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

S. Gail Eckhardt[1], W. Larry Gluck[2], Martin Gutierrez[3], Christine Peterson[4], Reza Mazhari[4] and Ely Benaim[4]

[1]University of Colorado Cancer Center, Anschutz Medical Campus, Aurora, CO, [2]Translational Oncology Research, Greenville, SC, [3]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [4]Rexahn Pharmaceuticals, Inc., Rockville, MD

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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. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. As a single agent, RX-5902 inhibits tumor growth, alters cell migration and enhances survival in a variety of in vivo animal 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 treat solid tumors.

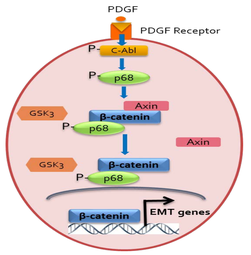
Methods: This is a Phase 1 study (NCT02003092) designed to evaluate safety, tolerability and pharmacokinetics following increasing doses of RX-5902 at varying schedules. Primary objectives include safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were pharmacokinetics (PK) and antitumor activity (RECIST v1.1). Eligible subjects (aged ≥ 18 years) with relapsed/refractory solid tumors received oral RX-5902 at 1, 3, 5 or 7 times per week for 3 weeks 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, 18 subjects have been enrolled (8 Females, 10 males). No dose limiting toxicities or treatment related SAEs have been reported. Six subjects have experienced stable disease; three subjects are currently receiving treatment for > 1 year. The most common side effects were grade 1 related adverse events: nausea, vomiting and fatigue; 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.

Conclusions: Data from this study support that RX-5902 is safe and well tolerated at the doses and schedules tested. Early Antitumor activity has been observed. A recommended phase 2 dose for RX-5902 for the treatment of triple negative breast cancer and advanced ovarian cancer will be presented.

RX-5902 Proposed Mechanism

- p68 phosphorylation at Tyr593 by c-Abl (Yang et al. Cell 2006)
- Phospho-p68 promotes EMT via promoting β-catenin nuclear translocation (Yang et al Cell 2006)
- Phospho-p68 mediates PDGF stimulated cell proliferation via promoting transcription of cyclin D1 and c-Myc genes (Yang et al J Biol Chem 2007)
- Phospho-p68 correlates with cancer progression
- β-catenin translocates 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/lymphoid enhancer factor [TCF/LEF] transcription factors) is required for the EMT process
- Studies underway to further characterize β-catenin interaction



Wang et al, Mol Cell Proteomics 2012; Yang et al, Cell 2006; He Cell, 2006, Yang J Biol Chem 2007

Study Design

This is a Phase 1/2a study (NCT02003092) designed to evaluate safety, tolerability and pharmacokinetics (PK) 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 PK and antitumor activity. Eligible subjects (aged ≥ 18 years) with relapsed/refractory solid tumors received oral RX-5902 at 1, 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest or for 4 weeks. Based on the RP2D of the Phase 1, a Phase 2a is ongoing in patients with advanced TNBC and OC in a 2-stage design.

Patient Demographics and Prior Treatments

Parameter	Overall
Gender, n (%)	24
Female	11 (46%)
Male	13 (54%)
Median age (range)	58 (25-86)
Race, n (%)	
White	23 (96%)
Other	1 (4%)
ECOG performance status, n (%)	
0	6 (25%)
1	18 (75%)
Number of prior anticancer treatments, n (%)	
1	3 (13%)
2	5 (22%)
3	2 (9%)
4+	13 (56%)

Baseline Characteristics of Patients. 28 potential patients were screened of which 24 were enrolled and 21 were treated with RX-5902. All 24 patients enrolled entered with Stage IV disease.

Safety Profile

Adverse Event	Number of Subjects per severity grade, n			
	Grade 1	Grade 2	Grade 3	Overall
Constipation	1			1
Diarrhea	1	1		2
Fatigue	3	2	1	6
Generalized weakness	1			1
Headache	1			1
Hypotension	1			1
Myalgias	1			1
Nausea	2	3		5
Neutropenia	1			1
Somnolence		1		1
Weight Loss	3		2	5
Vomiting	3	1		4

For further information about RX-5902 and Rexahn Pharmaceuticals please contact Dr. Ely Benaim: benaime@rexahn.com, (240) 268-5300 x304

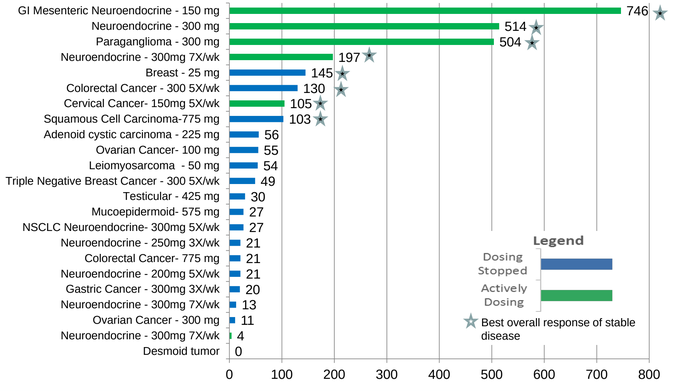
Pharmacokinetics

Pharmacokinetic (PK) samples were collected on Day 1 (for single weekly dosing) and Day 15 (multiple weekly doses) 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 and used for pharmacokinetic/pharmacodynamics assessments.

Dose (mg)	N	Dose Scheme	Dose Number	Cmax (µg/L)	Tmax (hr)	T1/2 (hr)	AUClast (hr*µg/L)	AUClast/Dose (hr/L*1000)
100	1	1 / Week	1	252	2		2341	23
150	1	1 / Week	1	226	6	11.4	3280	22
225	1	1 / Week	1	364	4	12.0	4312	19
300	2	1 / Week	1	385	3.8	16.6	5847	19
425	1	1 / Week	1	660	2		14673	35
575	1	1 / Week	1	707	4		10098	18
775	2	1 / Week	1	571	2.8		6570	8
250	1	3 / Week	1	394	2	14.0	5211	21
250	1	3 / Week	7	403	2		7774	31
300	1	3 / Week	1	288	6	10.3	4555	15
300	1	3 / Week	7	301	2		4143	14
150	1	5 / Week	1	227	2		2152	14
150	1	5 / Week	11	347	1		3721	25
200	1	5 / Week	1	337	4	8.5	2752	14
200	1	5 / Week	11	440	2		4034	20
300	2	5 / Week	1	433	1.8		4200	14
300	2	5 / Week	11	498	1.3		4359	15

Pharmacokinetic profiles of RX-5902. Dose proportional increase in plasma exposure up to dose of 575 mg daily, with slight accumulation from Days 1 to 15. Rapid oral absorption, with elimination half life suitable for once daily dosing.

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 cancers.
- Continuous dosing is currently being tested
- The study was recently amended to target triple negative breast cancer or ovarian cancer in a 2-stage Phase 2

Investigator Disclosures

1. Christine Peterson, PhD,, Reza Mazhari, PhD, and Ely Benaim, MD – Rexahn Pharmaceuticals