Background: Supinoxin (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. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. As a single agent, Supinoxin inhibits tumor growth and enhances survival in a variety of in vivo animal xenograft tumor models (e.g., breast, ovarian, pancreas, and melanoma). The impact emerging data from the first 6 weeks of treatment in a single-agent context with Supinoxin was described in this study.

Methods: This is a Phase 1 study designed to evaluate safety, tolerability, and pharmacokinetics following increasing doses of Supinoxin. Primary objectives include safety, tolerability, and determination of the MTD and a recommended phase 2 dose. The study is a single-arm, dose escalation trial. Subjects were treated as inpatients in the Clinical Research Unit or as outpatients, depending on apparent half-life (21–43 hr), usually followed by a steady, rising plasma phase. Tmax was calculated using WinNonlin, Version 6.4. Results: Supinoxin given orally to fasted subjects as API in capsules, sometimes displayed an apparent, short lag time (0.25 hr), usually followed by a steep, rising plasma phase. Tmax was somewhat variable, being observed from 1.5 to 6 hr after dosing. After Tmax, oral distribution phase was often exponential, followed by the apparent terminal phase. Safety, over 75% of AUCmax at 775 mg was observed by 24 hr. Apparent terminal half-life for the parent compound was 63–108 hr for 225 and 350 mg doses and 106–117 hr for 425 mg doses. Long-range elimination was the predominant elimination pathway for RX-5902 and metabolites. The plasma concentrations were modeled with a 3-compartment oral administration model.

Conclusions: At the selected doses, plasma exposure to Supinoxin appeared to be well tolerated. The MTD was not reached within the range of 25–425 mg/day.

Study Design

This is a Phase 1 multicenter, dose finding, open-label, single agent study of RX-5902 administered orally to subjects with advanced or metastatic solid tumors. One subject will be treated per dose group until the appearance of a related grade 2 or greater adverse event, after which 3 subjects will be treated using the modified Fibonacci schedule.

Subjects will be treated for up to 6 cycles of therapy. RX-5902 will be taken on Days 1, 8, and 15 followed by a week of rest on Day 22 of a 28-day cycle. All subjects will be followed for at least 30 days after the last dose of RX-5902. Additional cycles allowed for subjects receiving benefit.

For the population PK compartmental modeling, the concentration data was analyzed using Phoenix NLME and WinNonlin. Plasma concentrations were modeled with 3 compartment oral administration models (panels A and B). The actual pharmacokinetic data were initially used to validate the simulation model (panels A and B). 3 week at 200 mg/day (C) or 5 week at 200 mg/day (D) simulation were generated to predict exposures at each anticipated dose (3 week dosing regimen).

Conclusions

Based on the pharmacokinetic profile of RX-5902 administered weekly, a more frequent dosing schedule should be effective.

Preliminary pharmacokinetic data helped to validate the pharmacokinetic simulations to predict pharmacokinetic profiles at more frequent dosing.

Investigator Disclosures

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