Results of a Phase 1 Study of RX-5902, an Orally Bioavailable Inhibitor of Phosphorylated p68, Targeting Solid Tumors

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Background: RX-5902 is a novel compound that targets phosphorylated p68 RNA helicase (also known as DDX5), a member of the DEAD box family of RNA helicases. Phosphorylation of p68 promotes EMT via promoting transcription of cyclin D1 and c-Myc genes (Yang et al J Biol Chem 2007) and alters cell migration and enhances survival in a variety of in vivo xenograft tumor models (e.g., breast, ovarian, renal, pancreatic). We report the data from the first clinical study of RX-5902 as a single agent to solid tumors.

Methods: This is a 1 study (NCT02003092) designed to evaluate safety, tolerability and pharmacokinetics following increasing doses of RX-5902 at varying schedules. Primary objectives include safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were pharmacokinetic (PK) and antitumor activity (RECIST v1.1). Eligible subjects (age ≥ 18 years) with relapsed/refractory solid tumors received oral RX-5902 at 3, 5 or 7 times per week followed by 1 week of rest or for 4 weeks without a rest. Plasma concentrations were measured using a validated LC-MS/MS assay, and non-compartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4. Results: As of January 2016, 16 subjects have been enrolled (8 Female, 10 male). No dose limiting toxicities or treatment related SAEs have been reported. Six subjects have experienced stable disease; no grade 2 related events have been reported. RX-5902 was orally bioavailable with median Tmax of 2 hours and median elimination half-life of 12 hours.

Safety Profile

RX-5902 Proposed Mechanism

• p68 phosphorylation at Tyr593 by c-Abl (Yang et al. Cell 2006)
• Phospho-p68 promotes EMT via promoting transcription of cyclin D1 and c-Myc genes (Yang et al, J Biol Chem 2007)
• Phospho-p68 mediates PDGF stimulated cell proliferation via promoting transcription of cyclin D1 and c-Myc genes (Yang et al at Cell 2006)
• Phospho-p68 correlates with cancer progression
• Phospho-p68 correlates into the nucleus, where it binds to diverse DNA-binding partners to regulate gene transcription
• The β-catenin nuclear translocation and subsequent interaction with various targets (including T-cell factor/helix-loop-helix) transcription factors is required for the EMT process
• Studies underway to further characterize β-catenin interaction

Pharmacokinetics

Pharmacokinetic (PK) samples were collected on Day 1 (for single weekly dosing) and Day 15 (multiple weekly dosing) for 48 hours. Plasma concentrations were measured using a validated LC-MS/MS assay, and non-compartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4. Population PK model was built for pharmacokinetic/pharmacodynamics assessments.

Treatment (Days) and Best Response

Conclusions

• RX-5902 is safe and well tolerated at the doses and schedules tested.
• Early anti-tumor activity was observed in patients with breast, neuroendocrine, paraganglioma, head and neck and colorectal cancer.
• Continuous dosing is currently being tested.
• The study was recently amended to include patients with HER2 negative breast cancer or ovarian cancer in a 2-stage Phase 2