blood flow, possibly due to inherent technical difficulties associated with PET imaging method. In part 2 of the study, dynamic contrast MRI will be used to detect blood flow changes.

Conclusion. Maximum tolerated dose of SPI-1620 is defined as 11µg/m^2 in combination with docetaxel. SPI-1620 is well tolerated both as a single agent as well with docetaxel. Encouraging anti-tumor activity was seen in patients with docetaxel pretreated patients.