Phase 1 study of RX-5902, a novel Orally Bioavailable Inhibitor of Phosphorylated P68, which prevents β-catenin Translocation in Advanced Solid Tumors

J. Diamond[1], G. Eckhardt, W. Larry Gluck[2], Martin Gutierrez[3], Christine Peterson[4], Ruby Pila[4] and Ely Benaim[4].

[1]University of Colorado, Anschutz Cancer Center, 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

Abstract # 258P

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 through inhibition of β-catenin translocation. We report preliminary results of the Phase 1 study of RX-5902 as a single agent to treat advanced solid tumors.

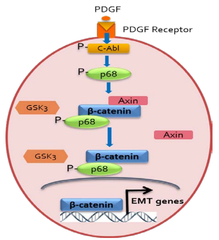
METHODS: The dose finding portion of the Phase 1 study (NCT02003092) was designed to evaluate safety, tolerability and dose limiting toxicities, to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were pharmacokinetics (PK) and antitumor activity (RECIST v1.1). Eligible subjects (aged ≥ 18 years), with relapsed/refractory solid tumors that had been heavily pretreated, received oral RX-5902 ranging from 25 mg to 350 mg and administered at 1, 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest or for 4 weeks without rest.

RESULTS: As of May 2017, 35 subjects (23 Females, 12 males) were treated with oral RX-5902. The dose limiting toxicities were G4 hyponatremia (n=1) and G3 fatigue (n=1) at 300 mg administered daily for 4 weeks. The maximum tolerated dose of 250 mg, will be studied further in the Phase 2a portion. Of the 35 subjects treated, 15 subjects (breast ER+/PR+/Her2-, triple negative breast (n=2), cervical (n=2), neuroendocrine (n=3), paraganglioma, colorectal (N=3), pancreatic, ovarian, head and neck cancers) experienced stable disease with 2 subjects receiving treatment for > 2.5 years. The most common related adverse events were G1 nausea, vomiting, diarrhea, weight loss and fatigue. Oral RX-5902 was bioavailable with median T_{max} 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. The RP2D of 250 mg of RX-5902 administered daily for 5 consecutive days for 4 weeks is being studied further in metastatic triple negative breast cancer in the Phase 2 portion of this study.

RX-5902 Validated Mechanism of Action

- p68 RNA helicase has been identified as the binding protein for RX-5902
- ^{3}H-RX-5902 binds to phosphorylated p68 and not p68 in a concentration dependent manner
- RX-5902 does not inhibit normal p68 RNA unwinding/helicase activity, but inhibits p-p68 ATPase activity
- RX-5902 decreases nuclear β-catenin in cancer cell lines but not in normal fibroblasts
- RX-5902 downregulates the downstream genes of β-catenin signaling in cancer cells but not in normal fibroblast cells



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 include evaluation of PK and antitumor activity. Eligible subjects (aged ≥ 18 years) with relapsed/refractory solid tumors who receive oral RX-5902 for 1, 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest or for 4 weeks. Preliminary data are presented for subjects in the phase 1 dose escalation.

Upon identifying the MTD or RP2D in the Phase 1, a 2-stage Phase 2a will commence in subjects with advanced TNBC and ovarian cancer.

Demographics

Parameter	Overall
Gender, n (%)	39
Female	24 (61.5%)
Male	15 (38.5%)
Median age (range)	62 (25-86)
Race, n (%)	
White	39 (100%)
ECOG performance status, n (%)	
0	13 (33.3%)
1	26 (66.7%)
Number of prior anticancer treatments, n (%)	
1	3 (7.7%)
2	4 (10.3%)
3	7 (17.9%)
4+	25 (64.1%)

Pharmacokinetics

Pharmacokinetic (PK) samples were collected on Day 1 (for single weekly dosing) and Day 15 (multiple weekly doses) for at least 8 hours. A Population PK model was built and used for pharmacokinetic/pharmacodynamics assessments. There is a trend towards dose proportionality despite the low number of subjects at some of the doses. The drug is absorbed orally moderately rapidly without a great deal of variability in Tmax.

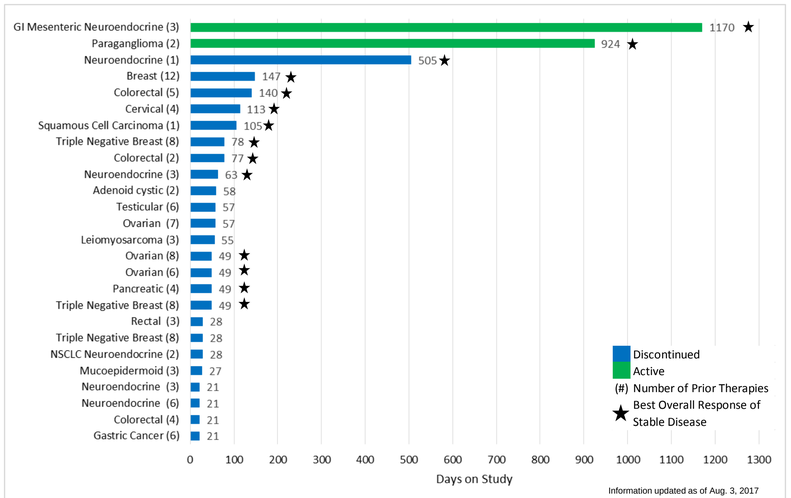
Dose	N	Dose Scheme	Dose Number	Cmax (ug/L	Tmax (hr)	T 1/2 (hr)	AUC0-8 hr*ng/mL)
250	1	3 / Week	1	394	2	14.0	1820
250	1	3 / Week	7	403	2		2158
300	1	3 / Week	1	288	6	10.3	1810
300	1	3 / Week	7	301	2		1551
150	1	5 / Week	1	227	2		1042
150	1	5 / Week	11	347	1		1687
200	1	5 / Week	1	337	4	8.5	1648
200	1	5 / Week	11	440	2		2268
250	10	5 / Week	1	605	2.4		2722
250	7	5 / Week	11	522	1.5		2243
300	4	5 / Week	1	477	2.4		2156
300	4	5 / Week	11	533	1.6		2199
300	4	7 / Week	1	439	2.9		2322
300	1	7 / Week	15	1250	6		6947
350	1	7 / Week	1	750	1.5		3378

Safety Profile

Most Frequent Adverse Events	Related Events n (%)	Highest Severity Grade Per Related AE (n) Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	18 (46.1%)	4	11	3	0
Nausea	12 (30.7%)	8	4	0	0
Diarrhoea	8 (20.5%)	6	2	0	0
Decreased appetite	8 (20.5%)	4	4	0	0
Asthenia	6 (15.3%)	3	0	3	0
Vomiting	5 (12.8%)	4	1	0	0
Somnolence	5 (12.8%)	1	4	0	0
Weight decreased	4 (10.2%)	4	0	0	0
Insomnia	4 (10.2%)	3	1	0	0
Cognitive disorder	4 (10.2%)	2	1	1	0
Gait disturbance	3 (7.6%)	3	0	0	0
Dehydration	3 (7.6%)	0	3	0	0
Arthralgia	2 (5.1%)	2	0	0	0
Constipation	2 (5.1%)	2	0	0	0
Headache	2 (5.1%)	2	0	0	0
Hypotension	2 (5.1%)	2	0	0	0
Muscle spasms	2 (5.1%)	2	0	0	0
Myalgia	2 (5.1%)	2	0	0	0
Pyrexia	2 (5.1%)	2	0	0	0

Most related adverse events were Grade 1 (n = 79) or Grade 2 (n=44). Twelve adverse events were Grade 3 and one related Grade 4 event, hyponatremia, was reported in a single patient (some data not shown above). 2 DLTs (Grade 4 hyponatremia and Grade 3 fatigue) were observed at 300 mg daily for 4 weeks. 250 mg/ day for 4 weeks was determined to be the recommended phase 2 dose.

Treatment Duration and Best Overall Response in Evaluable Subjects



Information updated as of Aug. 3, 2017

Conclusions

- RX-5902 is safe and well tolerated.
- Early anti-tumor activity was observed in patients with breast (including triple negative), ovarian, neuroendocrine, paraganglioma, colorectal, cervical, squamous cell, and pancreatic cancers.
- There is a trend towards dose proportionality despite the low number of subjects at some of the doses.
- The recommended phase 2 dose is 250 mg/day for 5 consecutive days with 2 days off for 4 weeks per cycle.
- The Phase 2 portion of the study targeting triple negative breast cancer or ovarian cancer is ongoing.

Investigator Disclosures

1. Christine Peterson, PhD, Ely Benaim, MD and Ruby Pila, MPH – Rexahn Pharmaceuticals

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