Single Agent Supinoxin Targeting Phosphorylated p-68 Preliminary Phase 1 Data

W. Larry Gluck[1], S. Gail Eckhardt[2], Martin Gutierrez[3], Christine Peterson[4]and Ely Benaim[4], [1]Translational Oncology Research, Greenville, SC, [2]University of Colorado Cancer Center, Anschutz Medical Campus, Aurora, CO, [3]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ [4]Rexahn Pharmaceuticals, Inc., Rockville, MD

Abstract # 344

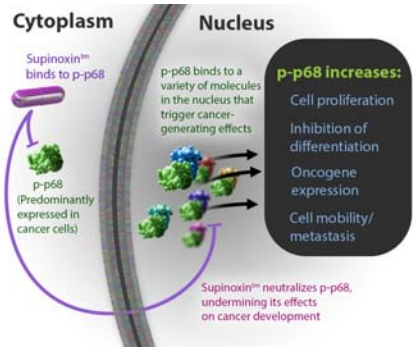
Background: Supinoxin (RX-5902) is a novel compound that targets phosphorylated p68 RNA helicase (also known as DDX5), a member of the DEAD box family of RNA helicases. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. As a single agent, Supinoxin inhibits tumor growth and enhances survival in a variety of in vivo animal xenograft tumor models (e.g., renal, ovarian, pancreatic, melanoma). We report emerging data from the first clinical study of Supinoxin as a single agent in patients with solid tumors.

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 to determine the MTD and a recommended phase 2 dose/schedule (RP2D); secondary objectives were pharmacokinetics (PK) and antitumor activity (RECIST v1.1). Patients received from 25 to 425 mg Supinoxin for up to 6 dosing cycles, with each cycle consisting of 1 dose of Supinoxin per week for 3 weeks followed by 1 week of rest. Plasma concentrations were measured using a validated LC-MS/MS assay, and noncompartmental pharmacokinetic parameters were 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. However, T_{max} was somewhat variable, being observed from 1.5 to 6 hr after dosing. After T_{max}, a short distribution phase was often observed, followed by the apparent terminal phase. Usually, over 75% of AUC_{last} (0-48 hr) was observed by 24 hr. Apparent terminal $T_{1/2}$ over the dose range 25 to 425 mg ranged from 5.8 to 27.6 hr, but most individual values were near the mean value of 14.0 hr. C_{max} and AUC_{last} increased fairly linearly with dose. AUC_{last} increased in a dose-proportional manner overall, but C_{max} increased a less than proportional manner. Over the dose range of 25 to 425 mg, C_{max} in fasted subjects ranged from 99 to 660 ng/mL. Over the same dose range, AUC_{last} in fasted subjects ranged from 894 to 14,673 hr*ng/mL. The most frequent related adverse events noted to date were mild nausea, vomiting and fatigue; no grade 2 related events have been reported.

Conclusions: At the tested dose levels, Supoinxin appears to be well tolerated.

RX-5902 Proposed Mechanism



Study Design

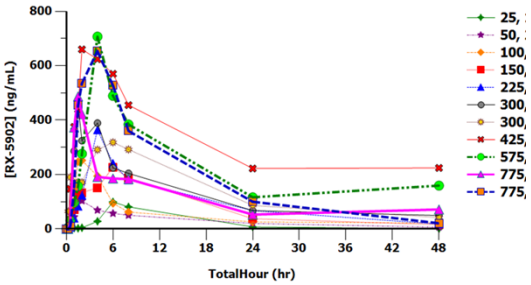
This is a Phase 1 multicenter, dose finding, open-label, single agent study of RX-5902 administered orally to subjects with advanced or metastatic solid tumors. One subject will be treated per dose group until the appearance of a related grade 2 or greater adverse event, after which 3 subjects will be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

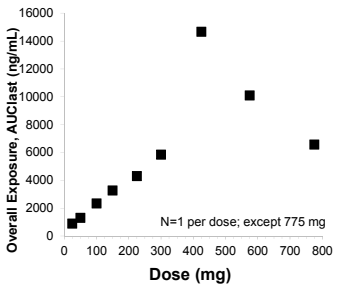
Pharmacokinetic sampling was done at 0.5 hours ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 10 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes and 8 hours ± 10 minutes, 24 hours ± 10 minutes and 48 hours ± 10 minutes, after the oral administration of RX-5902 on Cycle 1 Day 1

Preliminary Pharmacokinetic Results

Plasma Concentrations of Supinoxin After 1st Dose



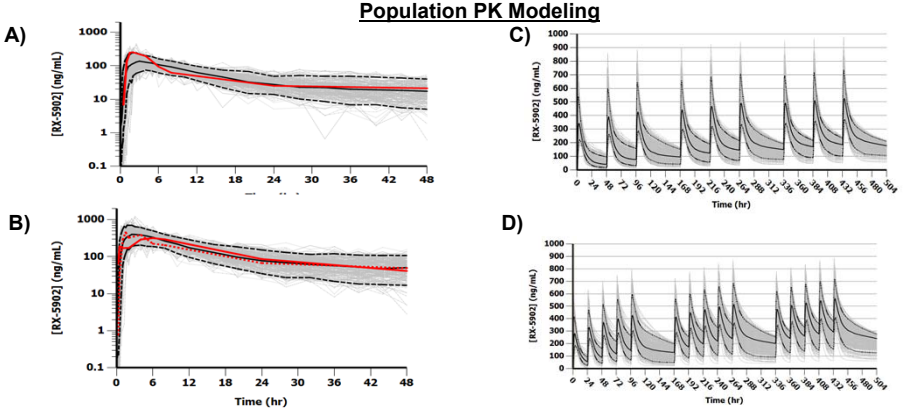
Dose-dependent Total Exposure



Pharmacokinetic Summary

Dose (mg)	Site #	Subject #	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUClast (hr*ng/mL)
25	1	1	99.1	6	5.75	894
50	1	2	109	1.5	13.2	1308
100	2	1	252	2	27.6	2341
150	2	4	226	6	11.4	3280
225	1	4	364	4	12.0	4312
300	1	5	318	6	14.6	6141
425	2	6	660	2	--	14673
575	2	7	707	4	--	10098
775	1	7	571	2.75	--	6569

Population PK Modeling

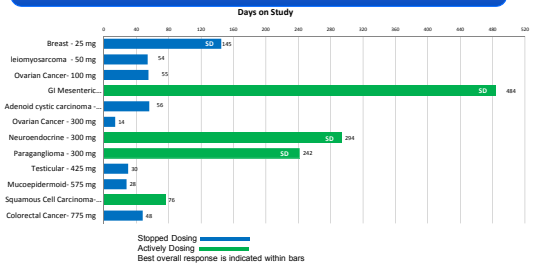


For the population PK compartmental modeling, the concentration data was analyzed using Phoenix NLME and WinNonlin. Plasma concentrations were modeled with a 3 compartment oral administration models (panels A and B). The actual pharmacokinetic data were initially used to validate the simulation model (panels A and B), and 3/week at 250 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).

Predicted Plasma Exposures

Dosing Frequency	Dose (mg)	Total cycle dose (mg)	Cmax Day 1	AUC Day 1	AUC Week 1	Cmax Week 3	AUC Week 3
1X week	425	1275	612	7087	15844	679	23897
	1050	3150	1507	17626	40076	1672	60015
3X week	250	2250	356	4179	23986	534	41354
	300	2700	432	5020	28607	644	49280
	350	3150	508	5861	33228	755	57207
5 Days on /2 Days off	100	1500	145	1682	16168	284	27673
	150	2250	217	2513	24000	424	41217
	200	3000	289	3345	31832	563	54760

Treatment and Safety Profile



Adverse Event	# of events	Severity
Vomiting	N = 3	Mild
Nausea	N = 1	Moderate
Anorexia	N = 1	Mild
Arthralgia`s	N = 1	Mild
Constipation	N = 1	Mild
Elevated triglycerides	N = 1	Mild
Fatigue	N = 1	Mild
Fever	N = 1	Mild
Insomnia	N = 1	Mild
Low appetite	N = 1	Mild
Lower back pain	N = 1	Mild
Muscle cramps	N = 1	Mild
Myalgia`s	N = 1	Mild
Nausea	N = 1	Mild
Neuropathy in Fingers and toes	N = 1	Mild
Night sweats	N = 1	Mild
Weight loss	N = 1	Mild

Conclusions

- Based upon 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

1. Christine Peterson, PhD – Rexahn Pharmaceuticals
2. Ely Benaim, MD – Rexahn Pharmaceuticals

For further information about RX-5902 and Rexahn Pharmaceuticals please contact Dr. Ely Benaim: benaime@rexahn.com, (240) 268-5300